Neural Correlates of Episodic Memory in Behavioral Variant Frontotemporal Dementia

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Abstract. Impaired episodic memory is currently an exclusion criterion for behavioral variant frontotemporal dementia (bv-FTD), although prior studies have shown that neuropsychological memory performance varies from very impaired to intact in such patients. Our study investigated i) whether this variability might be due to the admixture of true bv-FTD and phenocopy syndrome patients and ii) the neural correlates of episodic memory deficits in bvFTD. Groups of patients with true bvFTD (n = 14), phenocopy syndrome (n = 6), Alzheimer’s disease (AD) (n = 14), and healthy controls (n = 15) underwent memory testing and had MRI scanning with ratings of regional brain atrophy. Phenocopy patients did not differ to controls on memory scores or atrophy ratings. By contrast, bvFTD and AD patients were impaired on both measures in comparison to controls and more importantly, bvFTD and AD did not differ on memory scores. Atrophy patterns differed, with AD showing typical medial temporal lobe atrophy, while bvFTD patients had predominantly prefrontal cortex atrophy. In bvFTD neuropsychological memory performance correlated with frontal atrophy ratings while in AD significant correlations were found between memory and both medial temporal lobe and frontal atrophy ratings. Taken together, our data shows that bvFTD patients can show a similar degree of episodic memory impairment on neuropsychological tests to AD patients, however, the neural correlates differ. The previously variable reported memory performance in bvFTD is likely due to the inclusion of phenocopy patients, who are mostly undistinguishable from controls. These findings have implications for the diagnosis of bvFTD.

Keywords: AD, behavioral variant frontotemporal dementia (bvFTD), episodic memory, MRI, phenocopy syndrome

INTRODUCTION

Patients presenting with behavioral variant frontotemporal dementia (bvFTD) have a range of symptoms including apathy, disinhibition, impulsivity, social dysfunction, stereotypic behavior, and alterations in eating [1]. The current diagnostic criteria for bvFTD recognize the centrality of such symptoms but also emphasize the relative preservation of memory function and stipulate that early, severe amnesia, in contrast to Alzheimer’s disease (AD), is an exclusion feature for bvFTD [2].

Recent studies, however, question the premise of intact episodic memory in bvFTD. Clinically, around 10% of pathologically proven bvFTD patients show memory problems at presentation [3] and occasional cases can present with severe amnesia [4]. Neverthe-
less, formal comparisons of memory in bvFTD versus AD have yielded contradictory results [5, 9].

The inconsistency of results seems at first puzzling but could be explained by the inclusion of patients with the so-called phenocopy syndrome of bvFTD. Recent studies show a dichotomy of disease prognosis in bvFTD: some patients progress rapidly while others show little or no change over many years. Crucially, the non-progressive or phenocopy patients have similar behavioral disturbances to progressive or real bvFTD patients but show relatively normal cognition, structural and functional neuroimaging [10, 11]. This heterogeneity of bvFTD might explain previous findings: if only the progressive group shows brain atrophy then this group is more likely to exhibit memory deficits, while the phenocopy group will present little or no memory dysfunction. Exactly this pattern was found in a retrospective study [12], in which bvFTD patients were divided into true and phenocopy cases based upon their progression over time. Once the phenocopy patients were excluded, true bvFTD patients showed a memory deficit similar to that seen in AD on standard neuropsychological memory measures, although it still needs to be established whether there is a qualitative difference in memory impairment between bvFTD and AD.

The neural basis for memory impairment in bvFTD remains unclear. Neuropathological analyses have also identified early atrophy of medial temporal lobe structures [3], including the hippocampus [13, 14]. Selective hippocampal atrophy is one of the hallmarks of early AD and is thought to be the cause of the amnesic symptoms [15]. There is some evidence of medial temporal lobe involvement early in the course of bvFTD but very few studies so far have investigated the contribution of frontal cortex or medial temporal lobe pathology to the impaired memory performance in bvFTD [16]. Frontal brain regions, in particular dorsolateral prefrontal cortex, have been shown to be involved in episodic memory tasks [17, 18], and it is possible that dysfunction of this brain region, and not medial temporal lobe structure, is responsible for the memory impairment in bvFTD.

Our primary goal was to compare episodic memory in a series of prospectively assessed bvFTD patients, divided into those with the phenocopy syndrome and true bvFTD and contrast those to AD patients and healthy controls. A second goal of our study was to relate memory function to involvement of cortical brain structures, in particular frontal and medial temporal regions, using MRI findings. We used a validated MRI visual rating scale to assess the pattern of brain atrophy, and correlated this with the episodic memory findings in bvFTD and AD.

**MATERIALS AND METHODS**

**Case selection**

A total of 59 subjects participated in the study: 20 with a clinical diagnosis of bvFTD, 14 with AD and 15 healthy controls, all selected from the FRONTIER database.

All bvFTD patients met core clinical diagnostic criteria for FTD with insidious onset, decline in social behavior and personal conduct, emotional blunting, and loss of insight reported by care givers [1]. They also all fulfilled proposed new criteria for possible bvFTD [19]. The 20 bvFTD cases were then subdivided into: 1) phenocopy syndrome (n = 6), as defined by relatively stable, non-progressive behavioral disturbance with a lack of progression over two years or more and preserved activities of daily living; and 2) classical bvFTD (n = 14), which exhibited continuously worsening behavior and cognition over a two year period. This classification was independent of the cognitive and imaging data reported here. The 14 AD patients met diagnostic criteria for probable AD [20]. Healthy controls were volunteers or were spouses/carers of patients. All patients were assessed by a multidisciplinary team to exclude other neurological or psychiatric (e.g., schizophrenia, depression, mania, alcohol, and substance abuse) etiologies. In particular, psychiatric symptoms were checked via structured clinical interviews with the patient and career. All patients and spouses gave informed consent. Importantly, the current patient sample was entirely independent of our previous study on episodic memory in bvFTD versus phenocopy syndrome [12]. The study was approved by the local research ethics committee.

**Image acquisition & analysis**

All patient and controls underwent whole-brain T1-weighted images using a 3-tesla Philips MRI scanner with standard quadrature head coil. The 3D T1-weighted sequences were acquired with the following sequences: coronal orientation, matrix 256 × 256; 200 slices, 1 × 1 mm² in-plane resolution, slice thickness 1 × 5 mm, TE/TR = 2.6/5.8 ms, flip angle α = 19°. One rater (CP), blind to the clinical diagnosis, rated T1 coronal MRIs based on a validated rating scale [21] that involves reviewing 4 standardized coronal MRI...
slices; the first at the level of the anterior temporal pole, the second at the level of the insula, the third at the level of the lateral geniculate nucleus and the fourth at the level of the fornix. A total of 15 regions were scored bilaterally. On the first slice the anterior temporal pole, basal ganglia, orbitofrontal cortex, dorsolateral frontal cortex, and anterior cingulate were rated; on the second slice the anterior hippocampus, the entorhinal cortex, the perirhinal cortex, the anterior fusiform gyrus, and the lateral temporal region; on the third slice the mid-hippocampus and superior temporal gyrus; and on the fourth slice the posterior hippocampus and Brodmann’s area 37. Atrophy within each region was rated on a 5-point Likert scale ranging from 0 to 4 (0 = normal; 1 = borderline appearances, possibly normal; 2 = definite atrophy present; 3 = marked atrophy; 4 = severe atrophy). Composite scores were formed by summing the scores of the appropriate areas and dividing the total by the number of areas (e.g., for the left hippocampus the scores for the left anterior, mid and posterior hippocampus were summed then divided by three). Bilateral scores were formed by summing right and left scores and dividing by two.

The rater was trained on an independent set of 29 MR scans that included different dementia populations with varying degrees of severity, as well as healthy controls. Scoring was repeated for a sub-set of the experimental MRIs in order to assess intra-rater reliability, which was high (raw proportion of scores in agreement 74.6%; weighted kappa 0.768).

Cognitive tests

General cognition was assessed using the ACE-R. For verbal recall and recognition we used the Rey Auditory Verbal Learning Test (RA VLT) with the following scores: immediate recall after an interference list; 30 minute recall; and recognition after thirty minutes. Visual recall was investigated with the Rey-Osterrieth Complex Figure Test (RCF) and visual recognition with the Doors and People test (part A). Subjects first copied the RCF; then three minutes later were asked to recall it; the recall score was calculated as the percentage of the figure copied that was correctly recalled. All neuropsychological test scores were converted into percentage correct to allow comparison across tests and calculation of composite scores.

Disease severity was assessed using disease duration (the time from the first symptoms noted by the family to the time of MRI) and the Frontotemporal dementia Severity Rating Scale (FRS), a recently developed measure sensitive to disease progression [22]. The FRS utilizes a carer questionnaire to assess the degree of functional impairment across a range of everyday abilities, with the responses being converted to a logit score which corresponds to the severity of disease.

Statistics

Data were analyzed using SPSS15.0 (SPSS Inc., Chicago, Il, USA). Variables were plotted and checked for normality of distribution by Kolmogorov-Smirnov tests. Atrophy scores were compared across the four groups via ANOVAs followed by Tukey post-hoc where the data was normally distributed; where the data was not normally distributed the Kruskal-Wallis test was applied followed by post-hoc Mann-Whitney tests. The bivariate correlation was used to assess relationships between variables (Pearson’s for normally distributed data or Spearman’s for non-parametric data).

RESULTS

Demographics

There were no significant differences in demographic variables between the groups (all p’s > 0.1), other than a higher percentage of males in the phenocopy group (p < 0.05, ANOVA; Table 1). Disease duration was significantly longer in the phenocopy group compared to the AD (p < 0.01) and bvFTD groups (p < 0.05), but equivalent in the AD and bvFTD groups (p > 0.1). Disease severity as measured by the FRS was significantly worse in the bvFTD group compared to the AD group (p < 0.05) but no other inter-group differences emerged (all p’s > 0.1). Due to the higher disease severity in the bvFTD group, we used disease severity as a covariate in the remaining analyses. We did not covary our analyses for disease duration as it is a more crude measure of severity and severely distorted by the phenocopy group, which is has the longest disease duration but is cognitively intact (see below).

Global cognitive function

Unsurprisingly, the bvFTD and AD groups were significantly impaired on the ACE-R compared to controls (p < 0.000). Importantly, performance by the phenocopy group was not significantly different to controls (p > 0.1).
Table 1

<table>
<thead>
<tr>
<th>Demographics &amp; Cognitive Tests</th>
<th>Controls</th>
<th>bvFTD</th>
<th>Phenocopy</th>
<th>AD</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at MRI</td>
<td>56.8 (6.3)</td>
<td>59.7 (8.6)</td>
<td>63.8 (7.7)</td>
<td>64.7 (5.8)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Education</td>
<td>10.2 (2.8)</td>
<td>10.5 (4.8)</td>
<td>12.8 (3.5)</td>
<td>13.2 (2.4)</td>
<td>n.s.</td>
</tr>
<tr>
<td>Gender (M/F)</td>
<td>60</td>
<td>104</td>
<td>104</td>
<td>60</td>
<td>7.9*</td>
</tr>
<tr>
<td>Disease duration (months)</td>
<td>76.7 (34.6)</td>
<td>40.2 (33.0)</td>
<td>32.5 (14.8)</td>
<td>5.8*</td>
<td>NA</td>
</tr>
<tr>
<td>FRS logit score</td>
<td>–0.09 (0.8)</td>
<td>–0.7 (1.8)</td>
<td>1.3 (1.3)</td>
<td>5.8*</td>
<td>NA</td>
</tr>
<tr>
<td>ACE-R</td>
<td>84.8 (10.2)</td>
<td>75.2 (10.8)</td>
<td>78.4 (10.3)</td>
<td>95.5 (3.1)</td>
<td>1.1***</td>
</tr>
</tbody>
</table>

Note. F values indicate significant differences across groups; Tukey post hoc tests compare differences between group pairs. n.s. = non significant; *** \( p < 0.001 \); ** \( p < 0.01 \); * \( p < 0.05 \).

Disease duration was unknown for 1 bvFTD case; the FRS logit score was unknown for 3 bvFTD cases and 3 AD cases.

Memory function

The results of the memory tests are shown in Fig. 1 and Table 2. The bvFTD group was significantly impaired compared to controls (all \( p's < 0.01 \)) on all tests except the recognition component of the RA/VT (\( p > 0.1 \)). By contrast, performance of the phenocopy group did not differ from controls (all \( p's > 0.1 \)). As expected, the AD group was impaired on all tests (all \( p's < 0.05 \)) compared to controls. Moreover, there were no significant differences between the AD and bvFTD groups (all \( p's > 0.1 \)).

Regional brain atrophy

Figure 2 shows the summed scores for homologous regions in the two hemispheres across groups. It can be seen that controls obtained scores of less than 1 for all regions except the dorsolateral frontal cortex. The most atrophic group was the bvFTD group who demonstrated significant involvement of all fronto-temporal regions. Notably, the hippocampal (\( p < 0.025 \)) and parahippocampal (\( p < 0.025 \)) structures were also abnormal, with the exception of the perirhinal cortex (\( p > 0.1 \)). By contrast, the phenocopy group...
Table 2

<table>
<thead>
<tr>
<th>Memory scores Phenocopy bvFTD AD Controls</th>
<th>F values Phenocopy bvFTD AD Controls</th>
<th>F values Phenocopy bvFTD AD Controls</th>
<th>F values Phenocopy bvFTD AD Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediate verbal recall 48.9 (25)</td>
<td>26.7 (22)</td>
<td>24.7 (20)</td>
<td>64.4 (12)</td>
</tr>
<tr>
<td>Delayed verbal recall 52.2 (32)</td>
<td>14.4 (18)</td>
<td>19.5 (18)</td>
<td>66.2 (20)</td>
</tr>
<tr>
<td>Verbal recognition 92.2 (13)</td>
<td>68.2 (41)</td>
<td>67.6 (27)</td>
<td>88 (10)</td>
</tr>
<tr>
<td>Visual recall 54.6 (24)</td>
<td>21.4 (18)</td>
<td>14.1 (13)</td>
<td>52.7 (18)</td>
</tr>
<tr>
<td>Visual recognition 88.9 (9)</td>
<td>63.7 (19)</td>
<td>64.3 (20)</td>
<td>89.4 (12)</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>
| Note. F values indicate significant differences across groups; Tukey post-hoc tests compare differences between group pairs. n.s. = non significant; *** = p < 0.001; ** = p < 0.01; * = p < 0.05.

A bivariate correlation analysis was used to explore the relationship between the degree of brain atrophy and performance on neuropsychological tests. The group was comparable to controls. The AD group had diffuse changes affecting all regions except the anterior temporal, orbito-frontal cortex, entorhinal cortex, and perirhinal cortices. Inter-group comparisons revealed no significant differences between bvFTD and AD (all p's > 0.1). Compared to the phenocopy group the bvFTD group showed more severe atrophy of the anterior temporal (p < 0.05), orbitofrontal cortex (p < 0.025), entorhinal cortex (p < 0.025), anterior hippocampus (p < 0.05), area 37 (p < 0.01), as well as a statistical trend for the insula (p = 0.06).

Turning to the composite atrophy scores, the same pattern emerges as that described for individual regions, with equivalent degrees of atrophy in the bvFTD and AD groups for the frontal, temporal, parahippocampal, and hippocampal regions (all p's > 0.1), while the phenocopy group did not differ significantly from controls (all p's > 0.1).

The degree of atrophy seen on the right and left was compared within each group for the following composite regions: frontal, temporal, parahippocampal, hippocampal, and entire hemisphere. No significant differences for the degree of lateralization (left vs. right) of the composite atrophy scores were found (all p's > 0.1).

Correlations between brain atrophy and neuropsychological test scores

A bivariate correlation analysis was used to explore the relationship between the degree of brain atrophy and performance on neuropsychological tests.
phenocopy group was excluded from this analysis because of its small size. The following targeted candidate brain regions were entered: hippocampal region; dorso-lateral and the orbito-frontal cortices. Bilateral scores were used. The bvFTD group showed a significant correlation between verbal recognition memory and the orbito-frontal cortex \((r = 0.536, p < 0.05)\) only, and between visual recognition (Doors and People A) and degree of dorso-lateral frontal cortex atrophy \((r = 0.464, p < 0.05)\). By contrast, in the AD group there were significant correlations between immediate verbal recall and hippocampal atrophy \((r = 0.533, p < 0.05)\), as well as delayed verbal recall and atrophy of both frontal and hippocampal regions \((r = 0.422, p < 0.05)\) respectively.

An additional logistic regression (employing the Enter method) was performed to test whether a classification of memory scores and regional atrophy could explain the overall variance in the data. However, the logistic regression revealed no significant classifications \((p > 0.1)\).

**DISCUSSION**

We have confirmed in a prospective cohort that bvFTD patients have marked anterograde episodic memory deficits on neuropsychological recall tests which can make a distinction from AD difficult. The bvFTD patients also displayed diffuse brain atrophy of a severity equivalent to that seen in AD. Both hippocampal and frontal regional atrophy contributed to the memory problems of the AD group. In contrast, the memory deficits seen in bvFTD appeared to be mediated primarily by damage to frontal regions, with no significant correlations found between memory performance and hippocampal atrophy. Findings in the phenocopy group were strikingly different, with patients performing at control level on memory tests and having no significant brain atrophy.

The cognitive profile of bvFTD has been the subject of much debate. Some authors have reported memory to be intact in early bvFTD, while others have observed significant impairment \([5, 6]\). This is highly likely to be due to an admixture of those with true progressive bvFTD and those with the phenocopy syndrome in some studies. As confirmed by this study, phenocopy patients do not display significant memory impairment, and their inclusion would therefore skew the analysis of neuropsychological test results.

On a neural level, brain atrophy was more severe in the bvFTD group than in the AD group for all measured regions except the lateral temporal, insula, mid- and posterior hippocampus. In the AD group widespread atrophy was seen, with only the anterior temporal, orbitofrontal, entorhinal, and perirhinal cortices being spared. These results are in keeping with previous neuroimaging studies, which have found an equal degree of atrophy in bvFTD and AD patients \([23]\). In addition, we observed the posterior hippocampus was more severely affected than the anterior in AD, whilst in bvFTD the converse was true. These findings are again consistent with previous observations \([23, 24]\).

Correlations in the AD patients were found as expected between hippocampal atrophy and verbal and visual recall. Additional contributions of the dorso-lateral and orbitofrontal cortices to verbal memory were also observed. The only correlations seen in the bvFTD were between the orbito-frontal cortex and verbal recognition, and between the dorso-lateral frontal cortex and visual recognition. These findings have implications for our understanding to the brain networks subserving episodic memory. Hippocampal damage is not the sole cause of impairment on tests of memory, disruption of frontal cortical pathways also results in defective recall and recognition \([18, 25]\), with the contributions of specific frontal regions to episodic memory retrieval still unclear \([18]\).

On a clinical level, our results again replicate previous findings that bvFTD phenocopy patients perform similarly to controls on standard neuropsychological memory tests. More importantly, our data suggests that AD and bvFTD cannot be distinguished on the basis of the neuropsychological memory performance alone, although their deficits rely on different neural structures. Thus, significant memory dysfunction on neuropsychological tests in a patient should not be taken as an exclusion criterion for bvFTD, in particular in light of the emerging evidence of frontal dysfunction influencing memory performance in AD patients \([26]\).

Instead clinicians are advised to carefully corroborate any presenting behavioral features as well as neuroimaging atrophy measures to discriminate bvFTD and AD. The reliance on behavioral features and neuroimaging for a bvFTD diagnosis is also embodied in the revised diagnostic criteria of bvFTD \([19]\) which are currently undergoing validation. The application of these new criteria is therefore advisable as it will greatly reduce the risk of misdiagnosing bvFTD.

Finally, the etiology of the phenocopy syndrome is still unknown and to date there is no neuropathological data available. Some of the individuals in our study might have a decompensated personality or Asperger’s spectrum disorder. Further, some of our patients had a
history of mood disturbance, insufficient to reach criteria for a diagnosis of bipolar disorder. This is discussed more fully in prior studies [27]. Until there is definite neuropathological confirmation, the possibility that these patients suffer from an underlying neurodegenerative process cannot be excluded. Long-term clinical follow-up as well as neuropathology should shed light on this condition in the future and should further refine the bvFTD diagnostic criteria.

Taken together, our findings show that bvFTD patients show impaired neuropsychological memory performance at presentation, similar to AD patients. Notably, the neural correlates of the memory impairments seem to differ between the groups, with amnesia in AD caused by medial temporal lobe atrophy and amnesia in bvFTD more likely to be caused by frontal cortex atrophy. For future studies, it would be important to replicate our prospective findings in a bigger sample as well as to replicate our results via atomized whole-brain imaging analysis protocols (e.g., voxel-based morphometry). It is also unclear at this stage whether bvFTD and AD patients also have qualitative differences in their memory performance, which should be investigated with more experimental episodic memory task targeting prefrontal cortex versus medial temporal lobe dependent memory processes more specifically. Nevertheless, our current findings have implications for the diagnostic distinction of bvFTD and AD, which in turn will provide better treatment options for patients and their carers.

DISCLOSURE STATEMENT

Authors' disclosures available online (http://www.j-alz.com/disclosures/view.php?id=600).

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