Multidimensional measures of person knowledge and spatial associative learning: can these be applied to the differentiation of Alzheimer’s disease from frontotemporal and vascular dementia?

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Abstract

Patients with early stage Alzheimer’s disease (AD) show deficits in person knowledge and spatial associative memory. The current investigation examined the ability of impairment in these domains to differentiate AD from other overlapping conditions. In experiment 1, 14 AD patients, 21 vascular dementia (VaD) patients, 11 frontal variant frontotemporal dementia (fvFTD) patients and 41 controls were administered a graded faces test. VaD patients demonstrated a level of impairment comparable to the AD group on both the naming and person identification elements of the task. A mild naming deficit was revealed in the fvFTD group. In experiment 2, 22 AD patients, 23 patients with mild cognitive impairment (MCI), 11 fvFTD patients, 13 semantic dementia (SD) patients, and 23 elderly controls were administered the face–place test, a newly developed task that combines naming of famous faces, item recognition and spatial location. The naming component of the face–place test clearly differentiated SD patients from all dementia groups. All patient groups, except those with fvFTD, showed substantial deficits in the item recognition and spatial components. Consistency analyses indicated a fairly robust association between the two episodic components (item recognition and placing), but not between semantic and episodic elements of the FPT. Person knowledge deficits are, therefore, not specific to AD and the employment of face stimuli may influence the performance of SD patients on tasks of episodic memory.

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1. Introduction

Early diagnosis of Alzheimer’s disease (AD) is an important goal in individual and economic terms, as the prospect of effective treatments becomes more realistic. Efficient diagnostic strategies require not only the identification of early deficits, but also their differentiation from other overlapping conditions such as depression, old age and other types of dementia (Hodges, 2001).

Neuropsychologically, AD is characterised by deficits in anterograde, remote and semantic aspects of memory, attention and executive function and, in the later stages, spatial and visuoperceptual ability (Perry, Watson, & Hodges, 2000; Storey, Kinsella, & Slavin, 2001). Various classification schemes have been adopted to describe the prodromal characteristics of AD (Collie & Maruff, 2002) and in recent years the term mild cognitive impairment (MCI) has frequently been utilised to refer to individuals at the transition between normal ageing and AD (Petersen et al., 1999). MCI is defined by impaired memory function, relative to age and education matched controls, in contrast to preserved ability in other domains, intact activities of daily living and the absence of frank dementia (Petersen et al., 2001a). Studies charting progression from MCI to dementia or AD have found conversion rates ranging from 6 to 25% annually (Petersen et al., 2001b).
Of the various domains of semantic memory, knowledge about famous people, as tested by the ability to name and identify photographs appears to be compromised at a particularly early stage (Greene & Hodges, 1996; Hodges, Salmon, & Butters, 1993). In a recent study, Thompson, Graham, Patterson, Sahakian, and Hodges (2002) administered a graded difficulty people-naming test to 28 patients with MCI. Of the seven who converted to dementia over the next 2 years, six showed impairment on the task at baseline, suggesting that such a test might be useful in disease prediction. Tasks dependent upon crossmodal associative learning, such as the paired associate learning (PAL) task, have been found in recent studies to be sensitive to the early stages of AD (Blackwell et al., 2003; Fowler, Saling, Conway, Semple, & Louis, 1995; 2002) and to successfully differentiate AD from clinical depression (Swainson et al., 2001). These findings are compatible with frequent reports of impaired object location memory in association with focal hippocampal lesions (Kessels, de Haan, Kappelle, & Postma, 2001).

Taking advantage of potential deficits in crossmodal associative learning and person identification, Dudas, Clague, Thompson, Graham and Hodges (in press) recently contrasted MCI and established AD groups on a task combining aspects of people knowledge, item recognition and spatial associative memory called the face–place test (FPT). Both AD and MCI groups demonstrated impaired relative to matched controls on all elements of the FPT. Although highly sensitive to these groups, the issue of specificity in comparison with other types of dementia has not been explored. Experiments outlined here addressed the question of whether individuals with frontal and temporal variants of frontotemporal dementia and vascular dementia also show deficits in person identification and/or crossmodal associative learning.

Frontotemporal dementias are an important cause of dementia in the under 65 age group (Ratnamalli, Brayne, Dawson, & Hodges, 2002). Temporal variant frontotemporal dementia, referred to here as semantic dementia (SD), is characterised by progressive anoma, loss of memory for words and breakdown of semantic knowledge reflected by comprehension impairments (Hodges & Miller, 2001). Frontal variant frontotemporal dementia (fvFTD) patients, in contrast, present with progressive changes in social conduct and personality often in the context of good cognitive skills (Perry & Hodges, 2000).

In contrast to the extensive studies of episodic memory in AD, much less is known about anterograde memory in FTD syndromes. Patients with SD show excellent performance on recognition memory tests using pictures of objects as long as the study and test item are perceptually identical (Graham, Simons, Pratt, Patterson, & Hodges, 2000; Simons, Graham, Galton, Patterson, & Hodges, 2001). A recent study also found that patients with SD exhibited good performance on an associative memory task in which subjects were required to learn the associations between pairs of door and sofa pictures (Simons et al., 2002b). The same study also found impaired source discrimination in five patients with fvFTD (Simons et al., 2002b), but there has been little experimental work on episodic memory in this patient group. On the PAL test, SD and fvFTD groups perform significantly better than AD groups suggesting that memory for spatial location is relatively preserved in these groups (Lee, Rahman, Hodges, Sahakian, & Graham, 2003).

Person knowledge is severely impaired in semantic dementia, particularly in patients with predominantly right temporal lobe atrophy (Hodges & Graham, 1998; Thompson et al., 2004). A study by Simons et al. (2001) found that while patients with predominantly left temporal atrophy performed at a similar level to controls on a face recognition memory test (RMF; Warrington, 1984), bilateral and right temporal atrophy resulted in impaired performance. The status of person knowledge is unknown in the fvFTD group but previous studies have shown preservation of general semantic knowledge in this group (Perry & Hodges, 2000).

Vascular dementia (VaD) is a common cause of dementia, especially in older age groups, but the differentiation of VaD from AD on a neuropsychological basis remains problematic (Hodges & Graham, 2001). There is some evidence to suggest that the degree of episodic memory impairment in VaD may be less pronounced than in AD while the reverse trend occurs in executive function tests (Loos & Sachdev, 1999; Traylor et al., 2002; Yusuph, Vanderploeg, Crowell, & Mullin, 2002). Naming and semantic deficits have been found in VaD patients, but there are some contradictory results and the extent to which VaD and AD groups can be differentiated on this basis is unclear (Laine, Vuorinen, & Rinne, 1997; Lukatela, Malloy, Jenkins, & Cohen, 1998; Paul et al., 2001). Bentham, Jones, and Hodges (1997) found equivalent impairment on a battery of semantic tests in AD and VaD patients. Ricker, Keenan, and Jacobsen (1994) explored recognition memory for novel faces and a three-choice task that required matching of famous faces to one of three famous names. While both VaD and AD groups were impaired on the recognition memory task, the AD group showed a disproportionate impairment on the famous faces task leading the authors to propose that this pattern was a consequence of the visual semantic nature of the test material.

The two experiments described here examine whether tests of person knowledge can be employed to differentiate AD from FTD and VaD. The first experiment compared the ability of FvFTD, VaD and AD patients to name and provide semantic identification information about famous person items, graded according to familiarity (Thompson et al., 2002). Naming and semantic impairment in VaD might be predicted on the basis of findings of general anomic and semantic deficits in this group (Bentham et al., 1997). In contrast, the results of Ricker et al. (1994) suggest that VaD patients might also demonstrate sparing of semantic knowledge about famous people relative to individuals with AD.

In the second experiment, performance on the face–place test was compared in SD and fvFTD patients relative to existing data in AD and MCI (Dudas et al., in press). We
hypothesised that SD patients would show severe naming impairment, but spared performance on the placing and possibly recognition, components of the task. Predictions were unclear regarding whether the fVFTD patients would exhibit impaired ability to remember locations of faces in space. While findings from the PAL task suggest relatively good spatial memory (Lee et al., 2003), other studies have reported source memory impairment in fVFTD (Simons et al., 2002b) albeit for temporal judgements, a difficulty that might potentially lead to impaired performance on the FPT.

2. Experiment 1

2.1. Method

2.1.1. Participants

Four groups took part in the study: 14 Alzheimer’s disease (AD) patients, 21 cases diagnosed with subcortical vascular dementia (VaD), 11 frontal variant frontotemporal dementia (fVFTD) patients and 41 neurologically intact controls. One-way ANOVAs followed by post hoc Tukey testing revealed no significant differences between groups on mini-mental state examination (MMSE) (Folstein, Folstein, & McHugh, 1975) and years of education, but that subjects were not age-matched (see Table 1). All subjects (or caregivers, where appropriate) gave informed consent to participate and the study was approved by the local ethics committee.

AD subjects were selected from patients undergoing prospective evaluation at the Memory Disorders Clinic at Addenbrooke’s Hospital and were from the patient group already described by Thompson et al. (2002). The AD diagnosis was made by a senior neurologist using NINCDS-ADRDA criteria (McKhann, Drachman, Katzman, Price, & Stadlan, 1984).

The VaD group consisted of an unselected consecutive series of patients presenting to the Memory Disorders Clinic in Cambridge between 1999 and 2000, who were willing to be enrolled into the study. To avoid the pervasive problem of heterogeneity across patients with vascular dementia we selected patients who had substantial subcortical white matter pathology on T2 weighted MRI, together with vascular risk factors plus a history of transient ischaemic attacks and/or focal neurological signs on examination. Focal signs included mild facial paresis, clumsiness of fine finger movements, reflex asymmetry, extensor plantar responses and cortical sensory signs. None of the patients exhibited visual field defects on clinical testing. Formal perimetry was not performed. We did not apply the National Institute for Neurological Diseases and Stroke Association–Association International pour la Recherche et l’Enseignement en Neurosciences (NINDS–AIREN) criteria for probable VaD since these require a chronological relationship between a major vascular event and cognitive impairment, and the presence of focal neurological signs (Roman et al., 1993). We also excluded patients who have had major cortical strokes or strategic thalamic infarcts.

fVFTD subjects fulfilled the Lund–Manchester consensus criteria for frontotemporal dementia (Neary et al., 1998) and local criteria applied in previous studies (Bozeat, Gregory, Ralph, & Hodges, 2000; Perry & Hodges, 2000).

All subjects underwent a standard neuropsychological evaluation comprising backwards and forwards digit span, Logical Memory from WMS – III (Wechsler, 1987), copying and delayed recall of the Rey figure (Osterrieth, 1944), a 64 item naming test and category fluency both from a battery of general semantic tasks (Hodges, Graham, & Patterson, 1995), verbal fluency (FAS), the Wisconsin card sorting task (Heaton, Chelune, Talley, Kay, & Curtis, 1993) and visual object space perception battery (Warrington & James, 1991), the results of which are shown in Table 2. In brief, the AD group were impaired on all measures of episodic memory, category fluency and the cube analysis component of the VOSP. The VaD group showed a similar pattern to the AD group with the addition of impairment on tests of attention and executive function (FAS, digit span, WCST), naming and object decision from the VOSP. The fVFTD group performed less well than controls on measures of verbal and category fluency as well as showing a mild naming impairment (see Table 2).

2.2. Materials

The graded faces test (GFT) is a test of naming and knowledge of famous people comprising items of graded difficulty (Thompson et al., 2002). The stimuli consist of 30 faces, half of which consist of recently famous individuals and half non-recent celebrities, matched item by item to stimuli from the graded naming test (GNT) on the basis of control naming data. Item age was balanced across the set of stimuli and famous people were drawn from many categories including politicians, statesman and personalities from the worlds of acting, music or sport.

2.3. Procedure

Each black and white photograph was administered to the subject beginning with the easiest item. There were two task components, naming and identification. During naming,
subjects were asked to provide the first name and surname of the person in each photograph and were subsequently awarded one point if either the correct full name or correct surname was given (which did not significantly differ). The examiner did not provide the name of any items, but points were given if the subject offered accurate identification information without giving the name of the famous person. 

2.4. Results

Fig. 1 illustrates the performance of the three dementia groups and controls on the identification and naming components of the GFT. Since groups were not age-matched, a 3 × 2 ANCOVA with age as the covariate was carried out, that revealed a significant effect of group (F(3,82) = 28.08, P < 0.001), but no significant effect of test component. The absence of an effect of test component is slightly surprising and may indicate that age is a partial determinant of apparent performance differences between groups on the naming and identification tasks. Significant interactions between group and test component (F(3,82) = 14.81, P < 0.001) and between age and test component were found (F(1,82) = 6.68, P < 0.05), further suggesting that performance could be affected by age as well as task. Post hoc analyses (with Bonferroni correction for multiple comparisons at revised alpha level P = 0.0042) indicated significant differences between the AD and control group for both identification (t(53) = 5.27, P < 0.001) and naming (t(53) = 9.883, P < 0.001). VaD and fVFTD patients were impaired relative to the controls on the naming part of the task (t(60) = 4.89, P < 0.001, t(50) = 4.36, P < 0.001), but only the VaD group showed significant impairment on the identification component (t(60) = 4.89, P < 0.001). AD patients were impaired relative to the fVFTD group on naming (t(23) = 2.037, P < 0.01) but not identification. No other significant differences were found between the AD and VaD groups or between the vascular and fVFTD patients.

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### Table 2

<table>
<thead>
<tr>
<th>Component</th>
<th>AD Mean</th>
<th>S.D.</th>
<th>VaD Mean</th>
<th>S.D.</th>
<th>fVFTD Mean</th>
<th>S.D.</th>
<th>NC Mean</th>
<th>S.D.</th>
<th>P value for group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>VOSP (cube analysis)</td>
<td>7.9 ± 0.9</td>
<td>5.9</td>
<td>1.5 ± 0.4</td>
<td>4.8</td>
<td>1.7 ± 0.4</td>
<td>5.4</td>
<td>1.4 ± 0.4</td>
<td>0.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Logical memory (immediate)</td>
<td>4.0</td>
<td>2.3 ± 1.0</td>
<td>5.8</td>
<td>2.4 ± 1.0</td>
<td>9</td>
<td>3.0 ± 1.0</td>
<td>10.4</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Logical memory (delayed)</td>
<td>1.0</td>
<td>0.9 ± 0.5</td>
<td>0.4</td>
<td>2.5 ± 1.0</td>
<td>6.7</td>
<td>3.6 ± 1.0</td>
<td>8.3</td>
<td>4.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Rey copy</td>
<td>26.3</td>
<td>10.3 ± 2.5</td>
<td>7.6 ± 1.5</td>
<td>34.4</td>
<td>12.2 ± 3.4</td>
<td>34.1</td>
<td>1.5</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Rey delayed</td>
<td>4.3</td>
<td>5.7 ± 1.0</td>
<td>7.1</td>
<td>6.3 ± 1.0</td>
<td>15.6</td>
<td>7.4 ± 1.0</td>
<td>18.7</td>
<td>5.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Category fluency (total correct living)</td>
<td>36.1</td>
<td>12.9 ± 3.8</td>
<td>34.3</td>
<td>12.0 ± 3.0</td>
<td>43</td>
<td>12.8 ± 3.0</td>
<td>62.4</td>
<td>11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Category fluency (total correct mammal)</td>
<td>33.1</td>
<td>8.8 ± 3.2</td>
<td>31.2</td>
<td>14.3 ± 3.0</td>
<td>39.4</td>
<td>12.8 ± 3.0</td>
<td>57.7</td>
<td>10.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WCST (categories)</td>
<td>4.1</td>
<td>2.1</td>
<td>3.6</td>
<td>1.7 ± 1.0</td>
<td>1.1</td>
<td>0.3 ± 1.0</td>
<td>5.9</td>
<td>0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>WCST (perseverations)</td>
<td>8.0</td>
<td>7.0</td>
<td>7.3</td>
<td>7.8 ± 2.8</td>
<td>4.6</td>
<td>1.1</td>
<td>2.3</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>WCST (errors)</td>
<td>0.6</td>
<td>5.7</td>
<td>12.3</td>
<td>6.5 ± 4.0</td>
<td>4.0</td>
<td>2.0 ± 2.5</td>
<td>2.5</td>
<td>2.1</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>VOSP (incomplete letters)</td>
<td>15.9</td>
<td>5.4</td>
<td>17.5</td>
<td>3.0</td>
<td>19.4</td>
<td>0.8</td>
<td>19.3</td>
<td>0.8</td>
<td>n.s.</td>
</tr>
<tr>
<td>VOSP (subject decision)</td>
<td>16.6</td>
<td>2.50</td>
<td>15.8</td>
<td>3.2 ± 3.2</td>
<td>18.2</td>
<td>1.3 ± 3.2</td>
<td>17.1</td>
<td>2.2</td>
<td>n.s.</td>
</tr>
<tr>
<td>VOSP (dot counting)</td>
<td>8.6</td>
<td>2.79</td>
<td>8.9</td>
<td>2.0</td>
<td>9.5</td>
<td>0.7</td>
<td>10.0</td>
<td>0.21</td>
<td>n.s.</td>
</tr>
<tr>
<td>VOSP (number location)</td>
<td>7.3</td>
<td>7.3</td>
<td>2.2</td>
<td>8.7</td>
<td>1.8</td>
<td>9.0</td>
<td>3.1</td>
<td>n.s.</td>
<td></td>
</tr>
<tr>
<td>VOSP (cube analysis)</td>
<td>7.4</td>
<td>3.03 ± 1.0</td>
<td>8.9</td>
<td>1.7</td>
<td>10.1</td>
<td>2.3</td>
<td>&lt;0.05</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For these comparisons a different group of control subjects with similar levels of age and education to patients was used. Number of individuals given each test varied within the following ranges: AD (9–14), VaD (15–20), fVFTD (9–11) and controls (22–23). Of note, the fVFTD group are not precisely age-matched. Letters (a: significantly different to controls; b: significantly different to AD; c: significantly different to VaD; d: significantly different to fVFTD) indicate significant differences between groups on post hoc testing (P < 0.05); n.s.: non-significant.
To explore the effects of item familiarity on naming in fvFTD (see Fig. 2), the test items were split into 15-item blocks of high and low familiarity. A repeated measures ANOVA revealed a significant interaction between group and familiarity rating ($F(1,28) = 5.99, P < 0.05$) in accordance with the apparent divergence between groups in the middle of the item series. Subsequent post hoc paired $t$-tests demonstrated significant differences between the control and fvFTD groups in both the highest ($t(14) = 2.397, P < 0.05$) and lowest ($t(14) = 8.155, P < 0.001$) familiarity item sets.

In order to investigate how well the GFT predicted membership of diagnostic groups, a stepwise discriminant analysis was carried out. Table 3 indicates that the GFT misclassified nearly a quarter of controls as fvFTD patients, and that the VaD group overlaps significantly with AD and fvFTD patients. Overall naming performance on the GFT resulted in the correct classification of 48.3% of the original cases.

2.5. Comment

The fact that the fvFTD group, while impaired on naming performed within the normal range on the identification component of the GFT, is indicative of an underlying anomia rather than a breakdown of semantic knowledge. The naming deficit in the fvFTD group appears to relate to the familiarity of items. It is unclear whether familiarity is the sole factor influencing these findings since performance is quite uneven, even among the higher familiarity items and the groups appear to diverge most markedly in the middle of the item series (Fig. 2).

The pattern found in the fvFTD patients contrasts with the AD and VaD groups who have both naming and identification impairments. These deficits appear to be comparable in the two groups, a result that runs contrary to the suggestion by Ricker et al. (1994) that semantic knowledge might be spared in VaD relative to AD.

In summary, while Thompson et al. (2002) findings, in which the GFT identified individuals at early risk of developing AD, clearly illustrate that person knowledge is affected at the early stages of AD and perhaps MCI, the current data demonstrate that the GFT is unlikely to effectively differentiate AD from other dementia groups, thereby limiting its overall clinical applicability. The results of the discriminant analysis indicate that the GFT correctly predicted patient group membership in just under half of the overall subject group, indicating a level of specificity insufficient for diagnostic testing. Differentiation of AD and VaD was particularly poor.

3. Experiment 2

3.1. Method

3.1.1. Participants

Five subject groups participated: 22 patients diagnosed with Alzheimer’s disease (AD), 23 mild cognitive impairment (MCI) patients, 13 semantic dementia (SD) patients, 11 frontal variant frontotemporal dementia (fvFTD) patients and 23 healthy elderly control subjects. Groups were matched on the basis of age and years of education, but not according to MMSE (Folstein et al., 1975) score (see Table 4). All subjects (or caregivers, where appropriate) gave informed consent to participate and the study was approved by the local ethics committee.

The AD and MCI subjects, were selected from patients undergoing prospective evaluation at the Memory Disorders Clinic at Addenbrooke’s Hospital. The diagnosis of MCI was based on clinical consensus grounds following evaluation in the clinic by a senior neurologist (JRH), psychiatrist and clinical neuropsychologist. The MCI group were classified according to recent criteria used by Grundman et al. (2004) and Petersen et al. (2001a, 2001b), namely (1) memory complaint corroborated by an informant, (2) abnormal (<1.5 SD) memory function,
documented by delayed recall of the logical memory subtest of the WMS-R, (3) normal general cognitive function as determined by the clinician after assessment of the patient and informant interview plus an MMSE score greater than 24, (4) normal or minimally impaired activities of daily living (ADL), as determined by the clinician after assessment of the patient and an informant, and (5) not sufficiently impaired, cognitively or functionally to meet NINCDS-ARDA criteria for AD. Of note is the fact that patients with abnormal performance on stringent tasks such as category fluency can fulfill criteria for MCI. The AD diagnosis was made using the NINCDS-ARDA criteria for probable AD (McKhann et al., 1984). The AD and MCI groups corresponded to 1 and 0.5 on the clinical dementia rating scale (Berg, 1988), respectively.

The SD group fulfilled proposed local criteria and international consensus, namely impoverished semantic knowledge with comparative preservation of visuospatial abilities, episodic memory and non-semantic features of language (Hodges, Patterson, Oxbury, & Funnell, 1992; Neary et al., 1998). fvFTD subjects fulfilled the consensus criteria for frontotemporal dementia (Neary et al., 1998) and local criteria applied previously (Perry & Hodges, 2000). Control subjects were recruited from the relatives of patients and the MRC-CBU volunteer panel. Background neuropsychological data (see Table 5) for all four patient groups was collected, comprising digit span, logical memory (Wechsler, 1987), Rey figure (Osterrieth, 1944), recognition memory test (Warrington, 1984), category fluency, naming and word–picture matching from a battery of general semantic tests (Hodges et al., 1995), the pyramids and palm trees test (Howard & Patterson, 1992), the Wisconsin card sorting test (Heaton et al., 1993) and the visual object and space perception battery (Warrington & James, 1991). The SD patients performed well than the fvFTD, MCI and control groups on semantically based tasks including category fluency, pyramids and palm trees and naming and also demonstrated impairment on the logical memory and RMT (faces). The

Table 4
Means scores for age, years of education and mini-mental state examination (MMSE) in Alzheimer’s disease (AD), mild cognitive impairment (MCI), semantic dementia (SD), frontal variant frontotemporal dementia (fvFTD) and normal control groups.

<table>
<thead>
<tr>
<th>Age (S.D.)</th>
<th>AD</th>
<th>MCI</th>
<th>SD</th>
<th>fvFTD</th>
<th>Normal controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>67.6 (6.5)</td>
<td>67.7 (4.1)</td>
<td>64.9 (6.5)</td>
<td>63.3 (5.3)</td>
<td>63.3 (7.9)</td>
<td></td>
</tr>
</tbody>
</table>

Means and standard deviations of items in the supporting neuropsychological battery for the face–place test

Table 5

<table>
<thead>
<tr>
<th>SD</th>
<th>AD</th>
<th>MCI</th>
<th>SD</th>
<th>pvFTD</th>
<th>NC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Digit span (forwards)</td>
<td>6.4</td>
<td>1.2</td>
<td>6.2</td>
<td>1.3</td>
<td>6.5</td>
</tr>
<tr>
<td>Logical memory (immediate)</td>
<td>3.6</td>
<td>0.9</td>
<td>3.3</td>
<td>1.8</td>
<td>3.4</td>
</tr>
<tr>
<td>Logical memory (delayed)</td>
<td>1.4</td>
<td>0.8</td>
<td>0.7</td>
<td>1.2</td>
<td>0.9</td>
</tr>
<tr>
<td>Rey-copy</td>
<td>24.3</td>
<td>10.8</td>
<td>31.3</td>
<td>8.3</td>
<td>33.9</td>
</tr>
<tr>
<td>Rey-delayed</td>
<td>13.2</td>
<td>8.0</td>
<td>1.9</td>
<td>2.3</td>
<td>21.6</td>
</tr>
<tr>
<td>RMT (words)</td>
<td>32.8</td>
<td>8.4</td>
<td>13.2</td>
<td>3.7</td>
<td>20.6</td>
</tr>
<tr>
<td>Category fluency (total correct)</td>
<td>8.4</td>
<td>7.1</td>
<td>30.13</td>
<td>54.2</td>
<td>9.9</td>
</tr>
<tr>
<td>Pyramid and palmtrees (words)</td>
<td>36.4</td>
<td>7.4</td>
<td>49.1</td>
<td>2.4</td>
<td>50.7</td>
</tr>
<tr>
<td>Pyramid and palmtrees (pictures)</td>
<td>39.2</td>
<td>7.9</td>
<td>49.3</td>
<td>2.2</td>
<td>50.3</td>
</tr>
</tbody>
</table>

A different group of controls matched to the patient groups for age and education was used for these comparisons. Of note, the MCI and fvFTD groups are not precisely matched to the AD and SD groups on MMSE. Number of individuals given each test varied within the following ranges: SD (4–12), AD (10–18), MCI (17–21), fvFTD (3–11), NC (15–20). Letters (a: significantly different to controls; b: significantly different to SD; c: significantly different to fvFTD; d: significantly different to AD; e: significantly different to MCI) indicate significant differences between groups on post hoc testing; n.s.: non-significant.
AD patients were also impaired on semantic tasks, measures of episodic memory, attention and executive function (digit span, WCST) and the cube analysis component of the VOSP. The MCI group in contrast performed significantly below the control range on measures of episodic memory, naming and category fluency only. The fvFTD group showed mild impairments on tasks of category fluency and word–picture matching.

3.2. Construction of the face–place test

After preliminary pilot studies we determined that 2 × 2 arrays were ideal with two famous faces in each array (see Fig. 3). Twenty photographs of famous persons from three categories (politicians, actors/TV personalities, and singers) with enduring fame and relatively high familiarity, balanced across categories for age, sex, and familiarity score. The test items were selected from a database of 250 famous faces covering the second half of the 20th century. Familiarity data on the faces in this database had been collected in a control group (n = 24) during the pre-piloting phase. The photographs of 20 famous and 20 non-famous people were matched for general facial features (moustache, beard, etc.), and the use of accessories (hat, glasses, etc.) on each page of the study phase.

After two rounds of pilot testing, nine target items were replaced to achieve around 75% correct naming by healthy control subjects.

3.3. Test administration

Subjects were shown 10 pages in turn, each displaying a 2 × 2 array with two famous and two non-famous faces in each array (see Fig. 3). The position of the famous target faces in the array was balanced so that all four quadrants of the pages were used with the same frequency. Subjects were told that each array contained two famous faces. In the study phase, the subject was asked to point to each of the two famous persons (familiarity). If the subject incorrectly pointed to a non-famous person they were corrected. Subjects were then asked to name the famous people on the page (naming). If the subject provided only the surname, they were prompted to provide the full name if possible, but no cues were given. The maximum score for both familiarity and naming was 20.

In the test phase, subjects viewed the 40 cards sequentially with a photograph of a face on each. Half of these items had been seen in the study phase (targets), and half were new famous faces (foils) in the same familiarity range as the targets (e.g. Tom Jones as a foil for Cliff Richard). The subject was first asked whether or not she/he had seen the picture on the card in the arrays presented in the study phase (recognition). The order of the cards in the test phase was systematically randomised in two clusters (the first 10 target faces with the corresponding 10 foils, and then the second 10 targets randomised with their foils) so that the target faces would appear in a similar chronological order to that used in the study phase. If the face on the card was a foil, the subject was allowed to answer, and then the examiner passed directly onto the next test card, whether or not the subject had answered correctly. If the subject was unsure, they were asked to guess. If the face on the card was presented previously and the subject answered ‘No’, the examiner tactfully corrected the subject in order to subsequently test for place. For recognition, all responses were recorded: true positive, true negative, false positive or false negative. The main measure of recognition was hits – false alarms. Once recognition had been tested, the subject was asked, for all previously presented faces, in which position the photograph had been seen at study. Responses were indicated on a blank 2 × 2 template with the four positions marked 1, 2, 3, and 4 (placing). If the subject was unsure, they were asked to guess. Correct indication of the quadrant in which the target previously appeared was rewarded with one point (maximum = 20). Administration of the whole test took approximately 15 min.

4. Results

4.1. Analyses

The analyses focused on the performance of the fvFTD and SD patients relative to the MCI and AD groups who are reported by Dudus et al. (in press). Subject groups were well matched for age and education, but the groups could not be matched on the basis of dementia severity as measured by MMSE, since this measure is rather insensitive to the behavioural disturbances seen in fvFTD and to the MCI group on account of the very nature of the early diagnosis. As a consequence of these factors effective MMSE matching
Fig. 4. Performance of the four patient groups (Alzheimer’s disease (AD), mild cognitive impairment (MCI), semantic dementia (SD), and frontal variant frontal dementia (fvFTD)) and a group of neurologically normal control subjects on the four components of the face–place test. The graphs show mean performance and standard error bars for (a) familiarity and naming components and (b) recognition memory (hits – false alarms) and placing components of the FPT.

was only achieved between group pairings AD/SD and fvFTD/MCI, respectively.

ANOVAa were not carried out on the familiarity scores since this variable was highly skewed and at, or close to, ceiling in all groups apart from the SD patients and therefore of little value in differentiating the groups (see Fig. 4a).

In order to assess how well the FPT predicted membership of the different patient groups, a stepwise discriminant analysis was conducted. A consistency analysis was also carried out to assess the degree of intercorrelation between different components of the FPT. Odds ratios were calculated on an individual subject by subject basis and covaried according to performance on other test components to assess association between different pairs of task components. To aid interpretation of the data, the odds ratios were logged and exponentiated. Confidence intervals were calculated on the same basis to investigate the distribution of responses.

4.2. Naming

Fig. 4a illustrates the naming scores in all five groups and clearly indicates poor naming in a number of patient groups, especially in SD where the patients’ performance is at floor. A one-way ANOVA comparing performance among the different subject groups revealed a significant effect of group ($F(4,87) = 30.764, P < 0.001$) and post hoc testing confirmed that the SD group was significantly impaired relative to all other subject groups ($P < 0.05$). As already described (Dudas et al., in press), AD and MCI patients exhibited similar naming ability and both groups performed less well than controls ($P < 0.001$). The fvFTD group achieved significantly higher naming scores than AD patients ($P < 0.05$) but did not differ statistically in their performance from the MCI group. In summary, SD < AD = MCI < NC, MCI = fvFTD and NC = fvFTD > AD.

4.3. Item recognition

Hits – false alarms was used as a measure of item recognition (see Fig. 4b) in this study, since it could be easily computed by those who might want to use the FPT or develop similar tasks in a clinical context. A one-way ANOVA revealed a significant effect of group ($F(4,87) = 24.186, P < 0.001$). Post hoc tests indicated that the SD patients were significantly impaired relative to both the fvFTD group and controls ($P < 0.05$) and performed at a similar level to the AD and MCI groups. The AD and MCI groups were significantly impaired relative to controls ($P < 0.001$) and fvFTD ($P < 0.001$). There was no significant difference between the fvFTD and control groups. In summary, NC = fvFTD > AD = MCI = SD.

4.4. Placing

An effect of group was also found on the placing element of the FPT ($F(4,87) = 50.9, P < 0.001$). Post hoc testing indicated a graded decline among the control, MCI and AD groups (control > MCI > AD) whereby both patient groups were impaired relative to controls ($P < 0.001$) and MCI significantly outperformed AD ($P < 0.05$). The SD group scored significantly lower on the placing component of the task than either controls or fvFTD patients ($P < 0.001$). Despite numerically lower performance in MCI relative to SD (see Fig. 4b) this difference failed to reach statistical significance. The SD group demonstrated significantly better performance than AD patients ($P < 0.05$). The fvFTD group also performed statistically better than both the AD and
Table 6
Odds ratios and their confidence intervals in the subject groups regarding the naming-recognition, naming-placing, and recognition-placing consistencies in normal controls (NC), mild cognitive impairment (MCI), Alzheimer's disease (AD) and frontal variant frontotemporal dementia (fvFTD)

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Covarying</th>
<th>NC OR CI</th>
<th>MCI OR CI</th>
<th>AD OR CI</th>
<th>fvFTD OR CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naming-recognition</td>
<td>Placed</td>
<td>2.83 1.8-4.5</td>
<td>1.25 0.7-2.4</td>
<td>0.79 0.4-1.4</td>
<td>2.33 0.8-3.9</td>
</tr>
<tr>
<td></td>
<td>Not placed</td>
<td>1.8 0.7-2.4</td>
<td>1.6 0.8-2.4</td>
<td>0.82 0.5-1.4</td>
<td>1.08 0.4-2.8</td>
</tr>
<tr>
<td>Naming-placing</td>
<td>Recognised</td>
<td>2.32 1.4-3.9</td>
<td>1.24 0.7-2.1</td>
<td>0.86 0.5-1.4</td>
<td>1.45 0.8-3.6</td>
</tr>
<tr>
<td></td>
<td>Not recognised</td>
<td>1.19 0.6-2.1</td>
<td>1.47 0.9-2.6</td>
<td>1.95 1.2-3.1</td>
<td>1.18 0.7-2.1</td>
</tr>
<tr>
<td>Recognition-placing</td>
<td>Named</td>
<td>0.99 0.5-1.8</td>
<td>0.99 0.5-1.8</td>
<td>1.05 0.6-1.8</td>
<td>0.86 0.5-1.4</td>
</tr>
<tr>
<td></td>
<td>Not named</td>
<td>3.3 1.4-8.0</td>
<td>2 1.1-3.3</td>
<td>1.01 0.6-1.9</td>
<td>3.85 2.1-7.1</td>
</tr>
</tbody>
</table>

MCI patients on this measure ($P < 0.001$). In summary, NC = fvFTD > MCI = SD > AD.

4.5. Consistency analysis

Examination of the relationships between naming, item recognition and placing according to individual odds ratios for each group, revealed low degrees of association between naming and recognition, and between naming and placing in controls, contrasting with a high degree of intercorrelation between recognition and placing (see Table 6). The MCI group, in contrast, shows a low level of association between the recognition and placing aspects of the FPT, but no association between the other components. The AD group showed a very low degree of association between naming and placing in items that were not recognised. The fvFTD group showed low degrees of association between naming and placing on items that were not named. Since the SD group performed at floor on naming, but just below ceiling on familiarity, the relationships between familiarity, recognition and placing only were investigated in these subjects (see Table 7). No significant familiarity-recognition or familiarity-placing associations were found, but a significant relationship was found between recognition and placing in those items that the subject originally found familiar. Overall, there was a fairly consistent association between recognition and placing across groups (especially controls and MCI), but other associations were not robust.

4.6. Discriminant analysis

Table 8 illustrates the accuracy with which a discriminant function analysis based on the naming and placing components of the FPT classified subjects into the five groups. Not surprisingly, there is a considerable overlap between the AD and MCI, but the FPT classified virtually all patients in these two groups as pathological. The test was extremely good at predicting SD: all but one was correctly classified. The fvFTD were classified as either normal or fvFTD, but never as MCI. Overall 56.3% of the originally grouped cases were correctly assigned.

Table 7
Odds ratios and their confidence intervals in the subject groups regarding the familiarity-recognition, familiarity-placing, and recognition-placing consistencies in semantic dementia (SD)

<table>
<thead>
<tr>
<th>Correlation</th>
<th>Covarying</th>
<th>SD OR CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Familiarity-recognition</td>
<td>Placed</td>
<td>2.1 0.7-2.5</td>
</tr>
<tr>
<td></td>
<td>Not placed</td>
<td>1.4 0.7-2.5</td>
</tr>
<tr>
<td>Familiarity-placing</td>
<td>Recognised</td>
<td>1.5 0.9-2.5</td>
</tr>
<tr>
<td></td>
<td>Not recognized</td>
<td>0.9 0.5-1.7</td>
</tr>
<tr>
<td>Recognition-placing</td>
<td>Familiar</td>
<td>2.4 1.4-4.0</td>
</tr>
<tr>
<td></td>
<td>Not familiar</td>
<td>1.1 0.6-1.9</td>
</tr>
</tbody>
</table>

Table 8
Group classification table based on discriminant analysis of face-place test

<table>
<thead>
<tr>
<th>Predicted group membership</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NC</td>
</tr>
<tr>
<td>----------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>Original count</td>
<td>AD 0</td>
</tr>
<tr>
<td></td>
<td>MCI 1</td>
</tr>
<tr>
<td></td>
<td>NC 13</td>
</tr>
<tr>
<td></td>
<td>SD 0</td>
</tr>
<tr>
<td></td>
<td>fvFTD 4</td>
</tr>
</tbody>
</table>

Percentage

<table>
<thead>
<tr>
<th></th>
<th>AD 0</th>
<th>27.3</th>
<th>54.5</th>
<th>18.2</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MCI 4.3</td>
<td>34.8</td>
<td>39.1</td>
<td>13</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>NC 61.9</td>
<td>9.5</td>
<td>0</td>
<td>28.6</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>SD 0</td>
<td>0</td>
<td>9.1</td>
<td>90.9</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>fvFTD 40.0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>60.0</td>
</tr>
</tbody>
</table>

* indicates significant result (lower limit of CI > 1.0).
The only component of the FPT which clearly differenti-ated the MCI from the AD and SD groups was naming. No-tably however, all patient groups were impaired on naming, and only the fvFTD group performed normally on the recog-nition and placing components of the FPT. It is interesting that contrary to the initial hypothesis of spared recognition mem-ory in SD, this group performed at a similar level to both AD and MCI patients. While the SD group demonstrated some spared placing ability relative to AD patients, they were also significantly impaired relative to controls, despite excellent placing of objects (Lee et al., 2003). At the other extreme fvFTD were unimpaired even on the most difficult placing component of the task. The ability of the FPT to classify subjects, as assessed by discriminant analysis, suggests that MCI, early AD and SD cases were quite successfully discrim-inated, but that it was much less sensitive tofvFTD. Consis-tency analyses to assess the relationships between different components of the FPT, suggested that while performance on the naming part is not entirely independent from placing and item recognition in controls, the levels of association were very low. In contrast, no association between these aspects of performance was found in the MCI group. In both con-trols and MCI subjects there was a significant association between the recognition and placing components, indicating a more robust intercorrelation between these variables. The AD group did not demonstrate these patterns of association, which might reflect a smaller range of naming and placing responses in this group. The results of consistency analyses in the fvFTD and SD groups did not mirror those of the other patient groups and indicated little, if any, association between variables, except perhaps in the case of recognition and plac-ing for familiar items in SD. The findings in the SD and fvFTD subjects should however be interpreted with caution due to the relatively small group sizes.

5. General discussion

The key findings of experiment 1 were the presence of a person naming deficit in the fvFTD patient group and impair-ment in naming and identification in VaD patients, equivalent to that already observed by Thompson et al. (2002) in the AD group. Experiment 2 revealed impaired performance on tasks of both recognition memory and placing in the SD patients, which initially seems at odds with the original hypotheses that these abilities would be relatively spared. Patients with fvFTD performed within normal limits on the FPT.

One apparent contradiction between the two sets of data was the presence in thefvFTD group of a naming deficit in one task (the GFT) but not in the other (FPT). This finding can, albeit certainly, be explained on the basis of stimulus familiarity: in contrast to the high familiarity of items cho-sen for the FPT, the GFT consists of stimuli, which become steadily less familiar in a graded fashion. Fig. 2 confirms that the fvFTD patient group typically found items at an interme-diate level of familiarity more difficult than controls. These results suggest that a significant naming deficit infvFTD is likely to be masked if tests are based on high familiarity items.

While studies have demonstrated that naming does not occur without semantics in AD and SD (Hodges & Graham, 1998; Hodges & Greene, 1998), less is known about knowl-edge of famous people infvFTD. Unlike individuals with AD, who tend to exhibit impairments on tasks of both per-son naming and identification, the fvFTD patients appeared to have difficulty naming items despite intact performance on the identification component of the GFT. This pattern is compatible with the existence of a lexical access deficit in this group, but more detailed investigation of person seman-tic knowledge and its relationship to naming infvFTD is obviously required to substantiate this hypothesis.

Equivalent levels of impairment in naming and identifica-tion of famous people in VaD, to that seen in AD, is consistent with reports of anomia and partial breakdown of semantic knowledge in this group (Bentham et al., 1997) but is po-tentially at odds with the findings of Ricker et al. (1994). The earlier study found AD patients to be relatively more impaired than VaD patients on a task that required them to match the face of a famous person to one of three names. It is likely that the AD group reported in experiment 1 were at a milder stage of the illness than the group described by Ricker et al. (1994). It is possible, therefore, that the differences seen between the AD and VaD group might emerge with increasing disease severity. VaD and AD can be distinguished on other grounds including greater attentional and perceptual deficits early in the course of VaD than AD (Graham, Emery, & Hodges, 2004) but do not appear separable on the basis of semantic knowledge for people.

A consistency analysis examining the interrelationships between the different components of the face-place test revealed low levels of association between the ability to name and subsequently place or recognise items in controls, but a fairly consistent relationship between the ability to place and recognise items. The finding of association between recogni-tion and placing but not between other task components in MCI is furthermore consistent with the proposition that these two tasks both draw strongly on elements of episodic mem-ory but that episodic and semantic components are relatively independent. The findings of the consistency analysis were harder to interpret in SD and AD groups because of smaller group sizes and the more limited range of naming responses. There was, however, a suggestion in the SD group that item familiarity at the outset of the test influenced subsequent abil-ity to perform the recognition and placing tasks.

The most surprising finding from experiment 2 was the poor item recognition and placing impairment in the SD group. These deficits were almost as severe as those seen in AD and MCI, and have interesting implications. Experiments by Graham and colleagues have documented excellent item recognition memory for pictures of objects and animals in SD (Graham, Becker, & Hodges, 1997; Simons, Graham,
suggestions that person knowledge tests are sensitive to the
sure (Hodges & Graham, 1998). Our findings confirm prior
in the dementias other than AD but as an assessment tool, it
tiation. Person knowledge has not been investigated widely
to the overall goals of early dementia diagnosis and differen-
containing two famous faces with an inevitable recurrence of
the FPT is the length of the test phase. In the PAL, subjects
deficits with respect to famous people rendering them highly
demonstrated impaired fame judgement and severe naming
mantic content compared to famous faces. The SD patients
the geometric shapes used in the PAL have little, if any, se-
other major factor influencing performance. That is to say,
leashed macaques demonstrate impairment on perceptual
task specific variables already discussed.
Lesion studies in non-human primates suggest that the
perirhinal cortex is implicated in both perceptual process-
formation, and in the representation of semantic informa-
tion (Murray & Bussey, 1999). More specifically, Buckley,
Booth, Rolls, and Gaffan (2001) have shown that perirhinal-
imals has been invaluable. Elizabeth Milwain kindly made available her
The statistical advice of Ian Nimmo-Smith and Peter Watson
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Placing Test which was an inspiration for the development of the
Face Place Test.

References
semantic memory in vascular dementia and dementia of Alzheimer’s
Blackwell, A. D., Sahakian, B. J., Novey, R., Tempel, J. M., Robbins,
T. W., & Hodges, J. R. (2003). Detecting dementia: novel neuropsy-
chological markers of preclinical Alzheimer’s disease. Dementia and
Geriatric Cognitive Disorders, 17, 14–20.
neuropsychiatric and behavioural features distinguish frontotemporal
don dementia from Alzheimer’s disease? Journal of Neurology, Neurosurgery


