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IMPLICIT LEARNING IN PATIENTS WITH PROBABLE ALZHEIMER'S DISEASE

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The purpose of the present study was to determine whether patients with probable Alzheimer's disease (AD) were capable of implicit procedural learning. AD patients and elderly control subjects were given a serial visual reaction time task with an embedded repeating sequence. The AD patients responded more slowly than the controls, but many nonetheless showed learning of the repeating sequence. Patients who failed to learn the sequence were similar in age and overall severity of dementia to those who learned, but they scored lower on some tasks of nonverbal reasoning. Keywords:

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IMPLICIT LEARNING IN PATIENTS WITH PROBABLE ALZHEIMER'S DISEASE

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RUNNING HEAD: Implicit learning in Alzheimer's Disease

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ABSTRACT

The purpose of the present study was to determine whether patients with probable Alzheimer's disease (AD) were capable of implicit procedural learning. AD patients and elderly control subjects were given a serial visual reaction time task with an embedded repeating sequence. The AD patients responded more slowly than the controls, but many nonetheless showed learning of the repeating sequence. Patients who failed to learn the sequence were similar in age and overall severity of dementia to those who learned, but they scored lower on some tasks of nonverbal reasoning.

Acquisition of new information is usually assessed by measures of explicit recall or recognition. Learning can also be expressed implicitly, as when the performance of a task is facilitated as a result of prior experience. The terms "declarative" and "procedural" learning have been used for these two types of learning[1]. In patients with circumscribed pathology such Korsakoff's syndrome, bilateral medial temporal lobe lesions or medial thalamic lesions, procedural learning may be preserved when declarative learning is profoundly impaired[2,6-11]. Patients with Alzheimer's disease (AD) may have widespread neuropathological changes[12,13], and it is not clear whether procedural learning would or would not be preserved. The present study was undertaken to explore the integrity of procedural learning in AD patients.

METHODS

Subjects. We studied 35 patients with probable AD by ADRDA-NINCDS criteria[14] (19 women and 16 men; ages 52 to 87 yrs; mean age 70.4 yrs). None had a history of stroke or alcoholism, or had focal abnormalities on neurological examination. Hachinski scores[15] were less than 2. All had CT scans within one year, with no evidence of stroke or other lesions. Thyroid hormone levels, vitamin B12 levels, and other routine chemistries were normal. Scores on the Mini-Mental State examination[16] were 25 or lower. No patients recalled any of the three words in the memory item of the test. Sixteen of the AD patients had additional psychometric testing.

Control subjects. A group of 13 normal elderly individuals served as control subjects (5 women and 8 men;

ages 61 to 78 yrs; mean age 68.5 yrs). Eight of these subjects were administered the entire Wechsler Memory Scale [17], and their scores ranged from 108 to 143. The other five control subjects received a different set of memory tests. All five scored 4 or higher (range 4-10) on immediate recall of the Wechsler Memory Scale[17] visual reproduction subtest, and recalled after 60 minutes a minimum of 7 words (range 7-13 words) from a 15 word, five trial Rey list[18].

Procedures. The procedural memory task[6] employed a visual reaction time (RT) paradigm. The subjects were seated in front of a CRT screen immediately below which was a response board with four buttons. An asterisk appeared in one of four positions that were spaced horizontally across the bottom of the screen, and aligned with the positions of the response buttons. The patients were instructed to push the button that was below the position in which the light appeared. The RT to each stimulus was determined to the nearest millisecond, and the median of RT within each block was calculated. The stimulus remained on the screen until the correct button was pushed. The stimulus was then removed, and following a 500-msec delay, the next stimulus appeared. For the first four blocks of 100 responses each, a 10-trial sequence of light positions repeated itself ten times. Beginnings and ends of the sequence were not marked. The patients were not told that learning or memory was being assessed, nor that a repeating sequence was present. Immediately following the first four blocks, a fifth block of

100 stimuli was given in which the sequence of light positions was random, with the only constraint being that a given position was not repeated immediately. Learning was assessed by a decreasing median RT over the first four blocks (reflecting both nonspecific facility with the task and acquisition of the specific repeating sequence), and by longer median RT in the random block compared to the last (fourth) repeating block (indicating that the learning of the repeating sequence had contributed to the facilitation of responses in the first four blocks). Analyses of response latencies excluded trials on which an incorrect button was pushed.

Increased facility with the motor task itself could be manifested by decreasing RT without any learning of the sequence. In that case, however, it is likely that responses in the random block would be at least as fast as those in the last repeating block. If the sequence itself were learned, then RT would increase in the random block relative to the sequenced blocks.

A 10-item repeating sequence was chosen because 10 items is clearly beyond normal immediate span, yet short enough that a large number of sequence repetitions can be given without being excessively tedious to the subjects.

RESULTS

All control subjects responded faster in Block 4 than in Block 1 (figure 1). The mean latency in Block 4 (the last of the repeating sequence blocks) was 320 msec (S.D.= 154). The slope of the RT function from Block 1 to Block 4 was -68 msec (S.D.= 36). The average increase in latency in Block 5 (the random sequence block) compared to Block 4 was 181 msec (S.D.= 84 msec). All control subjects demonstrated increased RT latencies in Block 5, with the minimum increase being 55 msec. Error rates were between 0% and 6% in Blocks 4 and 5.

[Figure 1 about here]

For seven of the 35 AD patients, the task requirements proved too difficult in that their error rates exceeded 30% in Blocks 4 and 5. They were excluded from further analysis. The remaining 28 patients all had error rates that were less than 30% in Blocks 4 and 5.

As a group, these 28 AD patients (mean age, 71.7 yrs; 15 women and 13 men) responded more slowly than control subjects (figure 1). Median RT in Block 4 for the AD patients was 778 msec, almost 450 msec slower than the elderly controls. Only eight patients had median RT's that were faster than the slowest of the control subjects in Block 4. Nevertheless, compared to the control group, the AD patient group had a similar reduction in RT over Blocks 1 - 4: their average slope was -120 msec (S.D.=113) (using log-transformed slopes, t=1.86, 34.7 df, ns). They showed an increase in RT from Block 4 to Block 5 of 110 msec (S.D.= 162) (t=1.85, 39 df, ns), which was similar to that of control subjects. Thus, as a group, the AD patients showed learning of the repeating sequence that was like that of the normal elderly controls. An analysis of variance confirmed these observations. There was a significant effect of group (F=27.2,1 df, p<.001) and block (F=13.5, 4 df, p<.001) but no significant interaction (F=2.0, 4 df, p=.1). While most of the control subjects recognized that there was a repeating sequence, only one of the AD patients recognized that there was a pattern when asked at the end of the study. Error rates were higher in the AD patients, but within the AD patient group, error rates did not differ between Blocks 4 and 5.

Examination of the performance of individual AD patients revealed that the range was substantial. All but one patient had a negative slope over Blocks 1 - 4 (ie, median RT decreased from Block 1 to Block 4). However, nine patients failed to show evidence of specific learning, in that their median RT in Block 5 was as fast or faster than that in Block 4. To determine whether these "nonlearners" differed from the patients who showed evidence of learning the sequence ("learners"), where learning was defined by an increase in response latencies in block 5, we compared demographic characteristics and psychometric performance.

The nonlearner subgroup was slightly younger than the learner subgroup, but the difference was not significant (mean age of learners=73.7 years, nonlearners = 67.3 years). The proportion of women to men was also similar in the two groups. There were no systematic differences between the nonlearners and learners in their Mini Mental State examination scores (figure 2). There was a trend toward faster responses in the learners, but this difference reached significance only in Block 4 (Table 1), when the effects of learning the sequence would have given the learners the most advantage. Furthermore, learners and non-learners did not differ in error rates. Comparison of psychometric performance of the two groups was limited to the 14 individuals (10 learners and 4 nonlearners) who had had complete testing. Scores on two tests, the Block Design subtest of the WAIS and the Porteus mazes, were significantly lower in the nonlearners than the learners (Table 2 and figure 3). The scatterplots showed that all of the patients who had high performance on the Block Design test and the Porteus mazes were able to learn the sequence in the serial reaction time task, whereas individuals with low scores on those tests tended to be the patients who failed to learn.

[Figures 2 & 3 and Tables 1 & 2 about here]

DISCUSSION

The stimulus-response learning in this study was a kind of procedural learning. AD patients learned the procedure or skill required for increasingly efficient responses to the repeating sequence without an awareness of, or ability to, explicitly report the sequence. The procedural learning took place in the absence of apparent parallel declarative learning, suggesting that neural systems that can support learning are not uniformly damaged in AD. Studies of procedural learning in the rotary pursuit task also show preservation in AD patients[23,24]. The defining characteristics of procedural learning have yet to be fully enumerated; the implicit nature of the learning is a critical feature, but the complexity of the task also plays a role[7]. It is possible that preservation of learning in the pursuit rotor paradigm or the serial reaction time paradigm may not imply learning in other putative procedural tasks.

Acquisition of knowledge about the stimulus-response sequence occurred despite the patients' markedly slow simple reaction times compared to the control subjects. Furthermore, the fact that some patients performed the task accurately yet failed to learn the specific sequence suggests that the brain structures that support procedural learning can be compromised without disturbing performance of the elementary functions upon which learning would be built. Within the range of intellectual decline of the patients we tested, procedural learning ability was not related to severity of dementia as indexed by Mini-Mental State scores. Other studies of AD patients using performance measures of learning have also shown no relationship to global intellectual level[23,25]. On the other hand, learning of this task was related to performance on tests of nonverbal reasoning, ie Block Design and Porteus mazes. This finding should be replicated in a larger sample, but it leads to the speculation that learning of this particular paradigm was facilitated by right hemisphere-mediated functions.

Procedural learning may be impaired in patients with Huntington's disease[26,27]. The major and possibly exclusive involvement of the caudate nucleus in Huntington's disease[28] has raised the possibility that neostriatal pathology is a sufficient lesion to impair procedural learning. Caudate nucleus involvement in implicit learning and memory has been proposed by Mishkin[29] as the substrate for a "habit" system in primates, which may be analogous to procedural memory in humans. Caudate nucleus changes have been reported in AD [30].

It is somewhat easier at present to enumerate the neural systems NOT required for procedural learning than it is to point to the neural systems that are necessary. Studies of patients with temporal lobe lesions, medial dorsal thalamic lesions, and patients with Korsakoff's syndrome have shown intact procedural learning in the setting of impaired declarative learning[1,2,6-11]. One such study of Korsakoff patients used the same serial reaction time task used here[6]. Those patients learned the sequence and showed that they retained it for one week[31]. In addition, we have recently shown that young adults given subcutaneous scopolamine have preserved procedural learning in the presence of substantial impairment of formally parallel declarative learning[32].

It is worth emphasizing that not all of our AD patients demonstrated intact procedural learning. Failure to learn in this particular paradigm may also occur in normal subjects under conditions of divided attention. Nissen and Bullemer[6] have shown that when normal young adults were given the serial reaction time task while being instructed to keep track of the occurrence of a tone, their performance deteriorated compared to subjects performing the serial reaction time task alone. Under divided attention conditions, responses were much slower even in Block 1, and subjects failed to learn the repeating sequence[6]. There might have been attentional factors that affected the performance of the AD patients who failed to learn, although a difference between learners and nonlearners was not evident in their Block 1 RT's, which would be expected to vary with the degree to which the individuals were attending to the task.

If there exists more than one memory system for ongoing events, it seems reasonable to hypothesize that the systems operate in parallel. In any particular task, both systems may be operative, but one may dominate depending upon the learning conditions. The explicit declarative system is capable of (but alas, not always successful at) acquiring and storing information that may be presented only once; this high-efficiency memory system is critical for human achievement and is the one that is impaired in the amnesias. The other system, the implicit procedural system, is effective for other memory operations: learning a set of stimulus-response associations in which learning is manifested in task performance. The information gained in the procedural mode may not necessarily be accessible to explicit awareness, but can only be used in an implicit way, ie through one's actions. Studies of amnesic patients have shed considerable light on the relationship between these two types of learning operations, by showing that, under circumstances favorable to the procedural system, amnesics may learn at rates comparable to normal subjects.

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TABLE 1. PERFORMANCE OF PATIENTS WHO LEARNED OR FAILED TO LEARN THE SERIAL REACTION TIME SEQUENCE

MEASURE	NONLEARNERS (N=9)	LEARNERS (N=19)
Reaction time	Mean response times (S.D.)	
block 1	1431 (624)	1005 (396)
block 2	1180 (646)	816 (241)
block 3	970 (340)	764 (317)
block 4	931 (273)	705 (240) *
random block 5	874 (268)	893 (282)
Slope of function		
blocks 1-4	171 (160)	95 (76)

* difference significant by two-tailed t-test, $p < .05$

All other differences were nonsignificant

TABLE 2. PSYCHOMETRIC TEST SCORES OF PATIENTS WHO SHOWED PROCEDURAL LEARNING VERSUS THOSE WHO FAILED TO LEARN

TEST	Nonlearners (n=4)	Learners (n=10)	T-test
	(scores: mean (S.D.)		
WMS visual reproduction[17]	1.4 (1.8)	2.4 (1.3)	-1.16
Prose passage[18]	4.0 (3.9)	3.6 (2.8)	0.22
Rey Verbal List Learning[18] (Words recalled on post-interference trial)	3.3 (2.9)	2.4 (2.1)	0.62
WAIS block design[17] (raw score)	5.0 (7.8)	16.2 (7.2)	-2.61 *
WAIS digit symbol[17] (raw score)	11.3 (8.2)	19.2 (7.8)	-1.70
Word Fluency[19]	24.5 (7.1)	28.5 (7.1)	-0.10
Token Test[19]	131.5 (34.1)	155.0 (11.2)	-1.36
Boston Naming[20]	29.8 (13.4)	28.9 (13.1)	0.11
Figural fluency[21]	12.3 (18.0)	9.9 (4.5)	0.23
Porteus Mazes[22]	6.4 (1.1)	9.9 (3.8)	-2.68 *

*p <.05 (two-tailed)

WMS - Wechsler Memory Scale; WAIS - Wechsler Adult Intelligence Scale

LEGENDS FOR FIGURES

Figure 1. Median reaction times for the five Blocks of responses for controls (n=13) and probable AD patients (n=28). For each block, the median RT for 100 responses is shown. A repeating sequence of stimuli was presented in first four blocks, and a pseudo-random pattern was presented in the fifth block.

Figure 2. Scatterplot of Mini-mental State scores versus Block 5 minus Block 4 RT median latencies in milliseconds, a measure of the specific sequence learning. All Block 5 -Block 4 differences less than zero indicate that Block 5 RT's were faster than Block 4, and that specific sequence learning did NOT occur. The vertical line indicates the mean Block 5 minus Block 4 difference for the 13 elderly controls.

Figure 3. Scatterplots comparing scores of nonlearners and learners on (A) WAIS block design subtest (raw scores), and (B) Porteus Mazes (test ages). The mean for the groups is given as horizontal line.

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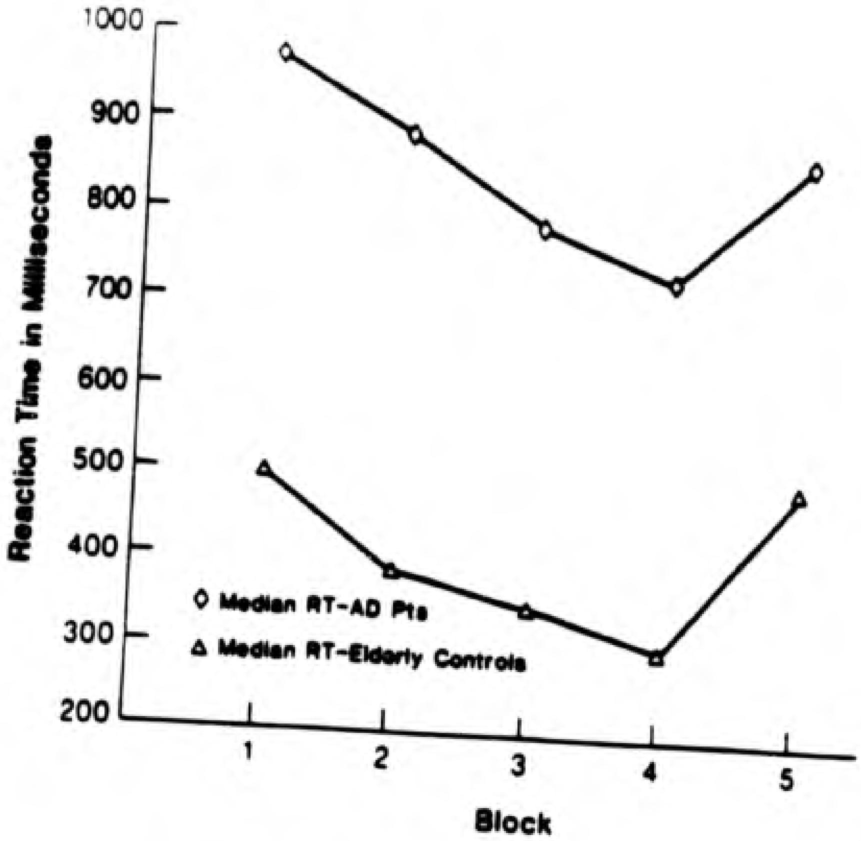
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Reaction Time in Milliseconds
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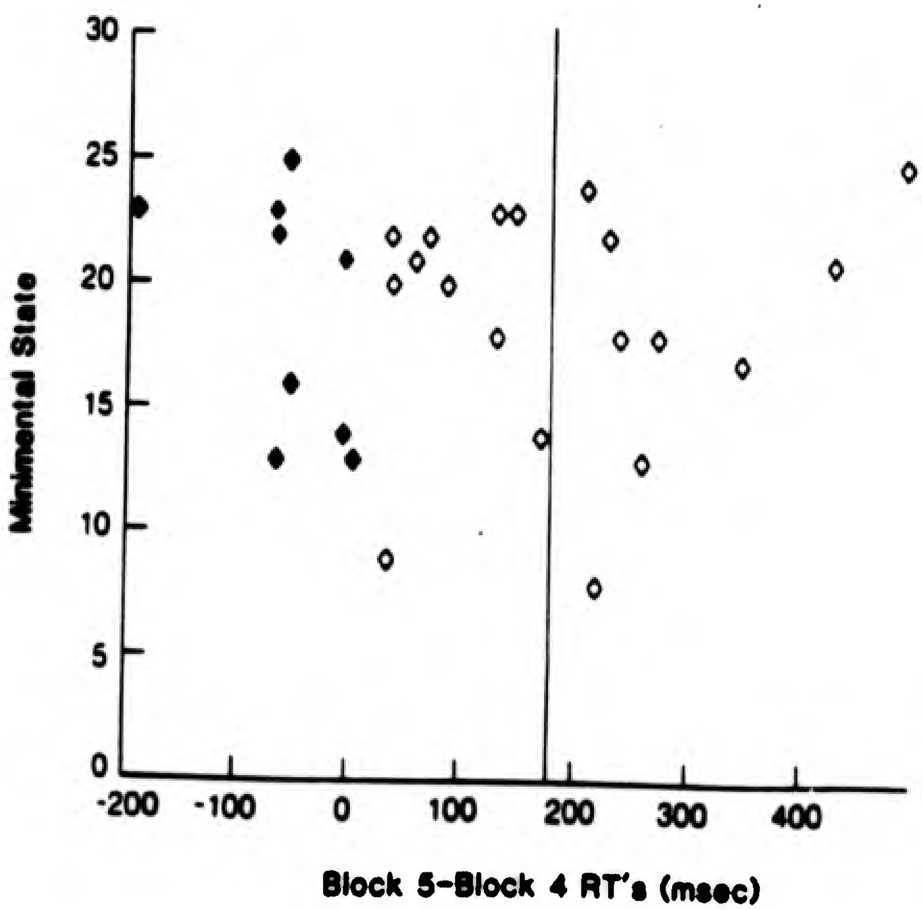
Block
Median RT-AD Pts
Median RT-Elderly Controls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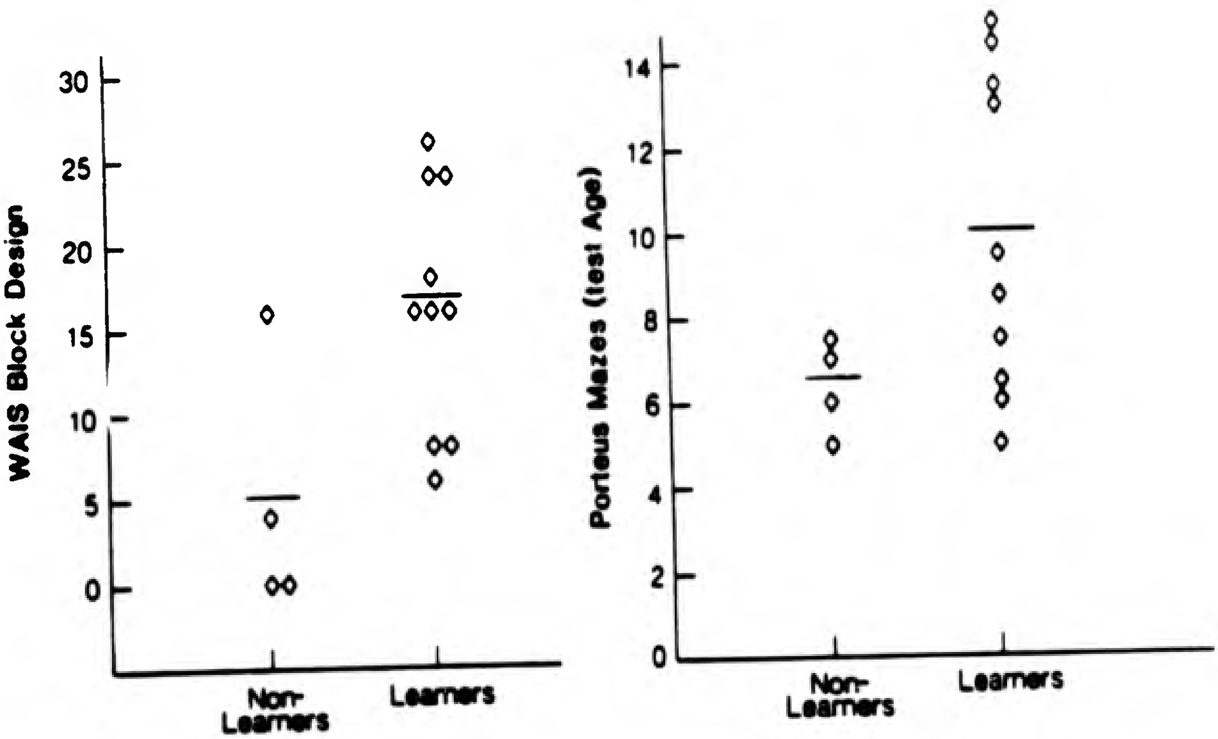
400
Block 5-Block 4 RT's (msec)



WAIS Block Design
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Non-Learners
Learners
Porteus Mazes (test Age)
14
12
10
8
6
4
2
0
Non-Learners
Learners

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