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Semantic Relations and Repetition of Items Enhance the Free Recall of Words by Multiple Sclerosis Patients

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ABSTRACT

We compared 25 patients with multiple sclerosis (MS) and 24 normal controls on a test of free recall of words. Some lists contained words that were all unrelated, while in others the intermediary words were semantically related. In another set, the mid-list words were repeated across the lists, or, in addition to the repetition, were semantically associated. Immediate recall was assessed using these lists. Delayed recall was assessed using different lists (delay-unrelated and delay-related) after distractor tasks. Recency was not affected in MS patients, but the primacy effect was lower than in controls, this effect being interpreted as due to a deficiency in articulatory rehearsal. The delay interval after each list abolished recency in both groups and resulted in impaired recall in MS patients. However the patients, like the controls, benefited from semantic relations in the middle of the lists and from spaced repetition of words across the lists, in either immediate and delayed recall. The enhancing effects of word relatedness and of spaced repetition are seen as being due to automatic processes preserved in MS patients.

Multiple sclerosis (MS) is a chronic demyelinating disease of the central nervous system resulting in a variety of problems in vision, cognition, upper-extremity function, bladder and bowel control, mobility and fatigue. The average age of onset is 32 years. This early onset often leads to restricted health and well-being of patients during their most productive years. Depending on the evolutive course, MS can be classified as progressive, if the symptoms worsen progressively with an accumulation of disabilities, or relapsing-remitting if there are acute relapses with partial or complete recovery and no progression between attacks.

Several investigators have reported memory impairment in MS patients. In particular, long-term memory, as assessed by a variety of measures, is consistently impaired (for reviews see: Grafman, Rao, & Litvan, 1990; Minden, Moes, Orav, Kaplan, & Reich, 1990; Rao, 1986), whereas short-term memory, as assessed by measures of span, is usually unimpaired (Jambor, 1969; Jennekens-Schinkel, van der Velde, Sanders, & Lanser, 1990; Litvan et al., 1988b). Impairment of working memory, as conceptualized by Baddeley and Hitch (1974), has been reported in MS patients (Grigsby, Ayarbe, Kravasin, & Busenbark, 1994; Litvan et al., 1988b; Rao et al., 1993).

Semantic knowledge has been found to be intact (Goldstein, McKendall, & Haut, 1992; Rao et al., 1993), in spite of consistent reports of

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impaired access to semantic memory in verbal fluency tests (Beatty, Goodkin, Monson, & Beatty, 1989; Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988; Caine, Bamford, Schiffer, Shoulson, & Levy, 1986; Rao, Leo, Bernardin, & Unverzagt, 1991). One explanation for this discrepancy may lie in the automaticity of the former tasks against the purposeful process required by the search efforts of the latter.

Free recall of supraspan word lists evaluates the ability to remember occurrences of words on a given occasion; it is one of the most frequently used tests in research into episodic memory. The results of a free recall task may be plotted in the form of a serial position curve and analysed to provide useful clues to the functioning of several aspects of memory. For instance, words presented at the start of a list of items are better remembered than words presented mid-list (Deese & Kaufman, 1957; Murdock, 1962). This is called the primacy effect and is thought to be due to the greater amount of rehearsal given to the first words of the list (Fischler, Rundus, & Atkinson, 1970; Rundus & Atkinson, 1970). The recency effect, the words presented at the end being better remembered than those in the middle, is widely used as a measure of short-term memory, since the effect disappears if recall is delayed some minutes after presentation of the word list (Glanzer & Cunitz, 1966; Postman & Phillips, 1965). However, this interpretation is controversial as recency effects can be seen in situations that involve more than short-term memory capacity (Baddeley & Hitch, 1977).

Alterations in primacy and recency effects of normal subjects have been achieved through experimental manipulation such as varying list length and rate of presentation of the items to be recalled (Murdock, 1962); varying the input modality (Arenberg, 1976) and varying the amount of rehearsal (Atkinson & Shiffrin, 1971). In some studies, the central portion of the serial position curve has been manipulated to show that recall of semantically related words is greatly enhanced, even when they are clustered in the intermediary (mid-list) positions, which are less well remembered when the words are unrelated (Craik & Levy, 1970; Tulving & Patterson, 1968). Spaced repetition effect is a well known and robust phenomenon in which recall of words repeated after some time is greater than nonrepeated words or words repeated immediately after the first presentation (Toppino, 1991). The repetition of intermediary words across several lists amounts to a spaced repetition procedure and has therefore been found to enhance recall of these words (Bueno, Abrisqueta, Ueta, & Bertolucci, 1997).

Normal recency and reduced primacy in MS patients have been found previously (Rao, 1986; Rao, Leo, & St. Aubin-Faubert, 1989a). Caine et al. (1986) and Rao et al., 1989a found no decrease in the final portion of the list.

The main purposes of the present study were to detect possible contributions of semantic relations and spaced repetition of words as memory enhancers in MS patients, and secondarily to examine alterations in primacy and recency effects in verbal free recall. As they have preserved semantic memory and the enhancement effect of semantic association seems to be an automatic process (Oliveira, Pompéia, Vaz, Ruiz, & Bueno, in preparation), we predict that MS patients would benefit normally from semantic relations, and from spaced repetition of words, an automatic process also not impaired in these patients (Grafman, Rao, Bernardin, & Leo, 1991).

METHODS

Subjects

Patients ($n = 25$) with clinically definite MS participated in the present study. They were diagnosed according to the criteria of Poser et al. (1983) and classified as having the relapsing remitting course of the disease. At the time of evaluation, the disease was in a clinically inactive state. All patients were physically independent, with scores between 0 and 6 in the Expanded Disability Status Scale (EDSS; Kurtzke, 1983), and no signs of aphasia, apraxia or agnosia. The patients were recruited through the Department of Neurology of the Universidade Federal de São Paulo-Escola Paulista de Medicina. All the patients were receiving symptomatic medication, either interferon-beta 1b (on alternate days), azathioprine or methotrexate. Steroids were only prescribed to treat acute relapses of the disease. They were compared to 24 healthy volunteers (CON – control group) with no history of neurological or psychiatric diseases. Both

Table 1. Demographic Characteristics and General Cognitive Performance of the Subjects.

Variables	MS patients	Controls	Student *t*	*p*
Age (years)	38.5 ± 9.6	35.3 ± 10.7	1.093	.28
Education (years)	12.4 ± 13.3	13.9 ± 3.6	1.216	.23
Sex (males/females)	6/19	6/18		
Full Scale IQ	104.8 ± 17.0	111.1 ± 14.6	1.364	.17
Verbal IQ	109.8 ± 17.0	110.8 ± 14.3	0.21	.82
Performance IQ	96.4 ± 14.9	108.1 ± 15.9	2.596	.01

Note. Test statistic from a *t* test.
$p > .05$.

groups were similar in relation to age and education (see Table 1).

Neuropsychological Assessment

The participants were submitted to batteries of cognitive ability and memory tests, and other psychiatric evaluation measurements, in three sessions of 2 hr each. Tests included a shortened version of the Wechsler Adult Intelligence Scale – Revised (WAIS–R), (Vocabulary and Design Block subtests), subtests of the Wechsler Memory Scale (WMS), Stroop Color Test, Rey-Osterrieth Complex Figure, Corsi Block-Tapping Test, FAS and Naming and Memory for Objects. All participants answered the Beck Depression Inventory and the State-Trait Anxiety Inventory. The order of evaluation was pseudo-random to avoid a possible bias produced by fatigue or by task presentation order. Testing of free recall of words was performed during the first half of the sessions, intermingled with the tests listed above. Compared to controls, the patients were found to be impaired in learning/memory tasks (immediate and delayed recall), in timed tasks, and in tasks with a motor component. However, their global intellectual achievement was as good as the control's results (see Table 1). Detailed results of the neuropsychological evaluation of these patients may be found in Andrade et al. (1999).

Verbal Free Recall

Thirty word lists were prepared and tested in advance. Each list had 15 common Portuguese words taken from a pocket dictionary. Each word had 2 or 3 syllables and was a common noun or adjective. The following lists were used: (a) six lists of unrelated words (unrelated); (b) six lists in which the three intermediary words (corresponding to input positions 7–9) were semantically related (related), as, for example, the Portuguese words for milk, cheese and butter; (c) six lists of unrelated words but in which the words in the middle were the same across the lists (repeated); (d) six lists in which the intermediary words were semantically related and were repeated in all of them (repeated-related); (e) three lists of unrelated words recalled after a delay interval (delay-unrelated); and (f) three lists recalled after a delay interval in which the three words in the middle were semantically related (delay-related). Besides the midlist words of the related lists, no other words within the same list were semantically related. The order of distribution of the words between the lists was semi-random, but phonetic relations within the same list such as rhymes and sequences of more than three words starting with the same letter were avoided.

Procedure

Each list was read at the rate of one word per second to each subject. The recall test was performed at the end of each list, either immediately after the last word was read or after a delay interval of 2 min, during which the subject had to perform a distracting activity. The subjects were instructed to say out loud as many of the words as possible without worrying about the order. In 24 lists, recall was immediate and in six lists recall was delayed. The experimenter took note of the answers.

Data Analysis

For statistical analysis and graphic presentation, the input positions were organized into groups of three, making a total of five clusters, such that the first group was considered the primacy effect generator and the last group was considered the recency effect generator. The three intermediary positions (7–9) were those which were manipulated by the introduction of semantic relations or repetition through the lists. To evaluate the number of words recalled, a two-way ANOVA with a repeated factor (factors: group and type of list or position in the list) was used. When appropriate, the ANOVA was followed by a Tukey's

post hoc test. A measure of the rate of forgetting was obtained by comparing the words recalled per list in the immediate and delayed tests. In order to analyze the rate of forgetting a three-way ANOVA was used (factors: group; delay; type of list). For all other measurements Student's t test was used. All analysis was performed using STATISTICA for Windows software (Release 5.1, 97 Edition) from Stat Soft Inc.

RESULTS

Intelligence and Memory Tests

Table 1 summarizes the demographic characteristics of the participants and their general performance in cognitive tests. The Full Scale IQ and the Verbal IQ, as evaluated by WAIS–R were also similar, indicating a preserved general intelligence in the MS patients. Their Performance IQ, however, was significantly inferior than that of controls, probably because the performance subtests are more affected by execution time (see Andrade et al., 1999 for details).

Overall Immediate Recall Data

The total immediate recall of MS patients was impaired as compared to controls. There was a significant difference between the lists $F(3, 141) = 6.82$; $p < .0002$, but no difference between the groups $F(1, 47) = 0.29$; $p = .58$, or interaction between groups and lists, $F(3, 141) = 1.53$; $p = .2$. The Tukey's test showed that the repeated-related lists were the easiest to remember ($p \leq .05$), and the unrelated lists were more difficult than the others.

Serial Position: Immediate Recall

In the unrelated lists the groups were not different, $F(1, 47) = 1.3$; $p = .26$, but there was a difference in relation to the word positions, $F(4, 188) = 1.18$; $p < .0001$. Tukey's post hoc test ($p \leq .05$) showed that positions 1–3 were more remembered than positions 4–6, indicating that a primacy effect was present. Positions 7–9 were less remembered than positions 1–3 and 13–15, demonstrating the usual intermediary reduction. Positions 13–15 were more remembered than positions 10–12 indicating the presence of a recency effect. Interaction between groups and positions was detected, $F(4, 188) = 2.65$; $p = .03$. A Tukey's post hoc test ($p \leq .05$) of this interaction showed that the patients performance was inferior when compared to the controls only in positions 1–3 (Fig. 1A).

In the related lists the groups were similar, $F(1, 47) = 1.09$; $p = .30$, but a significant difference between the positions was detected, $F(4, 188) = 92.88$; $p < .0001$; they were all different between themselves (Tukey; $p \leq .05$), except 1–3 versus 10–12. The increase in the number of the remembered words in positions 7–9 demonstrated an enhancing effect of the semantic relatedness among these words. There was no interaction between groups and positions, $F(4, 188) = 1.14$; $p > .3$ (Fig. 1B).

In the repeated lists there were no significant differences between the groups, $F(1, 47) = 0.06$; $p > .81$. There were significant differences in relation to the positions, $F(4, 188) = 98.01$; $p < .0001$, all of which were different between themselves, except 1–3 versus 7–9 (Tukey $p \leq .05$). Peak recalls appeared in positions 7–9 due to repetition of the intermediary words across the lists. No interaction between groups and positions, $F(4, 188) = 1.1$; $p = .33$, was detected (Fig. 1C).

In the repeated-related lists the groups did not differ between themselves, $F(1, 47) = 0.04$; $p = .8$, but there were significant differences in relation to the positions, $F(4, 188) = 100.2$; $p < .0001$, all the positions differing between themselves except 1–3 versus 10–12 and 7–9 versus 13–15 (Tukey $p \leq .05$). The increase in the number of recalls in positions 7–9 is a result of the semantic relatedness coupled with the repetition of the same words across the lists. There was no interaction between groups and positions, $F(4, 188) = 2.4$; $p = .052$ (Fig. 1D).

Overall Delayed Recall Data

The total number of delayed recalls from the lists showed a significant difference between the groups, $F(1, 47) = 12.89$; $p = .0007$, and between the different lists, $F(1, 47) = 15.59$; $p = .0002$, but there was no interaction between the groups and lists, $F(1, 47) = 0.02$; $p = .86$. Tukey's post hoc test showed that the patients remembered

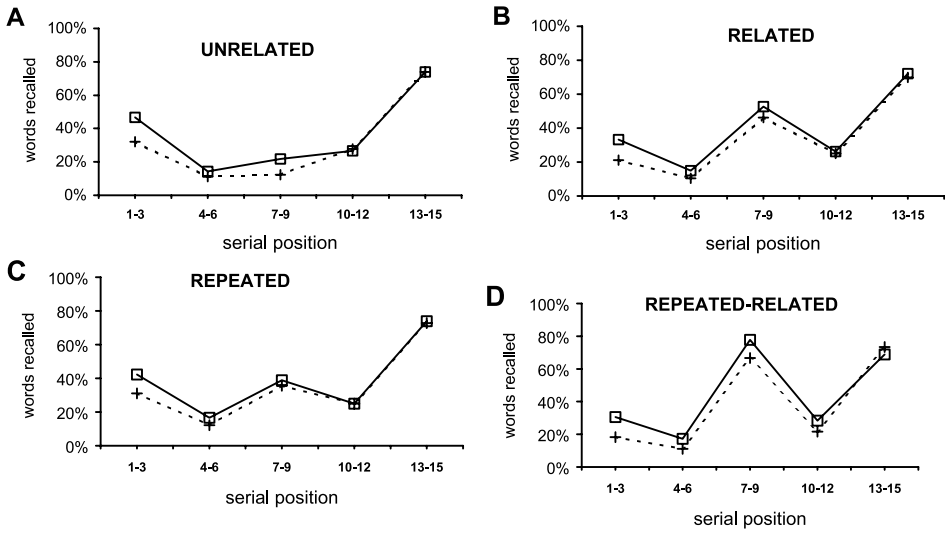

Fig. 1. Serial position curves derived from immediate verbal free recall tests. (A) Lists of Unrelated (UNRELATED) words. (B) Lists with semantically related (RELATED) words in mid-list positions. (C) Lists with repeated (REPEATED) words in mid-list positions. (D) Lists with repeated and semantically related (REPEATED-RELATED) words in mid-list positions. Positions were clustered in groups of 3 words. (□ □) Control group; (+-----+) multiple sclerosis group.

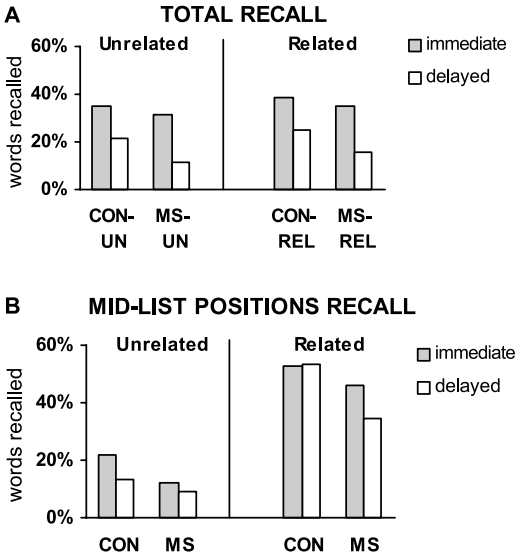

Fig. 2. Percentage of words recalled in immediate and delayed verbal free recall tests. (A) Total words recalled. (B) Mid-list positions (7–9) recalled. CON – control; MS – multiple sclerosis.

fewer words than the controls and that the delay-related lists were more remembered than the delay-unrelated lists ($p < .05$). (Fig. 2A).

Serial Position: Delayed Recall

A significant group main effect, $F(1, 47) = 13.17$; $p = .0007$, followed by Tukey's post hoc test ($p \leq .05$) showed that MS patients presented a general reduction in the serial position curve of delay-unrelated lists when compared to the control group. There were also significant differences between the positions, $F(4, 188) = 18.79$; $p < .0001$. Tukey's post hoc test indicated that the primacy effect continued to be exhibited as the words in positions 1–3 were more remembered than those in the other positions ($p \leq .05$), and that the recency effect was lost in both groups. No interaction between groups and positions was seen, $F(4, 188) = 2.3$; $p > .10$.

In the delay-related lists there were significant differences between the groups, $F(1, 47) = 9.66$; $p = .003$, and Tukey's test showed a reduction in the patients' serial position curve when compared to the controls ($p \leq .05$). There were differences between the positions, $F(4, 188) = 33.25$; $p < .0001$, positions 7–9 being more remembered than all others, showing that there was a peak of recall within the delay-related lists even after the delay. There was a reduction in recall in positions 13–15 indicating that the recency effect

was lost. The primacy effect can still be observed, as positions 1–3 were more remembered than positions 4–6 and 13–15. There was no interaction between groups and positions, $F(4, 188) = 1.16$; $p > .32$ (Fig. 2B).

Rate of Forgetting

The 2-min delay interval before recall reduced the number of remembered words, $F(1, 47) = 114$; $p < .0001$, and the patients remembered less words than the controls, $F(1, 47) = 7.17$; $p = .01$. Furthermore, the words from the delay-related lists were more remembered than those from the delay-unrelated lists, $F(1, 47) = 28.33$; $p < .0001$. The only statistically different interaction was the one between group and delay, $F(1, 47) = 4.67$; $p = .03$. Tukey's post hoc test ($p < .05$) showed that this was due to the fact that the delay caused a greater decrease in the correctly recalled words of MS patients when compared to controls. There was no interaction between group versus delay versus type of list, $F(1, 47) = 0.05$; $p = .8$, suggesting that the decrease in the MS patients' performance was independent of the type of list.

DISCUSSION

A deficit in immediate and delayed free recall was shown by the MS patients as compared to the control participants. Regarding immediate free recall, the MS patients presented a specific impairment in the primacy effect. Reduced primacy was already noted by others (Rao et al., 1989a). A visual inspection of the position curves published by Litvan and collaborators (1988a, 1988b) and by Caine et al. (1986) suggests that a small decline in primacy occurred in their patients also, but this is not mentioned by the authors. It seems that, when detected, the primacy reduction is rather small. The decreased primacy can be accounted for by a diminution of the number of rehearsals caused by an impairment of the articulatory loop, as there is evidence for a defective articulatory rehearsal mechanism in MS patients (Jennekens-Schinkel et al., 1990; Rao et al., 1993).

In the present study, the recency effect was not impaired. This is in accordance with results observed previously. Normal recency and reduced primacy in MS patients have been found by Rao et al. (1989a). Other authors have also failed to find a decrease in the final portion of the list (Caine et al., 1986; Rao et al., 1989a). Using the method developed by Tulving and Colotla (1970) to separate the relative contributions of short and long-term memory to verbal free recall, Rao, et al. and Faubert (1989a) found that MS patients recalled significantly fewer words from long-term memory, but not from short-term memory. In addition, results from digit span tests, either in our patients (Andrade et al., 1999) and in patients studied by others (Klonoff, Clark, Oger, Paty, & Li, 1991), did not show any deficits in comparison with controls. These results and the preserved recency effect strongly suggest that short-term memory is not affected by the disease.

The introduction of a distracting activity between the end of the list and the recall test produced the expected effect of abolishing the end peak of the serial position curve in the control group as well as in the MS group, which is consistent with a short-term memory interpretation of the recency effect (Glanzer & Cunitz, 1966; Postman & Phillips, 1965) in the conditions of the present study. In the MS group, the delay affected not only the recency effect, but also produced a widespread reduction in remembering throughout the entire list, decreasing the total number of recalled items, compared to controls in similar condition. Impairment in delayed recall in MS patients has been reported in studies using several kinds of to-be-remembered material, including visual stimuli, prose passages and word lists. However, these reports do not reveal, in general, an impairment of delayed recall proportionally greater than that of immediate recall. As a result, a difficulty in the acquisition rather than in the retention of new information have been usually attributed to MS patients (e.g., Beatty et al., 1988; van den Burg, van Zomeren, Minderhoud, Prange, & Meijer, 1987). Our results demonstrate a much more severe impairment in the delayed recall than in the immediate recall of word lists. Differences in procedure may partly explain this finding. Most studies of free recall of word lists in which delayed recall was also assessed have consisted of multi-trial learning

tasks. In these studies immediate recall followed the first presentation of the list, while the delayed recall was assessed after a time interval that followed the last trial, or, in other words, after a gradual learning of the word list. This contrasts with the present experiment in which delayed recall was performed after a single exposure to each list, giving the subjects no opportunity to relearn the lists. Neither encoding deficit nor a retrieval impairment would seem to provide a satisfactory explanation for the present results since when asked to recollect the words immediately after the presentation of each list, the patients' recall was near normal (except for a small decline in primacy that can be explained by other reasons), suggesting that both mechanisms, encoding and retrieval, were operating normally. On the other hand, the performance of the same patients after the delay was reduced proportionally more than the performance of the controls. Although this finding may suggest that the patients have a greater forgetting rate, it should be noted that delayed recall versus immediate recall was not computed for the same lists at different times. This point deserves further investigation in order to be clarified.

The MS subjects, like the controls, benefited from inter-list repetition of words. They were also able to use semantic relations between words to improve recall of intermediary items. This contrasts sharply with moderately demented Alzheimer's patients who do not benefit from any of these memory enhancers when immediately recalling similar word lists (Bueno et al., 1997); in the latter patients, this impairment occurred alongside with a deficit of total recall and of episodic memory failures in other tests. Despite an impairment in a variety of other tasks, such as prose passage, picture recall, paired associate learning, as reported in Andrade et al. (1999), our MS patients presented only a small deficit confined to the first three words in the immediate recall of the word lists. Therefore, it could be argued that the beneficial effects of semantic relations and of spaced repetition are related to the overall word recall, and so it is not surprising at all that the enhancing effect was preserved. However, a striking decline in performance was observed in the delayed recall test as compared to the controls. In spite of this severe memory impairment, the beneficial effect of the semantic relations of the words in the middle of the list was preserved in the same proportion of that seen in the healthy subjects (in both groups, a fourfold increase in recall was produced by mid-list word relatedness). Therefore, the cognitive processes required for the semantic relation enhancement effect seem to be independent of the processes required for episodic memory, being resistant to increased retention intervals. In consonance with the present results is the normal release from proactive inhibition encountered by Rao et al. (1993) in MS patients, an effect that implies normal semantic encoding. In contrast with our results, Troyer, Fisk, Archibald, Ritvo, and Murray (1996) found that MS patients are less likely to use semantic encoding or category clustering strategies than controls. However, this contradiction may be only apparent, as the strategies required in the latter study are active and effortful (the subjects have to generate the category clusters by themselves). In the present experiment, on the contrary, active generation of words associations was not necessary. The participants had only to perceive the strong semantic relations between words in the middle of the related lists, so it is reasonable to assume that this task that does not require effortful processing. It is relevant to the present interpretation that normal release from proactive inhibition has been found in MS patients (Rao et al., 1993).

Also, spaced repetition is considered to have an automatic effect in improving memory (Toppino, 1991). Thus, the present results is not in disagreement with to the proposal that MS patients perform normally in memory measures requiring automatic processing, while in those requiring effortful processing their performance is impaired, in agreement with the interpretation of Grafman et al. (1991).

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