RBANS analysis of verbal memory in multiple sclerosis

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Abstract

Patients with neurodegenerative diseases that cause mainly subcortical pathology often exhibit impairment when required to recall lists of unrelated words, but their memories are supposedly improved by test procedures that promote retrieval such as recognition or improve the organization of the to-be-remembered materials. Difficulties with floor effects on free recall and ceiling effects on recognition and other methodological concerns raise doubts about the validity of existing studies that tested these ideas. Using the verbal memory subtests of the RBANS, we [Arch. Clin. Neuropsychol. 18 (2003) 509] expressed each patient’s performances on Story Memory, List Learning, Story Recall, List Recall, and List Recognition as Z scores relative to his or her age group. Then, the Z scores were subtracted pairwise to test hypotheses about the nature of memory in Parkinson’s disease (PD). Contrary to expectation, patients with PD did not show better immediate or delayed recall of stories relative to lists and they did not show better recognition than recall.

In the present investigation, the same methodology was used to study verbal memory in multiple sclerosis, a disease that primarily affects subcortical structures. In contrast to previous results for patients with PD, the patients with MS exhibited better recall of stories than of lists and better List Recognition than Recall. Differences in the pathology of entorhinal regions in PD and MS may contribute to the differing patterns of memory impairment of these patients. The results emphasize that most patients with MS with memory impairments have deficits that are relatively mild and potentially remediable.

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1. Introduction

The memory disturbances that accompany Parkinson’s disease (PD) and multiple sclerosis (MS) appear to differ qualitatively as well as quantitatively from those associated with Alzheimer’s disease (AD) and temporal lobe amnesia. Manipulations of the test format that promote encoding or facilitate retrieval are reported to improve memory by patients with PD or MS, but the same procedures are much less effective for patients with AD or amnesia (Cummings, 1990). These observations support the view that retrieval failure is the major cause of memory impairment in PD (Weingartner, Burns, Diebel, & DeWitt, 1984) and MS (Rao, Leo, & Aubin-Faubert, 1989). Other findings, however, are inconsistent with the idea that defective retrieval is the main factor in the memory disturbances of patients with PD or MS. Impairments in recognition as well as recall have been noted in a number of studies of patients with PD or MS (Beatty, Staton, Weir, Monson, & Whitaker, 1989; Carroll, Gates, & Johnson, 1984; Sullivan & Sagar, 1989).

Devising a valid way of comparing performances on memory tests using different formats is not simple. Free recall measures may be vulnerable to floor effects while recognition tests may be insensitive because of ceiling effects. Recently, we compared performance by patients with PD or AD on the verbal memory components of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS; Randolph, 1998). We (Beatty et al., 2003) utilized the excellent norms for this test to calculate Z scores for each subject on each of the relevant subtests. Then, the Z scores were subtracted pairwise to test specific hypotheses about memory and other cognitive functions. Both patient groups performed more poorly on tests that required motor skill or cognitive speed and this was true for all cognitive domains (Language, Visuospatial/Construction and Attention) examined. Thus, PD patients exhibited the expected mental slowing observed in many other studies (Beatty et al., 1989; Cummings, 1990). In contrast to prediction, the patients with PD did not learn or remember stories better than unrelated word lists and they also did not perform better on recognition than on recall tests for memory for word lists. This finding raises questions about the validity of the retrieval failure explanation of impaired memory in PD. In the present study, the performance of patients with MS examined using the same battery of measures and analyses from the RBANS employed in the earlier study of patients with AD or PD (Beatty et al., 2003). Based on neuropsychological studies of the average performance of large groups of patients, cognitive deficits in MS fit in the typical pattern of subcortical disease (Rao, 1986).

2. Method

2.1. Participants

The participants were 58 patients (27 M, 31 F) with clinically definite MS. Fifty of the patients (20 M, 30 F) attained scores of at least 27 on the MMSE (the lower limit of healthy controls from central Oklahoma; Folstein, Folstein, & McHugh, 1975). The remaining MS patients (7 M, 1 F) scored between 22 and 26 on the MMSE. The proportion of men was significantly higher in the low MMSE-MS group than in the MS group of normal mental
status $\chi^2(1) = 4.49, P < .05$. Of the patients who scored at least 27 on the MMSE, 29 had a relapsing-remitting disease course and 21 had a secondary progressive disease course. Of the patients who scored less than 27 on the MMSE, three had a relapsing-remitting course and five had a secondary progressive course.

All patients underwent extensive medical and neurologic workups. They were excluded if they had any of the following conditions: history of neurologic disease other than MS (e.g., stroke, traumatic brain injury); history of schizophrenia or bipolar disease; history of alcoholism, drug abuse, or mental retardation; history of or a current serious medical illness (e.g., recent heart attack, poorly controlled diabetes).

Patients met criteria (Poser et al., 1983) for clinically definite MS. They were recruited from the clinic at the Oklahoma City Veterans Affairs Medical Center and from the practices of area neurologists. Utilizing the Ambulation Index (AI; Hauser et al., 1983) as a measure of physical disability, the patients in the group with MMSE scores in the normal range averaged $3.6 \pm 2.7$ on the AI while the patients in the group with low MMSE scores averaged $4.6 \pm 3.3$ on the AI. This difference was not significant ($t < 1$).

All patients received medications as prescribed by their attending physicians with doses adjusted for optimal clinical benefit. Details of the medications used are given another report (Aupperle, Beatty, Shelton, & Gontkovsky, 2002). Statistical analyses of the data for the MS patients indicated that the use or non-use of any of six classes of medications (immunomodulators and drugs to reduce spasticity, fatigue, depression, anxiety, or pain) was not significantly associated with neuropsychological (NP) test performance (Aupperle et al., 2002).

### 2.2. Procedure

Participants received the RBANS (Randolph, 1998), the MMSE and a self-report measure of depression as part of a larger battery. The Chicago Multiscale Depression Inventory (CMDI; Nyenhuis et al., 1995), which partitions depression into three components: mood, evaluative and vegetative was administered.

### 2.3. Data analysis

Scores for the six indexes (Immediate Memory, Visuospatial/Construction, Language, Attention, Delayed Memory, Total) were computed as described in the RBANS test manual (Randolph, 1998). To test the hypotheses about relative performance on the various measures of verbal memory, norms for the means and standard deviations on the individual subtests were obtained from the test publisher. Like the norms for the RBANS Indexes, norms for the individual subtests are blocked by decade for individuals from 20 to 89 years of age. Using the normative data for each patient’s age group, performances on the Story Memory, List Learning, Story Recall, List Recall, List Recognition, Naming, and Semantic Fluency were converted to Z scores. Then the Z scores were subtracted pairwise to test each a priori hypothesis about memory. Specifically, three comparisons were conducted to evaluate learning and memory: Z Story Memory–Z List Learning, Z Story Recall–Z List Recall, and Z List Recognition–Z List Recall. A fourth comparison, Z Naming–Z Semantic Fluency, tested the hypothesis that patients with MS should show slowed information processing. Each of the predicted patterns
was analyzed in two ways: (a) was the average difference in Z scores for each of the patient groups significantly different from 0; and (b) were there significant differences between the MS groups?

3. Results

Table 1 summarizes results on the demographic measures, the RBANS Indexes and the scales of depression. The two groups of patients did not differ significantly in age, education, disease duration or on any of the measures of depression. However, based on the recommended cutoffs for the CMDI, 28% of the patients had elevated scores on the Mood scale, 36% showed elevated scores on the Evaluative Scale, and 52% showed elevated scores on the Vegetative Scale.

Patients with low scores on the MMSE performed more poorly than patients who scored within the normal range on the MMSE (Wilks lambda = 0.773, $F(6, 51) = 2.499$, $P < .05$), but these differences were significant only for Immediate Memory, Delayed Memory, and Total.

Table 2 summarizes performance (raw scores) on the various subtests which comprise the Immediate Memory and Delayed Memory Indexes. Figure Copy is actually part of the Visuospatial/Construction Index, but is reported here because it serves as the “learning” trial for Figure Recall. Multivariate analysis of variance of the verbal tests showed a significant overall effect of MMSE level (Wilks lambda = 0.802, $F(5, 52) = 2.569$, $P < .05$). As shown

<table>
<thead>
<tr>
<th>Table 1</th>
<th>MMSE ≥ 27</th>
<th>MMSE &lt; 27</th>
<th>$F(1, 56)$ for groups</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>50</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>49.7 (8.4)</td>
<td>46.8 (11.0)</td>
<td>0.61</td>
</tr>
<tr>
<td>Education</td>
<td>14.6 (2.2)</td>
<td>14.0 (1.6)</td>
<td>0.52</td>
</tr>
<tr>
<td>Disease duration</td>
<td>13.6 (8.5)</td>
<td>12.8 (6.2)</td>
<td>0.07</td>
</tr>
<tr>
<td>MMSE</td>
<td>28.6 (1.1)</td>
<td>24.9 (1.2)</td>
<td>79.90***</td>
</tr>
<tr>
<td><strong>RBANS Index</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Immediate Memory</td>
<td>96.4 (14.7)</td>
<td>79.1 (14.3)</td>
<td>11.82***</td>
</tr>
<tr>
<td>Visuospatial/Construction</td>
<td>102.7 (15.7)</td>
<td>101.3 (21.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Language</td>
<td>94.0 (10.9)</td>
<td>90.6 (11.7)</td>
<td>0.89</td>
</tr>
<tr>
<td>Attention</td>
<td>91.7 (15.5)</td>
<td>87.8 (17.9)</td>
<td>0.56</td>
</tr>
<tr>
<td>Delay Memory</td>
<td>95.5 (14.9)</td>
<td>77.6 (22.8)</td>
<td>9.12**</td>
</tr>
<tr>
<td>Total</td>
<td>94.5 (13.4)$^p$</td>
<td>83.1 (19.2)</td>
<td>4.67$^*$</td>
</tr>
<tr>
<td><strong>CMDI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood</td>
<td>56.9 (13.3)</td>
<td>62.5 (16.4)</td>
<td>1.15</td>
</tr>
<tr>
<td>Evaluative</td>
<td>59.0 (16.9)</td>
<td>68.8 (24.2)</td>
<td>2.06</td>
</tr>
<tr>
<td>Vegetative</td>
<td>67.5 (15.3)</td>
<td>71.7 (14.4)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

$^p P < .05$.

$^* P < .01$.

$^{***} P < .001$.
in the table, patients with MMSE scores of less than 27 performed significantly more poorly in the learning of lists and stories and the recall of lists. Differences between groups on the other learning and memory measures were not significant.

Table 3 summarizes the intercorrelations among the various RBANS Indexes. Comparison with Table 4.1 in the RBANS manual (Randolph, 1998, p. 45) will reveal that the patterns of intercorrelations computed from the data of the patients in the present study and those for the data of the normative sample are quite similar.

To determine the association of depression and cognition, product moment correlations were computed between each of the three CMDI and the six RBANS Indexes. Of the 18 correlations calculated, two were significant at the 0.05 level. Immediate Memory and Mood were negatively correlated ($r = -0.32, P < .05$) and Delayed Memory and Mood were negatively correlated ($r = -0.26, P < .05$). These associations should be interpreted cautiously because the probabilities are not corrected for the number of correlations computed.

Table 4 reports the mean differences in $Z$ scores for the four hypotheses about memory and information processing speed. As predicted, both patient groups performed significantly better (relative to age-adjusted control norms) on the Naming test compared to the Semantic Fluency test. Both tests measure the ability to retrieve information from semantic memory, but...

Table 4
Mean (S.D.) difference between Z scores

<table>
<thead>
<tr>
<th></th>
<th>MMSE ≥ 27</th>
<th>MMSE &lt; 27</th>
<th>F(1, 56) for groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>50</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Naming–Semantic Fluency</td>
<td>0.84 (1.21)$^*$</td>
<td>1.28 (1.06)$^*$</td>
<td>1.14</td>
</tr>
<tr>
<td>Story Memory–List Learning</td>
<td>0.22 (1.15)</td>
<td>0.56 (0.95)</td>
<td>0.84</td>
</tr>
<tr>
<td>Story Recall–List Recall</td>
<td>0.94 (1.38)$^*$</td>
<td>1.25 (1.50)$^*$</td>
<td>0.30</td>
</tr>
<tr>
<td>List Recognition–List Recall</td>
<td>0.67 (1.51)$^*$</td>
<td>−0.26 (3.75)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

$^*$ Significantly different from 0.

the fluency test places a premium on speed while the naming test does not. Single sample $t$ tests showed that the means for both groups differed from 0 ($t$s > 3.41, $P$s < .025), but there was no significant difference between groups.

Next consider the learning and memory measures. For the comparison of Story Memory and List Learning, both groups attained positive scores indicating somewhat better story acquisition, but the effect was not significantly different from 0 ($t$s < 1.68). Recall of the story, however, was significantly better than for the word list for both MS groups. The mean difference in Z scores was significantly greater than 0 ($t$s > 2.35, $P$s < .05) for both groups.

For the comparison of List Recognition versus List Recall, only MS patients with MMSE scores in the normal range showed the expected benefit of recognition testing ($t(49) = 3.12, P < .01$). Performance by the patients with low MMSE scores on this measure was highly variable and not significantly different from 0. Differences between groups were not significant on any of the learning and memory measures. For the MS patients, correlations of Immediate Memory, Delayed Memory, and Total with the differences in Z scores were small in magnitude and statistically insignificant (absolute $r$s < .17, $P$s > .25).

4. Discussion

Unlike PD patients of normal mental status (Beatty et al., 2003), the MS patients of normal mental status exhibited relatively better performance on Story Recall and List Recognition than on recall of unrelated words. The MS patients of low mental status also showed relatively better recall of stories than of lists, but they did not show the relative advantage of recognition over recall exhibited by the patients of normal mental status.

Recent neuropathological studies may account for the similarities in the patterns of verbal memory deficits in AD and PD (Beatty et al., 2003). The brains of patients with PD exhibit lesions in the transentorhinal region, the second sector of the hippocampus and some nuclei of the amygdala (Braak & Braak, 2000; Braak, DeTredici, Bohl, Bratzke, & Braak, 2000), and this pathology develops before the neocortex is involved. The entorhinal region is among the first areas affected in AD (Braak & Braak, 1991) and is thought to be responsible for the substantial and early impairment in anterograde episodic memory in this disease.

To my knowledge, brains of MS patients have not been studied using the techniques the revealed temporal lobe pathology in PD. Traditionally, the initial pathological process in MS
has been presumed to be inflammatory, affecting the myelin (Raine, 1990). Lesions might occur anywhere in the white matter of the CNS, but a concentration in the periventricular regions has been documented repeatedly. More recent studies demonstrate that this analysis is incomplete. Axonal damage is evident at the earliest clinical stage (Filippi et al., 2003) and the loss of brain volume continues steadily independent of the pattern of relapses and remissions (Confavreaux & Vukusic, 2002).

Recent studies also suggest specific derangement of the temporal lobes in MS. Approximately 5% of MS patients exhibited epileptic seizures of temporal lobe origin which were associated with lesions in the temporal lobe (Gambardella et al., 2003). Furthermore, compared to healthy controls and patients without cognitive impairment, memory-impaired MS patients showed reduced regional cerebral glucose metabolism in the left thalamus and both hippocampi (Paulesu et al., 1996). Thus, recent studies suggest that dysfunction of the temporal lobes may contribute to the memory disturbances in both PD and MS. Presumably, the mechanisms are not identical.

Several psychometric properties of the verbal memory tests from the RBANS may account for the absence of an advantage of recognition over recall for the patients of low mental status. First, the average score for List Recall by control subjects ranges from 3.9 to 7.5 out of 10 depending on age. For recognition, the average score ranges from 18.8 to 19.8 out of 20. In other words, control performance on recognition is near ceiling. The second consideration is that the standard deviations for recall are more than twice as large as for recognition. The effect of these two influences is to inflate the size of $Z$ scores for deficits in recognition relative to recall. Recall $Z$ scores are limited, potentially artificially, by the fact that one cannot recall fewer than 0 words.

The comparison of Story Recall and List Recall is not troubled by either of the above psychometric problems. The average score for Story Recall by control subjects ranges from 7.4 to 10.1 out of 12 and the standard deviations for Story and List Recall are almost the same. For the normative sample (Randolph, 1998), the ratio of S.D.s for Story Recall:List Recall = 1.03:1.00, averaged across ages. Because of these psychometric considerations, comparisons of Story and List Recall using the method employed in this study are more likely to be valid than are comparisons of List Recognition and Recall. The methods are not perfect, but they represent an improvement over the tactic of inferring a qualitative difference in the nature of memory impairment from a significant deficit in recall and a non-significant deficit in recognition.

The impairments in memory and other cognitive functions in MS are quite variable. In a study of 103 MS patients, Beatty et al. (1995) found that 20.4% of patients performed within normal limits on tests that measured seven different cognitive domains, 43.9% were impaired in one or two domains, 40.8% were impaired in three or more domains. The number of domains on which patients were impaired was not significantly associated with age, disease duration, severity of disability, or level of depression. Because impairments can occur in almost any cognitive domain, given sufficiently large samples, statistically significant differences will be obtained. However, it has been consistently found that tests of anterograde episodic memory, rapid processing of novel information, or working memory are the most sensitive to deficits in MS, while measures of abstract reasoning, visuospatial function, and verbal intelligence are less sensitive (Rao, Leo, Bernardin, & Unverzagt, 1991; Wishart & Sharp, 1997).
Because of the heterogeneity of cognitive performance in MS, a typical study in which the average results of a moderately large sample are presented may not be representative of many or most of the individuals. For example, Rao et al. (1989) administered the Selective Reminding Test (SRT) to MS patients and controls. On average, the patients recalled fewer words during learning and after delay, but delayed recognition was normal. The patients also recalled fewer words from long-term storage (LTS) and from consistent long-term retrieval (CLTR), but more words from random long-term retrieval (RLTR). The patients tended to recall more words from short term memory, but this difference was not significant. On this basis they concluded that the verbal memory deficit in MS is mainly a problem of retrieval.

In a subsequent study of 99 patients and 32 controls (Beatty et al., 1996), we successfully replicated the findings of Rao et al. (1989) if only the average performance of the groups is considered. Subsequent study with cluster analysis, however, revealed that the MS group was actually comprised of three subgroups: 24 patients with normal verbal memory, 22 patients with severe impairment, suggestive of amnesia or dementia, and 53 patients with relatively mild deficits. To provide a rigorous test of the retrieval failure hypothesis at the level of the individual patient, we determined the number of patients who met all of the criteria for a pure retrieval deficit (impaired recall during learning and after delay, impaired CLTR, increased percentage of words recalled from RLTR, but normal performance on LTS and delayed recognition). Only 2 of 53 patients met all of these criteria. These findings raise problems for the theory of retrieval failure, but for cognitive therapy in MS they have no obvious implication. The important practical aspect of that study is the demonstration that there is a large subgroup of MS patients with relatively mild and potentially remediable memory problems. The present study provides additional evidence that the verbal memory deficits of most MS patients are mild. Although mild, disturbances in memory along with fatigue and physical disability are a significant prediction of premature retirement from the work force (Beatty, Blanco, Wilbanks, Paul, & Hames, 1995).

MS is a disease of young adults. More than 85% of patients experience their first symptoms between 20 and 50 years of age and the majority are diagnosed by age 30 (Ebers, 1986). Because of its demographics, MS may shorten the period of gainful employment by as much as 35 years. Reducing this impact would clearly benefit both individual patients and society. Therapeutic interventions aimed at improving memory offer the prospect of helping to achieve this goal, but the cognitive impairments of individual MS patients are just as varied as their physical disabilities. Fortunately, the development of brief, easily administered screening tests with good sensitivity and specificity (see Aupperle et al., 2002) should make it practical to identify patients who could benefit from memory training. Adding the RBANS to the Screening Examination for Cognitive Impairment (SEFCI; Beatty et al., 1995) would create a relatively comprehensive neuropsychological battery that could be administered in less than one hour. The SEFCI adds measures of abstract reasoning and speeded information processing that the RBANS lacks.

References


