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Abnormal Long-Term Episodic Memory Profiles in Multiple Sclerosis?

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Abstract

Objective: Various verbal episodic memory impairments have been demonstrated in multiple sclerosis (MS), including encoding, retrieval and storage processes. Our clinical experiment suggests that a subset of MS patients may show another pattern with a distinctive evolution of performances after a 20 minutes delay (short-delay versus long-delay free recall).

Methods: The current study assessed performances on the California Verbal Learning Test (CVLT) in MS with a special focus on evolution after delay to identify a subgroup of patients who may show a significant spontaneous improvement of long-delay free recall in comparison with short-delay free recall. Data from 52 MS patients were compared with those from 32 controls. Group analyses were conducted on classical scores. Individual MS performances were also analyzed, according to confidence intervals calculated using control data.

Results: From individual analysis, memory comorbidities were frequently observed in a MS patient (17% of MS patients had only one impaired score, 17% had two or three scores, 27% had four or five scores and 38% had six or more). Regarding the evolution after delay, three profiles were highlighted: two classical (stable and worsening, i.e. storage deficit) and a third showing a significant degree of improvement. The improvement was significantly correlated with processing speed, primacy effect and sensitivity to retroactive interference only in this third MS subgroup. This benefit from delay was not related to the effect of semantic clustering.

Conclusion: The current study suggests that a subgroup of MS patients might present a previously unreported abnormal long-term memory profile, in which an impaired short-term performance contrasts with a significant spontaneous improvement with delay. Previous studies have demonstrated the relevance of spaced learning in MS rehabilitation. If our results are corroborated in a larger sample, the CVLT may help to select patients that are likely to benefit from this temporal memory care.

Keywords: Retroactive interference; Primacy effect; Free recall; Retrieval; California Verbal Learning Test; Rehabilitation; Processing speed

Introduction

Although cognitive impairment is part of the clinical picture in Multiple Sclerosis (MS), the diagnosis of this disease does not require neuropsychological evaluation, unlike other neurological diseases such as Alzheimer's disease and lobar atrophies. Nevertheless, neuropsychological assessment allows the description and quantification of cognitive deficits in MS patients and may be particularly useful in elaborating rehabilitation programs. At a time when the effectiveness of memory stimulation has been well demonstrated in MS patients [1-6], it seems relevant to precisely identify which processes are impaired or preserved in this population. When considering episodic memory abilities, it is usual to dissociate, on the one end, the long-term maintenance of information over the period of a few minutes to a lifetime (storage). On the other hand, the manipulation of information, which may include multiple executive sub-processes such as encoding, retrieval, sensitivity to interference and learning strategy [7-9].While executive impairments can be targeted by cognitive intervention, storage deficits are more likely to require prosthetic strategies (agenda or other external help).

MS patients are prone to cognitive comorbidities. Neuropsychological assessment of their memory functions requires therefore tools that are specially designed to detect potential impairments in each component. The California Verbal Learning Test (CVLT [10] and its revised version CVLT-II [11]) is recognized as a standard clinical test for verbal episodic memory and a consensus conference has recommended its use in MS, based on its psychometric properties [12]. It has also been included in the MACFIMS (Minimal Assessment of Cognitive Function In MS [13]), a standardized

cognitive battery for MS patients. CVLT comprises a shopping list of 16 words (List A) belonging to four categories. Five free-recall trials are carried out by the patient after oral presentation of the List A. Then, an interferent 16 item list (list B) is presented to the patient, followed by a single free-recall of list B. List B is comprised of two categories of items that are shared with List A, as well as two new categories. This interference trial is followed by a short-delay free recall and a cued (by the category names) recall of the List A. After a 20 minute delay, a long-delay free recall and a cued recall are carried out, followed by a long-delay recognition trial.

As a result of its complexity, the CVLT offers many valuable indices that can be used to analyze memory impairments. Firstly, the first trial can be used to assess encoding abilities reflecting initial short-term processing [14,15], while the recall progression through the first five trials may be considered an index of learning (or acquisition) corresponding to short-term and storage processes [15,16]. The learning strategy may be characterized by the spontaneous organization of material (semantic organization in categories or semantic clustering) by the subject, based on the four categorical groupings, on a serial (serial clustering) or random recall. Furthermore, the recall consistency, i.e. the words common to several recalls, may also be considered. The free recall usually varies as a function of an item's position within the list (serial position effect), the items at the beginning and at the end of the list being better recalled than those in the middle (primacy and recency effects respectively). Importantly, the primacy effect is interpreted as a transfer into long-term memory, while the recency effect is interpreted as maintenance in short-term memory. Short-term memory is distinguishable from long-term memory based on specific properties including temporal decay and chunk capacity limits [17]. In psychometric assessments, long-term memory classically implies survival of delays extending a few minutes (CVLT [10]; Grober and Buschke [18]; RAVLT [19]; WMS-IV [20]). A significant improvement with cueing as compared to low free recall usually characterizes retrieval impairment in the patient. The comparison of the first recall of List A with the recall of List B assesses sensitivity to proactive interference: an abnormal decrease in performance for the second list demonstrates a difficulty in learning new information due to interference with previous learning. Finally, the evolution between the fifth recall and the short-delay free recall of list A (i.e performances just before and after the List B) is used to evaluate retroactive interference (the tendency for retention of learned material to be impaired by subsequent learning) while a significant loss of information between short-delay and long-delay cued-recalls allows the clinician to diagnose a potential storage impairment.

Despite the existence of these numerous indices, approximately half of all the published experimental studies that used the CVLT to examine MS memory have only considered a few scores, the most popular being the total recall of the first five trials [9,27,29,30]. Among the most comprehensive studies [7,8,21,23-26,28], only Diamond and colleagues [21] and Stegen and colleagues [8] exhaustively reported on raw scores. In a large sample (351 patients), the latter study reported impaired performances for all the described indices. However, regardless of the scores in consideration, results in the literature remain controversial and some processes have been only rarely considered (Table 1). In terms of discrepancies in the literature, one issue may be linked to the type of statistical analyses used, which, in previous studies, have tended to be based on classical group analysis. Indeed, although this method is useful in highlighting central (mean) tendencies within groups, it has the limitation of potentially obscuring relevant individual profiles which are often heterogeneous in MS.

Results from previous studies	Normal	Impaired
First free recall	Diamond et al., 1997 [21]; Olivares et al., 2005 [22]	Panou et al., 2009 [23]; Sartori et al., 2006 [24];Stegen et al., 2010 [8]
Fifth free recall	Olivares et al., 2005 [22]; Tinnefeld et al., 2005 [25]	Diamond et al., 1997 [21]; Panou et al., 2009 [23]; Sartori et al., 2006 [24];Stegen et al., 2010 [8]
Mean or total learned words for the first five trials	Tinnefeld et al., 2005 [25]	Diamond et al., 1997 [21]; Defer et al., 2006 [26]; Fink et al., 2010 [27]; Griffiths et al., 2005 [7]; Lafosse et al., 2013 [9]; Marié and Defer, 2001 [28]; Sartori et al., 2006 [24]; Scarrabelotti et al., 1998 [29], 1999 [30]; Stegen et al., 2010 [8]
Sensitivity to interferent list	Diamond et al., 1997 [21]; Tinnefeld et al., 2005 [25]	Stegen et al., 2010 [8]
Short-delay and/or long-delay trials	Diamond et al., 1997 [21]; Tinnefeld et al., 2005 [25]	Defer et al., 2006 [26]; Griffiths et al., 2005 [7]; Lafosse et al., 2013 [9]; Marié and Defer, 2001 [28]; Panou et al., 2009 [23]; Sartori et al., 2006 [24]; Stegen et al., 2010 [8]
Recognition	Diamond et al., 1997 [21]; Lafosse et al., 2013 [9]; Olivares et al., 2005 [22]; Scarrabelotti et al., 1998 [29]; 1999 [30]; Tinnefeld et al., 2005 [25]	Defer et al., 2006 [26]; Fink et al., 2010 [27]; Griffiths et al., 2005 [7]; Marié and Defer, 2001 [28]; Sartori et al., 2006 [24]; Stegen et al., 2010 [8]
Semantic organization in categories	Diamond et al., 1997 [21]; Lafosse et al., 2013 [9]; Stegen et al., 2010 [8]	
Recall consistency	Diamond et al., 1997 [21]	Lafosse et al., 2013 [9]; Stegen et al., 2010 [8]
Primacy effect	Diamond et al., 1997 [21]; Stegen et al., 2010 [8]	
Recency effect	Diamond et al., 1997 [21]	Stegen et al., 2010 [8]
Sensitivity to proactive interference	Diamond et al., 1997 [21]; Griffiths et al., 2005 [7]; Stegen et al., 2010 [8]	
Sensitivity to retroactive interference		Griffiths et al., 2005 [7]; Stegen et al., 2010 [8]
Loss of information after delay	Diamond et al., 1997 [21]; Stegen et al., 2010 [8]; Kiy et al., 2011 [31]	

Table 1: Previously published results on CVLT raw scores in MS patients (only studies focused on the CVLT or having made the connection with CVLT scores and cognitive processes).

Another issue is related to the possibility that MS patients may suffer simultaneously from several cognitive deficits. Thus, the crude comparison of raw scores to norms may hide episodic memory

comorbidities. For instance, impaired raw scores for the first five trials may hide the impact of a supplementary learning deficit corresponding to a low progression (the learning rate) throughout the five trials.

In our clinical experience, we have observed that some MS patients have an unexpected pattern on the CVLT, whereby they show a significant improvement, over time, of their delayed free recall in comparison with their short delay free recall (evolution after delay). To our knowledge, whereas a benefit of spaced versus massed verbal learning was demonstrated in MS [3,32], spontaneous improvement after delay has not been reported in these patients.

We therefore designed the present study to both assess the reality of this pattern and to describe the potential mechanisms that may underlie it. The uniqueness of this study lies in the fact that, besides assessment of the usual measures of raw scores and intra-individual indices, we also carried out further analyses of individual performances. This allowed us to obtain a more sophisticated diagnosis of memory impairments in individual MS patients according to confidence intervals in controls. We hypothesized that a proportion of MS patients would show a significant improvement of their delayed free recall. We further hypothesized that cognitive slowing during the first trials could contribute to this pattern. We proposed, that if these hypotheses are true, the evolution after delay would be a) negatively correlated with processing speed and with the sensitivity to retroactive interference (the second list adding confusion in the on-line processing of words), and b) positively correlated with the primacy effect (patients being unable to process the subsequent words in the list due to a limited temporal capacity).

Method

Participants

We retrospectively studied the CVLT performance of 52 patients, assessed within the remit of clinical practice and meeting diagnostic criteria [33] for clinically definite MS (42 remitting-reminding, 6 primary progressive and 4 secondary progressive) using the French version of the CVLT test (ECPA manual [34]). Data included in this study were obtained in compliance with the Helsinki Declaration. 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 or alcohol dependence, (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. A group of 32 healthy controls volunteering for neuropsychological evaluation was also tested (Table 2).

Statistics

The data of the control group were first compared to the only published norms for the French version of the CVLT [34]. According to regression equations in this French manual (including the age, education and gender variables), none of the scores from our control group were found to be significantly below the norm (cut-off: standard deviation ≥-1.65 σ; percentile ≤5) for any of the following: a) the first trial, the fifth trial, and the total of the first five trials for List A; b) List B; c) the short and long delays free and cued recalls; d) the recognition of List A. These initial results thus confirmed that there were no pathological performances in our healthy participants in comparison with the 337 controls included in the French norms.

Demographic and main disease characteristics	MS (n=52)	Controls (N=32)	Statistical test
Male/female ratio	17/35	14/18	Chi2: 0.62, NS
Age (years)	Mean: 39.29 (±11.89) Range: 20-64	Mean: 40.9 (12.6) Range: 22-66	Mann-Whitney: U=771.5, NS
Education (years)	Mean: 12.27 (±2.4) Range: 8-21	Mean: 12.5 (2.5) Range: 8-17	Mann-Whitney: U= 816, NS
Expanded Disability Status Scale (EDSS)	Median: 3.5 Range: 0-7	/	
Disease duration since the onset of the first symptom	Mean: 9.1 years (±8.7)	/	
Mean duration since diagnosis	Mean: 8 years (±6.6)	/	

Table 2: Demographic and main disease characteristics in MS and control groups.

As most of our data did not meet the assumption of normality (normality of distribution, homogeneity of variances), simple comparisons were tested with non-parametric tests (Mann-Whitney and Wilcoxon), and regressions were assessed using the Spearman Rho. Statistical analyses were performed using Stat View for Windows (SAS Institute Inc. Copyright©1992-1998, Version 5.0) and statistical significance was set at a significance level of 0.05. The null hypothesis was rejected with $p \leq 0.05$ [35]. For group analysis (Table 3), we calculated classical scores, as per the French CVLT. Intra-individual indices, based on scores between retrieval conditions, were also calculated for the group and individual analyses.

Results

Group analysis

Classical scores were estimated (see Table 3 for results and operationalization of memory processes). Half of them revealed significant differences.

We calculated additional intra-individual indices (Table 3), assessing supplementary cognitive processes. A pathological retroactive interference was shown in the MS group however no significant difference was observed for proactive interference, learning, short-term retrieval or long-term retrieval. Neither the long-term evolution (i.e. the improvement, stability or worsening of recalls after delay for both free and cued recalls) nor recollection (which is taken to reflect the benefit of familiarity versus recollection retrieval), was statistically different between the two groups. For MS patients, we found no significant correlations between these variables and age, disease duration, and EDSS.

Classical scores	MS mean	MS SD	NC mean	NC SD	U	p
Trial 1 (T1), encoding	7.46	2.37	8.78	2.06	563	**.013**
Trial 2 (T2)	10.77	2.53	12	2.48	606.5	**.038**
Trial 3 (T3)	12.19	2.27	13.34	1.87	596	**.03**
Trial 4 (T4)	12.92	2.06	13.8	1.92	616	**.046**
Trial 5 (T5)	13.71	2.11	14.31	1.59	711	.265
Total Recall Trials 1-5 (5T)	57.06	9.74	62.28	8.41	574	**.017**
List B	7.73	2.74	9.53	2.71	547	**.009**
Short Delay Free Recall (SDFR)	11.56	3.32	13.18	2.29	595.5	**.029**
Short Delay Cued Recall (SDCR)	12.63	2.84	13.81	2.07	637.5	.073
Long Delay Free Recall (LDFR)	12.19	3.11	13.46	2.09	652	.097
Long Delay Cued Recall (LDCR)	12.77	2.85	14.06	1.70	624	**.05**
Delayed recognition	15.08	1.45	15.84	0.45	609	**.04**
Semantic clustering[1]	2.47	2.02	2.89	2.44	756.5	.49
Serial clustering[2]	1.2	0.95	- 1.5	0.74	702	.23
Consistency index[3]	65.57	7.03	67.73	7.31	665.5	.125
Primacy recall[4]	28.44	4.02	26.57	3.35	628	**.06**
Recency recall[5]	26.01	4.92	24.55	3.60	712	.27
Intra-individual indices	MS mean	MS SD	NC mean	NC SD	U	P
Proactive interference List B minus T1	0.27	2.64	0.75	2.83	747.5	.436
Retroactive interference SDFR minus T5	-2.15	2.06	-1.12	1.45	601	**.033**
Learning T5 minus T1	6.25	2.33	5.53	1.80	677.5	.155
Short-term retrieval (SDCR minus SDFR)	1.08	1.41	0.62	1.1	678.5	.157
Long-term retrieval (LDCR minus LDFR)	0.58	1.09	0.59	0.80	565	.89
Long delay evolution for free recall (LDFR minus SDFR)	0.63	1.75	0.28	0.96	717.5	.29
Long delay evolution for cued recall (LDCR minus SDCR)	0.13	1.14	0.25	0.84	782.5	.648
Recollection (Delayed recognition minus LDFR)	2.88	2.61	2.38	2.00	771.5	.573

Table 3: CVLT classical scores and intra-individual indices for MS patients (MS) and controls (NC): means, standard deviations and Mann-Whitney tests (U). Underlined: executive scores for which the prevalence was calculated.

[1]Semantic clustering: Observed semantic clusters according to the expected clusters for the five first trials

[2]Serial clustering: Observed serial clusters according to the expected clusters for the five first trials

[3]Consistency index: Percent of correct responses common to two successive immediate trials related to the total of correct responses for the five first trials

[4]Primacy recall: Percent of correct responses for the first four words of the list A related to the total of correct responses for the five first trials

[5]Recency recall: Percent of correct responses for the last four words of the list A related to the total of correct responses for the five first trials

In bold: significant results ($p \leq .05$); In bold and italics: statistical trends.

Individual analysis

While basic research studies tend to use group results to provide useful information about the mean tendency of memory deficits observed in MS patients, clinical practice necessarily involves the consideration of individual cases. For this purpose, we defined confidence intervals as a range of values which is likely to include an unknown parameter, the estimated range being calculated from a given set of a sample data (data from normal controls here).

Individual data were considered for two reasons: firstly, to identify potential multiple memory impairments in each MS patient and secondly, to identify, if present, the subgroup of our interest (one showing a significant improvement of their recall after delay). This last profile may be hidden at the group level by the reverse pattern (storage deficit with a significant worsening of the recall after delay) observed in some other patients.

Confidence intervals

Confidence intervals were measured in the control group to set a "highest" and a "lowest" limit for 11 strategic variables (underlined and defined in the Table 3).The performances of MS patients were then individually compared to these limits (99% confidence interval). Scores below the lower limit of the confidence interval were considered indicative of pathological performance (as for the encoding on the Trial 1), the exceptions being for the retrieval deficit, the serial clustering and the primacy and recency effects, where pathological scores were defined as being above the higher limit of the confidence interval.

Impaired encoding was observed in 50% of MS patients. Retrieval difficulties had a prevalence rate of 31% for short-term retrieval and 48% for long-term retrieval. A pathological sensitivity to proactive interference was demonstrated in 42% of MS patients and in 56% for retroactive interference. Pathological learning and an impaired consistency index were observed in 23% and 40% of MS patients, respectively. Insufficient semantic clustering was shown in 44% of MS patients while 37% showed excessive serial clustering. Finally, higher primacy and recency effects were observed in 44% of MS patients.

For these eleven scores, an impairment of several processes simultaneously was frequently observed in a MS patient. All patients showed at least one impaired score: 17% had only one impaired score,

17% had two or three scores, 27% had four or five scores and 38% had six or more.

Long-term evolution profiles based on confidence intervals

Because of the high prevalence of retrieval impairments in MS (32% and 50%) of MS patients for short-term retrieval and long-term retrieval respectively), we focused on free recalls (where the patient received no external help for the retrieval) when considering evolution after delay. This also maximized ecological validity. As mentioned previously, group analysis revealed no significant difference between controls and patients. However, based on our clinical experience we hypothesized that these mean data could be masking the presence of two abnormal MS subgroups with regard to performance after a long delay (twenty minutes for the CVLT): one subgroup tending to show an increasing loss of information after delay (or storage deficit) and another with a tendency to show an atypical improvement after delay. To test this hypothesis, we considered the frequency distribution of the long-delay evolution of performances for free recall at the individual level for MS patients according to confidence intervals calculated in controls.

We next defined, for analysis purposes, 3 subgroups of patients based on their individual evolution of delayed free recall according to confidence intervals. Patients with a score below the lower limit of the 99% confidence interval in controls (12 patients, 23%) were assigned to the 'worsening' MS subgroup while patients with a score above the higher limit of the confidence interval in controls (25 patients, 48%) constituted the 'improving' MS subgroup. The remaining patients (15 patients, 28%) were assigned to the 'stable' MS subgroup. As improvement in MS patients could have been overestimated due to a ceiling effect in controls (a high free recall after interference reducing the scope for improvement after delay), we verified that the improving MS patient subgroup remained the same, even after comparison with the performances of the weakest controls.

Characteristics of patients with long-term improving and worsening

We then compared the main scores of these three MS subgroups (stable, improving, worsening) with the entire control group and observed no significant differences for the stable MS subgroup ($p>0.05$). As indicated in Table 4, a significant impairment was found in the improving subgroup for all the free immediate and delayed recalls (T1, T5, 5T, List B, SDFR, and LDFR) as well as delayed recognition in comparison to controls. The improving subgroup also showed a pathological sensitivity to retroactive interference, a deficit in the primacy recall and an impaired learning consistency (consistency index), despite a normal number of learned words (T5 minus T1). For the worsening subgroup, free recall impairment was also shown, but only for T1, total 5T, and LDFR. This pattern of results suggests a progressive normalization of learning in the worsening subgroup throughout the five immediate recalls (normal T5), with thus a higher progression between T1 and T5 (larger learning) as compared to controls and a selective loss of information after delay (LDFR, LDFR minus T5). Pathological scores for delayed recognition and recollection were also observed.

Classical scores and intra-individual indices in improving and worsening MS subgroups	**Improving MS subgroup (n=25)**		**Worsening MS subgroup (n=12)**		**Comparison between subgroups**
	Mean (SD)	*Mann-Whitney Improving vs controls*	*Mean (SD)*	*Mann-Whitney Worsening vs controls*	*Mann-Whitney Improving vs worsening*
Trial 1 (T1), encoding	7.20 (±2.45)	U=249.5, **p=.015**	6.75 (2.30)	U=94, **p=.01**	U= 132, NS
Trial 5 (T5)	12.88 (2.20)	U=248, **p=.014**	13.92 (1.83)	U=168, NS	U= 106, NS
Total Recall Trials 1-5 (5T)	54.16 (9.29)	U=205.5, **p=.002**	55.33 (8.61)	U=111.5, **p=.034**	U= 145, NS
Primacy recall	29.34 (4.26)	U=242, **p=.011**	26.6 (2.99)	U=191.5, NS	U=90, **p=.05**
Consistency index	63.75(6.24)	U=259, **p=.023**	64.58 (6.41)	U=136.5, NS	142.5, NS
Learning T5 minus T1	5.68 (2.44)	U=390.5, NS	7.17 (2.08)	U=104, **p=.02**	U=93.5, **p=.06**
List B	7.28 (3.01)	U=241, **p=.01**	7.92 (2.87)	U=127, NS	U=135, NS
Short Delay Free Recall (SDFR)	9.88 (2.85)	U=147, **p<.0001**	12.50 (2.81)	U=166.5, NS	U=76, **p=.016**
Retroactive interference	-3.00 (2.18)	U=192.5, **p=.0008**	-1.42 (1.44)	U=167, NS	U=87.5, **p=.042**
Long Delay Free Recall (LDFR)	11.96 (2.67)	U=274, **p=.043**	10.92 (3.53)	U=107.5, **p=.03**	U=127, NS
Delayed recognition	14.84 (1.65)	U=275.5, **p=.045**	14.92 (1.56)	U=116, **p=.045**	U=145, NS
Recollection	2.88 (2.45)	U= 366.5, NS	4.00 (2.22)	U=116, **p=.045**	U=102, NS

Table 4: Impaired scores either for the improving or for the worsening MS groups in comparison to controls: means, standard deviations and Mann-Whitney tests (U).

Cognitive explanations of the long-term improvements in the improving subgroup

Either of two mechanisms may account for the better performance after delay observed in the improving subgroup. The first explanation would be that such a pattern of performance is a result of the cueing introduced before the long-term recall. This factor would be reflected in a change in long-term semantic clustering but no significant difference was shown between the improving MS subgroup and controls for the percentage of semantic clustering in list B (U=394.5, NS), the SDFR (U=293, NS), the LDFR (U=314.5, NS), or the evolution of the semantic organization between the SDFR and the LDFR (U=355, NS). The same results were obtained for the stable and

the improving MS subgroups. Furthermore, a significant correlation between semantic clustering before and after the explicit introduction of categories (R=0.816, p=<0.0001) was demonstrated in the improving MS subgroup. When we considered individual scores, we observed that, in 84% of patients from this MS subgroup, the superior performances in LDFR in comparison with SDFR could not be explained by semantic improvement.

A second explanation could be based on the slowness occurring during the processing of the first trials. According to this hypothesis, the sensitivity to retroactive interference and the primacy recall of this improving MS subgroup might be higher when compared with controls. Indeed, only this MS subgroup showed a significant pathological sensitivity to retroactive interference (improving: U=192.5, p<.0008; stable: U=238.5, NS and worsening: U=167, NS) and a very strong primacy effect (improving: U=242, p=0.011; stable: U=193.5, NS and worsening: U=191.5, NS). For these two indices, significant differences were shown between the improving and the worsening groups (Table 4). Moreover, as predicted, significant correlations were obtained only for the improving subgroup between the percentage of delayed improvement and processing speed (Symbol Digit Modalities Test; SDMT, R=-0.43, p=0.034), primacy recall (R=0.53, p=0.009) and retroactive interference(R=-0.52, p=0.01). The same results were obtained after Bonferroni correction was applied and were not shown for the two other MS subgroups (worsening and stable).

Discussion

The objective of the present study was to apply a cognitive approach to the assessment of memory performance in MS patients based on the many scores derivable from the CVLT. The originality of our work was to examine the individual performance of these patients, after carrying out classical analyses at a group level. At the group level, most classical scores were clearly reduced in MS patients, as compared with controls (except T5, SDCR, LDFR and executive scores), suggesting extensive memory dysfunctions in the MS population. However, for all these scores, data reported in the literature are controversial. Discrepancies between studies cannot be explained in terms of sample sizes, since conflicting results have been reported both in relation to small (n<30 MS patients [28]; Randolph et al., 2005 [36] for examples) and large study samples (n>200, [8,37]). For similar disease durations (11.5 years), differences in the EDSS score may influence performances, but only when disability increases (no significant difference below and above 1.5 [25]; selective deficit for 4.7 group versus 2.8, [26]). We suggest that an alternative explanation for these discrepancies may be a large variability in the memory profiles in MS patients, probably due to the variability of lesion topography. Such variability suggests a need for individual memory assessment in the interest of improved clinical care.

The present analysis of individual data revealed both executive and storage impairments in MS (100% of MS patients presented with at least one strategic dysfunction and 25% of them a storage dysfunction). In previous group studies, executive memory difficulties in MS have been widely reported [8,26-28] and have generally been described as encoding impairments [8,23]. Some authors are operationalized this deficit as a pathological score for both cued recalls and delayed recognition [28,26], although a storage deficit could also explain this long-term profile. For others, encoding refers either to the first recallT1 [21,38-41] which corresponds to the change of information from sensory input into a form that the memory system can store, or to the evolution throughout the first five trials (learning or acquisition), which corresponds to the change resulting from practice [9,16,27, 42-46]. Our individual results point to the existence of both these latter deficits, with encoding deficits being three times more common than learning deficits (58% and 19% of MS patients respectively). Besides the rate of recalls, the implied processes also appeared to differ with abnormal consistency between trials, pathological sensitivity to proactive and retroactive interferences, larger primacy and recency effects, reduced semantic clustering and excessive serial clustering. For the clinical case, the high prevalence of comorbidities (at least six impaired processes in 38% of our MS patients) underlined the requirement of intra-individual indices to identify the greatest number of disturbed processes.

A retrieval deficit for short and long-term recalls was revealed in a high proportion of patients (one-third and one half of MS patients respectively). To our knowledge, retrieval abilities, operationalized as the difference between free and cued recalls, have only rarely been reported in association with the CVLT in MS [27]. In the past, most authors compared delayed recall and recognition. However, the latter also involves familiarity mechanisms to access facilitation to stored information. We believe that identification of retrieval difficulties, as presently defined, is clinically relevant since once acknowledged, efficient rehabilitation programs may consequently be proposed to relevant patients [1,2,5].

Storage impairment, defined as a loss of information after delay, has rarely been studied with the CVLT. Here, we have been able to show a storage impairment using supplementary scores to classical CVLT scores. From a clinical point of view, storage deficits are important to identify because mnemonics training usually fails to provide any improvement and it seems preferable to train patients with external memos (like diary, time switch, layout of environment, etc). Our work suggests that a more extensive range of CVLT scores should be considered in MS assessment, in addition to the classical raw scores typically reported in experimental studies.

The most widely agreed-upon cognitive symptoms of MS are fatigue and slowing. In this study, we found normal sensitivity to proactive interference, suggesting no pathological effect of fatigue on the learning of the second list due to the learning of the first list. On the contrary, impaired sensitivity to retroactive interference was revealed. This dissociation between interference effects is in agreement with previous studies [7,8] with larger samples, 83 and 351 patients respectively). A comparison between the beginning and the interferent material is usually proposed as the explanatory mechanism of the retroactive effect [47-49]. This effect has been reported for short-term, long-term and implicit memories [47,50-53]. Impairment of retroactive sensitivity is usually shown on long-term retrieval [47,54-56]. However, the present study suggests a different memory pattern in MS. Despite an excessive sensitivity to retroactive interference in our patients, no effect on long-term performance was shown, as the evolution after delay for free and cued recalls was similar in MS and controls. This unexpected result favours the idea that a distinct mechanism could be present in some MS patients.

In the improving MS subgroup, we observed an excessive primacy recall effect and a pathological sensitivity to retroactive interference. We also found a significant correlation between the delayed improvement and processing speed, measured with the SDMT, the retroactive interference and the primacy recall only in this MS subgroup. Interactions between processing speed and verbal learning have been frequently reported in MS, these patients needing more

trials to learn the same amount of information as controls [42-46,57] and the spaced learning trials being a successful method in MS memory rehabilitation [3,32,46]. Here, we can hypothesize that a slower processing speed may explain the memory profile of the improving subgroup. Short-term memory is a limited capacity system. These patients would correctly process the beginning of the list (primacy recall). However, as a result of their slowness, their working memory would be more rapidly filled, preventing the processing of the following items. If learning of the first list is disturbed by slowing, we might also expect that the introduction of a second list will have a stronger interference effect in the improving subgroup in comparison with the other subgroups. Their interference sensitivity may be increased by both the non-stabilization of their memory trace for the first list and the addition of new items (difficult to learn in a single trial according to their short-term impairment). If these hypotheses account correctly for the situation, the improving subgroup may be help by spaced learning, as previously shown in MS [3,32,46]. The present study would provide a way to select patients likely to benefit from this temporal rehabilitation based on their performances in a classical clinical test (the CVLT).

Taken together, our results confirm that the MS group is not a homogenous one, and can be divided into distinct subgroups with differing levels of memory impairment. Thus, simply comparing the CVLT measures between a healthy control group and a single MS group could be problematic, and lead to conclusions of the absence of differences, when comparison with appropriate subgroups would reveal relevant differences. In the future, it will be important to compare these memory profiles within the different MS phenotypes (primary progressive, secondary progressive and relapsing-remitting). In the present work, we observed the presence of each of the 3 long-term evolution subgroups (stable, worsening and improving) in all the main MS phenotypes, but our sample was too small to compare the incidence of the subgroups, across them.

In conclusion, this study underlines the high prevalence of memory comorbidities in MS when individual performances are considered. Regarding performance after delay, our results show that, in addition to normal performance and storage impairment, MS patients may present an unexpected pattern of spontaneous improvement after delay. These results should be corroborated with a follow up study using a larger sample that would also allow assessment of the cause of this unusual improvement. We suggest that cognitive slowness is a likely explanation. Such an explanation would also account for the excessive primacy effect and pathological sensitivity to retroactive interference observed in this MS subgroup. When a cognitive rehabilitation is planned on MS patients, it will be crucial to identify such memory profiles, as proposed strategies should depend on the mechanism of impairment. If, as suggested by the present data, some short-term deficits are linked to slowness, a simple adaptation of the presentation rate could help patients in daily life.

Conflict of Interest

The information in this manuscript and the manuscript itself has never been published either electronically or in print and the authors have no conflicts of interest. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

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