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Can episodic memory tasks differentiate semantic dementia from Alzheimer’s Disease?

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The aim of the current investigation was to contrast the neuropsychological profile of patients with Alzheimer’s disease (AD) with that seen in semantic dementia (SD), the temporal variant of frontotemporal dementia, focusing in particular on episodic memory. Previous studies have suggested that this domain of cognition is differentially affected in these two dementing conditions (Hodges et al., 1999; Simons et al., 2002a; Kramer et al., 2003; Piolino et al., 2003), raising the possibility that the use of anterograde memory tasks in the clinical setting may provide a viable method for distinguishing between these two diseases. The published studies have been limited, however, by a number of factors, in particular (a) difficulties in systematically matching patients across dementing conditions (e.g., Graham et al., 1997; Piolino et al., 2003); and, more importantly, (b) virtually no consideration of whether laterality (predominant involvement of right versus left temporal structures) influences performance on episodic tasks, especially in SD in which there is often asymmetric temporal lobe atrophy (Galton et al., 2001; Rosen et al., 2002). The goal of this study, therefore, was to investigate whether any well-established, standardized test of episodic memory provided a means of reliably differentiating between patients with AD and SD, and whether the division of SD patients into those with predominantly right or left atrophy of the temporal lobe facilitated this differentiation.

Patients with probable AD typically present with prominent complaints of memory difficulty (e.g., forgetting appointments, or where the car has been left in a car park). Neuropsychological testing confirms that the major impairment early on in the disease is in anterograde episodic memory, with patients typically showing poor recall of a story (Chapman et al., 1997), or complex figure after a delay (Bigler et al., 1989; Siri et al., 2001) and impaired recognition memory for previously studied words and faces (Dalla Barba, 1997; Lekeu et al., 2003). Tests designed to aid the early detection of AD have focused on episodic memory, with tasks measuring object-place memory showing particular promise (Swainson et al., 2001; Blackwell et al., 2003). Notably, however, patients with AD also suffer from significant and progressive impairment in attentional executive function (Swanberg et al., 2004), language (Murdoch et al., 1987), semantic knowledge (Hodges and Patterson, 1995) and visuospatial abilities (Kaskie and Storandt, 1995), especially later in the disease.

Structural MRI studies have consistently demonstrated bilateral, symmetrical medial temporal lobe atrophy, involving particularly the hippocampus and entorhinal cortex at an early stage of AD (for a review, see Chetelat and Baron, 2003), a finding that presumably reflects the predominant pathological locus in AD (Braak and Braak, 1991; Van Hoesen et al., 1991). Use of FDG-PET has highlighted involvement of other brain regions, with posterior cingulate hypometabolism often the earliest cortical abnormality (Minoshima et al., 1997). This finding has recently been extended to mild cognitive impairment (MCI; see Burns and Zaudig, 2002; Chertkow, 2002), implicating in particular the retrosplenial cortex (BA 29/30), a sub-region of the posterior cingulate (Nestor et al., 2003a; Nestor et al., 2003b).

In contrast, patients with SD present with a progressive yet relatively selective breakdown in semantic knowledge. These patients demonstrate poor performance on tests of semantic
memory involving a wide variety of stimuli from different modalities (Snowden et al., 1996a; 2004; Bozat et al., 2000; Graham et al., 2000). In contrast, episodic memory can be relatively intact, with normal performance on recognition-based tests with visual material, and relative preservation of recent autobiographical memory (Hodges and Graham, 2001; Simons, Verfaellie et al., 2002; Piolino et al., 2003). A study by Lee et al. (2003) showed that whereas, as previously mentioned, AD patients perform poorly on a task assessing object-place memory, SD patients showed good performance on this episodic task. Notably, however, patients with SD do not show unequivocal preservation of episodic memory, with deficits on word list learning even for still familiar stimuli (Graham et al., 2002). This is likely to make the differential diagnosis of SD and AD more challenging, given the heavy reliance on verbal memory tests in clinical practice.

The profile of atrophy in SD differs from that in AD. Studies report progressive atrophy of anterior and inferolateral regions of the temporal lobes, involving particularly the polar, anterior fusiform and inferior temporal gyri (Chan et al., 2001; Galton et al., 2001; Davies et al., 2004). Early on, this atrophy can be predominantly unilateral (affecting either the right, Evans et al., 1995; or left, Simons et al., 2001), but, as the disease progresses, eventually involves both temporal lobes (Snowden et al., 1992; Andersen et al., 1997; Whitwell et al., 2004). Although it was initially thought, based on visual inspection of MRI scans, that the medial temporal lobe was relatively preserved (Graham and Hodges, 1997), more systematic volumetric investigations have revealed asymmetric involvement of the hippocampal formation (Chan et al., 2001; Galton et al., 2001), and especially perirhinal cortex (Davies et al., 2004).

While initial studies focused on the overall neuropsychological profile of SD (Snowden et al., 1989; Hodges et al., 1992; Snowden et al., 1996b; Hodges et al., 1999), more recent investigations have started to consider whether there are significant clinical differences between patients with predominantly right or left temporal atrophy, using both behavioral and imaging assessments (Edwards-Lee et al., 1997; Simons et al., 2001; Thompson et al., 2003; Snowden et al., 2004). Thompson et al. (2003) reported more word finding difficulties and reduced comprehension in cases with predominantly left-sided atrophy (SDL), and greater person recognition difficulties in patients with predominantly right-sided atrophy (SDR). Interestingly, 20% of these SDR patients also reported navigation problems, whereas no such difficulties were noted in SDL patients. This finding suggests that patients with greater right temporal lobe atrophy might show more pronounced memory problems than patients presenting with predominant left temporal lobe atrophy. Support for this assertion comes from the study by Simons et al. (2001), which compared three groups of patients (categorized into predominantly right (SDR), predominantly left (SDL) and bilateral, according to rating of MRI scans). SDR patients were found to be at chance on the recognition memory test for faces (Warrington, 1984), while SDL patients performed normally.

Given these findings, it seems that anterograde memory may be differentially affected in patients with SD, with laterality of pathology a significant influencing variable. Once again this has implications for clinical diagnosis, suggesting that the differentiation of AD patients from SDR patients in particular might be difficult. Drawing firm conclusions, however, from the Simons et al. (2001) study is limited by two factors. First, although the groups did not differ significantly in Mini-Mental State Examination Score (MMSE, Folstein et al., 1975), they were not matched systematically on this measure of disease severity, with the SDL patients scoring on average 3 points higher than the SDR patients (27.5/30 vs. 24.5/30). Second, the groups employed by Simons et al. were relatively small, with only 4 patients in each of the SDR and SDL groups. We carried out a larger group study of laterality differences in SD by matching cases from our database pairwise on the basis of age, education and MMSE score. In addition, we contrasted the performance of these cases with a matched group of patients with presumed early AD in order to determine whether the two subgroups of SD could be easily differentiated from this disorder. We hypothesized, on the basis of previous smaller investigations, that SD patients with right predominant temporal lobe atrophy might be more likely to show broader impairment on anterograde memory tasks than cases with left predominant SD. Furthermore, these deficits might be more similar to those seen in AD, making it difficult to distinguish between SD and AD in the clinical setting.

Methods and materials

Participants

A retrospective search of our patient database from the last 12 years revealed 27 suitable patient participants, whose average length of time from initial presentation to testing was less than a year. All these individuals presented through the Memory and Cognitive Disorders Clinic at Addenbrooke’s Hospital, Cambridge, and were evaluated by a consultant neurologist, psychiatrist and clinical neuropsychologist prior to being enrolled in our longitudinal research program. In total, we identified 18 appropriate patients with semantic dementia, all of whom fulfilled the criteria for the temporal variant of frontotemporal lobar degeneration established by the Lund-Manchester group (Neary et al., 1998). Of note, the consensus criteria for semantic dementia exclude patients with “severe amnesia”. Given the difficulty in defining “severe” and our interest in episodic memory, we did not take episodic memory test performance into account when classifying patients. In all cases structural magnetic resonance imaging revealed local atrophy involving the polar and inferolateral regions of the temporal pole. On the basis of radiological evaluation from a senior neurologist (JRH), the cases
were further split into 9 individuals whose MRI scans at presentation revealed right predominant temporal involvement (SDR) and 9 cases in whom there was radiological evidence of left predominant temporal damage (SDL). Cases with obvious bilateral involvement were excluded. Figure 1 (a-d) shows illustrative scans of single cases from both groups. It should be noted that unlike some previous studies in which the performance of right and left semantic dementia patients were compared (Simons et al., 2001), here the cases were deliberately selected so that they could be pair-wise matched with each other on the basis of age, education and score on the MMSE. Nine further patients, this time with a diagnosis of probable Alzheimer’s disease, based on an informant confirmed history of progressive memory disorder, were selected from the database (matched according to age, education and MMSE performance to each semantic dementia pair). The diagnosis of probable AD was made according to the criteria developed by the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer’s Disease and Related Disorders Association (ADRDA), which consist of inclusion and exclusion criteria (McKhann et al., 1984). Two patients in this group had been given the diagnosis of MCI at the time the tests were administered; for both these patients, a later diagnosis of AD was made after further neuropsychological follow-up. Figure 1 (e-f) shows illustrative scans for an example case with AD.

While the majority of the patients are still living, pathological reports were available for four of the patients, three SDR and one SDL. Two were confirmed frontotemporal dementia with ubiquitin positive inclusions, one frontotemporal dementia with motor neuron disease type inclusions and the fourth “Pick’s disease, Pick body negative”.

In total, therefore, we report three patient groups (n = 9), all of whom were matched for basic demographic variables (age, education and MMSE, Fs < 1; see Table 1). Where Clinical Dementia Rating Scale (CDR) data was available (4 SDR, 7 SDL, 8 AD), this is also reported in Table 1, although due to the incompleteness of this data, this was not included as a matching variable. Data that were available suggest that for all three groups, patients were in similar, early stages of dementia. Normal controls were also selected from the database, again specifically chosen to be an appropriate match to each individual patient triplet (on the basis of age and education, Fs < 1). Unfortunately, not all controls had undertaken the complete battery of neuropsychological tests described here, so two sets of 9 matched controls were adopted, who together had completed all tasks, as shown in Table 2.

Although we tried as much as possible to make sure that the patients had undertaken each test, it was inevitable that there would be some missing data. In the situation where an individual patient had not completed a task, the data from this patient, and from the three subjects (two patients and one control) who were matched to that particular individual, were excluded from the analysis for that task only. This resulted in varying numbers of patients in each group for the different tasks (as noted in Table 2).

Case histories

Three illustrative case histories are provided below. These clearly indicate that semantic memory is the most obvious complaint in the two semantic dementia patients, while day-to-day memory problems are more evident in the case with Alzheimer’s disease. The SDR case history, however, also implies some broader problems with day-to-day memory.

WM: Semantic dementia (left predominant temporal lobe atrophy)

This 55-year-old biochemistry laboratory technician, with 15 years of education, presented with a 3-year history of progressive language problems. She complained initially of word-finding difficulties in general conversation, and of problems with comprehension, encountered mainly when reading books, or at times when several people were speaking together. She considered both her day-to-day memory and her memory for the past to be normal, opinions corroborated by her husband, although he reported ‘constant’ problems with his wife’s memory for names of objects and people, in keeping with the patient’s view.

On examination, WM’s speech was fluent, with only occasional word-finding pauses and circumlocutions. She scored 29 on the MMSE, but her score of 82/100 on the Addenbrooke’s Cognitive Examination (ACE, Mathuranath et al., 2000) revealed mild problems with verbal recall and reduced letter and category fluency. On formal neuropsychological testing, she also showed a significant degree of anoma, correctly naming only 2 out of the first 10 items on the Graded Naming Test (McKenna and Warrington, 1980), and had reduced immediate recall of a prose passage (Wechsler, 1987), but showed no loss of information over time. Recognition memory was average, with both memory for words and faces at the 50th percentile (Warrington, 1984), a probable reduction given this individual’s pre-morbid level of education. Working memory and visuospatial function, as assessed using subtests of the VOSP (Warrington and James, 1991), were also normal, and WM made no errors on the modified Wisconsin card sorting task (Nelson, 1976), a test of frontal executive function. An MRI scan at time of presentation revealed anterior left temporal lobe atrophy, and a SPECT scan performed 10 months later showed hypoperfusion in the left temporal region.

In summary, WM presented with complaints of problems with both word production and comprehension, but with preserved episodic memory.

AC: Semantic dementia (right predominant temporal atrophy)

This 58-year-old retired marketing manager, with 19 years of education, presented with a two-year history of increasing difficulty in the recognition of previously familiar people.
This was initially only with respect to distant acquaintances, but had worsened with time to affect his recognition of even quite familiar friends. He also complained of difficulty recalling people’s names and problems with comprehension of less frequent words, particularly when watching television, or again when in conversation with several people. His wife reported

Fig. 1. MRI scans representative of patients in Group SDR (a, b), Group SDL (c, d), Group AD (e, f). Left panels show the temporal poles, the right panels show the hippocampus approximately half way along its axis. For all images, the patient’s left is on the right as observed.
that he had day-to-day difficulties with memory, e.g., for conversations and appointments, and a tendency to ask the same questions over again. His wife also reported that his memory for the names of objects and people was poor, again on a daily basis.

On examination, AC spoke fluently, and there was no evidence of word-finding difficulties in his spontaneous speech. He scored 30 on the MMSE, and showed a mild decrease in both letter and category fluency on the ACE, scoring 87. Formal neuropsychological assessment revealed marked anomia; he named only 5 out of 30 items on the graded naming test (for comparison with WM, AC scored 4 out of the first 10 items). He too had reduced immediate recall of a prose passage, but showed some further loss of information over time. His recognition memory was poor, at the 5–10th percentile range for words and below the 5th percentile score for faces. Working memory and visuospatial function, as assessed using subtests of the VOSP, were normal, and he made no errors on the modified Wisconsin card sorting task. An MRI scan of his brain showed evidence of bilateral lobe atrophy, worse on the right than the left, and SPECT imaging revealed right temporal hypoperfusion.

In summary, AC presented with problems recognizing familiar people, both from face and voice, some anomia, and memory problems.

**CG: Alzheimer’s disease**

This 61-year-old copy editor, with 10 years of education, presented with a two-to-three year history of memory problems; she described her memory as “hopelessly unreliable”. She considered both day-to-day memory and her memory for the past to be affected, and mentioned that her daughter complained

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**Table 1. Means and standard deviations of demographic variables for Groups SDR, SDL, AD and Control**

<table>
<thead>
<tr>
<th></th>
<th>SDR</th>
<th>SDL</th>
<th>AD</th>
<th>Control 1</th>
<th>Control 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>MMSE</td>
<td>25.4 (4.6)</td>
<td>25.3 (4.6)</td>
<td>25.4 (4.0)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Age (yrs)</td>
<td>59.8 (6.0)</td>
<td>59.4 (5.5)</td>
<td>61.7 (8.1)</td>
<td>63.4 (5.4)</td>
<td>63.2 (5.7)</td>
</tr>
<tr>
<td>Education (yrs)</td>
<td>12.1 (3.8)</td>
<td>13.3 (3.0)</td>
<td>12.9 (2.2)</td>
<td>11.4 (2.6)</td>
<td>11.3 (1.3)</td>
</tr>
<tr>
<td>CDR⁴</td>
<td>0.4 (0.4)</td>
<td>0.9 (0.7)</td>
<td>0.9 (0.9)</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Gender ratio (F:M)</td>
<td>2:7</td>
<td>3:6</td>
<td>3:6</td>
<td>6:3</td>
<td>4:5</td>
</tr>
</tbody>
</table>

Numbers in brackets indicate the standard deviation of the population. Dashes indicate these tests were not administered to controls.

⁴For this test, data was available for 4 SDR patients, 7 SDL patients, and 8 AD patients.

**Table 2. Performance of Groups SDR, SDL, AD and Control on the battery of neuropsychological tests**

<table>
<thead>
<tr>
<th></th>
<th>SDR</th>
<th>SDL</th>
<th>AD</th>
<th>Control 1</th>
<th>Control 2</th>
<th>Pairwise comparisons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Logical memory</td>
<td>19.8 (12.0)</td>
<td>19.9 (7.3)</td>
<td>17.4 (8.6)</td>
<td>57.4 (14.4)</td>
<td>–</td>
<td>SDR = SDL = AD &lt; C1</td>
</tr>
<tr>
<td>Rey figure recall</td>
<td>32.3 (23.3)</td>
<td>50.3 (24.4)</td>
<td>13.7 (13.2)</td>
<td>53.1 (16.7)</td>
<td>–</td>
<td>AD &lt; C1 = SDL</td>
</tr>
<tr>
<td>RMT words</td>
<td>75.3 (10.8)</td>
<td>76.5 (8.0)</td>
<td>64.3 (13.2)</td>
<td>98.8 (1.4)</td>
<td>–</td>
<td>SDR = SDL = AD &lt; C1</td>
</tr>
<tr>
<td>RMT faces</td>
<td>57.5 (11.9)</td>
<td>76 (14.4)</td>
<td>81.3 (13.4)</td>
<td>89.5 (5.1)</td>
<td>–</td>
<td>SDR = SDL = AD &lt; C1</td>
</tr>
<tr>
<td>PPT words</td>
<td>74.7 (14.7)</td>
<td>77.7 (12.9)</td>
<td>96.2 (5.6)</td>
<td>98.6 (1.3)</td>
<td>–</td>
<td>SDR = SDL = AD &lt; C1</td>
</tr>
<tr>
<td>PPT pictures</td>
<td>66.5 (18.4)</td>
<td>83.5 (17.3)</td>
<td>95.1 (6.2)</td>
<td>–</td>
<td>98.9 (1.4)</td>
<td>AD &lt; C2&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Word-picture matching</td>
<td>75.8 (19.1)</td>
<td>83.2 (22.3)</td>
<td>98.2 (3.1)</td>
<td>–</td>
<td>99.4 (0.8)</td>
<td>SDR &lt; C2&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Category Fluency&lt;sup&gt;ad&lt;/sup&gt;</td>
<td>47.0 (14.5)</td>
<td>48.0 (33.5)</td>
<td>73.8 (22.7)</td>
<td>125.0 (13.4)</td>
<td>117.3 (16.9)</td>
<td>SDR = AD &lt; C1 = C2</td>
</tr>
<tr>
<td>Letter Fluency&lt;sup&gt;ad&lt;/sup&gt;</td>
<td>25.3 (16.5)</td>
<td>23.6 (15.2)</td>
<td>38.9 (11.5)</td>
<td>45.4 (11.2)</td>
<td>–</td>
<td>n/s</td>
</tr>
<tr>
<td>VOSP cube analysis&lt;sup&gt;c&lt;/sup&gt;</td>
<td>78.6 (29.5)</td>
<td>88.6 (24.2)</td>
<td>95.7 (4.9)</td>
<td>–</td>
<td>91.4 (21.0)</td>
<td>n/s</td>
</tr>
<tr>
<td>VOSP dot count&lt;sup&gt;c&lt;/sup&gt;</td>
<td>100 (0.0)</td>
<td>100 (0.0)</td>
<td>97.1 (4.5)</td>
<td>–</td>
<td>100 (0.0)</td>
<td>n/s</td>
</tr>
<tr>
<td>Rey figure copy&lt;sup&gt;b&lt;/sup&gt;</td>
<td>89.4 (13.2)</td>
<td>91.4 (10.3)</td>
<td>95.7 (4.2)</td>
<td>93.5 (11.6)</td>
<td>–</td>
<td>n/s</td>
</tr>
<tr>
<td>VOSP object decision&lt;sup&gt;c&lt;/sup&gt;</td>
<td>73.1 (7.5)</td>
<td>84.4 (16.7)</td>
<td>90.6 (7.7)</td>
<td>–</td>
<td>89.4 (3.9)</td>
<td>SDR &lt; AD = C2&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Except where indicated, all scores are percent correct or recalled. Numbers in brackets indicate the standard deviation of the population. Dashes indicate where a test was not administered to one of the control groups. Pairwise comparisons were carried out using Tukey’s Honestly Significant Difference. RMT, Recognition Memory Test; PPT, Pyramids and Palm Trees; VOSP, Visual Object and Space Perception battery; n/s, nonsignificant.

<sup>a</sup>For these tasks, n = 8 for each group.

<sup>b</sup>For these tasks, n = 9 for each group.

<sup>c</sup>For these tasks, n = 7 for each group.

<sup>d</sup>For these tasks, score is number generated.

<sup>e</sup>SDR group did not differ significantly from any other group.

<sup>g</sup>SDL group did not differ significantly from any other group.

<sup>f</sup>AD group did not differ significantly from any other group.

<sup>h</sup>AD group did not differ significantly from any other group.
that she was repetitive. She frequently lost track of current tasks, and reported using notes copiously as reminders, as she had trouble remembering arrangements from day to day. She also commented that she was “not as good as she used to be” at finding her way around, and while she had no difficulty using a map, she complained that she could not recall a route she had worked out in advance.

On initial bedside testing, CG achieved 27 on the MMSE, failing to recall any of the three items learned. The ACE (on which she scored 87) also revealed a severe and focal anterograde memory impairment, as she failed to remember a single element of the name and address after a delay, although she had learned it to perfection previously. Verbal and semantic category fluency were unimpaired, and she showed only mild difficulty in copying a cube line drawing. Formal neuropsychological testing revealed extremely poor delayed recall. Immediate recall of the prose passage was in the low normal range, but after a 30 minute delay, recall was nil, and recognition very poor. Copy of the Rey figure (Rey, 1941; Osterrieth, 1944) was poorly planned with spatial errors, and recall after a 45 minute delay was negligible. Further suggestion of visuospatial impairment was evident in her poor performance on the number location subtest of the VOSP, although she showed no difficulties with fragmented letters or cube analysis. CG managed the modified Wisconsin card sorting task without great difficulty, but showed slight dysexecutive problems as tested by the Stroop test (Stroop, 1935) and part B of the Trail Making test (Reitan and Wolfson, 1985). In sharp contrast to both WM and AC, CG scored 27/30 on the Graded Naming Test (95th percentile). An MRI scan showed focal bilateral atrophy to the hippocampi.

In summary, CG presented with a profound deficit in delayed recall, with some mild impairment in visuospatial and executive function, but with preserved semantic memory.

**Neuropsychological test battery**

**Episodic memory**

Verbal episodic memory was assessed with immediate recall of the logical memory subtest (Wechsler Memory Scale – Revised, Wechsler 1987; Wechsler Memory Scale – Third edition, Wechsler, 1997) and the words subtest of the Recognition Memory Test (RMT, Warrington, 1984; Warrington, 1996). Visual episodic memory was assessed with delayed recall of the Rey Complex Figure (Rey, 1941; Osterrieth, 1944), and the faces subtest of the RMT. All scores are reported as % correct or % recalled.

**Semantic memory**

Verbal and visual semantic knowledge was investigated by administration of the Pyramids and Palm Trees (PPT, Howard and Patterson, 1992), Word-Picture Matching (Hodges and Patterson, 1995), and category and letter fluency. For the fluency tests, scores are reported as number of correct responses generated; for the PPT and word-picture matching, scores are given as % correct.

**Perception**

Copy of the Rey Complex Figure and three subtests (cube analysis, dot counting and object decision) of the Visual Object and Spatial Perception battery (VOSP, Warrington and James, 1991) provided a measure of basic perceptual skill. All scores are given as % correct.

**Results**

Table 2 shows the results of the individual tests conducted in the different groups (SDR, SDL, AD and control groups 1 and 2). Immediate recall of a story, as assessed by the logical memory subtest of the WMS-R/WMS-III, was impaired in all three patient groups. A one-way ANOVA showed a highly significant effect of group, F(3,28) = 21.8, p < .001, and post-hoc pairwise comparisons (Tukey HSD, used in all pairwise comparisons in the following analyses) confirmed that all three patient groups were impaired relative to controls, but that their numerical scores did not differ significantly from one another. Recall of visual material was also impaired, as assessed by delayed recall of the Rey Complex Figure. A significant effect of group was revealed by a one-way ANOVA, F(3,32) = 6.8, p < .005. Pairwise comparisons revealed that this effect of group was predominantly driven by poor performance in the AD cases, who were impaired relative to both the SDL and control groups. Although numerically there was also a difference between the two SD groups, with poorer performance in cases with predominant right temporal lobe atrophy, this difference was not statistically significant, and neither SD group differed from controls.

Impairments in recognition memory were also present in the patient groups when compared to controls. One-way ANOVA s of the data from the RMT tasks revealed a significant effect of group for both words, F(3,28) = 16.4, p < .001 and faces, F(3,28) = 9.3, p < .001. Pairwise comparisons showed that all patients were impaired relative to controls on the words subtask, but did not differ statistically from one another. In contrast, only the SDR group were impaired relative

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1In two cases (one SDR and one SDL) the Logical Memory task was taken from the Wechsler Memory Scale – Third edition (Wechsler, 1997), in which the second story is repeated and a second recall required. In these two cases, only the percentage retained of the first recall of the two stories was used, in order to provide a more suitable comparison with the other patients.

2In four cases (one SDR and three AD), the short version of the RMT (Warrington, 1996), with 25 items in each subtest, had been administered. Thus percentage correct was used in the analysis as a measure of overall performance, in order to allow comparison between the two versions.
to controls on the faces task. This impairment was also greater than that seen in the left SD group and, surprisingly, the AD cases.

On all semantic tasks, ANOVA analyses revealed significant effects of group (PPT – words, $F(3,24) = 8.8, p < .001$; PPT – pictures, $F(3,24) = 7.5, p < .005$; Word-picture matching, $F(3,28) = 4.3, p < .05$; Category Fluency, $F(4,40) = 23.9, p < .001$). Pairwise comparisons confirmed that the AD group were impaired relative to controls on category fluency, but that they did not differ from the controls on any other semantic task. In contrast, the SDR group were impaired relative to controls on all semantic tasks, and were significantly worse than the AD group on all but category fluency. SDL were numerically impaired on all tasks relative to AD and controls; this reached significance in category fluency and the words subtest of the PPT. The two SD groups did not differ from one another on any semantic task.

A univariate ANOVA of the letter fluency data revealed a main effect of group, $F(3,24) = 3.5, p < .05$; pairwise comparisons showed that this was driven by an impairment in the SDL group that approached significance ($p = 0.051$). Basic visuoperceptual and spatial skills were reasonably well preserved in all three patient groups, with no main effect of group evident on the spatial tasks from the VOSP battery (cube analysis and dot counting, largest $F(3,24) = 2.4, p > .05$), or from the scores obtained from copying the Rey Complex Figure, $F < 1$. The one way ANOVA on the object decision data, however, did reveal a main effect of group, $F(3,28) = 4.4, p < .05$, with pairwise comparisons confirming poorer performance in the SDR group compared to both the AD and control groups, but no other differences between groups.

In summary, the AD patients performed normally on semantic and visuospatial tasks, but were severely impaired on tests of episodic memory (except notably recognition memory for unfamiliar faces). Both SD groups exhibited significant deficits on tests of semantic memory, although to differing degrees; they were also found to show significant deficits in episodic memory tasks. In particular, both SD groups were impaired on tests of verbal episodic memory (in recall of a story and recognition memory for words). In addition, the SDR group showed deficits on recognition memory for faces, a test of nonverbal episodic memory. All three groups of patients showed reasonable visuoperceptual ability, although the SDR group were impaired at object decision (a task which arguably requires visual semantic memory).

It is clear from these analyses that the differentiation of SD from AD is not simply a matter of looking for those patients with deficits in episodic memory: Both the clinical and experimental pictures are more complex than this. Thus we sought to delve further into the analyses, particularly to investigate the possibility that modality might hold a key to distinguishing between these patients. A composite episodic memory score was computed for tests using visual stimuli (Rey recall and RMT faces) and for tests using verbal stimuli (logical memory and RMT words) for the 7 patients in each group who had completed all these tasks. Note this composite combines one free recall and one recognition task for each modality, and therefore compares like with like. The scores for each group are presented as percentages in Figure 2. As is clear from the graph, and has been already stated, the patient groups do not differ in their performance on verbal memory tests. SDL patients, however, show a remarkable difference between their composite verbal and visual scores. This difference, evident only in the SDL group, was confirmed by a repeated measures ANOVA, with a between subject factor of group and a within subject factor of stimulus type (visual vs. verbal). There was a significant main effect of group, $F(3,24) = 14.3, p < .001$, which interacted with stimulus, $F(3,24) = 8.2, p < .005$. There was no main effect of stimulus, $F(1,24) = 3.6, p > .05$. Pairwise comparisons within the main effect of group revealed that all three patient groups were impaired overall relative to controls, but simple effects analysis of the interaction confirmed that only the SDL group showed an effect of stimulus, $F(1,24) = 21.8, p < .001$. Separate, univariate ANOVAs revealed significant effects of group for both verbal, $F(3,24) = 27.7, p < .001$, and visual, $F(3, 24) = 7.0, p < .005$ composite scores. Pairwise comparisons revealed that SDR and AD groups were significantly worse than controls on both composite measures. In contrast, the SDL group were impaired only on the verbal measure; they were no different from controls on the composite visual episodic memory score.

**Discussion**

Previous studies of SD have suggested that tests of episodic memory may provide a useful clinical tool for differentiating this syndrome from other neurodegenerative diseases (Hodges et al., 1999; Perry and Hodges, 2000; Lee et al., 2003; Piolino et al. 2003), in particular AD, in which the main neuropsychological symptom is poor anterograde memory. To date, however, no such study has specifically taken into account emerging evidence of differences between patients with SD based on the laterality of their atrophy. It has been suggested that good episodic memory is not characteristic of all SD patients, with a possible impairment in those with right predominant temporal lobe damage (Simons et al., 2001; Thompson et al., 2003). This paper therefore presents the first study to directly compare well-matched, separate groups of SDR and SDL patients with AD patients on a battery of standard neuropsychological measures of episodic memory. The results can be summarized as follows: (a) performance on verbal episodic memory tests was equally poor in AD and SD (regardless of side of atrophy); (b) performance on tests of visual episodic memory was also poor in SDR and AD, but significantly better (even close to normal for delayed recall of the Rey Figure) in SD cases with left predominant temporal lobe atrophy; and (c) tests of semantic memory were affected in both groups of SD patients but, with the exception of category fluency, not in patients with early AD.
These findings confirm that poor episodic memory in SD is more common than one would expect given the published literature (Graham et al., 1997; 2000; Simons, et al., 2002a; 2002b). Notably, however, many previous investigations have utilized visual tasks, in particular object recognition memory, and patient groups have typically included a large number of patients with left-sided atrophy (Lee et al., 2003). Studies of episodic memory that have controlled for side of atrophy (Simons et al., 2001; Snowden et al., 2004) report similar findings to those in this larger investigation, highlighting that the degree of impairment to semantic and episodic memory may be differentially affected by laterality of pathology (Edwards-Lee et al., 1997; Simons et al., 2001; Thompson et al., 2003; Snowden et al., 2004).

The relative preservation of visual episodic memory in patients with left-sided involvement is consistent with modality-specific memory deficits frequently reported after unilateral temporal lobe damage (Milner, 1958; Morris et al., 1995; Majdan et al., 1996; Glass et al., 1998). Importantly, however, the SDR group did not show better performance on verbal compared to nonverbal memory, with all SD cases showing equivalent levels of impairment on memory tasks involving meaningful verbal stimuli (words or stories). This result is compatible with the study by Graham et al. (2002), in which SD patients showed exceptionally poor learning and recall of word lists, with only a small advantage for ‘known’ over ‘degraded’ words. As suggested by these authors, a number of factors probably contribute to the strikingly poor verbal memory seen in SD, in particular impoverished activation of semantic representations from words compared to pictures (see also Lambon Ralph et al., 2000).

Surprisingly, the AD patients performed as well as the SDL group, and no different from controls, on the recognition memory test for faces, but were significantly impaired on the words component. Unlike the SDL group, this pattern did not seem attributable to overall improvement on tests that utilized visual stimuli, as this group showed severely impaired memory on the delayed recall of the Rey Figure (see also Becker et al., 1992; Greene et al., 1996). Lee et al. (unpublished observations) have also noted significant differences in episodic memory performance in AD and SD. In a mixed laterality SD group (ratio L:R = 4:3), performance on recall of the Rey Figure was normal (as it was for the SDL group reported here), but recognition memory for faces was severely impaired compared to controls. By contrast, the AD group were relatively good at recognizing previously studied faces, but showed virtually no memory for the Rey Figure after a delay (Lee et al., unpublished observations).

These findings initially seem confusing, except when considered alongside new theoretical developments in human memory. For many years, it was thought that structures in the medial temporal lobe (MTL) act as a single long-term memory system (Squire and Zola-Morgan, 1991; Manns et al., 2003). Some recent studies, however, imply functional specialization within the MTL (Aggleton and Brown, 1999; 2000).
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Buckley et al., 2001; Lee et al., 2004), with the hippocampus playing a critical role in spatial memory and the perirhinal cortex in recognition memory for complex visual stimuli. Interestingly, a recent investigation of the degree of atrophy to MTL structures in dementia found clear involvement of the perirhinal cortex in SD but less so in AD (Davies et al., 2004), a finding that is consistent with the pattern seen in this study. More systematic study of AD and SD, taking into account laterality, might reveal further behavioral dissociations between these two diseases, even within the domain of cognition (episodic memory) thought to be globally impaired in AD.

While this study continues to build on the corpus of work systematically comparing SD patients, and extends this to compare SDL, SDR, and AD patients simultaneously, one does need to be cautious in the interpretation of the data in the absence of confirmatory investigations. While we were careful to match the patients on a number of variables (age, educational level and score on the MMSE), it is possible that other factors may have skewed the findings. In particular, the MMSE is highly weighted towards memory and is likely to be most sensitive in patients with memory impairment. Unfortunately the CDR was not available in all patients in this study, and therefore we cannot directly confirm that our patient groups were at similar levels of dementia. That said, from the available data, this is likely to be the case. We reported the length of time between initial presentation at a memory clinic and the testing for this study, but note that this does not equate to symptom duration, and it is possible that our patient groups were not at equivalent stages in their illness. Further studies would benefit from undertaking even more rigorous matching.

Our interest in comparing the three groups of patients was predominantly clinical: could we use episodic tasks to differentiate between SD and AD? The answer to this question, based on our study, is clearly no, mainly due to the fact that SD is not a homogeneous condition, and SDR cases present with a much more complicated neuropsychological profile. Semantic tasks looked more promising: Even though we used tests in our analysis (e.g., PPT) on which controls performed close to ceiling, our two SD groups showed clear evidence of impairment on these tests, while, in the main, the AD group did not perform more poorly than controls. This is unsurprising considering that the diagnostic criteria for SD include a necessary impairment in semantic memory, but given the current widespread preference for verbal episodic memory tasks as diagnostic tools in dementia clinics, it is worth emphasizing the success of these tasks. A further complicating factor, however, is highlighted by the results of the category fluency test, in which AD patients were impaired. In contrast, AD patients showed good performance in the letter fluency test, in which AD patients were impaired. In contrast, AD

It should be emphasized that the semantic tests on which the AD group performed normally are relatively easy. It is well established that patients with even very early AD show impairment on more stringent tests such as category fluency, generation of detailed word definitions (Hodges and Patterson, 1995; Hodges et al. 1999) and on the graded picture naming test (Swainson et al., 2001; Blackwell et al., 2003). Patients with very early AD also show poor naming and knowledge of famous people (Thompson et al., 2002). Again, however, early detection and differentiation of AD from other dementias using tests of famous people is plagued by the fact that other disorders, most notably SD, also show significant problems with naming and knowledge about famous people (Hodges and Graham, 2001; Snowden et al., 2004).

The negative answer to our initial question, while disappointing, may help resolve another clinical puzzle: Why, at least in our clinic, and indeed in the literature, do we see more SD patients with left predominant temporal lobe damage than cases with greater right temporal lobe involvement? It seems quite possible that the reason for this skew in clinical presentation may reflect the poor verbal and visual episodic memory functioning seen in the SDR cases, even early on, which may lead clinicians to consider a preliminary diagnosis of probable AD rather than SD (this certainly was the case for one of the SDR patients included in this study, later confirmed by pathology to have FTD with ubiquitin positive inclusions). This would be an entirely reasonable assumption given that the current consensus criteria for FTD stress the presence of good day-to-day memory in this condition (Neary et al., 1998), a finding consistent with much of the published literature on SD. While this difficulty could be resolved by considering the neuropsychological profile of SDR patients as rather different from that seen in SDL patients, the findings from this study, and those that find significant semantic impairment in patients with probable AD or even MCI (Thompson et al., 2002) highlight the urgent need for revisions to diagnostic criteria for AD and FTD. Part of the difficulties with diagnosis may stem from the fact that a clinician’s review of day-to-day memory in cases presenting to a Memory Clinic is often based upon informal evaluation of memory for recent events. Certainly, in this context, patients with SD intuitively feel less clinically amnesic than cases presenting with possible AD (Warrington, 1975; Hodges et al., 1992), and studies of autobiographical memory have consistently demonstrated good, or even normal, retrieval of recently experienced events in this condition, albeit without consideration of laterality of atrophy (Graham and Hodges, 1997; Nestor et al. 2002; Piolino et al., 2003). As demonstrated here, however, this relative preservation of episodic memory does not necessarily result in good performance on anterograde memory tasks, leading one to wonder what aspects of episodic functioning might be supporting the recall of recent autobiographical memory in SD. Given the problems in differentiating SD and AD on the basis of standard anterograde memory tests, more emphasis should be placed upon the patterns of cerebral atrophy which appear to be very distinctive, with asymmetric temporo-polar, fusiform, and perirhinal atrophy in SD and symmetrical hippocampal and entorhinal atrophy in AD (Chan et al., 2001; Galant et al., 2001; Davies et al., 2004).
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