Episodic memory in Alzheimer’s disease: Separating response bias from discrimination

Andrew E. Budson a,b,c,*, David A. Wolk d, Hyemi Chong c, Jill D. Waring a,b,c

a Geriatric Research Education Clinical Center, Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA, USA
b Boston University Alzheimer’s Disease Center, Department of Neurology, Boston University School of Medicine, Boston, MA, USA
c Division of Cognitive and Behavioral Neurology, Department of Neurology, Brigham and Women’s Hospital, Boston, MA, USA
d Alzheimer’s Disease Research Center, Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA

Received 7 January 2006; received in revised form 25 April 2006; accepted 22 May 2006

Available online 3 July 2006

Abstract

Most studies examining episodic memory in Alzheimer’s disease (AD) have focused on patients’ impaired ability to remember information, leading to poor discrimination between studied and unstudied items at test. Poor discrimination, however, can also be attributable to an abnormally high rate of false alarms. One cause of a high false alarm rate is an abnormally liberal response bias; that is, responding “old” too liberally to the test items. In the present study, discrimination and response bias were evaluated when participants were given a series of progressively longer study–test lists of unrelated words. As expected, patients with AD showed overall worse discrimination and a more liberal response bias compared with older adult controls. Critically, patients with AD also showed a more liberal response bias than older adults when discrimination was matched between the groups after performance was equated by giving the older adult controls a more difficult test than the patients with AD. This result confirms that the patients’ abnormally liberal response bias is not simply attributable to their poor discrimination. Correlation analyses suggest that the patients’ liberal response bias is related to the degree of their episodic memory deficit, which may in turn be related to the severity of their disease. Thus, our research suggests that as AD progresses two distinct abnormalities of episodic memory develop: worse discrimination and a more liberal response bias. Possible explanations of this liberal response bias in patients with AD are discussed.

Keywords: Memory, Alzheimer’s disease; Response bias; Discrimination

1. Introduction

Two patients each receive a score of 6 on the recognition portion of the consortium to establish a registry for Alzheimer’s disease (CERAD) word list memory test (Morris et al., 1989), a test commonly used in clinical diagnosis of AD in which there are 10 studied and 10 unstudied words. The first patient correctly endorses only 6 of the 10 studied words and none of the unstudied words. The second patient correctly endorses all 10 studied words but also incorrectly endorses 4 of the unstudied words. Do these two patients have the same problems with their memory? The answer is likely no. The first patient shows a conservative response bias, that is, they responded “old” less than 50% of the time, while the second patient has a liberal response bias because they responded “old” greater than 50% of the time. Despite having the same recognition score, these two patients probably have different memory problems, which may be attributable to different anatomical and neurochemical dysfunction. Focusing on discrimination as the sole measure of memory performance would overlook such differences. In most clinical and experimental recognition memory tests, the rate of “old” responses to unstudied items (i.e., false alarms) is generally taken as a baseline false alarm rate and is simply subtracted from the number of hits (“old” responses to studied items) to obtain a corrected measure of recognition. To interpret these results however – especially in populations such as AD whose baseline false alarm rates are relatively high – it is critical to understand what factors contribute to the baseline false alarm rate. Most studies of recognition memory in AD have found that patients show higher rates of baseline false alarms to unstudied...
items than controls, but few studies have examined the causes of this outcome in patients with AD.

One such study by Snodgrass and Corwin (1988) found that patients with AD showed both poor discrimination and an abnormally liberal response bias compared with the control group. These results were in contrast to those of patients with amnesia due to mixed etiologies, who demonstrated a normal response bias despite showing the worst discrimination in the study. Bartok et al. (1997) also found that patients with AD showed a more liberal response bias as a group compared to controls.

Our previous studies in patients with AD and older adult controls examined false alarms to items that were semantically (e.g., Budson, Daffner, Desikan, & Schacter, 2000) or perceptually (e.g., Budson, Desikan, Daffner, & Schacter, 2001) related to the studied items. To begin our examination of response bias we first conducted post hoc analyses of these data from our laboratory to compare discrimination and response bias between the patients with AD and the older adult controls using \( d' \) as a measure of discrimination and \( C \) as a measure of response bias. We choose these measures because Snodgrass and Corwin (1988) note that models of \( d' \) and \( C \) demonstrate independence between discrimination and bias. \( C \) indicates greater discrimination; 0 indicates chance performance. Positive values of \( C \) indicate a conservative response bias, negative values indicate a liberal response bias, and 0 indicates a neutral bias. \( d' \) was calculated using \( \frac{\text{#hits} + 0.5}{\text{#studied items} + 1} \); \( FA = \frac{\text{#false alarms} + 0.5}{\text{#unstudied items}} \).

Values for \( d' \) and \( C \) of previous studies from our laboratory are shown in Table 1. We conducted post hoc analyses of these data from our laboratory to compare discrimination and response bias between patients with AD and the older adult controls, using \( d' \) as a measure of discrimination and \( C \) as a measure of response bias. We choose these measures because Snodgrass and Corwin (1988) note that models of \( d' \) and \( C \) demonstrate independence between discrimination and bias. \( C \) indicates greater discrimination; 0 indicates chance performance. Positive values of \( C \) indicate a conservative response bias, negative values indicate a liberal response bias, and 0 indicates a neutral bias. \( d' \) was calculated using \( \frac{\text{#hits} + 0.5}{\text{#studied items} + 1} \); \( FA = \frac{\text{#false alarms} + 0.5}{\text{#unstudied items}} \).

These results, as can be seen from Table 1, show that in addition to worse discrimination (\( F(1,32) = 53.34, P < 0.0005 \)), patients with AD also show a more liberal response bias (\( (1,32) = 14.04, P = 0.001 \)), compared to older adult controls.

There are many problems with these post hoc analyses, however, including unequal numbers of studied and unstudied items, and the fact that many of the unstudied items were either semantically or perceptually related to the studied items. When greater numbers of unstudied than studied items are present at test, individuals with worse discrimination will also appear to have a more liberal bias. For example, if two groups show the same tendencies toward a neutral response bias, when presented with a tested test consisting of 40% studied and 60% unstudied items, the group with impaired discrimination will tend to respond “old” to 50% of the items, whereas the group that shows normal discrimination will tend to respond “old” to 40% of the items because the latter group can better discriminate between the studied and unstudied items. Thus, the group with impaired discrimination will tend to exhibit a more liberal response bias compared to the group with normal discrimination. When unstudied items are semantically or perceptually related to studied items, greater numbers of false alarms may result from deficits in item-specific recollection—the ability to discriminate a studied item from a closely related foil—rather than differences in response bias.

The primary goal of the present study was therefore to examine response bias in patients with AD compared to healthy older adult controls in a more standard memory test. In particular, we wanted to examine response bias when these two groups were matched on discrimination in order to assure that any differences found in bias were not related to the patients’ worse discrimination relative to the older adult controls. We predicted that with discrimination matched between groups, patients with AD would show a more liberal response bias compared with older adult controls.

One reason for this prediction is that patients with AD show evidence of pathologic changes in frontal cortex (Buckner et al., 2005; Lisotrom et al., 1998), and neuropsychological and neuroimaging studies of patients with AD have demonstrated frontal lobe dysfunction (Baddeley, Bressi, Delia Sala, Logie, & Spinler, 1991; Buckner et al., 2005; Dalla Barba, Nedjam, & Dubois, 1999; Haxby et al., 1988; Mountjoy, Roth, Evans, & Evans, 1983). Patients with frontal lobe lesions have been previously noted to show elevated levels of false alarms (Budson et al., 2002a; Melo, Winocur, & Moscovitch, 1999; Parkin, Ward, Bindschedler, Squares, & Powell, 1999; Rapsack, Reminger, Gisky, Kasznia, & Comer, 1999; Rapsack et al.,

### Table 1

<table>
<thead>
<tr>
<th>Study name</th>
<th>AD</th>
<th>Older adults</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( d' )</td>
<td>( C )</td>
</tr>
<tr>
<td></td>
<td>( d' )</td>
<td>( C )</td>
</tr>
<tr>
<td>Budson et al. (2000)</td>
<td>0.92</td>
<td>-0.58</td>
</tr>
<tr>
<td>Test 1</td>
<td>1.29</td>
<td>-0.36</td>
</tr>
<tr>
<td>Test 2</td>
<td>1.79</td>
<td>-0.38</td>
</tr>
<tr>
<td>Test 3</td>
<td>1.78</td>
<td>-0.31</td>
</tr>
<tr>
<td>Test 4</td>
<td>1.95</td>
<td>-0.44</td>
</tr>
<tr>
<td>Average</td>
<td>1.55</td>
<td>-0.41</td>
</tr>
<tr>
<td>Budson et al. (2001)</td>
<td>0.59</td>
<td>-0.07</td>
</tr>
<tr>
<td>Budson et al. (2002b)</td>
<td>0.35</td>
<td>0.04</td>
</tr>
<tr>
<td>Budson et al. (2002a)</td>
<td>0.73</td>
<td>0.16</td>
</tr>
<tr>
<td>1 trial</td>
<td>1.15</td>
<td>-0.42</td>
</tr>
<tr>
<td>5 trials</td>
<td>1.08</td>
<td>-0.37</td>
</tr>
<tr>
<td>Budson et al. (2003b)</td>
<td>0.97</td>
<td>0.04</td>
</tr>
<tr>
<td>Budson et al. (2003a)</td>
<td>0.47</td>
<td>-0.07</td>
</tr>
<tr>
<td>Guillo et al. (2004)</td>
<td>1.16</td>
<td>0.02</td>
</tr>
<tr>
<td>Budson et al. (2005)</td>
<td>0.71</td>
<td>0.36</td>
</tr>
<tr>
<td>Word</td>
<td>0.53</td>
<td>0.16</td>
</tr>
<tr>
<td>Picture</td>
<td>0.91</td>
<td>-0.16</td>
</tr>
<tr>
<td>Pierce et al. (2005)</td>
<td>1.03</td>
<td>-0.16</td>
</tr>
<tr>
<td>Budson et al. (2006)</td>
<td>1.07</td>
<td>-0.18</td>
</tr>
<tr>
<td>Emotional</td>
<td>1.04</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

---

1 Note, however that as \( d' \) increases the range of possible biases decreases. See MacMillan and Creelman (2005) and Snodgrass and Corwin (1988) for discussion of this issue.

2 In order to provide a valid measure of bias, when the number of studied and unstudied items were unequal, hits and false alarms were weighted such that an old response to a studied item had the same impact as an old response to an unstudied item (MacMillan & Creelman, 2005). In addition, because \( d' \) and \( C \) are undefined when the proportion of responses equals 0 or 1, all responses were converted using the formulas provided by Snodgrass and Corwin (1988): 

\[
H = \frac{(\text{#hits} + 0.5)/(\text{#studied items} + 1)}{\text{#false alarms} + 0.5}/(\text{#unstudied items} + 1) \]

\[
\text{FA} = \frac{(\text{#false alarms} + 0.5)/(\text{#unstudied items})}{(\text{#unstudied items})}
\]
Frontal lobe dysfunction in patients with AD may therefore cause a liberal response bias. To test our prediction, we gave patients with AD and age, education, and gender matched healthy older adults a series of straightforward lists of words to memorize which differed only in their numbers of words at study and test. Level 1 consisted of 10 words at study and 20 words at test (10 studied and 10 unstudied), level 2 was similar but consisted of 20 words at study and 40 at test, level 3 consisted of 40 words at study and 80 at test, level 4 consisted of 80 words at study and 160 at test, and level 5 (given only to older adults) consisted of 160 words at study and 320 words at test. The critical analysis was the comparison of response bias between the patients and the older adult controls when they were matched for discrimination. The few previous studies that examined bias in AD (including our meta-analysis) compared subject groups that differed on both bias and discrimination — making it impossible to be assured that the bias observed in the patients was not attributable to their poor discrimination. Lastly, in addition to examining response bias in patients with AD when discrimination is matched to older adult controls, we were also interested in determining if the response bias of patients with AD is related to their lack of awareness (anosognosia) of their memory impairment and/or their frontal lobe dysfunction by correlating bias with an anosognosia measure (the anosognosia questionnaire-dementia, Migliorelli et al., 1995) as well as several tests of frontal lobe functioning.

2. Methods

2.1. Participants

Twelve patients with a clinical diagnosis of probable AD (NINCDS-ADRDA criteria, McKhann, Drachman, Folstein, Katzman, & Perry, 1984) were recruited from the Memory Disorders Unit, Brigham and Women’s Hospital (BWH) and the Boston University Alzheimer’s Disease Center (BU ADC), both in Boston, MA, USA. These patients were each assessed by one or more of the neurologists, psychiatrists, and neuropsychologists in these centers, all of whom are expert in the diagnosis of AD. The neuropsychological tests used for the patients’ clinical diagnosis of AD varied by center, and included use of the dementia scale (Blessed, Tomlinson, & Roth, 1968), the dementia rating scale (Mattis, 1988), verbal fluency to letters and categories (Monchul et al., 1992), the CERAD word list memory test (Morris et al., 1989), wechsler memory scale III logical memory (Wechsler, 1997b), the frontal assessment battery (Dubois, Slachevsky, Litvan, & Pillon, 2000), the Boston naming test (Kaplan, Goodglass, & Weintraub, 1983), and the geriatric depression scale (Koren, Micalos, Cohen & Blazer, 1988). Twelve healthy community-dwelling older adults were recruited from participants in a longitudinal study of normal aging at BWH, from the BU ADC, from spouses and friends of the patients studied by the use of flyers and other placed in senior centers in and around Boston. Written informed consent was obtained from all participants and their caregivers (where appropriate). The Human Subject Committee of BWH approved the study. Participants were paid $10/h for their participation. Older adults in the control group were excluded if they scored below 27 on the MMSE (Folstein, Folstein, & McHugh, 1975). Patients with AD showed either mild or very mild impairment on the MMSE (mean = 26.2, range = 23–29). Participants were excluded if they were characterized by clinically significant depression, alcohol or drug use, cerebrovascular disease, or traumatic brain damage. All participants had normal or corrected to normal vision. The patients were matched to the older adults on the basis of age (patient mean = 70.5 years, range = 66.85 years, older adult mean = 74.4 years, range = 67.88 years), and education (patient mean = 15.3 years, range = 12–21 years, older adult mean = 15.6 years, range = 12–22 years). There were five female patients and eight female older adult controls.

2.2. Materials

One thousand two hundred and sixty words were used in the experiment from the University of Western Australia MRC Psycholinguistic Database (http://www.psy.uwa.edu.au/MRCDatabase/uwapzenc.htm). A list of 1407 words were generated by using parameters of Nactera-Francis frequency of 10–700 and word length three to eight letters. One hundred and forty-seven words were removed (most because of their similarity to other words in the list, and several because of vulgarity, high emotional valence, or foreign spelling). The 1260 remaining words were divided into 63 lists of 20 words, counterbalanced by length and frequency. Free study–test levels were constructed. The levels consisted of the following numbers of words at study and test—level 1: 10/20, level 2: 20/40, level 3: 40/80, level 4: 80/160, level 5: 160/320. The lists were randomly assigned as studied and unstudied words for levels one through five, creating version A1. Studied and unstudied words were then switched, creating version A2. The lists were then randomly assigned as studied and unstudied words for levels one through five two additional times, creating versions B1, B2, C1, and C2. Thus, there were a total of 6 counterbalanced versions of the test. These versions were programmed using PsyScope software (Cohen, MacWhinney, Flatt, & Provost, 1997). To help participants distinguish words presented in each level, the study words were shown in a different color (against a white background) for each level. Test words were always shown in black. Study words were presented for 2500 ms each with a 400 ms interval between each word. Test words were present until the participant responded.

2.3. Procedure

Participants were first tested to assure that they could distinguish the different colors used (red, green, blue, pink, orange, and gray). Participants were instructed to read the words presented aloud and try to remember them for a subsequent test. After a 1 min filler in which participants performed simple math, participants were instructed to respond “old” verbally if they remember seeing the test word presented in the preceding color study list or “new” if they do not. The procedure was then repeated with the remaining levels. Patients with AD were presented with four study–test levels, and older adults with five. The levels progressed forward sequentially (shortest to longest) for half of the subjects (the forward test) and backward sequentially (longest to shortest) for the other half of the subjects (the backward test).

3. Results

We first present the results of the standard neuropsychological tests (Table 2). Next the analysis of “old” responses to studied (hits) and unstudied (false alarms) items are presented (Table 3). The results of discrimination and bias are then presented, first by an analysis of levels one through four, and then by a comparison of bias when discrimination is matched between the groups (Table 4). Lastly, we present the results of Pearson correlations between participants’ response bias and the results of the standard neuropsychological tests and the anosognosia questionnaire (Table 5). Scatter plots are provided for important correlations (Fig. 1).
chological tests compared with the healthy older adult controls, with the exception of arithmetic (Wechsler, 1997a).

3.2. Hits and false alarms

Comparing levels one through four between groups with a repeated measures ANOVA with group (patients with AD versus older adult controls) as a between-subject factor and level (1–4) and item type (hits versus false alarms) as within-subject factors showed effects of item type (F(1,22) = 216.96, P < 0.0005) and group (F(1,22) = 23.45, P < 0.0005) but not of level (F(3,66) < 1), and interactions of item type × group (F(1,22) = 29.13, P < 0.0005) and item type × level (F(3,66) = 13.89, P < 0.0005), but not of level × group (F(3,66) < 1) or item type × level × group (F(3,66) = 2.11, P = 0.107). The effect of item type is present because participants showed more hits than false alarms. The effect of group is present because patients with AD made more hits and false alarms combined than did older adult controls. To understand the interactions between item type and both group and level, additional analyses were performed.

Comparing levels one through four between groups with a repeated measures ANOVA for hits revealed an effect of level (F(3,66) = 6.42, P = 0.001), no effect of group (F(1,22) = 2.39, P = 0.136), and no interaction (F(3,66) < 1). The effect of level is present because overall participants showed worse discrimination than the older adults. The effect of level is present because overall subjects showed worse discrimination across the levels. The interaction is likely present because older adults showed no change in d′ across the first two levels and then a steep decline, whereas the patients showed a more gradual, continuous decline (Table 4).

An analogous ANOVA for false alarms showed effects of group (F(1,22) = 40.20, P < 0.0005), level (F(3,66) = 4.47, P = 0.002), and no interaction (F(3,66) = 1.06, P = 0.373). The effect of group indicates that patients with AD made significantly more false alarms than did older adult controls (Table 3). The effect of level is present because participants overall made greater false alarms as the study and test lists became longer.

3.3. d′ and C

We used d′ and C as our measures of discrimination and response bias, respectively. Greater d′ indicates greater discrimination; 0 indicates chance performance. Positive values of C indicate a conservative response bias, negative values indicate a liberal response bias, and 0 indicates a neutral bias. Because these measures are undefined when the proportion of responses equals 0 or 1, all responses were converted using the formulas provided by Snodgrass and Corwin (1988).2

3.3.1. Comparison of matched levels

Comparing levels one through four between groups with a repeated measures ANOVA for d′ yielded effects of group (F(1,22) = 35.47, P < 0.0005), level (F(3,66) = 12.50, P < 0.0005), and a group × level interaction (F(3,66) = 2.80, P = 0.047). The effect of group shows that the patients exhibit worse discrimination than the older adults. The effect of level is present because overall subjects showed worse discrimination across the levels. The interaction is likely present because older adults showed no change in d′ across the first two levels and then a steep decline, whereas the patients showed a more gradual, continuous decline (Table 4).

Table 2
Results of the neuropsychological tests for patients with AD and healthy older adult controls

<table>
<thead>
<tr>
<th>Test</th>
<th>Patients with AD, mean (S.D.)</th>
<th>Older adults, mean (S.D.)</th>
<th>dF</th>
<th>F</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE (Folstein et al., 1975)</td>
<td>26.17 (2.69)</td>
<td>20.75 (0.45)</td>
<td>1, 22</td>
<td>20.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Verbal fluency (Monsch et al., 1992)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Categories (animals, fruits, vegetables)</td>
<td>39.00 (12.56)</td>
<td>51.08 (7.94)</td>
<td>1, 22</td>
<td>7.94</td>
<td>0.01</td>
</tr>
<tr>
<td>Backward digit span (Wechsler, 1997a)</td>
<td>27.75 (12.39)</td>
<td>47.17 (8.78)</td>
<td>1, 22</td>
<td>19.62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Memory (CERAD, Morris et al., 1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word list memory</td>
<td>11.92 (5.86)</td>
<td>22.25 (4.80)</td>
<td>1, 22</td>
<td>29.49</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Word list recall</td>
<td>1.58 (1.44)</td>
<td>7.58 (1.38)</td>
<td>1, 22</td>
<td>108.41</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mental control (Wechsler, 1997a)</td>
<td>6.67 (2.84)</td>
<td>9.42 (1.10)</td>
<td>1, 22</td>
<td>10.02</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Backward digit span (Wechsler, 1997a)</td>
<td>6.36 (1.16)</td>
<td>9.00 (2.13)</td>
<td>1, 22</td>
<td>9.91</td>
<td>0.005</td>
</tr>
<tr>
<td>Arithmetic (Wechsler, 1997a)</td>
<td>11.09 (3.86)</td>
<td>13.54 (4.08)</td>
<td>1, 20</td>
<td>2.1</td>
<td>ns</td>
</tr>
<tr>
<td>Anosognosia questionnaire (AQ-D) (Migliorelli et al., 1995)</td>
<td>–</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AQ-D was not obtained in controls. The results for the mental control, digit span, and arithmetic were not available for one patient with AD. Results for arithmetic were not available for one control. Values for d, F, and P are from one-way ANOVAs between patients and controls. ns: non-significant, P > 0.10.

Table 3
Proportion of hits and false alarms in patients with AD and older adults

<table>
<thead>
<tr>
<th></th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hits</td>
<td>0.80 (0.11)</td>
<td>0.79 (0.11)</td>
<td>0.73 (0.09)</td>
<td>0.73 (0.10)</td>
<td>–</td>
<td>0.46 (0.27)</td>
<td>0.50 (0.18)</td>
<td>0.51 (0.15)</td>
<td>0.54 (0.20)</td>
<td>0.23 (0.16)</td>
</tr>
<tr>
<td>False alarms</td>
<td>0.50 (0.18)</td>
<td>0.50 (0.18)</td>
<td>0.51 (0.15)</td>
<td>0.54 (0.20)</td>
<td>0.56 (0.20)</td>
<td>0.47 (0.11)</td>
<td>0.47 (0.11)</td>
<td>0.47 (0.11)</td>
<td>0.47 (0.11)</td>
<td>0.47 (0.11)</td>
</tr>
</tbody>
</table>

Patients with AD were not tested on level 5. 1–5 denote the levels.
Table 4

| Discrimination (d′) and response bias (C) in patients with AD and older adults |
|----------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Average                          | AD (S.D.)       | Older adult (S.D.) |
| 1                                | 0.93 (0.75)     | 2.04 (0.66)     |                 |                 |                 |                 |                 |                 |
| 2                                | 0.80 (0.53)     | 2.19 (0.78)     |                 |                 |                 |                 |                 |                 |
| 3                                | 0.60 (0.39)     | 1.50 (0.51)     |                 |                 |                 |                 |                 |                 |
| 4                                | 0.52 (.40)      | 1.20 (0.34)     |                 |                 |                 |                 |                 |                 |
| 5                                | 0.72 (0.40)     | 0.92 (0.28)     |                 |                 |                 |                 |                 |                 |

Patients with Alzheimer’s disease at levels 1–5 cannot be tested on level 5.

Table 5

<table>
<thead>
<tr>
<th>Test</th>
<th>r</th>
<th>AD</th>
<th>Older adults</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global cognition score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE (Folstein et al., 1975)</td>
<td>0.59a</td>
<td>−0.08</td>
<td></td>
</tr>
<tr>
<td>Verbal fluency (Monsch et al., 1992)</td>
<td>0.00</td>
<td>−0.58a</td>
<td></td>
</tr>
<tr>
<td>Categories (animals, fruits, vegetables)</td>
<td>0.37</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Memory (CERAD; Morris et al., 1989)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word list memory</td>
<td>0.57</td>
<td>−0.55</td>
<td></td>
</tr>
<tr>
<td>Word list recall</td>
<td>0.86a</td>
<td>−0.54</td>
<td></td>
</tr>
<tr>
<td>Word list recognition</td>
<td>0.72a</td>
<td>−0.42</td>
<td></td>
</tr>
<tr>
<td>Mental control (Wechsler, 1997a)</td>
<td>0.46</td>
<td>−0.01</td>
<td></td>
</tr>
<tr>
<td>Arithmetic (Wechsler, 1997a)</td>
<td>0.24</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>Anosognosia questionnaire (AQ-D)</td>
<td>0.47</td>
<td>0.05</td>
<td></td>
</tr>
<tr>
<td>(Migliorelli et al., 1995)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Correlation significant at the P<0.05 level.

Fig. 1. Scatter plots showing the correlation between response bias as measured by C average and performance on word list recall, the delayed recall portion of the CERAD word list memory test (Morris et al., 1989) for (a) patients with Alzheimer’s disease and (b) healthy older adult controls.
An analogous ANOVA for C also yielded an effect of group \( (F(1,22)=20.40, P<0.0005) \). There was no effect of level \( (F(3,66)<0.1) \) and no interaction \( (F(3,66)=0.2) \). The effect of group was present because the patients showed a liberal response bias in comparison to the older adults’ conservative bias. That there was no effect of level and no interaction suggests that the response bias of participants in both groups were unchanged over the four levels.

As discussed in Section 2, half of the subjects started with level one and proceeded to level four (or five in the case of the controls), and the other half started with the highest level and proceeded to level one. To assure that the direction of testing, forward versus backwards, did not affect our results we performed the following analyses. Two ANOVAs were performed, one for direction and one for C, each with two between-subject factors of group (patients with AD versus older adult controls) and direction of test (forward versus backwards), and one within-subjects factor of level (1 through 4). For d there was no overall effect of direction of test \( (F(1,20)<0.1) \), and no interactions between direction of test and group \( (F(1,20)=1.39, P=0.251) \), between direction of test and level \( (F(3,60)=2.11, P=0.108) \), or between direction of test \( \times \) level \( \times \) group \( (F(3,60)=1) \). Similarly, for C there was also no overall effect of direction of test \( (F(1,20)<0.1) \), and no interactions between direction of test and group \( (F(1,20)<1) \), between direction of test \( \times \) level \( (F(3,60)<1) \), and between direction of test \( \times \) level \( \times \) group \( (F(3,60)=1) \). Thus, whether subjects started with level one and proceeded to higher levels or vice-versa did not significantly affect our results.

3.3.2. Comparison of matched discrimination

The critical analysis for the present study is comparison of the response bias of patients versus older adult controls when discrimination is matched between the groups. Matching discrimination is possible by comparing the first level for the patients to the fifth level for the older adults (Table 4). The discrimination measure d' was almost exactly matched between the groups \( (F(1,22)<0.01, P>0.95) \). The bias measure C was more liberal in the patients compared to the older adult controls \( (F(1,22)=12.38, P=0.002) \). Because age was not perfectly matched between the groups, the analysis of C was repeated with age as a covariate; again the difference between the groups was highly significant \( (F(1,21)=8.82, P=0.007) \).

To assure that our critical analysis was not affected by the direction that participants performed the different levels, we performed one-way ANOVAs with the between-subjects factor of direction of test for d' and C for the patients with AD for the first level, and for the older adult controls for the fifth level. These analyses revealed no effect of the direction of test on d' for the patients \( (F(1,10)<1) \) or controls \( (F(1,10)=1) \), and no effect on C for the patients \( (F(1,10)<0.1) \) or controls \( (F(1,10)<0.1) \).

3.3.3. Correlations

To gain insight into the liberal response bias of the patients, we performed correlations between the average of the bias measure C and a measure of the patients’ awareness of their memory deficit (anosognosia), along with several standard neuropsychological tests of cognitive functions (Table 5). Because a total of 10 comparisons were performed, using the Bonferroni correction to avoid type I error, we adjusted our \( \alpha \) to 0.05 divided by 10 or 0.005, indicating that only correlations with a \( \alpha \) value of <0.005 would be considered significant. To avoid a type II error and ignoring potentially meaningful results with small \( N \), however, we will also comment on correlations with a \( \alpha \) value of <0.05. For the patients, three correlations showed a \( \alpha \) value of <0.05: MMSE, delayed recall (word list recall) on the CERAD, and recognition (word list recognition) on the CERAD. However only the correlation with delayed recall on the CERAD reached significance after Bonferroni correction (Table 5 and Fig. 1a).

In the older adults only a single correlation showed a \( \alpha \) value of <0.05 (letter word fluency), which was not significant for our corrected \( \alpha \). Note that the correlation with delayed recall on the CERAD was not significant in the older adults (Fig. 1b).

4. Discussion

In post hoc analyses from our previous studies involving items that were semantically or perceptually related to studied items, patients with AD showed a more liberal response bias compared with older adults. We were concerned, however, that post hoc analyses of these studies may have lead to a finding of a liberal response bias for several spurious reasons: because greater numbers of unstudied compared to studied items were presented, because of the patients’ impaired ability to discriminate a studied item from a related but unstudied item, or because the patients’ discrimination was lower than that of older adult controls. In the present study we wanted to examine response bias in patients with AD when their discrimination was matched to that of older adult controls in a more standard memory test. We predicted that the patients would show a more liberal response bias compared to older adult controls in a memory paradigm using unrelated items and equal numbers of studied and unstudied items at test—even when the groups were matched for overall discrimination.

Our prediction was confirmed: we found that patients with AD did show overall lower levels of discrimination and a more liberal response bias compared with older adult controls. Critically, we demonstrated that patients with AD also show a more liberal response bias than healthy older adults when discrimination was matched between the groups. Thus, the primary question of this study has been answered. We have determined that the patients’ liberal response bias is not simply related to their poor discrimination on a particular memory test, but is a separate and distinct problem of memory in patients with AD.

The strongest evidence of the independence of discrimination and bias may be the lack of an effect of level or a group \( \times \) level interaction for the response bias measure C in our comparison of matched levels: response bias was not significantly affected by the level of discrimination in either patients or controls. A quick perusal of Table 4 shows the remarkable stability of C across the levels in both the patients with AD and the older adult controls, despite changes in d'. Although individual subject data had more variability, most of the participants’ biases were similar across the different levels of discrimination; in other words, a given individual tended to show a particular bias that...
was relatively unchanging regardless of discrimination and test difficulty, consistent with previous studies (Windmann, Urbach, & Kutat, 2002). Bias did differ between individuals, however. Fig. 1 shows the distribution of the bias averaged across the levels for the individual subjects. Fig. 1a shows the strikingly high correlation between response bias and word list recall (or delayed recall) on the CERAD in the patients with AD. This correlation indicates that as retrieval of episodic memory becomes more impaired in AD, their recognition response bias becomes more abnormally liberal. We will consider the implications of this correlation below. Note that this correlation was not present in the older adult controls (Fig. 1b).

Although the primary question of the study has been answered, the question of why patients with AD show a more liberal response bias than healthy older adults remains. We hypothesized that frontal lobe dysfunction in patients with AD may have contributed to their liberal response bias. The patients with AD were impaired relative to the older adult controls on many tests which have been associated with frontal lobe functioning (see Table 2) including verbal fluency to letters (FAS, Monsch et al., 1992), mental control (Wechsler, 1997a), and backward digit span (Wechsler, 1997a). We therefore expected correlations to be present between impairment on these tests of frontal lobe functioning and the liberalism of the patients’ response bias. To our surprise, however, such correlations were not found.

There are several possible reasons why correlations were not found between the patients’ frontal lobe deficit and their liberal response bias. One possibility is that because the frontal lobes constitute a large part of the brain with both functionally overlapping and separable regions, it is possible that the frontal lobe measures that we chose were simply not sensitive to the particular aspect of frontal lobe function that is also relevant for response bias in AD. Another possibility is that because these patients were in the earliest stages of AD, they may not have appreciable frontal lobe pathology. Although our patients showed impairment on neuropsychological tests sensitive to frontal lobe dysfunction, recent evidence suggests that parietal lobe dysfunction could also account for impairment on many tests of frontal/executive function (Asahi, Okamoto, Okada, Yamawaki, & Yokota, 2004; Kemmotou, Villalobos, Gaffrey, Courchesne, & Müller, 2005; Narayanan et al., 2005; Peers et al., 2005). Compared to frontal lobe involvement, parietal lobe involvement occurs very early in AD (Reisman et al., 1998). If frontal lobe dysfunction cannot explain our patients’ response bias, then the question remains: What is the etiology of their liberal response bias?

One possible explanation of why patients with AD show a liberal bias compared with older adult controls is related to the evidence that patients with AD demonstrate disordered semantic networks that may lead to an aberrant sense of familiarity (Chan, Butters, & Salmon, 1997). Patients with AD have been shown to make elevated levels of familiarity-based false alarms (Lekeu et al., 2003) attributable to impaired recollection (Gallo, Sullivan, Daffner, Schacter, & Budoson, 2004; Knight, 1998; Koivisto, Portin, Soinela, & Rinne, 1998; Smith & Knight, 2002), which in turn has been related to a number of factors including deficits in item-specific recollection (Budoson et al., 2000) and source memory (Dalla Barba et al., 1999; Pierce, Sullivan, Schacter, & Budoson, 2005; Tendolkar et al., 1999). An item that would not evoke a sense of familiarity in an individual with a normal semantic network may do so in a patient with AD with a disordered semantic network. An example might be, if the patient studied the word “snake” and then shown the word “rope” at test, the patient might say “old” because in her mind a snake and a rope are very similar because her semantic network is characterized by more interconnected associations (Chan et al., 1993, 1995). Support for this view may be inferred from the work of Balota, Burgess, Cortese, and Adams (2002) who found that patients with mild AD showed a more liberal response bias than older adults for high frequency words but not for low frequency words, since high frequency words typically have more semantic associations than low frequency words. (Alternatively, high frequency words may also be more familiar to patients with AD simply because they are more frequently encountered.) One way to test this hypothesis would be to evaluate patients with AD and controls with an experimental memory paradigm that contains words that are weakly related to studied words (e.g., study “snake” and test “rope,” using the example above). If the main cause of the patients’ liberal response bias is their disordered semantic network, then we would expect the patients to false alarm to such weakly related lures at a greater rate than truly unrelated words, in addition to showing a greater false alarm rate to these words compared with the older adult controls.

Although the expected correlations between our tests of frontal lobe functioning and response bias were not present in the patients with AD, one correlation was present with our stringent α of 0.005 (after Bonferroni correction), and two were present with the more lenient α of 0.05 (Table 5). Understanding these correlations between response bias and word list recall (r = 0.89, P < 0.005), word list recognition (r = 0.72, P = 0.008), and the MMSE (r = 0.59, P = 0.043) may be informative regarding the cause of the liberal response bias in patients with AD. In the CERAD memory test (Morris et al., 1989), word list recall measures free recall of the 10 studied words after a 10-min delay, and word list recognition (administered after word list recall) measures the ability to distinguish the 10 studied from 10 unstudied words. The MMSE (Folstein et al., 1975) is a widely used measure of global cognition that includes orientation in time and place, registration and recall of three words, attention and calculation, naming, repetition, following a three-step command, reading, writing, and copying a figure. We now speculate on the possible implications of these correlations.

First, we consider why the patients’ bias correlated more strongly with word list recall than with word list recognition. There are several possible explanations for the differences in the strength of the correlation between recall and recognition. We will consider two: (1) that recall requires different and/or greater frontal lobe activation compared to recognition, and (2) that recall requires the activity of the hippocampus whereas recognition may rely on other medial temporal lobe structures.

Apart from its role in response inhibition (Shimamura, 1995), evidence over the past 15 years has demonstrated that the frontal lobes are critical for memory processing (see Simons & Spiers,
A number of studies of patients with frontal lobe lesions have compared recall and recognition. In their meta-analysis of memory studies involving patients with these lesions, Wheeler, Stuss, and Tulving (1995) report that although recognition was affected by frontal lesions, recall was affected by frontal lesions in a greater number of studies and to a much greater extent. To understand which region or regions within the frontal lobes show greater activation for recall versus recognition, we turn to functional brain imaging studies. However, surprisingly few functional imaging studies have directly compared recall versus recognition, and here the data is mixed (see Davidson, Troyer, & Moscovitch, 2006, for review). Some studies, such as Cabeza et al. (1997), found that frontal activations were indistinguishable for recall and recognition. Other studies using similar (though not identical) paradigms have shown differences in frontal lobe activation for recall versus recognition. Fletcher, Shallice, Frith, Frackowiak, and Dolan (1998) found that right dorsolateral frontal cortex activity was increased for free relative to cued recall, whereas right ventrolateral frontal cortex was increased for cued relative to free recall. Petrides, Alivisatos, and Evans (1995) found greater activation of left ventrolateral frontal cortex in free relative to cued recall. Although additional work needs to be done to understand the differences in activation between recall and recognition, from the lesion literature it is clear that the frontal lobes are more critical for recall compared to recognition. Thus, one possible reason that the patients’ response bias correlated more with their performance on word list recall than word list recognition may relate to differences in frontal lobe activation during recall versus recognition. For example, dysfunction of right dorsolateral frontal cortex (or a sub-region within this area) may affect both the patients’ free recall of words and their response bias, causing them to be highly correlated. As mentioned above, it is possible that the lack of a correlation between response bias and our standard neuropsychological tests of frontal lobe function in the patients could be attributable to the insensitivity of the particular standard tests we choose to measure function in the critical area of frontal cortex (dorsolateral frontal cortex in this example).

Another possible reason that word list recall correlated more with the patients’ response bias relative to word list recognition may be related to the difference between the medial temporal lobe structures necessary for recall versus recognition. It has been postulated that the hippocampus is essential for recall, whereas the perirhinal cortex can support recognition (see Simons & Spiers, 2003, for review). Studies of individuals with selective hippocampal damage have shown impairment in recall with relative preservation of recognition (Aggleton & Shaw, 1996; Baddeley, Vargha-Khadem, & Mishkin, 2001; Giovanello & Vertenstein, 2001; Yonelinas et al., 2002). And patients studied with medial temporal lobe lesions that included perirhinal cortex have demonstrated worse recognition memory than patients whose lesions were confined to the hippocampus (Buffalo, Reber, & Squire, 1998; Holdstock, Gutnikov, Gaffan, & Mayes, 2000). Since response bias in the patients correlated more with word list recall than word list recognition, and recall is dependent on the hippocampus whereas recognition is dependent on the perirhinal cortex, one possibility is that damage to the hippocampus is responsible for the abnormally liberal response bias observed in patients with AD.

Next, we consider two possible explanations as to why the patients’ bias correlated with word list recall and recognition more strongly than the MMSE. Word list recall and recognition both measure retrieval of episodic memory. As mentioned above, retrieval of episodic memory is measured in the MMSE, but so are many other aspects of cognitive function. Thus one explanation as to why word list recall and recognition correlated with the patients’ response bias more strongly than the MMSE is that the patients’ response bias is related more to their impairment in retrieval of episodic memory than to their overall dementia severity.

There is, however, another explanation. We have considered how the correlations between bias and word list recall, word list recognition, and the MMSE are different from each other, it is also worth considering how they are similar to each other. Each of these three standard neuropsychological variables may be considered a measure of the stage or severity of the patients’ AD. While the MMSE is often considered the standard in measuring the stage of patients with dementia, the CERAD memory test may actually be considerably more sensitive, particularly in the very mild stage of AD (Gillen, Gregg, Yuan, Kurth, & Klosnian, 2001; Neumann et al., 2001). This is not surprising since in AD the patients’ episodic memory impairment is related to the severity of their Alzheimer’s pathology (Price & Morris, 1999). Considered together, therefore, our correlation analyses may suggest that not only is the liberal response bias in patients with AD related to their impairment of their retrieval of information from episodic memory, it is also related to the progression of their AD. We believe that this explanation may be correct, and therefore suggest that as AD progresses, two distinct abnormalities of episodic memory develop: worse discrimination and a more liberal response bias.

To summarize, our correlation analyses found that the patients’ response bias was strongly correlated with their ability to retrieve information from episodic memory, particularly in a delayed recall task, and less strongly correlated with their performance on the MMSE. Given the differences of recall versus recognition tasks in episodic memory, we speculated that the abnormally liberal response bias observed in these patients with very mild AD may be attributable to either dysfunction of particular regions of frontal cortex that are also important for the free recall of information, or to dysfunction of the hippocampus versus perirhinal cortex. We also speculated that disorganization of the patients’ semantic networks might explain their liberal response bias.

One possible way to discern between these different possibilities would be to use structural magnetic resonance imaging techniques to measure a variety of brain regions – including dorsolateral and other areas of frontal cortex, hippocampus and other medial temporal lobe structures, and anterior and lateral temporal lobes which may be related to semantic networks – and then to examine whether correlations are present between these regions and the patients’ response bias during a straightforward memory test, such as the one used in the present study.
In fact, a recent study did perform a similar analysis. Kramer et al. (2005) measured a variety of brain volumes (including frontal lobes, hippocampus, and anterior temporal cortex) in patients with AD, patients with frontotemporal dementia, patients with semantic dementia, and controls, and correlated these volumes with subjects’ performance on a variety of aspects of the California verbal learning test-short form (CVLT-SF; Delis, Kramer, Kaplan, & Ober, 2000), including response bias. They found that whereas hippocampal volumes were the best predictor of delayed recall and recognition, frontal volumes were the best predictor of semantic clustering and response bias. This study would therefore suggest that regions of frontal cortex are most important for response bias. There are, however, important differences between the Kramer et al. study and ours. First, by MMSE score, the patients in their study were somewhat more impaired, averaging about 22. It may be frontal lobe dysfunction explains response bias in patients with mild to moderate AD but not in very mild AD. Second, while the CVLT-SF is advantageous in that it allows measurement of several different brain regions, it measures a variety of different aspects of cognition, its use of semantic clustering introduces confounds mentioned in the Introduction, such as the necessity to use item-specific recollection to distinguish between studied items and related lures. Others and we have previously shown that the frontal lobes are critical for item-specific recollection (Budson et al., 2002a; Schacter et al., 1996). Although addi-

Acknowledgements

This research was supported by the National Institute on Aging R01 AG025815, P30 AG13846, and the National Institute of Mental Health F32 MH68936. We thank Scott Slotnick, Brandon Ally, Daniel Press, Jon Simons, and Carl Gold for reading earlier versions of this manuscript, and also Joan Snodgrass, June Corwin, Ellen Beth, and Dan Schacter for their help. We also gratefully acknowledge the suggestions of the editor and reviewers of the previous submission of this manuscript.

References


...carcinic cholinergic receptors, whereas lorazepam activates the inhibitory neurotransmitter gamma-aminobutyric acid (GABA). Lastly, we hope that our research into recognition response bias in patients with AD will stimulate further research into response bias in normal subjects. We believe that understanding response bias will prove critical in understanding the function and dys-

function of episodic memory.


