Comparison of prefrontal atrophy and episodic memory performance in dysexecutive

Alzheimer's disease and behavioural-variant frontotemporal dementia

Stephanie Wong[a,b,c], Maxime Bertoux[d], Greg Savage[a,b], John R Hodges[a,c,e], Olivier Piguet[a,c,e] &

Michael Hornberger[a,f]

[a]*ARC Centre of Excellence in Cognition and its Disorders, Sydney, Australia*

[b]*Department of Psychology, Macquarie University, Sydney, Australia*

[c]*Neuroscience Research Australia, Sydney, Australia*

[d]*Department of Clinical Neurosciences, Cambridge University, UK*

[e]*School of Medical Sciences, the University of New South Wales, Sydney, Australia*

[f]*Norwich Medical School, University of East Anglia, UK*

Corresponding author:

Prof. Michael Hornberger

Norwich Medical School, University of East Anglia, NR4 7TJ, Norwich, UK

Tel: +44 1603 593540; Fax: +44 1603 593752; Email: m.hornberger@uea.ac.uk

Running title: Episodic memory in dysexecutive AD and bvFTD

Abstract

Alzheimer's disease (AD) sometimes presents with prominent executive dysfunction and associated prefrontal cortex atrophy. The impact of such executive deficits on episodic memory performance as well as their neural correlates in AD, however, remains unclear. This aim of the current study was to investigate episodic memory and brain atrophy in AD patients with relatively spared executive functioning (SEF-AD; n=12) and AD patients with relatively impaired executive functioning (IEF-AD; n=23). We also compared the AD subgroups with a group of behavioural-variant frontotemporal dementia patients (bvFTD; n=22), who typically exhibit significant executive deficits, and age-matched healthy controls (n=38). On cognitive testing, the three patient groups showed comparable memory profiles on standard episodic memory tests, with significant impairment relative to controls. Voxel-based morphometry analyses revealed extensive prefrontal and medial temporal lobe atrophy in IEF-AD and bvFTD, whereas this was limited to the middle frontal gyrus and hippocampus in SEF-AD. Moreover, the additional prefrontal atrophy in IEF-AD and bvFTD correlated with memory performance, whereas this was not the case for SEF-AD. These findings indicate that IEF-AD patients show prefrontal atrophy in regions similar to bvFTD, and suggest that this contributes to episodic memory performance. This has implications for the differential diagnosis of bvFTD and subtypes of AD.

Introduction

Alzheimer's disease (AD) is a neurodegenerative disorder characterised clinically by progressive memory impairment and declines in language and visuospatial abilities [1]. A proportion of AD patients however, present with prominent executive dysfunction [2, 3], even during the early disease stages [4, 5].

The cognitive profile of AD patients who present with executive dysfunction can be difficult to distinguish from patients with behavioural-variant frontotemporal dementia (bvFTD), who typically exhibit significant executive deficits [6]. In addition, bvFTD patients can also present with episodic memory impairment [7-9] and perform as poorly as AD patients on episodic memory tests [10-13]. Thus, overlap is present between AD and bvFTD in both executive and memory deficits, blurring the distinction between these two patient groups. Standard neuropsychological measures of executive function and episodic memory recall do not reliably distinguish between bvFTD and AD patients at presentation [14, 15]. Nevertheless, given that executive function is affected in some, but not all AD patients [2, 16], it is unclear whether previous findings have been driven by deficits in a subset of dysexecutive AD patients.

Previous studies comparing AD patients with or without prominent executive dysfunction have yielded mixed results. While some have reported similar levels of impairment on cognitive screening measures in both groups [4, 17], others have found executive-impaired AD patients to have significantly lower scores on cognitive and functional scales [2, 18, 19], with faster decline over time [20]. The impact of executive deficits on episodic memory in

3

AD also remains unclear, with some studies reporting worse performance on some memory tests in AD with executive dysfunction [17], but others finding no difference [4].

Clinicopathological studies have identified pathologically confirmed cases of AD presenting with predominant executive dysfunction. The relative distribution of pathology in these cases appears to be markedly atypical, involving the frontal cortex as well as medial temporal lobe (MTL) structures [21, 22]. Neuroimaging investigations further indicate that AD patients who display frontal hypoperfusion tend to show a more dysexecutive profile, as well as worse neuropsychiatric symptoms and functional impairment compared to typical AD patients [23]. Furthermore, AD patients with prominent executive dysfunction show increased frontal hypometabolism [24] and additional cortical thinning in frontoparietal regions, despite equivalent cortical thinning in MTL regions compared to predominantly memory-impaired AD patients [25]. Similar findings have also been reported in dysexecutive versus amnestic mild cognitive impairment (MCI) patients, with greater frontal involvement in the former group [26, 27]. It is currently unknown, however, whether frontal atrophy in executive-impaired AD patients resembles the pattern of atrophy characteristically seen in bvFTD [28].

This study addresses these issues by contrasting dysexecutive AD with bvFTD, with the aim of investigating the influence of executive function on memory, as well as identifying their neuroimaging correlates. Specifically, we compared episodic memory performance and brain atrophy between bvFTD patients and AD patients, who were classified into relatively spared and relatively impaired executive function subgroups (SEF-AD and IEF-AD), according to performance on standard neuropsychological tests of executive function. We also

compared the neural substrates of episodic memory performance in the three patient groups using voxel-based morphometry (VBM) covariate analyses. Based on previous evidence, we predicted that prefrontal cortex (PFC) and MTL atrophy would be least severe in SEF-AD patients, whereas IEF-AD and bvFTD patients would show more extensive atrophy in these regions. In addition, we expected that episodic memory performance would relate to divergent patterns of atrophy across the three groups, with greater PFC involvement in IEF-AD and bvFTD.

Materials and Methods

Case selection

A total of 95 participants were selected from the FRONTIER database, at Neuroscience Research Australia, Sydney. The sample included 35 AD and 22 bvFTD patients and 38 age- and education-matched controls (see Table 1 for demographic details). Based on extensive clinical investigations, cognitive assessment and structural brain neuroimaging, patient diagnoses were established by consensus among a senior neurologist, neuropsychologist and occupational therapist. All patients met the relevant clinical diagnostic criteria for AD [1] or bvFTD [6]. Biomarker data were available and considered when assigning diagnoses in a subset of the patients, via positron emission tomography (PET) imaging for the amyloid-β ligand, Pittsburgh compound-B (PiB). Of those who underwent PiB-PET imaging, PiB-positive status was confirmed in 2/2 SEF-AD patients and 3/3 IEF-AD patients, whereas PiB-negative status was confirmed in 2/2 bvFTD patients. All patients were seen for follow-up, approximately 12 months following their initial visit. Only patients showing clear evidence of

disease progression in accordance with their diagnosis were included. Disease duration was estimated as the number of years elapsed since the onset of symptoms.

The age- and education-matched healthy control group consisted of volunteers or spouses/carers of patients. Exclusion criteria included current or prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease (stroke, transient ischemic attacks), alcohol and other drug abuse and limited English proficiency.

Participants' overall level of cognitive functioning was established using the Addenbrooke's Cognitive Examination-Revised [ACE-R; 29]. The Frontotemporal Dementia Rating Scale [FRS; 30] and Clinical Dementia Rating Scale [CDR; 31] were used as measures of the disease severity in bvFTD and AD patients. In addition, the Cambridge Behavioural Inventory-Revised [CBI-R; 32] was used to quantify symptoms of behavioural disturbance reported by the family or carer, with higher scores indicative of more behavioural disturbance. All participants or their Person Responsible provided written informed consent in accordance with the Declaration of Helsinki. This study was approved by the South Eastern Sydney Local Health District and the University of New South Wales ethics committees.

Measures of executive function

The following neuropsychological tests of executive function were administered: the Backwards Digit Span test [DSB; 33], the Controlled Oral Word Association Test [COWAT; 34], the Trail Making Test [TMT; 35] and the Hayling Sentence Completion Test [36].

The DSB test is a measure of working memory, where participants are required to repeat series of numbers (which increase in length over trials) in reverse order. The COWAT is a timed verbal fluency task that involves generating a list of words that begin with a specified letter (over 3 trials, for F, A or S). The total number of correct responses on the DSB test and total number of correct words on the COWAT were included in our analyses.

The TMT is a measure of visual attention, psychomotor speed and cognitive flexibility. In Part A, participants are required to draw lines connecting numbers in a numerical sequence (1-2-3 etc.). This is followed by Part B, where participants are to draw lines connecting numbers and letters in an alternating numerical and alphabetical sequence (1-A-2-B-3-C etc.). Lines should be drawn as rapidly and accurately as possible and the time taken to complete each part is recorded, with a maximum time limit of 300 seconds for both sections. To obtain a measure of cognitive flexibility whilst accounting for psychomotor speed, Trails A time was subtracted from Trails B time (B-A time), with longer time indicative of greater impairment.

The Hayling Sentence Completion Test assesses the ability to inhibit prepotent verbal responses on a sentence completion task. An initial baseline phase requires completion of a series of sentences with a logical word as quickly as possible. The second phase involves inhibition of the automatic logical response for a new set of sentences, and instead, completion with a word that is semantically unrelated. According the scoring criteria, errors were classed as belonging to Category A (highly related) or Category B (somewhat related), before conversion into an 'A score' and a 'B score'. The sum of these scores (AB error score; maximum score=128) was included in our analyses.

Measures of episodic memory

Following previously reported procedures [12, 37] verbal and visual episodic memory tests were administered to all participants. The Rey Auditory Verbal Learning Test (RAVLT) [38] was used to assess memory recall and recognition for verbal information. The RAVLT involves learning a list of 15 words (List A), which is read aloud over five consecutive trials, each followed by a free recall test. This is followed by presentation of an interference list of 15 words (List B), with a free recall test for these words. Participants are then required to recall words from List A without further presentation (immediate recall trial A6). Following a 30-minute delay, recall of List A is reassessed (delayed recall trial A7), followed by a recognition test, containing all items from List A as well as words from List B and 20 new words. Scores from trials A6 and A7 were included in our analyses.

The Rey-Osterrieth Complex Figure Test [RCFT; 39] was administered to assess recall of visual information from a complex design. Three minutes after copying a complex figure as accurately as possible, participants were instructed to reproduce the figure from memory. The number of correctly recalled components (maximum score: 36) was included in our analyses.

To investigate relationships between patterns of grey matter atrophy and episodic memory recall performance, a memory composite score was created. Episodic memory recall scores from the RAVLT trials A6 and A7 and RCFT were converted into percentage correct scores before averaging to yield the memory recall composite score, which was then included as a covariate in the imaging analyses.

Classification of AD patients

Individual raw scores on the four executive tasks (TMT, COWAT, DSB and Hayling Test) were initially transformed into *z*-scores based on the mean and SD of the control group used in this study. *Z*-scores ≤ -1.5 (for COWAT and DSB total correct scores) or ≥ 1.5 (for TMT B-A time and Hayling Test AB error score) were classified to be within the impaired range. For the participants who were either unable to complete Part B of the TMT or failed to do so within the prescribed time limit (14.7% of participants; 10/35 AD and 4/22 bvFTD), the maximum Trails B time score of 300 seconds was used to compute their TMT B-A score. Following previously reported procedures [17, 40] AD patients who were impaired on 0 or 1 of the executive tasks were classified as having spared executive function (SEF-AD; n = 12). In contrast, AD patients who were impaired on >1 of the executive tasks were classified as having impaired executive function (IEF-AD; n = 23).

Statistical analyses

Data were analysed using SPSS 20.0 (SPSS Inc., Chicago, Ill., USA). Kolmogorov-Smirnov tests were used to check for normality of distribution in the demographic data, neuropsychological measures of executive function and memory composite scores. Where the data were normally distributed, scores were compared across the four groups (SEF-AD, IEF-AD, bvFTD and controls) using ANOVAs followed by Tukey post hoc tests. Data that were not normally distributed were analysed using Kruskal-Wallis tests followed by post hoc pairwise comparisons, which were performed using Dunn's [41] procedure with a Bonferroni correction for multiple comparisons. A chi-square test was used to check for

gender distribution across groups. Spearman rank correlations were used to investigate relationships between performance on measures of executive function and memory.

Image acquisition and voxel-based morphometry (VBM) analysis

All patients and controls underwent the same imaging protocol with whole-brain T1-weighted images using a 3T Phillips MRI scanner with a standard quadrature head coil (8 channels). The 3D T1-weighted sequences were acquired as follows: coronal orientation, matrix 256 x 256, 200 slices, 1 mm^2 in-plane resolution, slice thickness 1mm, TE/TR=2.6/5.8ms. 3D T1-weighted sequences were analysed using FSL-VBM, a voxel-based morphometry analysis [42, 43], which is part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html [44]. Following brain extraction from the images, tissue segmentation was carried out using the FMRIB Automatic Segmentation Tool (FAST) [45]. The resulting gray matter partial volume maps were aligned to the Montreal Neurological Institute standard space (MNI52) using the nonlinear registration approach with FNIRT [46, 47], which uses a b-spline representation of the registration warp field [48]. To correct for local expansion or contraction, the registered partial volume maps were modulated by dividing them by the Jacobian of the warp field. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8mm). Because we had strong regional a priori, a single region of interest mask of PFC and MTL regions was created using the Harvard-Oxford cortical and subcortical structural atlas. The following regions were included in the mask: hippocampus, parahippocampal gyrus, fusiform cortex, temporal pole, precentral gyrus, superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus, orbitofrontal gyrus, subcallosal cortex, medial prefrontal cortex, paracingulate gyrus, anterior cingulate gyrus and frontal pole.

A voxel-wise general linear model (GLM) was applied to investigate differences in grey matter intensity via permutation-based non-parametric testing [49] with 5000 permutations per contrast. As a first step, differences in PFC and MTL grey matter intensity between patients (SEF-AD, IEF-AD and bvFTD) and controls were assessed. For comparisons between patients and controls, a threshold of 100 contiguous voxels was used, uncorrected at the $p<.001$ threshold. For analyses between patient groups, we lowered the cluster-based threshold to 75 contiguous voxels. Next, correlations between memory performance and regions of grey matter atrophy were investigated in SEF-AD, IEF-AD and bvFTD patients combined with controls. This procedure has previously been used in similar studies including bvFTD and AD patients [12] and serves to achieve greater variance in test scores, thereby increasing the statistical power to detect brain-behaviour relationships. An overlap analysis was conducted to identify common regions of grey matter atrophy correlating with memory performance across groups. For all covariate analyses, a threshold of 100 contiguous voxels was used, uncorrected at the $p<.001$ threshold. Regions of significant grey matter density change were superimposed on the MNI standard brain, with maximum coordinates provided in MNI space, and localised with reference to the Harvard-Oxford probabilistic cortical and subcortical atlas.

Results

Demographics and global cognitive functioning

Based on the criteria detailed in the Methods section, 12 AD patients were classified into the SEF-AD group and 23 AD patients into the IEF-AD group (Table 1). Participant groups

were matched for age, sex and education (all *p* values >.1). The three patient groups were matched for disease duration and dementia severity, as indexed by the CDR Sum of Boxes score (all *p* values >.1). As expected, bvFTD patients were significantly more impaired in comparison to both AD subgroups on a specific measure of FTD symptom severity (FRS Rasch score; SEF-AD vs. bvFTD, *p*<.001; IEF-AD vs. bvFTD, *p*<.05). On the cognitive screening test (ACE-R), all patient groups were significantly impaired in comparison to controls (all *p* values <.001) but did not differ from each other (all *p* values >.1). Analysis of the CBI-R subscores revealed significant differences across groups. Post hoc group comparisons indicated that relative to controls, SEF-AD patients showed more disturbance in memory and orientation, everyday skills, mood, stereotypic and motor behaviours and motivation (*p* values <.05). Compared to controls, IEF-AD patients had disturbance in relation to memory and orientation, everyday skills, mood and motivation (*p* values < .05). In comparison to controls, bvFTD patients showed more symptoms of behavioural disturbance across all CBI-R subscores except abnormal beliefs (*p* values <.01). Post hoc comparisons between patient groups revealed more disturbance in eating habits in bvFTD relative to SEF-AD (*p*=.031) and IEF-AD (*p*<.001), as well as more symptoms of abnormal behaviour (*p*=.003), stereotypic and motor behaviours (*p*<.001) and reduced motivation (*p*=.015) in bvFTD relative to IEF-AD. Importantly, SEF-AD and IEF-AD patients did not differ on any of the CBI-R subscores (all *p* values >.05).

Executive function

Results for the executive function tests and correlations with memory performance are detailed in Supplementary Material.

Memory

Results for the episodic memory recall raw scores (RAVLT trials A6 and A7, RCFT 3-minute recall trial) are detailed in Supplementary Information. These raw scores were averaged to yield a memory recall composite score. A main effect of group was found for the memory recall composite ($F_{3,89}$=55.022, p<.001); see Figure 1. Tukey post hoc tests revealed that controls performed significantly higher than all patient groups (all p values <.001). Importantly, no significant differences were evident among the patient groups (all p values >0.1).

VBM Group Analysis

Patterns of atrophy

Participant groups were contrasted to reveal patterns of PFC and MTL atrophy. Compared to controls, SEF-AD patients demonstrated relatively circumscribed atrophy in the right hippocampus and left inferior and middle frontal gyri (Figure 2A, Supplementary Table 3). IEF-AD patients showed atrophy relative to controls in the hippocampus bilaterally, as well as regions in the bilateral temporal and frontal poles, left inferior, middle and superior frontal gyri, left orbitofrontal cortex and left fusiform cortex (Figure 2B, Supplementary Table 3). In comparison to controls, bvFTD patients showed widespread bilateral atrophy, encompassing the hippocampus, frontal pole, orbitofrontal cortex, paracingulate cortex, subcallosal cortex, anterior cingulate cortex, medial prefrontal cortex, inferior, middle and superior frontal gyri, precentral gyrus and temporal pole (Figure 2C, Supplementary Table 3).

Comparison of the SEF-AD and bvFTD groups indicated regions of greater atrophy in the latter group, involving the frontal pole, orbitofrontal cortex, paracingulate gyrus and superior frontal gyrus bilaterally, as well as left temporal pole and subcallosal cortex (Supplementary Figure 1A, Supplementary Table 4). In comparison to the IEF-AD group, bvFTD patients showed greater atrophy in the bilateral frontal and temporal poles, orbitofrontal cortex, subcallosal cortex, paracingulate cortex and superior frontal gyri (Supplementary Figure 1B, Supplementary Table 4). No PFC or MTL regions were found to be significantly more atrophic in IEF-AD or SEF-AD compared to bvFTD (Supplementary Table 4). Direct comparison of the two AD groups revealed significantly greater atrophy in the right superior frontal gyrus and frontal pole in the IEF-AD group (Supplementary Figure 1C, Supplementary Table 4). The reverse contrast did not reveal any regions of significantly greater atrophy in SEF-AD compared to IEF-AD patients.

Covariate analysis

Memory composite scores were entered as covariates in the design matrix of the VBM analysis. For all participants combined, memory performance correlated with atrophy in the bilateral hippocampi, frontal and temporal poles, fusiform cortex, parahippocampal gyrus and orbitofrontal cortex, as well as the right medial prefrontal cortex, subcallosal cortex and superior temporal gyrus and left inferior, middle and superior frontal gyri and precentral gyrus (Supplementary Figure 2, Table 2). While memory performance in SEF-AD patients combined with controls correlated with a circumscribed region of atrophy in the right hippocampus (cluster size= 39 voxels; MNI coordinates X=28, Y=-14, Z=-18), this was below the uncorrected significance level of $p<.001$ and cluster threshold of 100 contiguous voxels (Figure 3A, Table 2). In contrast, memory performance in IEF-AD patients combined with

controls covaried with bilateral regions of atrophy in the hippocampus and PFC, including

orbitofrontal, medial prefrontal and paracingulate cortices. The left lateral frontal cortices

were also implicated, including inferior, middle and superior frontal and precentral gyri, as

well as the left temporal pole, fusiform cortex and parahippocampal gyrus (Figure 3B, Table

2). In bvFTD patients combined with controls, memory performance correlated with

bilateral regions of atrophy in the hippocampus, fusiform cortex, parahippocampal gyrus,

temporal pole, orbitofrontal cortex, subcallosal cortex, medial prefrontal cortex,

paracingulate cortex, superior frontal gyri and frontal pole (Figure 3C, Table 2).

Next, we conducted an overlap analysis to investigate common regions of atrophy that

underlie memory performance in IEF-AD and bvFTD (Figure 4, Table 3). This overlap analysis

revealed that atrophy in the right frontal pole and bilateral hippocampi correlated

significantly with memory performance in both the IEF-AD and bvFTD groups.

A partial correlation analysis further explored whether atrophy in the prefrontal cortex

could have explained the significant correlations with memory performance in IEF-AD and

bvFTD. Indeed, PFC regions still correlated significantly ($p<.001$) with the memory composite

score in IEF-AD patients, when MTL atrophy was taken into account. Similarly, in bvFTD

patients, PFC regions remained significantly correlated ($p<.05$) with memory performance

once MTL atrophy was taken into account.

Discussion

This study investigated the neuroimaging correlates of memory impairment in AD patients with or without executive dysfunction, compared to bvFTD patients, who typically show a dysexecutive cognitive profile. On cognitive testing, SEF-AD, IEF-AD and bvFTD patients showed substantial episodic memory impairments relative to age- and education-matched control participants, but did not differ from each other. Imaging analyses revealed that the pattern of prefrontal atrophy in IEF-AD patients was similar to that seen in bvFTD. Importantly, divergent neural correlates of memory performance were identified across groups. While hippocampal atrophy was associated with memory performance across all patient groups, additional prefrontal involvement was found only in IEF-AD and bvFTD. These findings shed light on important differences underlying the memory impairments in these patient groups.

Converging evidence points to an atypical, frontal distribution of neuropathology in dysexecutive AD patients [21-25]. One significant contribution of the present study was the comparison of PFC and MTL atrophy between bvFTD patients and AD subgroups. Consistent with our hypothesis, imaging results indicate that the pattern of atrophy in IEF-AD resembles that seen in bvFTD patients, with bilateral involvement of the orbitofrontal and lateral prefrontal cortices, frontal pole as well as medial temporal regions. In contrast, SEF-AD patients showed relatively circumscribed regions of PFC and MTL atrophy, involving the right hippocampus and left inferior and middle frontal gyri only. Our findings mesh well with a recent study by Woodward and colleagues [24], where 'frontal' AD patients showed greater medial and orbitofrontal cortex hypometabolism compared to other AD patients,

16

despite showing similar levels of hypometabolism in the lateral prefrontal regions. Furthermore, the widespread prefrontal atrophy seen in our IEF-AD group is consistent with previous reports of cortical thinning [25], AD-type pathology and neuronal loss [21, 22] in the frontal lobes of dysexecutive AD patients. It is important to note, however, that PFC atrophy was more extensive in bvFTD compared to IEF-AD, despite the involvement of similar regions in these two patient groups. This is consistent with the typical pattern of atrophy reported in bvFTD [50].

On a cognitive level, our findings are consistent with a number of studies that have identified significant executive deficits in a subgroup of AD patients, using specific tests of executive function [2-4, 17, 51]. In keeping with previous studies [10-12, 37], episodic memory performance was similarly impaired in both AD and bvFTD. Furthermore, it was not possible to distinguish between SEF-AD and IEF-AD solely based on episodic memory performance. While this could be due to floor effects across all AD patients, it is also possible that measures of memory recall on the RAVLT and RCFT are not sensitive enough to detect the additional impact of executive deficits observed in the IEF-AD group.

Importantly, our findings extend prior research by demonstrating that poor memory performance in SEF-AD and IEF-AD is mediated by divergent patterns of PFC and MTL atrophy. While memory impairments were related to hippocampal atrophy in both AD subgroups, this showed additional associations with prefrontal atrophy in IEF-AD patients only. Similarly, prefrontal atrophy was related to memory performance in bvFTD. Our finding of PFC involvement in memory impairments in IEF-AD and bvFTD challenges the notion that different neural processes underlie memory dysfunction in AD and bvFTD. As

such, it has often been presumed that poor memory performance in AD is due to deficits in memory consolidation, a process presumed to be mediated by the medial temporal lobes [52]. On the other hand, memory impairment in bvFTD is generally thought to be secondary to deficits in the executive aspects of memory, including planning and organisation of information, monitoring and inhibition of responses and contextual memory [53]. Hence, this dichotomous view does not take into the account the contribution of frontally-mediated executive deficits to memory dysfunction in IEF-AD. In light of the significant PFC involvement in memory performance in IEF-AD but not SEF-AD, our findings point to important differences in the neural mechanisms underlying memory impairments in these AD subgroups.

Another novel finding to emerge from this study was the identification of shared prefrontal neural correlates of memory dysfunction in IEF-AD and bvFTD. Although atrophy in several PFC subregions correlated with memory performance in IEF-AD and bvFTD separately, the right lateral frontal pole was the only subregion commonly implicated across both patient groups. While associations between frontal polar atrophy and episodic memory performance have previously been reported in AD and bvFTD [12, 15], the specific mechanism through which this prefrontal subregion contributes to memory impairments in IEF-AD and bvFTD remains, to date, underexplored. Interestingly, the frontal pole (otherwise known as the rostral prefrontal cortex or Brodmann's Area 10) appears to be involved in various higher-order cognitive functions, with further functional specializations within its subregions. As such, the lateral frontal pole has been implicated in working memory and episodic memory retrieval, whereas medial regions are involved in mentalizing [54]. Furthermore, several studies have revealed divergent patterns of functional connectivity

across different frontal polar subregions, with strong projections between the lateral frontal

pole and nodes of the executive control network, such as the dorsolateral prefrontal cortex

and supplementary motor area [55, 56]. In light of evidence from neuroimaging studies,

which implicate the dorsolateral prefrontal cortex in executive aspects of episodic memory

recall [57, 58], it seems likely that the right lateral frontal polar involvement in memory

performance in IEF-AD and bvFTD patients reflects the impact of their executive deficits on

memory impairment, which needs further investigation in the future.

Our imaging analyses also revealed varying degrees of MTL involvement in memory

performance across the three patient groups. In the SEF-AD group, hippocampal atrophy

correlated with memory performance, but this was below the statistical threshold applied in

our analyses. This likely reflects the relatively circumscribed pattern of MTL atrophy found

in this group. Surprisingly, although MTL regions correlated with memory performance in

both IEF-AD and bvFTD, this was more extensive in bvFTD. In this context, it is important to

note that our imaging results were a priori masked for prefrontal and medial temporal

regions. Therefore, other brain regions may have contributed to the observed memory

deficits. In particular, the precuneus and posterior cingulate cortex have been shown to play

a relatively large role in memory impairment in AD [12, 59], as well as diencephalic atrophy

[60]. These regions were, however, not included in our imaging analyses and as such,

further exploration of the relative contributions of other brain regions to memory

dysfunction in these patient groups is warranted.

Given that both PFC and MTL regions correlated with memory performance in IEF-AD and

bvFTD, our findings suggest that memory impairments in these patients are not only due to

hippocampal but also frontal dysfunction. Along a similar vein, Bertoux, et al. [13] revealed two distinct profiles of episodic memory dysfunction in bvFTD, using the Free and Cued Selective Reminding Test (FCSRT). While one subgroup demonstrated impaired memory consolidation, consistent with the characteristic profile of memory impairments in AD, another subgroup showed deficits in the strategic aspects of memory recall, such that they benefited from cueing. The authors concluded that memory impairments in bvFTD may not be solely attributable to executive dysfunction. Although our memory measures did not allow this dissociation, our imaging findings, which indicate both PFC and MTL involvement, dovetail with this result. Given the overlap in executive deficits and memory impairment in IEF-AD and bvFTD, the implementation of memory measures that can disentangle these prefontally- and hippocampally-driven memory processes represents an important area of future inquiry.

Overall, our findings provide further support to the notion that memory impairments in AD and bvFTD are not solely driven by deficits in hippocampal or prefrontal memory processes, respectively. Indeed, the cooperative involvement of both PFC and MTL structures has been purported to be necessary for memory functioning in AD and bvFTD, with greater involvement of PFC regions in bvFTD [11, 37]. The current study extends existing findings by demonstrating PFC involvement in memory impairment in a subgroup of AD patients who show distinct profiles of executive dysfunction and prefrontal atrophy.

From a clinical perspective, the potential overlaps in executive and memory impairments in AD and bvFTD call into question the diagnostic value of conventional measures of executive function and memory that are commonly used in clinical settings. Our findings add to a

growing body of literature, which indicates that deficits in these areas are not specific to either disease and therefore, do not reliably distinguish between bvFTD and AD. Yet, current diagnostic criteria for bvFTD describes a predominantly dysexecutive cognitive profile, with relative sparing of episodic memory [6]. On the other hand, revised criteria for AD allow for atypical presentations with prominent executive dysfunction [1], yet this so-called 'frontal AD' can be clinically misdiagnosed as bvFTD [22, 61]. We and others [15, 62-64] have suggested that tests of social cognition may better distinguish between AD and bvFTD, as these measures target medial prefrontal cortex regions that are predominantly affected in bvFTD [28, 64]. In light of the present findings, it is unclear whether IEF-AD patients would have similar social-cognitive deficits, given that they show patterns of prefrontal atrophy in similar regions as bvFTD patients. Speculatively, it is possible that IEF-AD and bvFTD patients may be distinguishable on measures of social cognition and behavioural symptoms, although one previous study that did include these measures showed that 'frontal AD' patients could be impaired [51]. This should be addressed in future research, as improvements in diagnostic accuracy will help guide potential treatment choices in these patient groups.

A number of caveats warrant further discussion. Firstly, we did not have neuropathological confirmation for the clinical diagnoses, as the majority of our sample had not yet come to autopsy. As such, we cannot exclude the possibility that some bvFTD patients had underlying AD pathology and vice versa. Indeed, findings from several postmortem studies indicate that multiple pathologies may co-occur [65, 66]. Reassuringly, bvFTD patients showed a higher prevalence of behavioural symptoms on the CBI-R, including abnormal behaviour, stereotypic and motor behaviours, apathy and abnormal eating habits.

Furthermore, our patient sample included only those who showed clear evidence of disease progression in accordance with their diagnosis, within a minimum 12-month follow-up period. Nevertheless, our findings mesh well with a growing number of studies highlighting memory impairments in neuropathologically confirmed cases of bvFTD [8, 60], and executive dysfunction in neuropathologically confirmed cases of AD [20, 21].

Secondly, although measures of disease duration, dementia severity and behavioural disturbance were not statistically different between our two AD subgroups, IEF-AD patients tended to have longer duration and greater severity of symptoms. Additionally, given that estimated symptom onset was based on caregiver reports, the potential for overestimating disease duration may have differed for those with more dysexecutive symptoms. Taken together with our relatively small sample size, the possibility that IEF-AD patients represent a subgroup of AD patients with more advanced disease progression cannot be ruled out. Nonetheless, we and others [16, 25] have shown divergent patterns of prefrontal atrophy in AD patients presenting with or without significant executive dysfunction. Whether this represents typical neuropathological progression in more advanced stages of AD or an altogether different trajectory of degeneration in IEF-AD remains to be addressed. As such, replication of our findings in a larger patient cohort, in conjunction with longitudinal clinical and neuroimaging data, represents an important area of future enquiry.

Another limitation of this study concerns the range of executive abilities assessed by the tests included in our battery, which encompassed working memory, verbal response inhibition and cognitive flexibility. Future studies should incorporate a broader battery to include problem solving and reasoning skills. Furthermore, as age- and education-adjusted

normative data were not available for some executive measures, analyses were conducted using z-scores derived from control data. While the control and patient groups were matched in terms of age and level of education, this could potentially limit the applicability of our findings in other cohorts. In spite of these limitations however, our delineation of the AD subgroups point to important differences in the brain regions implicated in memory impairment in AD patients presenting with or without significant executive dysfunction.

Finally, although our findings suggest that both hippocampal and prefrontal mechanisms contribute to memory performance in both IEF-AD and bvFTD, our memory recall composite did not allow for distinctions to be made between these processes. More detailed investigations with measures that can tap into such aspects of memory function in these patient groups are therefore warranted. For example, the California Verbal Learning Test-Second Edition [67] yields process scores that assess executive aspects of memory, including semantic clustering, cued recall and discrimination indices for word and source recognition. Similarly, employing the Boston Qualitative Scoring System [68], which assesses planning, fragmentation, neatness, perseveration and organisation on the RCFT, could provide further insights into the relationship between the executive aspects of visual memory encoding and subsequent recall performance.

With these caveats in mind, this study provides additional evidence that a subgroup of AD patients have significant executive deficits and prefrontal atrophy in similar regions to those affected in bvFTD. Although profiles of memory dysfunction were indistinguishable in SEF-AD, IEF-AD and bvFTD, our findings reveal divergent neural correlates of memory impairment in these patient groups, with prefrontal involvement in the latter two groups

only. Taken together, considerable overlap exists between IEF-AD and bvFTD patients in terms of performance on memory and executive function tests, as well as neuroimaging measures of atrophy and neural correlates of memory dysfunction. Our findings have important clinical implications in that current measures of memory and executive function may lack sufficient sensitivity to distinguish between IEF-AD and bvFTD.

References

[1]   McKhann GM, Knopman DS, Chertkow H, Hyman BT, Jack CR, Jr., Kawas CH, Klunk WE, Koroshetz WJ, Manly JJ, Mayeux R, Mohs RC, Morris JC, Rossor MN, Scheltens P, Carrillo MC, Thies B, Weintraub S, Phelps CH (2011) The diagnosis of dementia due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dement* **7**, 263-269.

[2]   Swanberg MM, Tractenberg RE, Mohs R, Thal LJ, Cummings JL (2004) Executive dysfunction in Alzheimer disease. *Arch Neurol* **61**, 556-560.

[3]   Godefroy O, Martinaud O, Verny M, Mosca C, Lenoir H, Bretault E, Roussel M (2014) The Dysexecutive Syndrome of Alzheimer's Disease: The GREFEX Study. *J Alzheimers Dis* **42**, 1203-1208.

[4]   Binetti G, Magni E, Padovani A, Cappa SF, Bianchetti A, Trabucchi M (1996) Executive dysfunction in early Alzheimer's disease. *J Neurol Neurosurg Psychiatry* **60**, 91-93.

[5]   Zheng D, Sun H, Dong X, Liu B, Xu Y, Chen S, Song L, Zhang H, Wang X (2014) Executive dysfunction and gray matter atrophy in amnestic mild cognitive impairment. *Neurobiol Aging* **35**, 548-555.

[6]   Rascovsky K, Hodges JR, Knopman D, Mendez MF, Kramer JH, Neuhaus J, van Swieten JC, Seelaar H, Dopper EG, Onyike CU, Hillis AE, Josephs KA, Boeve BF, Kertesz A, Seeley WW, Rankin KP, Johnson JK, Gorno-Tempini ML, Rosen H, Prioleau-Latham CE, Lee A, Kipps CM, Lillo P, Piguet O, Rohrer JD, Rossor MN, Warren JD, Fox NC, Galasko D, Salmon DP, Black SE, Mesulam M, Weintraub S, Dickerson BC, Diehl-Schmid J, Pasquier F, Deramecourt V, Lebert F, Pijnenburg Y, Chow TW, Manes F, Grafman J, Cappa SF, Freedman M, Grossman M, Miller BL (2011) Sensitivity of revised diagnostic criteria for the behavioural variant of frontotemporal dementia. *Brain* **134**, 2456-2477.

[7]   Hodges JR, Davies RR, Xuereb JH, Casey B, Broe M, Bak TH, Kril JJ, Halliday GM (2004) Clinicopathological correlates in frontotemporal dementia. *Ann Neurol* **56**, 399-406.

[8]   Graham A, Davies R, Xuereb J, Halliday G, Kril J, Creasey H, Graham K, Hodges J (2005) Pathologically proven frontotemporal dementia presenting with severe amnesia. *Brain* **128**, 597-605.

[9]   Hornberger M, Piguet O (2012) Episodic memory in frontotemporal dementia: a critical review. *Brain* **135**, 678-692.

[10]   Hornberger M, Piguet O, Graham AJ, Nestor PJ, Hodges JR (2010) How preserved is episodic memory in behavioral variant frontotemporal dementia? *Neurology* **74**, 472-479.

[11]   Frisch S, Dukart J, Vogt B, Horstmann A, Becker G, Villringer A, Barthel H, Sabri O, Muller K, Schroeter ML (2013) Dissociating memory networks in early Alzheimer's disease and frontotemporal lobar degeneration - a combined study of hypometabolism and atrophy. *PLoS One* **8**, e55251.

[12]   Irish M, Piguet O, Hodges JR, Hornberger M (2014) Common and unique gray matter correlates of episodic memory dysfunction in frontotemporal dementia and Alzheimer's disease. *Hum Brain Mapp* **35**, 1422-1435.

[13]   Bertoux M, de Souza LC, Corlier F, Lamari F, Bottlaender M, Dubois B, Sarazin M (2014) Two distinct amnesic profiles in behavioral variant frontotemporal dementia. *Biol Psychiatry* **75**, 582-588.

[14]   Gregory CA, Orrell M, Sahakian B, Hodges JR (1997) Can frontotemporal dementia and Alzheimer's disease be differentiated using a brief battery of tests? *Int J Geriatr Psychiatry* **12**, 375-383.

[15]   Wong S, Flanagan E, Savage G, Hodges JR, Hornberger M (2014) Contrasting prefrontal cortex contributions to episodic memory dysfunction in behavioural variant frontotemporal dementia and Alzheimer's disease. *PLoS One* **9**, e87778.

[16]   Ossenkoppele R, Pijnenburg YA, Perry DC, Cohn-Sheehy BI, Scheltens NM, Vogel JW, Kramer JH, van der Vlies AE, Joie RL, Rosen HJ, van der Flier WM, Grinberg LT, Rozemuller AJ, Huang EJ, van Berckel BN, Miller BL, Barkhof F, Jagust WJ, Scheltens P, Seeley WW, Rabinovici GD (2015) The behavioural/dysexecutive variant of Alzheimer's disease: clinical, neuroimaging and pathological features. *Brain* **138**, 2732-2749.

[17]   Gleichgerrcht E, Torralva T, Martinez D, Roca M, Manes F (2011) Impact of executive dysfunction on verbal memory performance in patients with Alzheimer's disease. *J Alzheimers Dis* **23**, 79-85.

[18]   Woodward M, Brodaty H, Boundy K, Ames D, Blanch G, Balshaw R, PRIME Study Group (2010) Does executive impairment define a frontal variant of Alzheimer's disease? *Int Psychogeriatr* **22**, 1280-1290.

[19]   Woodward M, Jacova C, Black SE, Kertesz A, Mackenzie IR, Feldman H, ACCORD Investigator Group (2010) Differentiating the frontal variant of Alzheimer's disease. *Int J Geriatr Psychiatry* **25**, 732-738.

[20]   Mez J, Cosentino S, Brickman AM, Huey ED, Manly JJ, Mayeux R (2013) Faster cognitive and functional decline in Dysexecutive versus amnestic Alzheimer's subgroups: a longitudinal analysis of the National Alzheimer's Coordinating Center (NACC) database. *PLoS One* **8**, e65246.

[21]   Johnson JK, Head E, Kim R, Starr A, Cotman CW (1999) Clinical and pathological evidence for a frontal variant of Alzheimer disease. *Arch Neurol* **56**, 1233-1239.

[22]   Blennerhassett R, Lillo P, Halliday GM, Hodges JR, Kril JJ (2014) Distribution of pathology in frontal variant Alzheimer's disease. *J Alzheimers Dis* **39**, 63-70.

[23]   Fernandez-Calvo B, Ramos F, de Lucena V (2013) Frontal variant of Alzheimer's disease and typical Alzheimer's disease: A comparative study. *anales de psicologia* **29**, 293-300.

[24]   Woodward MC, Rowe CC, Jones G, Villemagne VL, Varos TA (2015) Differentiating the frontal presentation of Alzheimer's disease with FDG-PET. *J Alzheimers Dis* **44**, 233-242.

[25]   Dickerson BC, Wolk DA, Alzheimer's Disease Neuroimaging Initiative (2011) Dysexecutive versus amnesic phenotypes of very mild Alzheimer's disease are associated with distinct clinical, genetic and cortical thinning characteristics. *J Neurol Neurosurg Psychiatry* **82**, 45-51.

[26]   Pa J, Boxer A, Chao LL, Gazzaley A, Freeman K, Kramer J, Miller BL, Weiner MW, Neuhaus J, Johnson JK (2009) Clinical-neuroimaging characteristics of dysexecutive mild cognitive impairment. *Ann Neurol* **65**, 414-423.

[27]   Chang YL, Jacobson MW, Fennema-Notestine C, Hagler DJ, Jr., Jennings RG, Dale AM, McEvoy LK, Alzheimer's Disease Neuroimaging Initiative (2010) Level of executive function influences verbal memory in amnestic mild cognitive impairment and predicts prefrontal and posterior cingulate thickness. *Cereb Cortex* **20**, 1305-1313.

[28]   Seeley WW, Crawford R, Rascovsky K, Kramer JH, Weiner M, Miller BL, Gorno-Tempini ML (2008) Frontal paralimbic network atrophy in very mild behavioral variant frontotemporal dementia. *Arch Neurol* **65**, 249-255.

[29]   Mioshi E, Dawson K, Mitchell J, Arnold R, Hodges JR (2006) The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Int J Geriatr Psychiatry* **21**, 1078-1085.

[30]   Mioshi E, Hsieh S, Savage S, Hornberger M, Hodges JR (2010) Clinical staging and disease progression in frontotemporal dementia. *Neurology* **74**, 1591-1597.

[31]   Morris JC (1997) Clinical dementia rating: a reliable and valid diagnostic and staging measure for dementia of the Alzheimer type. *Int Psychogeriatr* **9 Suppl 1**, 173-176; discussion 177-178.

[32]   Wedderburn C, Wear H, Brown J, Mason SJ, Barker RA, Hodges J, Williams-Gray C (2008) The utility of the Cambridge Behavioural Inventory in neurodegenerative disease. *J Neurol Neurosurg Psychiatry* **79**, 500-503.

[33]   Wechsler D (1997) *Wechsler Adult Intelligence Scale® – Third Edition (WAIS®-III)*, The Psychological Corporation, San Antonio, TX.

[34]   Benton A, Hamsher K, Sivan A (1994) *Multilingual Aphasia Examination, 3rd ed.*, Psychological Corporation, San Antonio, TX.

[35]   Reitan R (1958) Validity of the Trail Making Test as an indicator of organic brain damage. *Percept Motor Skills* **8**, 271-276.

[36]   Burgess P, Shallice T (1997) *The Hayling and Brixton Tests*, Thames Valley Test Company, Thurston Suffolk.

[37]   Pennington C, Hodges JR, Hornberger M (2011) Neural correlates of episodic memory in behavioral variant frontotemporal dementia. *J Alzheimers Dis* **24**, 261-268.

[38]   Schmidt M (1996) *Rey Auditory and Verbal Learning Test: A Handbook*, Western Psychological Services, Los Angeles.

[39]   Meyers J, Meyers K (1995) *The Meyers Scoring System for the Rey Complex Figure and the Recognition Trial: Professional Manual*, Psychological Assessment Resources, Odessa, FL.

[40]   Gleichgerrcht E, Chade A, Torralva T, Roca M, Manes F (2011) Comparing the Neuropsychiatric Profile of Patients with Alzheimer Disease Who Present Spared versus Impaired Executive Functioning. *Curr Gerontol Geriatr Res* **2011**, 514059.

[41]   Dunn OJ (1964) Multiple Comparisons Using Rank Sums. *Technometrics* **6**, 241-&.

[42]   Ashburner J, Friston KJ (2000) Voxel-based morphometry--the methods. *Neuroimage* **11**, 805-821.

[43]   Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* **14**, 21-36.

[44]   Smith SM, Jenkinson M, Woolrich MW, Beckmann CF, Behrens TE, Johansen-Berg H, Bannister PR, De Luca M, Drobnjak I, Flitney DE, Niazy RK, Saunders J, Vickers J, Zhang Y, De Stefano N, Brady JM, Matthews PM (2004) Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* **23 Suppl 1**, S208-219.

[45]   Zhang Y, Brady M, Smith S (2001) Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE Trans Med Imaging* **20**, 45-57.

[46]   Andersson JLR, Jenkinson M, Smith S, Non-linear optimisation. FMRIB technical report TR07JA2, Accessed

[47] Andersson JLR, Jenkinson M, Smith S, Non-linear registration, aka Spatial normalisation. FMRIB technical report TR07JA2, Accessed

[48] Rueckert D, Sonoda LI, Hayes C, Hill DL, Leach MO, Hawkes DJ (1999) Nonrigid registration using free-form deformations: application to breast MR images. *IEEE Trans Med Imaging* **18**, 712-721.

[49] Nichols TE, Holmes AP (2002) Nonparametric permutation tests for functional neuroimaging: a primer with examples. *Hum Brain Mapp* **15**, 1-25.

[50] Kipps CM, Hodges JR, Fryer TD, Nestor PJ (2009) Combined magnetic resonance imaging and positron emission tomography brain imaging in behavioural variant frontotemporal degeneration: refining the clinical phenotype. *Brain* **132**, 2566-2578.

[51] de Souza LC, Bertoux M, Funkiewiez A, Samri D, Azuar C, Habert MO, Kas A, Lamari F, Sarazin M, Dubois B (2013) Frontal presentation of Alzheimer's disease: A series of patients with biological evidence by CSF biomarkers. *Dement Neuropsychol* **7**, 66-74.

[52] Alvarez P, Squire LR (1994) Memory consolidation and the medial temporal lobe: a simple network model. *Proc Natl Acad Sci U S A* **91**, 7041-7045.

[53] Kopelman MD (2002) Disorders of memory. *Brain* **125**, 2152-2190.

[54] Gilbert SJ, Spengler S, Simons JS, Steele JD, Lawrie SM, Frith CD, Burgess PW (2006) Functional specialization within rostral prefrontal cortex (area 10): a meta-analysis. *J Cogn Neurosci* **18**, 932-948.

[55] Liu H, Qin W, Li W, Fan L, Wang J, Jiang T, Yu C (2013) Connectivity-based parcellation of the human frontal pole with diffusion tensor imaging. *J Neurosci* **33**, 6782-6790.

[56] Moayedi M, Salomons TV, Dunlop KA, Downar J, Davis KD (2014) Connectivity-based parcellation of the human frontal polar cortex. *Brain Struct Funct*.

[57] Long NM, Oztekin I, Badre D (2010) Separable prefrontal cortex contributions to free recall. *J Neurosci* **30**, 10967-10976.

[58] Savage CR, Deckersbach T, Heckers S, Wagner AD, Schacter DL, Alpert NM, Fischman AJ, Rauch SL (2001) Prefrontal regions supporting spontaneous and directed application of verbal learning strategies: evidence from PET. *Brain* **124**, 219-231.

[59] Nestor PJ, Fryer TD, Hodges JR (2006) Declarative memory impairments in Alzheimer's disease and semantic dementia. *Neuroimage* **30**, 1010-1020.

[60] Hornberger M, Wong S, Tan R, Irish M, Piguet O, Kril J, Hodges JR, Halliday G (2012) In vivo and post-mortem memory circuit integrity in frontotemporal dementia and Alzheimer's disease. *Brain* **135**, 3015-3025.

[61] Larner AJ (2006) "Frontal variant Alzheimer's disease": a reappraisal. *Clin Neurol Neurosurg* **108**, 705-708.

[62] Possin KL, Feigenbaum D, Rankin KP, Smith GE, Boxer AL, Wood K, Hanna SM, Miller BL, Kramer JH (2013) Dissociable executive functions in behavioral variant frontotemporal and Alzheimer dementias. *Neurology* **80**, 2180-2185.

[63] Torralva T, Roca M, Gleichgerrcht E, Bekinschtein T, Manes F (2009) A neuropsychological battery to detect specific executive and social cognitive impairments in early frontotemporal dementia. *Brain* **132**, 1299-1309.

[64] Bertoux M, Funkiewiez A, O'Callaghan C, Dubois B, Hornberger M (2013) Sensitivity and specificity of ventromedial prefrontal cortex tests in behavioral variant frontotemporal dementia. *Alzheimers Dement* **9**, S84-94.

[65]   Woodward M, Mackenzie IRA, Hsiung G-YR, Jacova C, Feldman H (2010) Multiple brain pathologies in dementia are common. *European Geriatric Medicine* **1**, 259-265.

[66]   Forman MS, Farmer J, Johnson JK, Clark CM, Arnold SE, Coslett HB, Chatterjee A, Hurtig HI, Karlawish JH, Rosen HJ, Van Deerlin V, Lee VM, Miller BL, Trojanowski JQ, Grossman M (2006) Frontotemporal dementia: clinicopathological correlations. *Ann Neurol* **59**, 952-962.

[67]   Delis DC, Kramer JH, Kaplan E, Ober BA (2000) *California Verbal Learning Test - Second Edition, Adult Version*, The Psychological Corporation, San Antonio, TX.

[68]   Somerville J, Tremont G, Stern RA (2000) The Boston Qualitative Scoring System as a measure of executive functioning in Rey-Osterrieth Complex Figure performance. *J Clin Exp Neuropsychol* **22**, 613-621.

Table 1. Demographic characteristics across participant groups[a]

	Control	SEF-AD	IEF-AD	bvFTD	F	Post hoc
Age (years)	65.58 (5.53)	65.17 (7.87)	63.91 (7.87)	60.95 (6.24)	n.s.	
Gender (M:F)	19:19	6:6	13:10	17:5	n.s.	
Education (years)	12.5 (2.39)	12.25 (3.79)	12.5 (3.25)	11.83 (3.18)	n.s.	
Disease duration (years)	-	3.13 (1.19)	3.41 (2.10)	3.57 (2.14)	n.s.	
FRS Rasch score	-	1.74 (0.94)	0.78 (1.69)	-0.36 (0.98)	***	SEF-AD, IEF-AD > bvFTD
CDR sum of boxes score [18]	0.42 (0.53)	3.55 (1.77)	3.93 (2.13)	5.60 (2.60)	***	SEF-AD, IEF-AD, bvFTD > Controls
ACE-R total [100]	95.21 (3.48)	80.92 (7.25)	72.78 (7.62)	76.32 (11.75)	***	SEF-AD, IEF-AD, bvFTD > Controls
CBI-R subscores [100]						
Memory and orientation	5.41 (6.59)	47.73 (14.73)	45.92 (25.22)	42.69 (18.27)	***	SEF-AD, IEF-AD, bvFTD > Controls
Everyday skills	0.42 (1.40)	15.00 (17.32)	28.64 (25.36)	29.52 (22.80)	***	SEF-AD, IEF-AD, bvFTD > Controls
Self-care	0	2.27 (5.06)	4.62 (9.83)	8.33 (15.22)	**	bvFTD > Controls
Abnormal behaviour	3.13 (7.48)	11.74 (10.34)	9.60 (10.77)	36.59 (23.72)	***	bvFTD > Controls, IEF-AD
Mood	1.73 (4.12)	17.61 (17.41)	17.39 (18.84)	26.19 (22.67)	***	SEF-AD, IEF-AD, bvFTD > Controls
Beliefs	0	2.27 (3.89)	3.08 (12.19)	3.97 (11.96)	*	n.s.

Eating habits	3.30 (7.97)	13.64 (18.71)	9.24 (13.96)	38.39 (25.02)	***	bvFTD > SEF-AD, IEF-AD, Controls
Sleep	13.19 (16.08)	22.73 (18.39)	29.89 (29.61)	39.29 (32.66)	*	bvFTD > Controls
Stereotypic/motor behaviours	6.60 (14.48)	24.43 (21.55)	13.59 (19.28)	53.57 (28.82)	***	SEF-AD > Controls; bvFTD > IEF-AD, Controls
Motivation	1.81 (5.99)	25.91 (25.28)	18.80 (17.74)	62.38 (35.52)	***	SEF-AD, IEF-AD, bvFTD > Controls; bvFTD > IEF-AD

[a] Standard deviations in parentheses, maximum score for tests shown in brackets.

Frontotemporal Dementia Rating Scale (FRS); Clinical Dementia Rating Scale (CDR); Addenbrooke's Cognitive Examination-Revised (ACE-R);

Cambridge Behavioural Inventory-Revised (CBI-R).

*p<.05, **p<.01, ***p<.001, n.s. = non-significant

Table 2. Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with memory composite scores

Regions	Hemisphere (L/R/B)	MNI Coordinates			Number of voxels
		X	Y	Z	
All groups					
Temporal pole, orbitofrontal cortex, inferior frontal gyrus, middle frontal gyrus, frontal pole, fusiform cortex (anterior), parahippocampal gyrus (anterior and posterior), hippocampus	L	-40	4	-46	3075
Medial prefrontal cortex, frontal pole	R	2	46	-26	1323
Fusiform cortex (posterior), parahippocampal gyrus (anterior and posterior), hippocampus	R	40	-22	-36	1194
Orbitofrontal cortex, subcallosal cortex, medial prefrontal cortex	R	12	30	-18	300
Superior frontal gyrus, precentral gyrus	L	-20	-16	54	192
Superior temporal gyrus (anterior), temporal pole,	R	62	6	-12	128
SEF-AD and controls					
None above threshold					

IEF-AD and controls

Region	Side	X	Y	Z	Voxels
Frontal pole	R	28	52	-8	760
Orbitofrontal cortex, medial prefrontal cortex, paracingulate gyrus, frontal pole	B	8	32	-28	646
Orbitofrontal cortex, frontal pole, inferior frontal gyrus	L	-26	18	-10	465
Superior frontal gyrus, precentral gyrus	L	-20	-16	56	296
Hippocampus	L	-22	-16	-22	258
Temporal pole	L	-56	4	-14	251
Hippocampus	R	28	-14	-24	186
Fusiform cortex (anterior and posterior), parahippocampal gyrus (anterior)	L	-30	-12	-40	152
Middle frontal gyrus, inferior frontal gyrus	L	-40	12	30	109

bvFTD and controls

Region	Side	X	Y	Z	Voxels
Fusiform cortex (anterior and posterior), parahippocampal gyrus (anterior and posterior), hippocampus, temporal pole, orbitofrontal cortex, subcallosal cortex, medial prefrontal cortex, frontal pole	B	-26	-8	-48	6184
Frontal pole, paracingulate gyrus, superior frontal gyrus	B	12	72	-8	1863
Orbitofrontal cortex	R	26	20	-10	163

Superior frontal gyrus	L	-4	18	56	115

All results uncorrected at $p<.001$; only clusters with at least 100 contiguous voxels included. All clusters reported $t>3.87$. MNI = Montreal

Neurological Institute

Table 3. Voxel-based morphometry results showing common regions of significant grey matter intensity decrease that correlate with memory performance, which overlap in impaired executive function Alzheimer's disease (IEF-AD) and behavioura- variant frontotemporal dementia (bvFTD) patients

| | | MNI | | | |
| | | Coordinates | | | Number |
Regions	Hemisphere (L/R/B)	X	Y	Z	of voxels
Frontal pole	R	24	62	6	202
Hippocampus	R	28	-14	-24	159
Hippocampus	L	-22	-16	-20	151

All results uncorrected at p<.001; only clusters with at least 100 contiguous voxels included. All clusters reported t>4.53. MNI = Montreal Neurological Institute.

Figure captions

Figure 1. Mean memory recall performance (memory composite score) in controls, spared executive function Alzheimer's disease (SEF-AD), impaired executive function Alzheimer's disease (IEF-AD) and behavioural-variant frontotemporal dementia (bvFTD) participants. Error bars represent standard error of the mean. ***p<.001.

Figure 2. VBM analyses showing brain regions of decreased grey matter intensity in (A) SEF-AD patients in comparison with controls (B) IEF-AD patients in comparison with controls and (C) bvFTD patients in comparison with controls. Coloured voxels show regions that were significant in the analyses with p<.001, uncorrected for all contrasts, with a cluster threshold of 100 contiguous voxels. Clusters are overlaid on the MNI standard brain.

Figure 3. VBM analyses showing brain regions in which grey matter intensity correlates significantly with memory recall performance in (A) SEF-AD compared with controls, (B) IEF-AD compared with controls and (C) bvFTD compared with controls. Coloured voxels show regions that were significant in the analysis with p<.001 uncorrected, with a cluster threshold of 100 contiguous voxels in (B) and (C). Clusters are overlaid on the MNI standard brain.

Figure 4. VBM analyses showing brain regions in which grey matter intensity correlates significantly with memory recall performance in both IEF-AD and bvFTD. Coloured voxels show regions that were significant in the analysis with p<.001 uncorrected, with a cluster threshold of 100 contiguous voxels. Clusters are overlaid on the MNI standard brain.