

Dissociating perceptual and conceptual implicit memory in multiple sclerosis patients

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Abstract

Previous studies indicate that Multiple Sclerosis (MS) patients exhibit deficits in tests of explicit memory such as free recall, but show normal priming on implicit tests of memory such as word stem completion. However, the memory performance of patients with different MS disease subtypes has not been fully examined. In the current study, memory was assessed in Primary Progressive (PPMS), Relapsing Remitting (RRMS), and Secondary Progressive (SPMS) MS subgroups. Explicit memory as well as perceptual and conceptual implicit memory were examined using free recall, word fragment completion, and exemplar generation tests, respectively. All three groups of MS patients exhibited free recall deficits and normal priming on the exemplar generation test. However, the PPMS group exhibited a deficit in word fragment completion priming, whereas the RRMS and SPMS groups exhibited normal levels of priming on this task. Lesion load was assessed using magnetic resonance imaging and was negatively correlated with explicit memory performance, but it did not account for the observed deficits in perceptual implicit memory. The results indicate that PPMS patients exhibit a pattern of memory impairment that is distinct from that of the RRMS and SPMS groups. Moreover, the results indicate that perceptual implicit memory can be neurologically dissociated from conceptual implicit memory. © 2002 Elsevier Science (USA). All rights reserved.

1. Introduction

Multiple sclerosis (MS) leads to a deficit on tests of explicit memory, such as free recall and recognition (e.g., Beatty, Goodkin, Monson, & Beatty, 1990; Carroll, Gates, & Roldan, 1984; Grant, 1984; Rao, Hammeke, McQuillan, Khatri, & Lloyd, 1984, 1991). In contrast, these patients perform normally on tests of implicit memory, such as word stem completion (e.g., Beatty et al., 1990; Latchford, Morley, Peace, & Boyd, 1993; Scarrabelotti & Carroll, 1998, 1999), pursuit rotor learning

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(Beatty et al., 1990), and picture naming (e.g., Carroll et al., 1984). These previous studies, however, have not explored differences between subpopulations of MS patients, and it is not known whether memory performance is equally affected in these different populations.

There are at least two clinically distinct forms of MS, one which is progressive from the onset with no evidence of relapses or remissions (i.e., primary progressive, PPMS) and the other in which the disease initially begins with a relapse-remitting phase—the initial phase is referred to as relapsing-remitting MS (RRMS) and the later phase is referred to as secondary progressive (SPMS). PPMS demonstrates a more rapid progression to advanced disability (Thompson et al., 1997), despite fewer inflammatory lesions (Revesz, Kidd, Thompson, Barnar, & McDonald, 1994) and a lower MRI lesion load throughout the brain than the other form of MS (Thompson et al., 1990, Thompson, Kermode, & Wicks, 1991; Stevenson et al., 1999). There is also epidemiological (e.g., Cottrell et al., 1999; Andersson, Waubant, Gee, & Goodkin, 1999) and immunogenetic evidence (e.g., Olerup et al., 1989; Weinshenker et al., 1998) that these two forms of MS are distinct. Moreover, PPMS patients sometimes exhibit less severe deficits in explicit memory, attention, and reasoning, even when the degree of physical disability is comparable (e.g., Comi et al., 1995) with the other MS group.

The current study examined three distinct forms of memory in PPMS, RRMS, and SPMS patients in order to determine if the memory performance of these groups differs. Explicit memory was measured using a free recall test, perceptual implicit memory was measured using a word fragment completion test, and conceptual implicit memory was measured using an exemplar generation test. These three types of memory are functionally distinct in the sense that they are differentially influenced by several experimental variables, and they are neurologically distinct in the sense that they can be differentially disrupted in different patients populations (for reviews see Gabrieli, 1999; Roediger & McDermott, 1993). For example, selective hippocampal damage leads to selective explicit memory deficits, leaving implicit memory abilities preserved. In contrast, Alzheimer's disease generally disrupts conceptual implicit memory along with explicit memory but leaves perceptual implicit memory reserved.

No previous studies have examined conceptual implicit memory in MS patients, and thus it is not clear how these patients will perform on this form of memory test. Moreover, as mentioned above, perceptual implicit memory and explicit memory have been examined previously in MS patients; however, these studies have not separately examined the performance of patients with different MS subtypes, thus it is not known if the different subgroups will perform similarly on these tests.

In addition to the memory tests, each MS patient in the current study underwent an MRI scan in order to compare the lesions in the different groups and to assess the relationship between lesion load and memory performance. MS results in a progressive accumulation of juxtacortical and deep white matter lesions that disrupt connections between cortical and subcortical structures, and previous studies have indicated that MS patients with cognitive impairments, including impairments in explicit memory, exhibit higher lesion loads than patients who do not (e.g., Comi et al., 1995; Huber et al., 1992; Hohol et al., 1997; Rovaris et al., 1998; Franklin, Heaton, Nelson, Filley, & Seibert, 1988; Rao, Leio, & St. Aubin-Faubert, 1989a,b; Reischies, Baum, Brau, Hedde, & Schwindt, 1988). However, it is not known whether lesion load is related to implicit forms of memory. Consistent with previous studies, we used T1- and T2-weighted images to assess lesion load. T1 lesion load was assessed by hypointense (dark) lesions seen on a T1-weighted image, and T2 lesion load was assessed by hyperintense (bright) lesions seen on a T2-weighted image.

2. Methods

Subjects. Nineteen PPMS, 19 RRMS, 11 SPMS patients, and 16 healthy controls were recruited from the Mount Zion Multiple Sclerosis Center at the University of California, San Francisco. RRMS and SPMS patients were classified using criteria established by Poser et al. (1983) and they all met criteria for clinically definite multiple sclerosis (CDMS). RRMS patients exhibited acute relapses with clear recovery and no disease progression during the periods between relapses. SPMS patients exhibited an initial RRMS course followed by clinical progression of disability with or without occasional relapses, minor remissions, and plateaus. PPMS included patients with a purely progressive course from onset without relapses and with laboratory-supported evidence of MS via lumbar puncture. Laboratory support evidence was defined by the presence of two or more oligoclonal bands in the CSF in the absence of the same bands in the serum or by an elevated IgG synthesis rate and/or elevated IgG index. Patients with a diagnosis of any kind of neurodegenerative disease other than multiple sclerosis were excluded from this study.

The patient demographics are presented in Table 1, and the group scores were contrasted using Tukey–Kramer HSD. General physical impairment and disability was measured using the Expanded Disability Status Scale (EDSS) (Kurtzke, 1983). The SPMS group was more impaired on the EDSS than the PPMS, who were more impaired than the RRMS. The ages of the PPMS and RRMS groups did not differ from the control group, but the SPMS group was significantly older than the controls and the RRMS group. The potential effects of these age differences are addressed under “Discussion.” The groups did not differ with respect to gender.

MR acquisition. A 1.5-T GE Signa Scanner was used to obtain proton density and T2-weighted conventional spin-echo images for each MS patient. The proton density images were acquired (TR/TE = 2500/20 ms) as contiguous axial, 3-mm-thick slices (total slice = 44) with a matrix size of $192 \times 256 \times 44$ (FOV = $180 \times 240 \times 144$ mm). Similar parameters were used for the T2 image acquisition except that TE equaled 80 ms. The T1-weighted images were acquired (TR/TE = 27/6 ms, flip angle = 40°) as high-resolution contiguous axial, 1.5-mm-thick slices (total slice = 124) with a spoiled gradient-echo (SPGR) sequence and matrix size of $192 \times 256 \times 124$ (FOV = $180 \times 240 \times 186$ mm).

T2 lesions were identified by drawing regions of interest (ROIs) around lesions seen on proton density images from software developed at the Magnetic Resonance Science Center on a Sun Microsystems computer. Proton density images offer a higher contrast between ventricular CSF and lesions surrounding it and thus are used to identify MS lesions. The presence of each lesion was ascertained by comparing the proton-density-weighted images to acquired T2-weighted images. T1 lesions were identified by drawing ROIs around hypointense areas defined by a signal clearly lower than that of surrounding white matter, but not necessarily lower than that of gray matter. Lesions were drawn on every slice covering the entire brain for each patient. Brainstem lesions were not included. Each patients brain scan was linearly aligned using the automated image registration algorithm (Woods, Grafton,

Table 1
Demographics for the MS and control groups

Subject type	Mean age (years)	Mean disease duration (years)	Mean EDSS	Male/female
PPMS	48.7	9	4.68	8/11
SPMS	51.5	12.9	6.00	3/8
RRMS	43.3	9.3	2.03	7/12
Controls	41.1	N/A	N/A	9/7

Holmes, Cherry, & Mazziotta, 1998a,b) to a digital brain phantom template (MNI; Collins et al., 1998; Friston et al., 1995). The brain was segmented into four quadrants using the interhemispheric fissure to divide the right and left hemispheres and the line equidistant from the anterior and posterior commissures (AC/PC line) to divide the brain into posterior and anterior regions. The lesion ROIs for each patient were aligned using the same algorithm and transformation matrix as the scanned images. The lesion load data were calculated by multiplying the area of the lesion by the number of slices it penetrated. This resulted in a total lesion load and regional lesion load for each quadrant. Lesion load was divided by total tissue volume in each brain quadrant and is reported as a percentage.

Materials. For the word fragment completion test, 68 words, six to eight letters in length, were divided into two study lists (from Blum & Yonelinas, 2001). Each subject studied one of the two lists (the study lists were counterbalanced across subjects) and were tested on a randomized list of nonpronounceable word fragments (e.g., “_a_bi_” for the word “rabbit”) corresponding to the 34 studied and the 34 nonstudied words.

For the exemplar generation test, 5 exemplars from 40 different categories (e.g., “fruit—cherry, watermelon, plum, pineapple, and grape”) were selected from Battig and Montague (1969). Exemplars ranged from the 8th to the 24th most frequently occurring exemplars for a given category. The items were divided into two study lists (counterbalanced across subjects), with each list containing 5 exemplars from each of 20 different categories. All 40 category names were used as cues in the test phase.

Design and procedure. Subjects were first presented with a list of 34 words (to be used in the subsequent word fragment completion test) on a computer screen at a rate of one word every 2 s. They were required to indicate whether each item could be held in one hand by pressing one of two response keys. Subjects were then read 100 additional words by the experimenter (to be used in the subsequent exemplar generation test) and were asked to determine whether each word was concrete or abstract. Subjects responded verbally, and the task was self-paced.

Subjects were then presented with a word fragment completion test in which they were asked to complete word fragments with the first word that came to mind. Sixty-eight word fragments were presented on a computer screen at a rate of one fragment every 5 s. Subjects responded verbally and the experimenter recorded each response.

Following the word fragment test, subjects were presented with a category exemplar generation task in which they heard 40 category names and were required to generate five examples of each category as quickly as they could. Subjects were given 10 s for each category. They responded verbally and the experimenter recorded their responses.

Subjects were then asked if they had used memory for the earlier studied items to improve their performance on the fragment completion or exemplar generation tests in order to determine whether they used explicit memory on the implicit tests (e.g., Bowers & Schacter, 1990). Finally, subjects were asked to recall as many items from the earlier study lists as they could. They were given 5 min to complete the free recall test.

3. Results

Memory performance. Comparisons between the patient groups and the control group were conducted using Dunnett’s Method for planned *t* tests, and a significance level of $p < .05$ was selected for all statistical tests. Fourteen of the 65 subjects reported using explicit memory on the implicit tests, but when they were excluded from the analyses the overall pattern of results did not change; thus, we included all subjects in the results reported below.

Fig. 1 presents the number of words recalled for the MS and control groups. Compared to the control group, all three of the MS groups demonstrated a significant deficit in free recall performance ($p < .01$ for PPMS; $p < .03$ for SPMS; $P < .04$ for RRMS).

Table 2 presents the proportion of old and new items produced in the word fragment completion and exemplar generation tests for the MS and control groups. Priming was measured by subtracting the proportion of new target items produced from the proportion of old target items produced. Fig. 2 presents the priming effects on the word fragment completion test for the MS and control groups. Compared to the control group, the PPMS group exhibited a significant deficit in fragment completion priming ($p < .02$). In contrast, the SPMS and RRMS groups exhibited normal priming effects relative to controls (both $ps > .05$).

In the fragment completion test, the MS patients completed fewer new items than the control subjects (i.e., .19 versus .29). A subsequent analysis was conducted to determine if differences in new item performance influenced the pattern of priming effects on the word fragment completion test. The control subjects were divided into two equal groups based on their new item completion rate on the fragment completion test. The magnitude of the priming effects were identical for the subjects with the highest and those with the lowest new item completion rates. Moreover, the average new item completion rate for the latter group (.19) was the same as that of the MS patients. These results indicate that differences in new item performance did not influence the observed priming effects.

Fig. 3 presents the priming effects on the exemplar generation test. Compared to the control group all three MS groups exhibited normal priming in the exemplar generation test (all $ps > .05$).

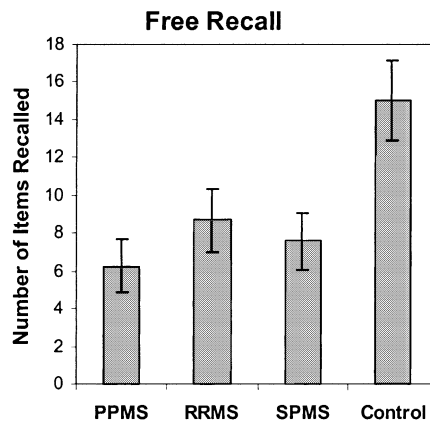


Fig. 1. Free recall performance in PPMS, RRMS, SPMS, and Control subjects. Error bars are standard errors.

Table 2

Mean proportion of old and new items produced in the word fragment completion and exemplar generation tests

	Fragment completion		Exemplar generation	
	Old	New	Old	New
PPMS	0.296	0.220	0.123	0.081
RRMS	0.387	0.220	0.115	0.079
SPMS	0.309	0.144	0.114	0.077
Controls	0.469	0.285	0.119	0.088

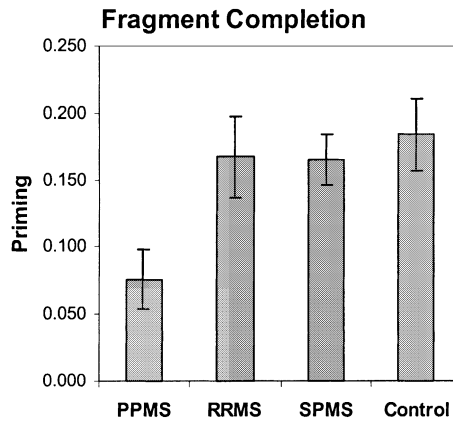


Fig. 2. Word fragment completion priming for PPMS, RRMS, SPMS, and Control subjects. Error bars are standard errors.

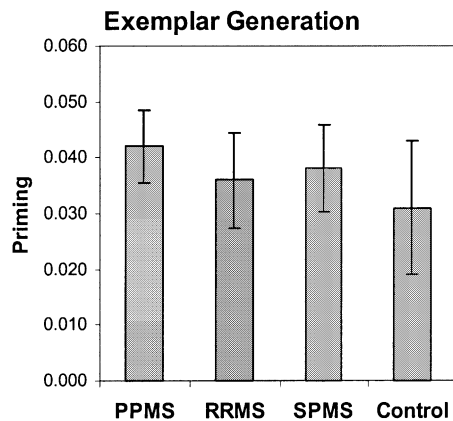


Fig. 3. Exemplar generation priming for PPMS, RRMS, SPMS, and controls. Error bars are standard errors.

In sum, the three groups of MS patients exhibited significant deficits on the recall test, whereas they all performed normally on the exemplar generation test. However, the PPMS group exhibited a significant deficit in fragment completion priming while the SPMS and RRMS groups exhibited normal priming on this task.

Lesion load. Table 3 presents the mean proportion of T2 lesion volume relative to total volume of each brain quadrant (anterior/posterior and left/right) for each MS group. An ANOVA indicated that there was a significant effect of group on lesion load [$F(2, 43) = 8.966, p < .001$] indicating that the MS patient groups differed in terms of lesion load. Subsequent analysis indicated that the SPMS group exhibited a greater lesion load than the two other groups ($ps < .05$), and the PPMS and RRMS

Table 3
Mean proportional T2 lesion load (lesion volume divided by total volume for each brain quadrant) for the three MS populations

Subject type	Right anterior %M(SD)	Left anterior %M(SD)	Right posterior %M(SD)	Left posterior %M(SD)
PPMS	0.9 (1.3)	0.9 (1.3)	1.4 (1.5)	1.3 (1.3)
RRMS	0.6 (0.8)	0.3 (0.4)	0.7 (0.9)	0.7 (1.3)
SPMS	3.7 (3.7)	3.7 (3.9)	4.1 (4.0)	3.7 (4.0)

Table 4
Correlations (Spearman's Rho) between memory performance and proportional T₂ lesion load in each quadrant for all MS patients combined

	Free recall	Word fragment priming	Exemplar generation priming
Left–anterior	–.224	.158	.154
Left–posterior	–.370*	.108	.083
Right–anterior	–.247	.101	.061
Right–posterior	–.334*	–.009	.060

* $p < .05$.

groups did not differ from each other. The proportional T2 lesion load was greater in the right than left hemisphere [$F(1, 43) = 4.106, p < .05$] and greater in the posterior than anterior regions [$F(1, 43) = 5.093, p < .05$]. Most important however, was that patient group interacted with no other factor (F 's < 1.8), indicating that the distribution of lesions across the four quadrants did not differ in the three MS groups. Similar analyses of T1 lesion load led to the same pattern of results and are discussed no further.

Lesion/memory correlations. To assess the relationship between total lesion load and behavioral performance, correlations were examined between memory performance and the proportional T2 lesion load in the left and right, posterior and anterior quadrants (see Table 4). When all MS groups were combined there was a significant negative correlation between free recall performance and both left and right posterior regions. The anterior regions were also negatively correlated but not significantly so. No significant correlations were observed between either fragment completion or exemplar generation priming and lesion load in any quadrant. Subsequent analyses further examined the correlations within each MS group separately, but no significant correlations were identified.

4. Discussion

The current results indicate that different subtypes of MS patients exhibit distinct patterns of memory impairments. PPMS patients exhibited a deficit in perceptual implicit memory as measured using a word fragment completion test, whereas the SPMS and RRMS patients exhibited normal priming on this test. In contrast, all three groups exhibited deficits in explicit memory as measured using a free recall test, and they all exhibited normal conceptual implicit memory as measured on an exemplar generation test.

Previous studies have indicated that MS patients, as a group, exhibit explicit memory deficits (e.g., Beatty et al., 1990; Carroll et al., 1984; Grant, 1984; Rao et al., 1984, 1991). The current results extend these results by indicating that these deficits are observed in all three MS subgroups. Previous studies also indicated that MS patients exhibit normal implicit memory on several perceptual implicit memory tests (e.g., Beatty & Monson, 1990; Latchford et al., 1993; Scarrabelotti & Carroll, 1998, 1999; Beatty et al., 1990; Carroll et al., 1984). The current results expand on these findings in showing that conceptual implicit memory is preserved in the three groups of MS patients.

The most important finding of the present study was that word fragment completion priming was preserved in SPMS and RRMS patients, whereas it was significantly disrupted in PPMS patients. As mentioned above previous studies have indicated that MS patients, as a group, exhibit no deficits in perceptual implicit memory. However, these studies have examined no separate subgroups of MS patients. The reason these previous studies report no deficits in perceptual implicit

memory in the average MS groups is likely because PPMS patients only made up a small proportion of the MS patients typically tested. For example, Scarrabelotti and Carroll (1999) examined a group of 49 MS patients and found that stem completion priming was normal in this group. However, the group contained only 3 PPMS patients. Thus, even if the PPMS patients did exhibit a deficit in priming, at the group level no priming deficit would be expected.

The fragment completion priming deficit observed in the PPMS group cannot be attributed to patient age. First, aging in itself does not generally lead to deficits on perceptual implicit memory tests like fragment completion (e.g., Fleishman & Gabrieli, 1998). Moreover, although the SPMS patients were slightly older than the control subjects, the ages of the PPMS and RRMS patients were comparable and were not significantly different from those of the controls. Overall disease severity, also does not appear to be responsible for the fragment completion priming deficits observed in the PPMS group. That is, for the PPMS group the level of physical impairment and disability as measured with the EDSS was intermediate between the other two MS patient groups, and the three groups exhibited comparable performance on the recall and conceptual implicit memory tests. Moreover, the PPMS group exhibited an intermediate lesion load compared to the other two MS groups.

These results demonstrate that perceptual implicit memory can be dissociated from conceptual implicit memory, and they join a growing body of literature indicating that the two forms of implicit memory are functionally and neuroanatomically distinct. For example, Alzheimer's disease patients exhibit deficits in conceptual implicit memory tests, but exhibit normal performance on perceptual implicit memory tests (for reviews see Fleishman & Gabrieli, 1998; Maki, 1995). The present results provide the opposite dissociation (i.e., a disruption of perceptual but not conceptual implicit memory), and together they show that the two types of implicit memory can be doubly dissociated. Such findings demonstrate that these two forms of memory are neurologically distinct.

The results of the MRI analyses are consistent with previous studies indicating that SPMS patients exhibit a greater lesion load than do the PPMS patients (e.g., Stevenson et al., 1999) and with studies indicating that explicit memory impairment is correlated with lesion burden (Franklin et al., 1988; Rao et al., 1989a,b; Reischies et al., 1988), particularly with posterior regions (Moriarty et al., 2000). The current study, however, contrasted the distribution of the lesion load across anterior/posterior and left/right quadrants in the different patient groups and found no evidence that the distribution of lesions differed across the groups. Moreover, an examination of the relationship between lesion load and memory performance revealed no significant correlation between implicit memory performance and T1 or T2 lesion load.

The observation that the PPMS group exhibited a deficit in perceptual implicit memory that did not influence conceptual implicit memory indicates that this form of MS selectively disrupts the processes that support perceptual implicit memory. Future studies are needed to further characterize the disrupted memory processes and to determine the physiological mechanisms underlying this deficit. The MRI examination of lesion load in the MS patients showed that the PPMS group exhibited a lower lesion load than the SPMS group, indicating that overall lesion load could not account for the implicit memory deficit in the PPMS group. Moreover, the distribution of lesions across anterior/posterior and left/right brain quadrants did not differ across the three MS groups. Thus, differences in lesion location do not appear to provide an explanation for the implicit memory impairment in the PPMS group. The lack of a relationship between lesion load and implicit memory may reflect limitations associated with the current MRI methods. Stevenson (1999) showed that PPMS patients have fewer white matter lesions than SPMS patients; thus, it could be the case that tissue damage in PPMS is simply not visible through conventional T1- and T2-weighted MRI, yet is still significant enough to contribute

to a behavioral deficit. It could also be that focal white matter lesions are less important to the deficit than diffuse normal appearing white matter microscopic changes. Future studies that use alternative imaging methods such as magnetization transfer ratio histograms, T2 relaxation time histograms, diffusion tensor imaging, and magnetic resonance spectroscopy may provide important insights into this issue.

The precise neuroanatomical substrates of perceptual implicit memory as measured in the fragment completion test are currently unknown. However, neuroimaging studies of healthy subjects and results from the study of patients with selective lesions to the occipital lobes suggest that this form of memory is supported by posterior neocortical regions (e.g., Schacter, Alpert, Savage, Rauch, & Albert, 1996; Fleishman, Gabrieli, Reminger, & Rinaldi, 1995), possibly including the right extrastriate cortex (e.g., Squire et al., 1992; Backman et al., 1997; Gabrieli, Fleishman, Keane, & Reminger, 1995; but see Yonelinas et al., 2001). Based on these previous findings one would expect the PPMS patients to exhibit a disproportionately large lesion load in the right posterior brain regions compared to the other MS patient groups. Although there was a significant lesion load in the right posterior quadrant in the MS patients, there was no evidence that it was greater in the PPMS group than in the other MS groups. However, as mentioned above, this may reflect a limitation of the imaging methods that were utilized in the current study. The current results do not show why the PPMS patients exhibited a deficit in perceptual implicit memory, but they do suggest that further studies of PPMS patients may provide a key to understanding the neuroanatomical substrates of this form of memory.

Previous results indicate that PPMS differs from SPMS and RRMS in terms of clinical, epidemiological, immunogenetic, and histopathological results. The present results extend these findings by showing that these groups also differ with respect to their associated memory deficits.

References

- Andersson, P., Waubant, E., Gee, L., & Goodkin, D. (1999). Multiple sclerosis that is progressive from the time of onset: Clinical characteristics and progression of disability. *Archives of Neurology*, *9*, 1138–1142.
- Backman, L., Almkvist, O., Anderson, J., Nordberg, A., Winblad, B., Reineck, R., & Langstrom, B. (1997). Brain activation in young and older adults during implicit and explicit retrieval. *Journal of Cognitive Neuroscience*, *9*, 378–391.
- Battig, W., & Montague, W. (1969). Category norms for verbal items in 56 categories: A replication and extension of the Connecticut category norms. *Journal of Experimental Psychology*, *80*, 1–46.
- Beatty, W., Goodkin, D., Monson, N., & Beatty, P. (1990). Implicit learning in patients with chronic progressive multiple sclerosis. *International Journal of Clinical Neuropsychology*, *12*, 166–172.
- Beatty, W., & Monson, N. (1990). Semantic priming in multiple sclerosis. *Bulletin of the Psychonomic Society*, *28*, 397–400.
- Blum, D., & Yonelinas, A. P. (2001). Transfer across modality in perceptual implicit memory. *Psychonomic Bulletin and Review*, *8*(1), 147–154.
- Bowers, J., & Schacter, D. (1990). Implicit memory and test awareness. *Journal of Experimental Psychology: Learning Memory and Cognition*, *16*(3), 404–416.
- Carroll, M., Gates, R., & Roldan, F. (1984). Memory impairment in multiple sclerosis. *Neuropsychologia*, *22*(3), 297–302.
- Collins, D., Zijdenbos, A., Kollokian, V., Sled, J., Kabani, N., Holmes, C., & Evans, A. (1998). Design and construction of a realistic digital brain phantom. *IEEE Transactions on Medical Imaging*, *17*(3), 463–468.
- Coltheart, M. (1989). Implicit memory and the functional architecture of cognition. In S. Lewandowsky, J. Dunn, & K. Kirsner (Eds.), *Implicit memory: Theoretical issues*. Hillsdale, NJ: Erlbaum.
- Comi, G., Fillipi, M., Martinelli, V., Campi, A., Rodegher, M., & Alboni, M., et al. (1995). Brain MRI correlates of cognitive impairment in primary and secondary progressive multiple sclerosis. *Journal of Neurological Sciences*, *132*, 222–227.
- Cottrell, D., Kremenutzky, G., Rice, G., Koopman, W., Hader, W., Baskerville, J., & Elbers, G. (1999). The natural history of multiple sclerosis: A geographically based study. *Brain*, *122*(4), 625–639.

- Fleishman, D., & Gabrieli, J. (1998). Repetition priming in normal aging and Alzheimer's disease: A review of findings and theories. *Psychology and Aging*, **13**(1), 88–119.
- Fleishman, D., Gabrieli, J., Reminger, S., & Rinaldi, J. (1995). Conceptual priming in perceptual identification for patients with Alzheimer's disease and a patient with right occipital lobectomy. *Neuropsychology*, **9**(2), 187–197.
- Franklin, G., Heaton, R., Nelson, L., Filley, C., & Seibert, C. (1988). Correlation of neuropsychological and MRI findings in chronic/progressive multiple sclerosis. *Neurology*, **38**, 1826–1829.
- Friston, K. J., Holmes, A., Worsley, K., Poline, J., Frith, C., & Frackowiack, R. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping*, **2**, 189–210.
- Gabrieli, J. (1999). The architecture of human memory. In J. K. Foster & M. Jelicic (Eds.), *Memory: Systems, process, or function?* New York: Oxford Univ. Press, pp. 205–231, xii, 297.
- Gabrieli, J., Fleischman, D., Keane, M., & Reminger, S. (1995). Double dissociation between memory systems underlying explicit and implicit memory in the human brain. *Psychological Science*, **6**(2), 76–82.
- Grant, I. (1984). Deficient learning and memory in early and middle phases of multiple sclerosis. *Journal of Neurology, Neurosurgery, and Psychiatry*, **47**(3), 250–255.
- Hohol, M., Guttmann, C., Orav, J., Mackin, G., Kikinis, R., & Khoury, S., et al. (1997). Serial neuropsychological assessment and magnetic resonance imaging analysis in multiple sclerosis. *Archives of Neurology*, **54**, 1018–1025.
- Huber, S., Bornstein, R., Rammohan, K., Christy, J., Chakeres, D., & McGhee, R. (1992). Magnetic Resonance imaging correlates of neuropsychological impairment in multiple sclerosis. *Journal of Neuropsychological Clinical Neuroscience*, **4**, 152–158.
- Kurtzke, J. K. (1983). Rating neurologic impairment in multiple sclerosis: An expanded disability status scale (EDSS). *Neurology*, **33**, 1444–1452.
- Latchford, G., Morley, S., Peace, K., & Boyd, J. (1993). Implicit memory in multiple sclerosis. *Behavioural Neurology*, **6**(3), 129–133.
- Maki, P. (1995). Is implicit memory preserved in Alzheimer's disease? Implications for theories of implicit memory. *Aging and Cognition*, **2**(3), 192–205.
- Moriarty, D. M., Blackshaw, A., Talbot, P. R., Griffiths, H. L., Snowden, J. S., Hillier, V. F., & Jackson, A. (2000). Neuropsychological impairments in multiple sclerosis correlates with T1 hypointense lesions demonstrated on 3D-high resolution T1 weighted MRI. *Proceedings of the International Society of Magnetic Resonance Medicine*, **8**.
- Olerup, O., Hillert, J., Frederikson, S., Olsson, T., Kam-Hansen, S., Moller, E., Carlson, B., & Wallin, J. (1989). Primarily chronic progressive and relapsing remitting multiple sclerosis: Two immunogenetically distinct entities. *Proceedings of the National Academy of sciences of the USA*, **86**, 7113–7117.
- Poser, C., Paty, D., Scheinberg, L., McDonald, W., Davis, F., Ebers, G., Johnson, K., Sibley, W., Silberberg, D., & Tourtelotte, W. (1983). New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Annals of Neurology*, **13**, 227–231.
- Rao, S., Leio, G., & St. Aubin-Faubert, P. (1989a). On the nature of memory disturbance in multiple sclerosis. *Journal of Clinical and Experimental Neuropsychology*, **11**, 699–712.
- Rao, S., Leo, G., Haughton, V., St. Aubin-Faubert, P., & Bernardin, L. (1989b). Correlation of magnetic resonance imaging with neuropsychological testing in multiple sclerosis. *Neurology*, **39**, 161–166.
- Rao, S. M., Hammeke, T. A., McQuillan, M. P., Khatir, B. O., & Lloyd, D. (1984). Memory disturbance in chronic progressive multiple sclerosis. *Archives of Neurology*, **41**, 625–631.
- Rao, S. M., Leo, G. J., Bernardin, L., & Unerzagt, F. (1991). Cognitive dysfunction in multiple sclerosis: Frequency, patterns and rediction. *Neurology*, **41**, 658–691.
- Reischies, F., Baum, K., Brau, H., Hedde, J., & Schwindt, G. (1988). Cerebral magnetic resonance imaging findings in multiple sclerosis: Relation to disturbance of affect, drive, and cognition. *Archives of Neurology*, **45**, 1114–1116.
- Revesz, T., Kidd, D., Thompson, A., Barnar, R., & McDonald, W. (1994). A comparison of the pathology of primary and secondary progressive multiple sclerosis. *Brain*, **117**, 759–765.
- Roediger III, H., & McDermott, K. (1993). Implicit memory in normal human subjects. *Handbook of Neuropsychology*, **8**(8), 63–131.
- Rovaris, M., Filippi, M., Falautano, M., Minicucci, L., Rocca, M., & Martinelli, V., et al. (1998). Relation between MR abnormalities and patterns of cognitive impairment in multiple sclerosis. *Neurology*, **50**, 1601–1608.
- Scarrabelotti, M., & Carroll, M. (1998). Awareness of remembering achieved through automatic and conscious processes in multiple sclerosis. *Brain and Cognition*, **38**, 183–201.
- Scarrabelotti, M., & Carroll, M. (1999). Memory dissociation and metamemory in multiple sclerosis. *Neuropsychologia*, **37**, 1335–1350.
- Schacter, D. L., Alpert, N. M., Savage, C. R., Rauch, S. L., & Albert, M. S. (1996). Conscious recollection and the human hippocampal formation: Evidence from positron emission tomography. *Proceedings of the National Academy of Sciences of the USA*, **93**, 235–321.

- Squire, L. R., Ojemann, J. G., Miezin, F. M., Petersen, S. E., Videen, T. O., & Raichle, M. E. (1992). Activation of the hippocampus in normal humans: A functional anatomical study of memory. *Proceedings of the National Academy of Sciences of the USA*, **89**, 1837–1841.
- Stevenson, V. L., Miller, D. H., Rovaris, M., Barkhof, F., Brochet, B., Dousset, V., Filippi, M., Montalban, X., Polman, C. H., Rovira, A., deSa, J., & Thompson, A. J. (1999). Primary and transitional progressive MA, a clinical and MRI cross-sectional study. *Neurology*, **52**, 839–845.
- Thompson, A., Kermode, A., MacManus, D., Kendall, B., Kingsley, D., Moseley, I., & McDonald, W. (1990). Major differences in the dynamics of primary and secondary progressive multiple sclerosis. *Annals of Neurology*, **29**, 53–62.
- Thompson, A., Kermode, D., & Wicks, et al. (1991). Patterns of disease activity in multiple sclerosis: Clinical and magnetic resonance imaging study. *British Medical Journal*, **300**, 631–634.
- Thompson, A., Polman, C., Miller, D., McDonald, W., Brochet, B., & Fillipi, M., et al. (1997). Primary progressive multiple sclerosis. *Brain*, **120**, 1085–1096 (Review).
- Weinshenker, B., Santrach, P., Bissonet, A., McDonnell, S., Schaid, D., Moore, S., & Rodriguez, M. (1998). Major histocompatibility complex class II alleles and the course and outcome of MS: A population-based study. *Neurology*, **51**, 742–747.
- Woods, R., Grafton, S., Holmes, C., Cherry, S., & Mazziotta, J. (1998a). Automated image Registration. I. General methods and intrasubjects, intramodality validation. *Journal of Computer Assisted Tomography*, **22**(1), 139–152.
- Woods, R., Grafton, S., Watson, J., Sicotte, N., & Mazziotta, J. (1998b). Automated Image Registration. II. Intersubject validation of linear and nonlinear models. *Journal of Computer Assisted Tomography*, **22**(1), 153–165.
- Yonelinas, A. P., Kroll, N. E. A., Baynes, K., Dobbins, I. G., Frederick, C. M., Knight, R. T., & Gazzaniga, M. S. (2001). Visual implicit memory in the left hemisphere: Evidence from callosotomy and occipital-lobe lesion patients. *Psychological Science* (in press).