The prefrontal cortex and episodic memory in dementia syndromes

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Abstract

Episodic memory impairment is commonly reported in neurodegenerative syndromes such as Alzheimer's disease (AD) and behavioural-variant frontotemporal dementia (bvFTD). These deficits have been attributed predominantly to medial temporal lobe atrophy and poor encoding/retrieval in AD, as opposed to prefrontal cortex (PFC) atrophy and impaired strategic retrieval processes in bvFTD. Evidence suggests, however, that the PFC contributes to episodic memory impairment across both patient groups, although it is unclear whether both lateral and medial subregions of the PFC are involved. This thesis aims to clarify the PFC contributions to episodic memory in AD and bvFTD by comparing performance on both established and novel measures of episodic memory and patterns of PFC atrophy using voxel based morphometry.

In a study comparing dysexecutive AD and bvFTD, the two patient groups showed significant overlap on measures of PFC atrophy, performance on standardised neuropsychological episodic memory tests, and correlations between PFC atrophy and memory performance. A second study contrasted the lateral and medial PFC contributions to episodic memory in AD and bvFTD, revealing that performance on standardised neuropsychological episodic memory tests correlated with lateral PFC atrophy across both groups, but correlated with medial PFC atrophy in bvFTD only. The next three studies employed novel experimental tasks to determine the role of the medial PFC in enhancing memory for 1) self-relevant, 2) socially relevant and 3) reward-related information. Collectively, these three studies revealed that value-related memory processes, which are mediated by the medial PFC, are disproportionately disrupted in bvFTD.

The main findings of the thesis are that the impact of lateral PFC dysfunction on episodic memory is not specific to bvFTD, and that greater emphasis is needed to try to understand the value-related processes through which the medial PFC augments episodic memory encoding and retrieval. These findings stand to improve differential diagnosis of AD and bvFTD, and improve understanding of the role of the PFC in episodic memory.

Certification by candidate

I hereby declare that the work included in this thesis has not been submitted for a higher degree to any other university or institution. All the work was carried out during my PhD candidature under the supervision of Prof Greg Savage (primary supervisor), Prof Michael Hornberger (adjunct supervisor) and Prof Olivier Piguet (adjunct supervisor). The studies reported in this thesis were carried out at the Frontier Frontotemporal Dementia Research Clinic, Neuroscience Research Australia (NeuRA). Information included in the projects was collected through direct participant contact and written informed consent was obtained from all the participants. The research presented in this thesis was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethics Committee of the South Eastern Sydney Local Health District, the University of New South Wales and Macquarie University (reference number 5201300764).

The manuscripts presented in this thesis have either been published in peer-reviewed journals or are currently under review. The inclusion of coauthors reflects that the work arose from active collaboration between researchers in team-based research. I declare that for all the manuscripts, my contribution to the work involved formulation of experimental design, data collection, data and neuroimaging analyses, interpretation of results, and writing of the manuscripts. Collection of data from a standardised neuropsychological test battery, which featured prominently in Chapters 2 and 3, and provided background information in analyses for Chapters 4–6, was carried out by research assistants and clinical neuropsychologists at Frontier.

The manuscripts are listed by their associated thesis chapters:

Chapter 1

Wong, S., Bertoux, M., Savage, G., Hodges, J. R., Piguet, O., & Hornberger, M. (2016). Comparison of prefrontal atrophy and episodic memory performance in dysexecutive Alzheimer's disease and behavioral-variant frontotemporal dementia. Journal of Alzheimer's Disease, 51(3), 889–903. http://doi.org/10.3233/JAD-151016

Chapter 2

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Chapter 3

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Chapter 4

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Chapter 5

Wong, S., Irish, M., Savage, G., Hodges, J.R., Piguet, O., & Hornberger, M. Strategic value-directed learning and memory in Alzheimer's disease and behavioural-variant frontotemporal dementia. (In submission).

For each publication listed above, I certify that this publication was a direct result of my research towards this PhD, and that reproduction in this thesis does not breach copyright regulations.

Stephanie Wong (student number: 42365643) ___/___/___

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Last but not least, an enormous thank you goes out to my friends and family, who have supported me through what seemed like an endless tertiary education. And to James Kane, whose unwavering patience and care helped me overcome setbacks and stay focused, words cannot describe how grateful I am for everything.

List of abbreviations

Aβ	Amyloid-beta
ACC	Anterior cingulate cortex
ACE-III	Addenbrooke's cognitive examination, 3rd edition
AD	Alzheimer's disease
bvFTD	Behavioural-variant frontotemporal dementia
CBI	Cambridge behavioural inventory
CDR	Clinical dementia rating scale
CDR SoB	Clinical dementia rating scale sum of boxes score
COWAT	Controlled oral word association test
CSF	Cerebrospinal fluid
CSIM	Conditional source identification measure
dlPFC	Dorsolateral prefrontal cortex
dmPFC	Dorsomedial prefrontal cortex
DSB	Digit span backward
DSF	Digit span forward
FDG-PET	Fluorodeoxyglucose positron emission tomography
FRS	Frontotemporal dementia rating scale
FUS	RNA-binding protein fused in sarcoma
IGT	Iowa gambling task
MCI	Mild cognitive impairment
MPFC	Medial prefrontal cortex
MRI	Magnetic resonance imaging
MTL	Medial temporal lobe

OFC	Orbitofrontal cortex
PET	Positron emission tomography
PiB	Pittsburgh compound-B
PFC	Prefrontal cortex
RAVLT	Rey Auditory Verbal Learning Test
RCFT	Rey Complex Figure Test
SI	Selectivity index
SIM	Source identification measure
SRE	Self-reference effect
SVS	Social vulnerability scale
TASIT	The Awareness of Social Inference Test
TDP-43	TAR-DNA-binding protein 43
TMT	Trail Making Test
VDM	Value-directed memory
VDR	Value-directed remembering
vlPFC	Ventrolateral prefrontal cortex
vmPFC	Ventromedial prefrontal cortex
VBM	Voxel based morphometry

Chapter 1
Introduction

Every day, we encounter enormous amounts of information, of which we remember only a small portion. The question of how the brain stores, maintains and retrieves such episodic memories continues to intrigue neuroscientists. Much of our current understanding of the neural substrates of episodic memory stems from studying individuals who have memory impairment due to brain damage. The most notable of these patients is undoubtedly HM, who underwent bilateral medial temporal lobectomy for treatment of intractable epilepsy. An unforeseen consequence of bilateral surgery was HM's subsequent inability to retain new episodic memories beyond a few minutes; this profound anterograde amnesia endured throughout his life (Corkin, 2002; Scoville & Milner, 1957). It is now widely accepted that the medial temporal lobe (MTL), and particularly the hippocampus, plays a central role in episodic memory (Squire & Zola-Morgan, 1991). Nonetheless, episodic memory impairment can also result from damage to other brain regions. For example, evidence from studies of frontal lobe lesions in animals (Konorski, 1972) and humans (Milner, 1982) indicates that damage to this region impairs the ability to learn and remember new associations between stimuli. Until recently, however, the role of the prefrontal cortex (PFC) in episodic memory has remained relatively underexplored in comparison to the MTL (Blumenfeld & Ranganath, 2007; Shimamura, 1995; Simons & Spiers, 2003).

Unlike MTL damage, focal damage to the PFC does not typically result in a severe amnestic syndrome. Instead, PFC damage affects distinct control processes that enhance the initial laying down of memory 'episodes' or traces and the subsequent retrieval of certain aspects of items or events (Blumenfeld & Ranganath, 2007). As a result, episodic memories may be poorly formed and inaccurately retrieved. Episodic memory deficits nevertheless tend to be overlooked relative to more obvious symptoms of PFC damage, such as executive dysfunction, disinhibition and apathy (Simons & Spiers, 2003). Indeed, patients with behavioural-variant frontotemporal dementia (bvFTD), which primarily affects the frontal lobe, have only recently been acknowledged as showing episodic memory deficits similar in severity to Alzheimer's disease (AD) patients, for whom episodic memory impairments are a hallmark clinical feature. The contributions of PFC damage to episodic memory dysfunction in both these neurodegenerative conditions is poorly understood. Greater understanding of these brain-behaviour relationships is crucial in order to improve diagnostic accuracy and inform the potential development of targeted, symptom-based interventions for these conditions.

This thesis investigates deficits in memory processes that are supported by the PFC in AD and bvFTD. In particular, focus is placed on identifying similarities and differences across these neurodegenerative patient groups, in terms of the severity and regional distribution of PFC atrophy, and how these impact on episodic memory processes. In doing so, the thesis employs both established and novel memory measures, in conjunction with voxel-based morphometric analysis of structural magnetic resonance imaging (MRI) brain scans to assess regional patterns of grey matter loss.

This chapter provides an overview of the PFC and its role in episodic memory. Clinical and pathological features of the two neurodegenerative conditions are then outlined, focusing on

symptoms of PFC dysfunction and the impact of PFC damage on episodic memory. This is followed by an overview of the thesis aims and structure.

1.1. The prefrontal cortex and its relationship to cognition and behaviour

The PFC forms the largest and most anterior portion of the frontal lobes, encompassing all frontal cortices except the precentral and premotor cortices. It is extensively interconnected with a vast number of sensory, motor, limbic, basal ganglia, brainstem and cerebellar regions (Fuster, 2015). Through these reciprocal pathways, the PFC functions as a convergence zone where information from sensory, arousal, memory, affective and motivational systems is integrated, evaluated and acted upon (Stuss & Knight, 2002). As such, the PFC plays a central role in complex cognition and behaviour, serving critical adaptive functions for human survival. Indeed, in evolutionary terms, the PFC is the most recently developed region of the brain (Passingham & Wise, 2012; Semendeferi et al., 2002; Sherwood, Subiaul & Zawidzki, 2008). In humans, the PFC does not reach full maturation until the third decade of life, consistent with the trajectory of development in higher order cognitive functions (Fuster, 2015; Sowell et al., 1999). Furthermore, the PFC is one of the first brain regions to be susceptible to age-related degeneration, and is particularly vulnerable to neuropathological changes in dementia (Fuster, 2015; Jernigan et al., 2001).

Boundaries of PFC subdivisions may be delineated according to cytoarchitecture, connectivity or functional activity in neuroimaging studies in healthy participants. However, a more clinically relevant approach is to subdivide the PFC based on clusters of cognitive and behavioural symptoms that arise from separable lesion sites (Fuster, 2015; Lezak, Howieson, Bigler, & Tranel, 2012). By this definition, the PFC is broadly subdivided into the dorsolateral, ventromedial and dorsomedial PFC, as illustrated in Figure 1.1.

1.1.1. Dorsolateral prefrontal cortex

The dorsolateral prefrontal cortex (dlPFC) encompasses Brodmann areas 8, 9, 46 and 10. Patients with dlPFC lesions show deficits in working memory (Barbey, Koenigs, & Grafman, 2013), attentional set-shifting (Yochim, Baldo, Nelson, & Delis, 2007), abstract reasoning (Kroger et al., 2002) and planning/organisation (Colvin, Dunbar, & Grafman, 2001). Damage to the dlPFC is also linked with poor performance on tasks assessing verbal fluency (Stuss et al., 1998) and verbal strategy generation (Robinson et al., 2015). As such, damage to the dlPFC is broadly associated with impaired performance on the majority of neuropsychological tests of executive function that are commonly used in the clinic. Furthemore, it should be noted that lesions to the region immediately ventral to the dlPFC—the ventrolateral PFC (vlPFC)—often extend to include regions of the dlPFC or orbitofrontal cortex (Szczepanski &Knight, 2014). While damage to the vlPFC has been associated with deficits in spatial attention (Stone, Reynolds & Leuthardt, 2011) and control of motor responses (Aron et al., 2003), the specificity of these impairments to vlPFC damage requires further confirmation.

1.1.2. Ventromedial prefrontal cortex

The ventromedial prefrontal cortex (vmPFC) includes the medial part of the orbitofrontal cortex (OFC) and the ventral part of the medial PFC, encompassing Brodmann areas 11, 12, 25, and 32 and the medial portions of 9 and 10. The vmPFC is involved in inhibitory control, social behaviour and value-based decision-making. Lesions to the vmPFC have been linked with symptoms of disinhibition and impulsivity (Berlin, Rolls, & Kischka, 2004; Eslinger, 1999), socially inappropriate behaviour and impaired moral judgment (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999; Barrash et al., 2011). Patients with vmPFC lesions also show disturbance in decision-making, which appears to be guided by immediate rewards rather than future consequences (Bechara, Tranel, & Damasio, 2000). Converging evidence

suggests that this may be driven by broad impairments in reward-related processes, including reduced sensitivity to reward value (Fellows, 2011) and changes in reward value (Fellows & Farah, 2005; Hornak et al., 2004), as well as deficits in representing the emotional value of rewards (Bechara, 2004).

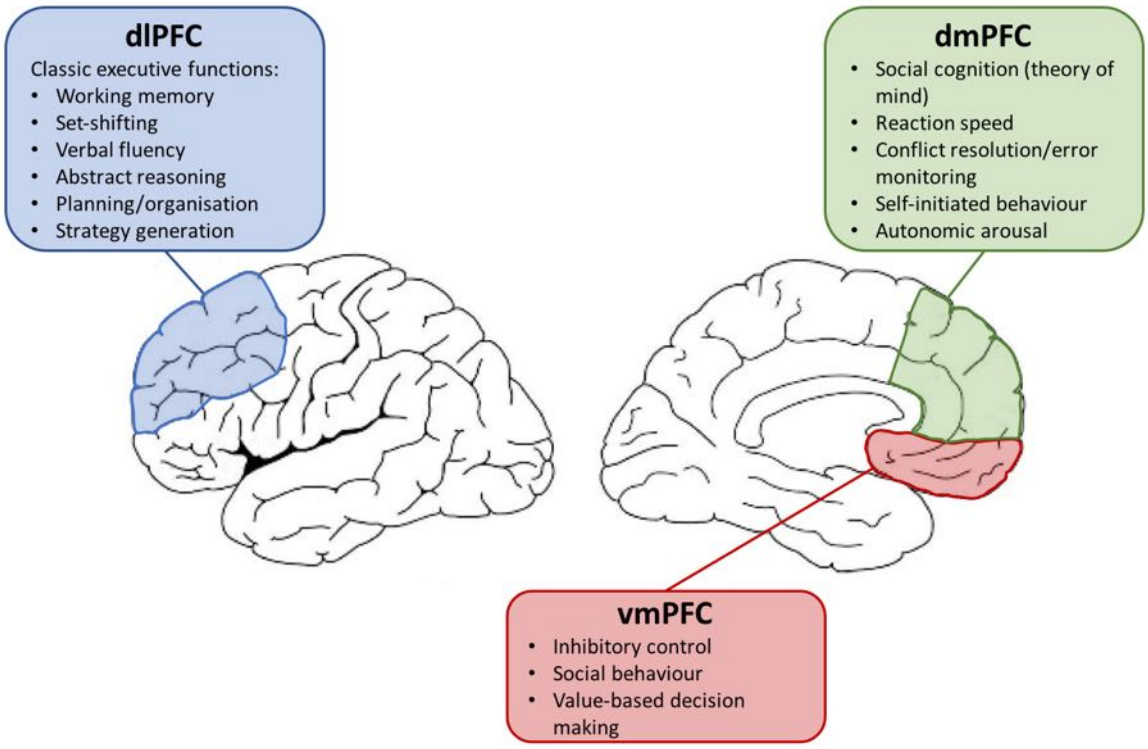

Figure 1.1. Approximate anatomical locations of the major subdivisions of the PFC and cognitive/behavioural symptoms associated with lesions to each subdivision.

1.1.3. Dorsomedial prefrontal cortex

The dorsomedial PFC (dmPFC) comprises prefrontal cortical areas on the medial surface of the brain that lie superior to the vmPFC, including the anterior cingulate cortex (ACC). This subdivision roughly corresponds to Brodmann areas 8, 9, 10, 24 and 32. However, it is important to note that there is no clear cytoarchitectural boundary between the dmPFC and

vmPFC. The dmPFC is broadly implicated in social cognition, where impairments in *Theory of Mind* have been reported in patients with bilateral ACC lesions (Baird et al., 2006; Stone, Baron-Cohen, Calder, Keane, & Young, 2003), and are associated with abnormal dmPFC activity in autism (Mundy, 2003). Lesions to the dmPFC, and particularly those involving the ACC, are also associated with slowed reaction times (Stuss et al., 2005) and deficits in cognitive control processes, such as conflict resolution and error monitoring (di Pellegrino, Ciaramelli, & Làdavas, 2007; Stemmer, Segalowitz, Witzke, & Schönle, 2004). Furthermore, reduced self-initiation of behaviour has been reported in cases of bilateral anterior cingulotomy (Cohen et al., 1999), and ACC lesions are linked with blunted autonomic arousal in the context of mental stress (Critchley et al., 2003).

1.2. The role of the prefrontal cortex in episodic memory

As described by Tulving (1972), episodic memory involves the conscious recollection of personally experienced events within a specific spatial and temporal context. This information undergoes processes of encoding, consolidation and retrieval. Encoding involves the conversion of perceived information into a memory trace that can be stored and subsequently retrieved. This memory trace may undergo consolidation, which stabilises and converts the memory trace from short-term to long-term memory. Finally, retrieval involves the re-accessing of stored memory traces, commonly known as 'remembering'. These processes are largely mediated by structures within the medial temporal lobe (MTL). Importantly, however, the MTL is richly interconnected with the PFC, and these two systems interact to support successful remembering (Simons & Spiers, 2003). Damage to the PFC may therefore impair episodic memory through disrupting the control processes that facilitate efficient encoding and retrieval (Dolan & Fletcher, 1997; Eichenbaum, 2017; Fletcher, Shallice, Frith, Frackowiak, & Dolan, 1998). These processes may be broadly categorised as those mediating the strategic and organisational aspects of encoding and

retrieval, and those enhancing certain aspects of information to facilitate preferential encoding and retrieval. Neuroanatomically, these two types of control processes are associated with lateral and medial regions of the PFC, respectively.

1.2.1. Lateral prefrontal cortex contributions to episodic memory

In line with its role in executive functions, the lateral PFC—encompassing both the dlPFC and vlPFC; see Figure 1.2)—is broadly implicated in the executive aspects of memory encoding and retrieval. The subdivisions of the PFC outlined previously, which are based on clusters of lesion-specific cognitive/behavioural symptoms, do not tend to make this dorsal-ventral distinction. Here, the added level of specificity in theories of lateral PFC contributions to memory results from combining findings from clinical studies of patients with dlPFC lesions and functional neuroimaging studies showing dlPFC and vlPFC activity in healthy participants. While the memory-related roles of the dlPFC and vlPFC are discussed separately in this section, these will be collectively referred to as lateral PFC contributions to memory for the remainder of this thesis, in the interest of maintaining consistency. In contrast, functions of the PFC will continue to be referred to using the dlPFC, vmPFC and dmPFC subdivisions described in Section 1.1.

In terms of encoding, converging evidence from dlPFC lesion patient and functional neuroimaging studies demonstrates that the dlPFC is involved in the organisation of information to be remembered (Blumenfeld & Ranganath, 2007; Simons & Spiers, 2003). In particular, tasks that involve organising or manipulating information in working memory are associated with increased dlPFC activity (Blumenfeld, 2006). Additionally, the dlPFC is recruited during the spontaneous implementation of organisational strategies such as ‘chunking’ or semantic clustering, where multiple pieces of information are organised into smaller bundles of information, or groups that contain semantically related information

(Gershberg & Shimamura, 1995; Hawco, Berlim, & Lepage, 2013; Savage et al., 2001). On the other hand, the vlPFC appears to be involved in top-down selection processes that direct attention towards goal-relevant information, as well as elaborative processing of semantic or phonological features of memory representations (Blumenfeld & Ranganath, 2007; Simons & Spiers, 2003). Importantly, the implementation of these organisational and selection processes during encoding results in detailed representations that are optimised for long-term storage, and supports subsequent memory retrieval. According to the framework proposed by Simons & Spiers (2003), these lateral PFC regions are also recruited during strategic retrieval processes. Specifically, the vlPFC is involved in the selection of retrieval cues that are used to search and reactivate stored memory representations, which are then monitored and verified by the dlPFC.

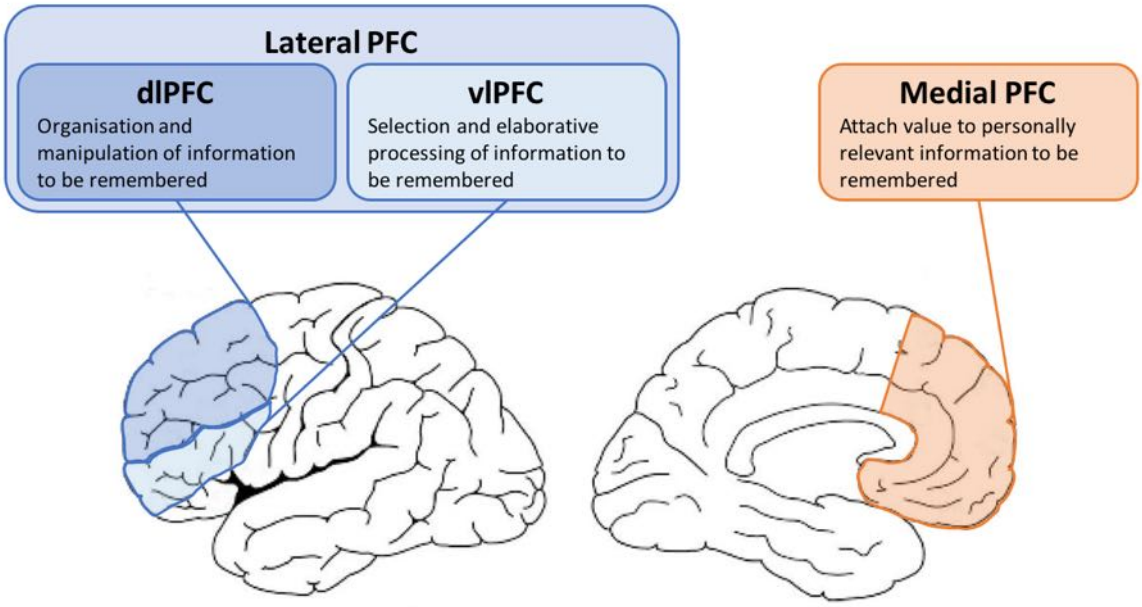

Figure 1.2. Summary of functions and approximate anatomical locations of lateral (dlPFC and vmPFC) and medial PFC subdivisions associated with episodic memory encoding processes.

Much of the proposed framework for the lateral PFC control of episodic memory is drawn from findings in the experimental literature. In clinical settings, performance on standardised neuropsychological measures of episodic memory also provides some insight into the lateral PFC contributions to memory. These tests typically assess learning, retention and retrieval of new information. During one or multiple learning trials, verbal or visual stimuli are presented, after which patients are asked to immediately recall the stimuli. Following a specified time period (usually between 20–45 min), delayed recall is assessed, where patients are asked to recall the stimuli without any further presentation of the stimuli. This is followed by a recognition test, where patients are required to discriminate between targets (i.e., previously seen) and distractors (i.e., not previously seen). The delayed recall test provides a measure of spontaneous retrieval of information, which is thought to reflect not only memory retention, but also strategic retrieval processes that are employed to organise and monitor newly learnt information (Lezak et al., 2012). In contrast, performance on the recognition test is considered to reflect memory retention, regardless of a patient's capacity to spontaneously retrieve the information, as presentations of target and distractor stimuli function as cues or reminders that can circumvent faulty strategic retrieval processes. As such, patients with lateral PFC damage tend to show greater impairments on recall tests, relative to recognition (Wheeler, Stuss, & Tulving, 1995). Lateral PFC-mediated control processes may also be inferred from measures of semantic clustering on verbal episodic memory recall tests that include words belonging to certain semantic categories (e.g., vegetables, modes of transport). Indices of semantic clustering assess the extent to which words from the same semantic category are recalled consecutively, and are associated with lateral PFC activity in healthy adults (Long, Öztekin, & Badre, 2010).

1.2.2. Medial prefrontal cortex contributions to episodic memory

Increasing evidence suggests that the medial PFC plays an important role in episodic memory, though most accounts do not delineate between the vmPFC and dmPFC subdivisions. Taking into account the functional heterogeneity and vast interconnectivity of the mPFC, it is unsurprising that it has been proposed to play a role in diverse range of memory functions, from signalling confidence in memory retrieval (Hebscher & Gilboa, 2016), to memory for self- and socially relevant information (Cassidy & Gutchess, 2012; Macrae, Moran, Heatherton, Banfield, & Kelley, 2004), memory for reward predictive cues (Bialleck et al., 2011) and memory for adaptive responses in specific spatiotemporal contexts (Euston, Gruber, & McNaughton, 2012). One unifying theme that has recently been proposed is that the primary function of the medial PFC is to add subjective value to personally relevant memory (Lin, Horner, & Burgess, 2016). As such, memories of higher subjective value are enhanced through preferential encoding and retrieval. This dovetails with the 'valuation hypothesis' put forward by D'Argembeau (2013), which posits that the medial PFC functions as a 'valuation' centre that attaches personal value or significance to incoming stimuli. The mechanisms through which the medial PFC interacts with MTL regions to augment subjectively valued memories are not well known. Arguably, important insights regarding these mechanisms may be garnered through the study of medial PFC contributions to episodic memory in patients with damage to this brain region.

From this review, it is clear that the PFC plays a critical role in the control of episodic memory processes. Damage to the PFC is therefore likely to have significant consequences for episodic memory functions.

1.3. Alzheimer's disease

1.3.1. Clinical presentation

Alzheimer's disease (AD) is the most common form of dementia. Clinically, patients show pervasive impairments of episodic memory, presenting insidiously with deficits in learning and recall of recently learned information. For a diagnosis of probable AD, dysfunction is also present in at least one other cognitive domain, including reasoning/judgment, visuospatial or language abilities, or personality, behaviour or comportment (McKhann et al., 2011). With disease progression however, impairment invariably spreads across multiple cognitive domains.

1.3.2. Neuropathology of AD

Pathologically, amyloid plaques and neurofibrillary tangles are the hallmark features of AD. Plaques are formed by the abnormal accumulation of insoluble extracellular amyloid-beta (Aβ) protein, whereas tangles result from progressive accumulations of intracellular phosphorylated tau (Braak & Braak, 1991; 1996). The sequence of pathological progression is well established, with the earliest neurofibrillary changes stemming from the transentorhinal and entorhinal cortices, spreading to the hippocampus and adjacent limbic areas, before reaching the neocortex, affecting virtually all subdivisions of the cerebral cortex (Braak & Braak, 1991). Degeneration and loss of the cholinergic neurons in the basal forebrain is also an early pathological feature of AD (Cullen & Halliday, 1998; Whitehouse et al., 1982). Importantly, dysfunction of the cholinergic system is associated with cognitive deficits in AD (Francis, Palmer, Snape, & Wilcock, 1999; Mesulam, 2004). While these deficits may improve with acetylcholinesterase inhibitor drug therapy in the mild-to-moderate stages of the disease (Kobayashi, Ohnishi, Nakagawa, & Yoshizawa, 2016; Lanctôt et al., 2003), the long-term benefits are limited (Hogan, 2014).

Increasingly, biomarker data that provide evidence of underlying AD pathophysiological processes have been used to support diagnoses of AD (Jack et al., 2011). This includes in vivo measures of AD-specific biochemical, physiological and neuroanatomical changes. For example, cerebrospinal fluid (CSF) measures of Aβ and tau serve as biomarkers that give an indication of the accumulation of AD pathology in the brain (Tapiola et al., 2009). Furthermore, advancements in biomarker neuroimaging methods have enabled in vivo visualisation of the distribution of Aβ pathology, through positron emission tomography (PET) tracer compounds such as Pittsburgh Compound-B (PiB) (Klunk et al., 2004; Rowe et al., 2007).

1.3.3. Neuroimaging in AD

Structural and functional neuroanatomical changes seen on MRI and 18-fluorodeoxyglucose PET (FDG-PET) scans are generally consistent with the established spread of pathology in AD (Csernansky et al., 2004; Mosconi et al., 2009; Vemuri et al., 2008). A meta-analysis of neuroimaging studies revealed that the earliest stage of AD is associated with hippocampal and transentorhinal atrophy, as well as hypometabolism in the inferior parietal lobule and precuneus (Schroeter, Stein, Maslowski, & Neumann, 2009). Likewise, significant atrophy in the hippocampus, inferior and middle temporal gyri, posterior cingulate and precuneus has been documented in amnestic mild cognitive impairment (MCI) patients who subsequently transition to a diagnosis of AD dementia (Chételat et al., 2002; Nestor, Fryer, Ikeda, & Hodges, 2003). Importantly, with progression of AD, the spread of atrophy from MTL to lateral temporal, parietal and frontal regions, is closely related to cognitive decline (Eskildsen et al., 2013; Thompson et al., 2007)**.** Atrophy of the basal forebrain is evident on structural MRI scans (Teipel et al., 2005), and may even precede the cortical spread of atrophy in AD (Hall, Moore, Lopez, Kuller, & Becker, 2008; Schmitz, Nathan Spreng,

Alzheimer's Disease Neuroimaging Initiative, 2016). The severity of basal forebrain atrophy also correlates with accumulation of Aβ pathology in the neocortex (Kerbler et al., 2015).

1.3.4. Atypical presentations of AD

The most recent revision to the diagnostic criteria for AD describes three non-amnestic presentations of AD, where the initial and most prominent cognitive deficits are in either language, visuospatial or executive functions (McKhann et al., 2011). Patients with such atypical presentations of AD show patterns of pathology and atrophy which deviate from the typical sequence described above. For reasons currently unknown, atypical presentations of AD are more common in younger onset (<65 years of age) compared to late onset (>65 years of age) AD patients (Koedam et al., 2010).

The language presentation of AD is termed logopenic progressive aphasia, which is characterised by impaired word retrieval in spontaneous speech and confrontation naming, as well as deficits in sentence repetition (Gorno-Tempini et al., 2011). Patients diagnosed with logopenic progressive aphasia show structural and functional changes on neuroimaging predominantly in the left posterior temporal and inferior parietal regions (Lam, Masellis, Freedman, Stuss, & Black, 2013; Leyton, Piguet, Savage, Burrell, & Hodges, 2012). This asymmetry is reflected in the distribution of neurofibrillary tangles, which is higher in temporoparietal than in hippocampal regions (Gefen et al., 2012; Josephs, Dickson, Murray, & Senjem, 2013). In contrast, patients with the visuospatial presentation of AD, termed posterior cortical atrophy, show progressive declines in visuospatial, visuoperceptual, literacy and praxic skills, in the context of relatively preserved episodic memory (Crutch et al., 2012; McMonagle, Deering, Berliner, & Kertesz, 2006). Structural and pathological changes in posterior cortical atrophy predominantly affect the occipito-parietal regions, with less involvement of the hippocampus (Lam et al., 2013; Tang-Wai et al., 2004). As these

atypical presentations of AD do not typically involve PFC atrophy or significant episodic memory impairment, these disorders are not discussed further.

Of relevance to this thesis is the dysexecutive or frontal presentation of AD, where patients present with disproportionate executive dysfunction and behavioural changes relative to memory deficits (Lam et al., 2013; Ossenkoppele et al., 2015). In terms of pathology, these patients show a greater distribution of Aβ plaques and neurofibrillary tangles and lower neuronal density in the frontal lobes, relative to typical AD patients (Blennerhassett, Lillo, Halliday, Hodges, & Kril, 2014; Johnson, Head, Kim, Starr, & Cotman, 1999). Furthermore, dysexecutive AD patients show frontal hypometabolism (Woodward, Rowe, Jones, Villemagne, & Varos, 2015) and additional cortical thinning in frontoparietal regions, despite equivalent cortical thinning in MTL regions compared to typical AD patients (Dickerson, Wolk, Alzheimer's Disease Neuroimaging Initiative, 2011). Taken together, the younger age of onset, predominant executive deficits and disproportionate frontal lobe pathology in dysexecutive AD patients resembles certain aspects of bvFTD. In this context, greater understanding of the overlapping features of AD and bvFTD remains an important goal, in order to improve diagnostic accuracy.

1.4. Behavioural-variant frontotemporal dementia

1.4.1. Clinical presentation

Frontotemporal dementia (FTD) encompasses a group of neurodegenerative diseases associated with atrophy of the frontal and temporal lobes. Onset of FTD symptoms typically occurs at a younger age than for AD (i.e., < 65 years of age), and FTD is the second most common form of younger onset dementia following Alzheimer's disease. Three main clinical variants of FTD are recognised: two language variants, termed semantic variant primary progressive aphasia (svPPA) and nonfluent/agrammatic variant primary progressive

aphasia (navPPA), and the behavioural-variant (bvFTD). Each clinical variant is characterised by distinct profiles of cognitive and behavioural symptoms and patterns of brain atrophy (Gorno-Tempini et al., 2011; Rascovsky et al., 2011). In particular, svPPA (otherwise known as semantic dementia) is characterised by a profound, multi-modal loss of semantic knowledge, with impaired confrontational naming and single-word comprehension (Gorno-Tempini et al., 2011; Hodges, Patterson, Oxbury, & Funnell, 1992). Patients with svPPA show predominant anterior temporal lobe atrophy, which is typically more severe on the left side (Galton et al., 2001; Mummery et al., 2000). In contrast, semantic knowledge remains relatively preserved in navPPA (otherwise known as progressive nonfluent aphasia), which is characterised by deficits in the motor aspects of language production, with effortful, halting speech, phonological errors and agrammatism (Gorno-Tempini et al., 2011; Turner, Kenyon, Trojanowski, Gonatas, & Grossman, 1996). Patients with navPPA show predominant atrophy of the left inferior frontal and insular cortices (Gorno-Tempini et al., 2004). As episodic memory impairment is not a primary clinical feature of svPPA or navPPA, these language variants of FTD are not discussed further.

The current thesis focuses on bvFTD, which represents a prototypical example of frontal lobe dysfunction. Patients with bvFTD present with predominant changes in social behaviour and personal conduct. Hallmark features include disinhibition, apathy, motor and verbal stereotypies, altered eating habits, loss of empathy and emotional blunting. Insight into the presence and severity of these symptoms is also impaired. In terms of cognition, current diagnostic criteria for bvFTD mandate a primarily dysexecutive profile, with relative sparing of episodic memory and visuospatial functions (Rascovsky et al., 2011). The diagnostic utility of this criterion has been questioned, however, in light of evidence that executive dysfunction is not specific to bvFTD (Harciarek & Cosentino, 2013) and that episodic memory is indeed impaired in these patients (Hornberger, Piguet, Graham, Nestor,

& Hodges, 2010a). As such, increasing emphasis is placed on other cognitive deficits in the neuropsychological profile of bvFTD, including impairments in inhibitory and socio-emotional functions, Theory of Mind and decision-making (Bertoux et al., 2015; Funkiewiez, Bertoux, de Souza, Levy, & Dubois, 2012).

1.4.2. Neuropathology of bvFTD

Despite continued refinement of the clinical diagnostic criteria, correctly diagnosing bvFTD remains a challenge. The gold standard for diagnostic confirmation is currently achieved through post mortem pathological analysis. Syndromes within the FTD spectrum are associated with several pathological subtypes, classified on the basis of protein depositions. These include tau, TAR-DNA-binding protein 43 (TDP-43) and RNA-binding protein fused in sarcoma (FUS) (Mackenzie et al., 2010). Considerable pathological heterogeneity underlies the clinical presentation of bvFTD, such that those presenting with the clinical syndrome have an almost equal chance of having underlying tau or TDP-43 pathology, with a small proportion of cases having FUS pathology (Chare et al., 2014; Hodges et al., 2004). Furthermore, a subset of patients, who meet clinical diagnostic criteria for bvFTD, will have underlying pathological changes consistent with AD (Chare et al., 2014; Seelaar, Rohrer, Pijnenburg, Fox, & van Swieten, 2011) or a combination of both FTD and AD pathology (Woodward, Mackenzie, Hsiung, Jacova, & Feldman, 2010). With advances in the development of pharmaceutical interventions that target these underlying pathological changes, there is a pressing need to establish associations between clinical and pathological phenotypes.

In bvFTD, the progression of brain atrophy resulting from the accumulation of pathology and associated neuronal loss is generally similar across pathological subtypes (Kril & Halliday, 2011). Post mortem disease staging has been established across pathologically-

confirmed cases of bvFTD with different disease durations (Broe et al., 2003). Atrophy of the OFC and medial prefrontal regions is evident from the earliest disease stage, followed by the hippocampus, temporal pole, dorsolateral prefrontal cortex and basal ganglia. This pattern of progression is related to clinical measures of dementia severity, as well as patterns of neuronal loss (Kersaitis, Halliday, & Kril, 2004).

1.4.3. Neuroimaging in bvFTD

Patterns of atrophy seen on structural MRI scans are consistent with those documented in post mortem studies. The severity and progression of atrophy can be assessed using visual rating scales (Kipps et al., 2007) or automated quantitative methods, such as voxel-based morphometry (VBM) and cortical thickness mapping. From the earliest disease stage, volumetric studies using VBM typically reveal atrophy in a network of frontal (OFC, dlPFC, vmPFC and frontal polar) and paralimbic (ACC, anterior insular cortices) regions, together with the hippocampus, striatum and thalamus (Schroeter, Raczka, Neumann, & Cramon, 2007; Seeley et al., 2008). Atrophy in these frontal-paralimbic regions continues to spread over time, encroaching into the basal ganglia, subcortical limbic regions and the parietal cortex (Seeley et al., 2008). Degeneration of white matter tracts has also been documented, with those connecting the frontal and temporal regions particularly vulnerable (Frings et al., 2014; Lam, Halliday, Irish, Hodges, & Piguet, 2013; Whitwell et al., 2010).

1.4.4. Diagnostic difficulties

In most cases, evidence of brain atrophy on MRI complements the clinical presentation of bvFTD. However, a subset of patients present with the clinical features in the absence of overt atrophy on MRI (Davies et al., 2006). Although these patients are clinically indistinguishable from typical bvFTD patients, they are usually less impaired on measures of general cognitive function, executive dysfunction and activities of daily living

(Hornberger, Shelley, Kipps, Piguet, & Hodges, 2009). Unlike frank bvFTD, these so-called *phenocopy* patients do not show progressive worsening of symptoms (Kipps, Hodges, & Hornberger, 2010). The aetiology of this phenocopy syndrome is still unknown, though it has been suggested that symptoms may be due to underlying autism spectrum disorder, personality disorder or subclinical mood disorder (Piguet, Hornberger, Mioshi, & Hodges, 2011). It is uncertain whether the clinical features in phenocopy patients result from an underlying neurodegenerative disorder. Until this is clarified, it is advisable that studies on bvFTD include only patients with clear evidence of change on neuroimaging, in order to minimise the confounding influence of phenocopy cases.

A pressing source of diagnostic difficulty arises from the overlap between bvFTD and AD. These patient groups show similarities in executive dysfunction and episodic memory impairment, as well as associated patterns of atrophy, which will be discussed in detail in the following sections. These overlapping features are particularly problematic when distinguishing between bvFTD and dysexecutive presentations of AD, which is characterised by prominent executive dysfunction and an atypically frontal distribution of pathology and atrophy (Blennerhassett et al., 2014; Dickerson et al., 2011; McKhann et al., 2011). An additional complicating factor is the fact that dysexecutive AD patients tend to have younger onset of symptoms, similar to bvFTD (Koedam et al., 2010). It is important to note that studies comparing AD and bvFTD typically include younger onset AD patients. As these patients tend to show more atypical features, findings may not be representative of late onset AD, which may share fewer overlapping features with bvFTD.

In terms of neuroimaging biomarkers, in vivo amyloid imaging methods may be useful in distinguishing between AD and bvFTD on the basis of absence or presence of AD pathology. However, this does not account for the possibility of multiple pathologies (Naasan et al.,

2015). Similarly, the specificity of in vivo tau imaging methods for FTD remains to be established (Villemagne & Okamura, 2016). In order to improve diagnostic accuracy, much progress is yet to be gained by refining the characterisation of bvFTD through cognitive, behavioural and neuroimaging methods.

1.5. The prefrontal cortex in AD and bvFTD

1.5.1. Prefrontal cortex atrophy

AD and bvFTD patients show distinct patterns of brain atrophy, with lateral parietal and occipital cortices more affected in AD and frontal paralimbic regions (including ACC, anterior insula and subcallosal gyrus) more atrophic in bvFTD (see Figure 1.3) (Landin-Romero et al., 2016; Rabinovici et al., 2007). Nonetheless, the presence of PFC atrophy does not exclude a diagnosis of AD. In particular, dlPFC atrophy is evident in both AD (Chételat et al., 2008) and bvFTD (Seeley et al., 2008), and does not serve as a reliable marker to distinguish between the two syndromes (Rabinovici et al., 2007). OFC atrophy is also present across both AD and bvFTD (Rabinovici et al., 2007), though this is more severe in bvFTD, with longitudinal neuroimaging data indicating more rapid declines in volume and cortical thickness (Frings et al., 2014; Landin-Romero et al., 2016). Additionally, regions adjacent to the OFC, such as the subcallosal medial PFC, are significantly atrophic in bvFTD but not in AD (Lindberg et al., 2012). Furthermore, ACC atrophy appears to be specific to bvFTD, especially early in the disease (Rabinovici et al., 2007). Although reduction in ACC cortical thickness becomes apparent with disease progression in AD, the rate and spread at which this occurs remains more severe in bvFTD (Landin-Romero et al., 2016). This is consistent with post mortem pathological findings, which show disproportionate ACC atrophy and neuronal loss in bvFTD compared to AD (Hornberger et al., 2012; Santillo, Nilsson, & Englund, 2013; Tan et al., 2013). With reference to the prefrontal subdivisions discussed earlier in this chapter, evidence from cross-sectional and longitudinal

neuroimaging studies comparing AD and bvFTD therefore suggests that the dlPFC may be affected to a similar degree across both diseases, whereas the vmPFC and dmPFC is disproportionately atrophic in bvFTD.

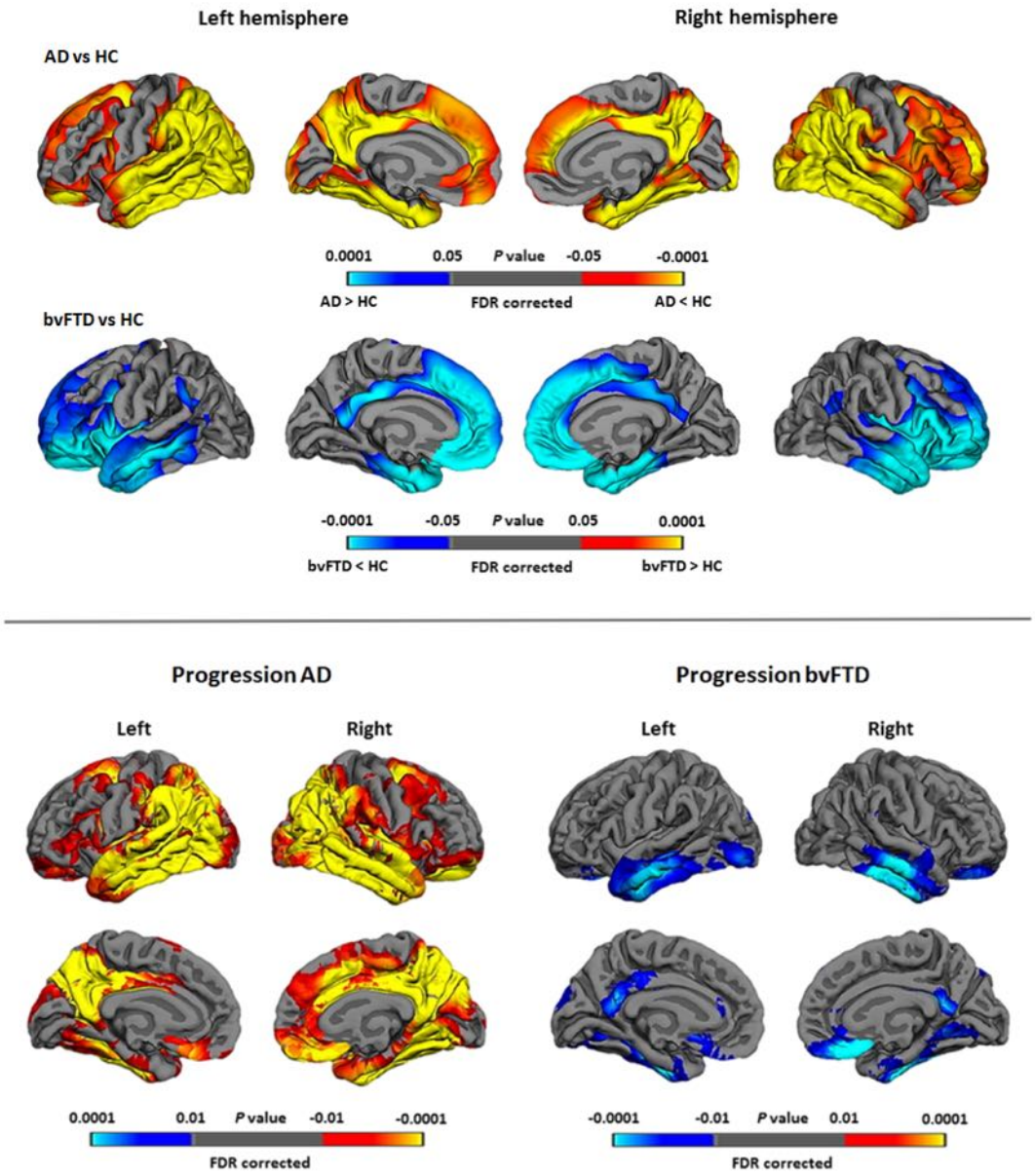

Figure 1.3. *Top panel*—Regions showing significantly greater reductions in cortical thickness in AD relative to healthy controls (red-yellow) and bvFTD relative to healthy controls (blue) at baseline. *Bottom panel*—Regions showing significant annual rates of cortical thinning with disease progression in AD (red-yellow) and bvFTD (blue). Figures adapted from Landin-Romero et al. (2016).

1.5.2. Dorsolateral prefrontal cortex functions

In addition to prominent deficits in episodic memory, AD patients commonly present with executive dysfunction, which worsens with disease progression (Grober et al., 2008; Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004). The profile of executive deficits in AD is largely consistent with dlPFC damage, with poor performance on clinical tests of executive function. Converging evidence from studies of executive function in AD demonstrates deficits in working memory, verbal fluency, attentional set-shifting, planning/organisation, problem solving and abstract reasoning (for a review, see Allain, Etcharry-Bouyx, & Verny, 2013; Baudic et al., 2006; Collette, Van der Linden, & Salmon, 1999; Lafleche & Albert, 1995; Rainville et al., 2002; Swanberg et al., 2004). Importantly, executive deficits in AD are associated with cortical thinning in the dlPFC (Dickerson et al., 2011), which is also atrophic in dysexecutive MCI patients (Chang et al., 2010; Pa et al., 2009).

As mentioned above, executive dysfunction is one of the core diagnostic criteria for bvFTD (Rascovsky et al., 2011). While some studies have found relatively intact performance on clinical tests of executive function (Lough, Gregory, & Hodges, 2001; Rahman, Sahakian, Hodges, Rogers, & Robbins, 1999), more recent studies have demonstrated widespread impairments across tests of verbal fluency, attentional set-shifting, planning/organisation, problem solving and abstract reasoning (Gansler, Huey, Pan, Wasserman, & Grafman, 2016; Giovagnoli, Erbetta, Reati, & Bugiani, 2008; Lagarde et al., 2013). One plausible explanation for this discrepancy is the potential admixture of phenocopy and progressive bvFTD cases. Importantly, only the latter group show consistent impairments on measures of working memory, verbal fluency and cognitive flexibility (Hornberger et al., 2009). Furthermore, longitudinal profiles of executive function in progressive bvFTD patients

indicate clear worsening of executive functions with disease progression (Ramanan et al., 2016).

Direct comparisons between AD and bvFTD patients reveal that these patient groups cannot be reliably differentiated on the basis of their performance on executive tests that target dlPFC function (Giovagnoli et al., 2008; Gregory, Orrell, Sahakian, & Hodges, 1997; Hutchinson & Mathias, 2007; Pasquier, Lebert, Grymonprez, & Petit, 1995). This is unsurprising, in light of the overlap in dlPFC atrophy reviewed above. The comparable profiles of executive dysfunction in AD and bvFTD therefore reduce the utility of such tests in differential diagnosis. As a result, there is an increasing need for tests of PFC function that can better detect early cognitive deficits that are specific to bvFTD. Given that the most pronounced sites of atrophy lie within the medial PFC (Seeley et al., 2008), it is argued that tests of executive function that are commonly used in the clinic—which largely target dlPFC functions—are insensitive to deficits in vmPFC and dmPFC functions (Rahman et al., 1999; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009). As such, increased focus is placed on measures of inhibition, decision-making and social cognition in bvFTD.

1.5.3. Ventromedial prefrontal cortex functions

In bvFTD, converging evidence from carer reports and objective measures indicates disproportionate impairments in inhibition, decision-making and reward processing—functions mediated by the vmPFC (which encompasses the OFC). Reports of behavioural disinhibition and performance on verbal and motor measures of inhibitory function reliably discriminate between AD and bvFTD patients, and correlate with OFC atrophy in the latter (Bertoux, Funkiewiez, O'Callaghan, Dubois, & Hornberger, 2013; Bozeat, Gregory, Ralph, & Hodges, 2000; Hornberger, Geng, & Hodges, 2011; Hornberger, Savage, Hsieh, Mioshi, Piguet, & Hodges, 2010b; O'Callaghan, Naismith, Hodges, Lewis, & Hornberger, 2013). On

decision-making tasks, increased risk-taking behaviour and difficulty making strategic choices that maximise rewards relate to OFC atrophy in bvFTD (Gleichgerrcht, Torralva, Roca, & Manes, 2010; Kloeters, Bertoux, O'Callaghan, Hodges, & Hornberger, 2013; Rahman et al., 1999; Strenziok et al., 2011). In contrast, while AD patients also show deficits on similar decision-making tasks, these appear to be driven by memory impairment and temporal-parietal atrophy (Kloeters et al., 2013; Sinz, Zamarian, Benke, Wenning, & Delazer, 2008). Accordingly, Perry and Kramer (2013) suggest that poor decision-making is underpinned by deficits in reward processing in bvFTD, but relates to memory impairments in AD. Furthermore, deficits in social decision-making and reward processing have also been demonstrated in bvFTD patients, who show reduced sensitivity to negative social outcomes (Grossman et al., 2010; Perry, Sturm, Wood, Miller, & Kramer, 2015)

1.5.4. Dorsomedial prefrontal cortex functions

Social cognitive dysfunction is well established in bvFTD, with widespread impairments across measures of Theory of Mind, emotion recognition, empathy and complex social reasoning (Bertoux et al., 2012; Dermody et al., 2016; Lough et al., 2006; Melloni et al., 2016; O'Callaghan et al., 2016; Torralva et al., 2009). Considering the multi-faceted nature of social cognition, however, it is difficult to pinpoint specific neural substrates of social cognitive deficits in bvFTD. While Bertoux et al. (2012) identified associations between dmPFC atrophy and performance on tests of Theory of Mind and emotion recognition, other studies implicate a wider fronto-temporo-insular network of regions, collectively termed the Social Context Network (Couto et al., 2013; Ibáñez & Manes, 2012). Nonetheless, tests of social cognition are sensitive to early deficits in bvFTD, especially in comparison to executive measures that are commonly used in the clinic (Funkiewiez et al., 2012; Torralva et al., 2009). Furthermore, although AD patients may also perform poorly on tests of Theory of Mind, these deficits are related to global cognitive dysfunction and disease progression,

rather than social cognitive deficits per se (Dermody et al., 2016; Dodich et al., 2016). As social cognition remains relatively intact in AD, particularly during the early stages of the disease, these measures can distinguish between bvFTD and AD (Bertoux et al., 2015; Possin et al., 2013).

From the evidence reviewed above, it is clear that AD and bvFTD are both associated with changes in the structural integrity and related functions of the dlPFC, whereas the vmPFC and dmPFC are more severely impacted in bvFTD. A question remains about whether the PFC contributions to episodic memory in AD and bvFTD may similarly vary across PFC subdivisions.

1.6. Episodic memory in AD and bvFTD

Whereas episodic memory impairment is the hallmark clinical feature of AD (McKhann et al., 2011), the presence of episodic memory impairment has been considered an exclusion criterion for diagnosis of bvFTD (Neary et al., 1998; Rascovsky et al., 2011). Increasing evidence, however, shows that bvFTD patients can present with clinically significant episodic memory deficits (for a review, see Hornberger & Piguet, 2012), even in pathologically confirmed cases (Caine, Patterson, Hodges, Heard, & Halliday, 2001; Graham et al., 2005; Hodges et al., 2004; Papageorgiou et al., 2016). It is now well established that AD and bvFTD patients cannot be reliably differentiated on the basis of performance on standardised neuropsychological measures of episodic memory (Frisch et al., 2013; Gregory et al., 1997; Hornberger, Piguet, Graham, Nestor, & Hodges, 2010a; Irish, Piguet, Hodges, & Hornberger, 2014b; Pennington, Hodges, & Hornberger, 2011). Furthermore, this pattern of findings has also been replicated in cohorts of AD and bvFTD patients with in vivo biomarker profiles in keeping with their diagnoses (Bertoux et al., 2014). These shared symptoms of episodic memory impairment have significant

implications for the differential diagnosis of AD and bvFTD, adding to the abovementioned difficulties posed by the substantial overlap in executive dysfunction.

1.6.1. The medial temporal lobe versus prefrontal cortex debate

Research in episodic memory has typically focused on the MTL as the neuroanatomical seat of memory. Indeed, MTL atrophy is evident in both AD and bvFTD, and does not serve as a reliable marker to distinguish between the two groups (de Souza et al., 2013; Hornberger et al., 2012; Rabinovici et al., 2007). However, evidence of contrasting features of episodic memory dysfunction in AD and bvFTD has led to the dominant perspective that such deficits are underpinned by divergent neurocognitive processes.

On clinical measures of episodic memory learning, delayed recall and recognition, AD patients are impaired consistently across all three components (Economou, Routsis, & Papageorgiou, 2016; Lekeu et al., 2010; Pasquier, Grymonprez, & Lebert, 2001; Salmon & Bondi, 2009). As such, AD patients show a typical amnestic profile of reduced learning and rapid forgetting of recently learnt material, resulting in poor performance across both recall and recognition tests. This pattern suggests deficits in memory encoding and retention, as the provision of cues through the recognition test format is thought to circumvent strategic retrieval deficits. Similarly, the provision of cues during cued recall procedures (where cue words that were associated with target words during learning are presented) does not appear to benefit recall performance in AD (Cerciello, Isella, Proserpi, & Papagno, 2016; Lemos, Duro, Simoes, & Santana, 2014). This suggests that impaired recall performance in AD is not driven by inefficient strategic retrieval due to executive deficits, but rather, by poor encoding and retention of the information in the first place. This is consistent with findings from neuroimaging studies, where memory impairments in AD have largely been attributed to atrophy of the MTL (Bonner-Jackson, Mahmoud, Miller, & Banks, 2015; Mori et al.,

1997). Evidence from other neuroimaging studies, however, indicates that performance on different components of memory tests may differentially recruit MTL and PFC regions. Whereas hippocampal atrophy and hypometabolism is implicated across learning, delayed recall and recognition, performance on delayed recall is also associated with structural and functional changes in the lateral PFC (Lekeu et al., 2003; Pennington et al., 2011; Rémy, Mirrashed, Campbell, & Richter, 2005). It remains to be elucidated whether AD patients are affected by dual sources of impairment on episodic memory tests, showing both an MTL-driven amnestic profile, as well as lateral PFC-mediated strategic retrieval deficits.

While bvFTD patients show impairments on episodic memory learning and delayed recall tests, performance on recognition tests is comparatively preserved, with many patients performing in line with age-matched healthy controls (Flanagan et al., 2016; Hornberger, Piguet, Graham, Nestor, & Hodges, 2010a; Hutchinson & Mathias, 2007). Similarly, providing cues that were associated with target words during learning can improve recall performance in bvFTD cases (Bertoux et al., 2014; Cerciello et al., 2016; Lemos et al., 2014; Pasquier et al., 2001). The relative sparing of recognition and cued recall performance, in the context of impaired learning and delayed recall performance, has led to the dominant perspective that memory impairment in bvFTD is driven by executive deficits, which are important for spontaneously implementing strategic and organisational processes during encoding and retrieval. This is supported by neuroimaging findings, which indicate that performance on recall and recognition measures is associated with an overwhelmingly frontal distribution of atrophy (Frisch et al., 2013; Irish, Piguet, Hodges, & Hornberger, 2014b; Pennington et al., 2011).

There are, however, exceptions to this AD-MTL versus bvFTD-PFC dichotomy. In the subset of AD patients showing an atypical dysexecutive presentation with a predominantly

frontal distribution of atrophy, the extent to which executive deficits impact on episodic memory remains unclear. Some studies report poorer memory performance in dysexecutive compared to typical AD patients (Gleichgerrcht, Torralva, Martinez, Roca, & Manes, 2011), but others detect no difference (Binetti et al., 1996). Whether dysexecutive AD patients show patterns of PFC atrophy and episodic memory deficits similar to bvFTD is unclear. Secondly, episodic memory deficits in bvFTD may not necessarily conform to a typical dysexecutive profile of episodic memory impairment, whereby memory can be improved with cueing or a recognition format (Bertoux et al., 2014; Mansoor et al., 2014). Indeed, Bertoux et al. (2014) suggest that two distinct amnestic profiles exist in bvFTD—one being primarily driven by executive deficits, and the other resembling the typical amnestic profile of AD patients. In support of these findings, two distinct profiles of cerebral hypometabolism and associated cognitive deficits have been identified in bvFTD—a frontal subtype showing predominant executive dysfunction, and a temporo-limbic subtype showing primary amnestic deficits (Cerami et al., 2016). Furthermore, Bertoux et al. (2016) used data-driven methods to demonstrate that executive dysfunction cannot fully account for memory impairments in bvFTD. Collectively, these exceptions further blur an already murky distinction between the profiles of executive function and episodic memory in AD and bvFTD. Development of novel memory tests which capitalise on functions that are disproportionately affected in bvFTD represents a promising approach to delineating episodic memory functions in these two disorders.

1.6.2. Medial prefrontal contributions to memory in AD and bvFTD

This review has established that executive dysfunction, episodic memory impairment, dlPFC atrophy and MTL atrophy are shared features of AD and bvFTD. In contrast, medial PFC dysfunction is overwhelmingly affected in bvFTD, yet the abovementioned MTL versus PFC debate has focused primarily on the contributions of the lateral PFC to memory. In the

context of investigating the impact of PFC dysfunction on episodic memory in these patient groups, memory tests that tap into medial PFC functions therefore represent a promising, yet unexplored, approach.

We have seen that the medial PFC regions are involved in control processes that enhance memories by attaching subjective value or significance. Previous studies demonstrate that memory for emotional stimuli is enhanced relative to non-emotional stimuli in AD patients and healthy controls, but not bvFTD (Kumfor, Irish, Hodges, & Piguet, 2013; 2014). Importantly, this attenuated impact of emotional value on memory in bvFTD is associated with atrophy of the OFC, which forms part of the medial PFC. As such, medial PFC atrophy in bvFTD may disrupt the valuation process which attaches levels of significance to enhance the encoding and retrieval of certain memories. This valuation process has been proposed to be important for the *self-reference effect*, a phenomenon where memory for self-related information is enhanced relative to memory for information related to another person (D'Argembeau, 2013; Kuiper & Rogers, 1979). In keeping with the marked changes to personality and interpersonal conduct, patients with bvFTD also show alterations in self-concept, as reflected in the striking discrepancies between patient and carer ratings of personality traits (Ruby et al., 2009). While disruption to self-relevant autobiographical memories has been shown to be related to medial PFC atrophy in bvFTD (Irish, Hodges, & Piguet, 2013; Irish, Hornberger, Wahsh, Lam, Lah, et al., 2014a), the self-reference effect has not been contrasted in bvFTD and AD. Examining this effect in two neurodegenerative patient groups with divergent patterns of medial PFC atrophy will provide insights into the impact of medial PFC atrophy on memory for self-relevant information.

Assessment of socially relevant memories represents another avenue for exploring medial PFC contributions to episodic memory. In particular, overly friendly or gullible behaviours

are frequently reported in bvFTD (Pressman & Miller, 2014), suggesting distinct alterations in processing socially relevant information. Recent studies have investigated social aspects of decision-making in bvFTD, revealing disruptions in social reward processing (Grossman et al., 2010; Perry et al., 2015), decision-making in social contexts (O'Callaghan et al., 2016) and strategic social bargaining (Melloni et al., 2016). This contrasts with AD, where social cognition and reward processing remains unaffected, particularly during the earlier stages of the disease (Bertoux et al., 2015; Perry et al., 2015; Possin et al., 2013). Examining the impact of social decision-making on episodic memory will shed new light on interactions between social cognition and memory, as well as the neural correlates, in these patient groups.

Another approach to investigating the medial PFC contribution to memory focuses on the enhancing effect of reward value on learning and memory. Evidence in healthy adults suggests that reward value plays a key role in shaping episodic memory (Shohamy & Adcock, 2010), allowing us to prioritise learning and memory for highly valued information (Castel, Benjamin, Craik, & Watkins, 2002). Increasingly, cognitive and behavioural symptoms in bvFTD have been attributed to underlying alterations in reward processing (Perry & Kramer, 2013). Strategic learning of information according to its value has not been explored in bvFTD or AD, and it is unclear how such preferential learning impacts on subsequent memory retrieval. Employing a value-directed learning paradigm in these patient groups will therefore offer new insights regarding interactions between reward valuation and strategic memory processes.

Investigation of these memory enhancement effects in bvFTD and AD provides valuable insights into the medial PFC control of memories that have personal, social or motivational significance. Along with continued refinement of episodic memory testing procedures,

further characterisation of the brain-behaviour relationships underpinning memory deficits in these patient groups stands to improve diagnostic accuracy and facilitate the development of targeted interventions.

1.7. Contextual overview and aims

The primary focus of this thesis is to investigate the PFC contributions to episodic memory impairments in AD and bvFTD. The studies presented include data collected from patients and healthy control participants, who were recruited through the Frontier Frontotemporal Dementia Research Clinic. Data were collected from July 2013 to November 2016. Some overlap exists in the participant samples across studies, as a proportion of participants were involved in multiple studies.

This thesis is presented in the form of five first-author manuscripts, three of which have been published in peer-reviewed journals (including one "in press" at the time of thesis submission) and two of which are currently under review. Each of these journals have different formatting requirements and referencing styles. While study-specific methods are outlined within each of the chapters, Chapter 4 includes an overview of the development of novel memory measures and source memory experimental methods and analyses, which are also relevant to Chapters 5 and 6. A more detailed description of the neuroimaging analysis techniques employed across Chapters 2–5 is provided in Appendix A. This format of thesis by publication necessitates some repetition of information, but redundancy has been minimised wherever possible.

Each manuscript is presented within a chapter of this thesis, and addresses the following specific aims:

1. **To contrast PFC atrophy and episodic memory performance in dysexecutive AD and bvFTD patients.** A subset of AD patients presents with prominent executive dysfunction and PFC atrophy. The impact of such executive deficits on episodic memory performance, as well as their neural correlates, remains unclear. Chapter 2 compares performance on standardised neuropsychological measures of episodic memory and brain atrophy in AD patients with or without significant executive dysfunction, as well as bvFTD patients, who typically have significant executive deficits. This study was published in the *Journal of Alzheimer's Disease* (Wong, Bertoux, et al., 2016a).
2. **To compare dlPFC and vmPFC contributions to episodic memory impairment using standardised neuropsychological tests in bvFTD and AD.** Evidence suggests that PFC atrophy impacts on episodic memory in AD and bvFTD, although the relative contribution of different subdivisions of the PFC is unclear. Chapter 3 contrasts dlPFC and vmPFC functions using standardised neuropsychological measures of executive function, emotion recognition and decision-making, and compares the dlPFC and vmPFC correlates of episodic memory. This study was published in *PLoS ONE* (Wong, Flanagan, Savage, Hodges, & Hornberger, 2014). Findings from this chapter informed the development of novel memory tests that target vmPFC functions in subsequent chapters of this thesis.
3. **To assess the self-reference effect on memory in bvFTD and AD.** Evidence from studies of autobiographical memory in bvFTD suggests a link between medial PFC atrophy and impaired retrieval of personally relevant memories from the past (Irish et al., 2013; Irish, Hornberger, Wahsh, Lam, Lah, et al., 2014a). Chapter 4 explores whether bvFTD and AD patients show differential enhancement of memory for self-

relevant information, and the neural correlates of this effect. This study was accepted for publication in *Cortex* in September 2016, and was made available online as an EPub ahead of print in October 2016 (Wong, Irish, et al., 2016b).

4. **To assess learning and memory of social interactions in bvFTD and AD.** Patients with bvFTD show disruptions in processing socially relevant information, though it is unclear how this impacts on learning and memory. Chapter 5 reports a study employing a novel neuroeconomic task based on the trust game paradigm, and explores the neural substrates underpinning learning and memory of socially relevant information in these patient groups. This manuscript is currently under review for publication.
5. **To assess strategic value-directed learning in bvFTD and AD.** Evidence suggests that bvFTD patients show deficits in reward processing, though it is unclear how this impacts on learning and memory of rewarding information. The study reported in Chapter 6 applied a novel value-directed remembering paradigm to contrast AD and bvFTD patients on learning and memory of stimuli associated with high versus low rewards. This manuscript is currently under review for publication.

Together, these five experimental chapters offer novel insights into the prefrontal contributions to episodic memory impairment in bvFTD and AD. Broad conclusions and implications are considered in the concluding chapter. Ultimately, the thesis demonstrates that the impact of lateral PFC dysfunction on episodic memory is not specific to bvFTD, and proposes that greater emphasis be placed on explicating the processes through which damage to the medial PFC impacts on value-related episodic memory.

Chapter 2
The prefrontal cortex and episodic memory in dysexecutive AD and bvFTD

2.1. Publication I

Wong, S., Bertoux, M., Savage, G., Hodges, J. R., Piguet, O., & Hornberger, M. (2016). Comparison of prefrontal atrophy and episodic memory performance in dysexecutive Alzheimer's disease and behavioral-variant frontotemporal dementia. Journal of Alzheimer's Disease: JAD, 51(3), 889–903. http://doi.org/10.3233/JAD-151016

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Comparison of Prefrontal Atrophy and Episodic Memory Performance in Dysexecutive Alzheimer's Disease and Behavioral-Variant Frontotemporal Dementia

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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. The 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 behavioral-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.

Keywords: Alzheimer's disease, executive function, frontotemporal dementia, memory, neuropsychology, prefrontal cortex

INTRODUCTION

Alzheimer's disease (AD) is a neurodegenerative disorder characterized clinically by progressive memory impairment and declines in language and

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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 behavioral-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 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 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

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 behavior	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 behaviors	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. FRS, Frontotemporal Dementia Rating Scale; CDR, Clinical Dementia Rating Scale; ACE-R, Addenbrooke's Cognitive Examination-Revised; CBI-R, Cambridge Behavioural Inventory-Revised. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$, n.s., non-significant.

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 behavioral disturbance reported by the family or carer, with higher scores indicative of more behavioral 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 while 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 analyzed 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 analyzed 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 256×256, 200 slices, 1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms. 3D T1-weighted sequences were analyzed 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: 8 mm). 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 $p < 0.001$ 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-behavior 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 $p < 0.001$ threshold. Regions of significant grey matter density change were superimposed on the MNI standard brain, with maximum coordinates provided in MNI space, and localized with reference to the Harvard-Oxford probabilistic cortical and subcortical atlas.

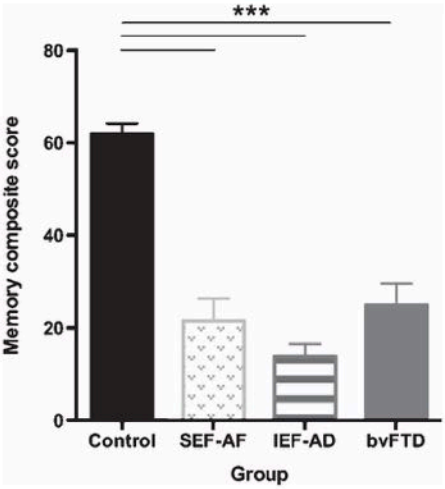

Fig. 1. Mean memory recall performance (memory composite score) in controls, spared executive function Alzheimer's disease (SEF-AD), impaired executive function Alzheimer's disease (IEF-AD), and behavioural-variant frontotemporal dementia (bvFTD) participants. Error bars represent standard error of the mean. $^{***}p < 0.001$.

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, gender, and education (all p values > 0.1). The three patient groups were matched for disease duration and dementia severity, as indexed by the CDR Sum of Boxes score (all p values > 0.1). 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 versus bvFTD, $p < 0.001$; IEF-AD versus bvFTD, $p < 0.05$). On the cognitive screening test (ACE-R), all patient groups were significantly impaired in comparison to controls (all p values < 0.001) but did not differ from each other (all p values > 0.1). 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 behaviors and motivation (p values < 0.05). Compared to controls, IEF-AD patients had disturbance in relation to memory and orientation, everyday skills, mood, and motivation (p values < 0.05). In comparison to controls, bvFTD patients showed more symptoms of behavioral disturbance across all CBI-R subscores except abnormal beliefs (p values < 0.01). *Post hoc* comparisons between patient groups revealed more disturbance in eating habits in bvFTD relative to SEF-AD ($p = 0.031$) and IEF-AD ($p < 0.001$), as well as more symptoms of abnormal behavior ($p = 0.003$), stereotypic and motor behaviors ($p < 0.001$), and reduced motivation ($p = 0.015$) 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 > 0.05).

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 the Supplementary Material. These raw scores were averaged to yield a memory recall composite score. A main effect of group was found for the memory recall composite ($F_{3,89} = 55.022$, $p < 0.001$); see Fig. 1. Tukey *post hoc* tests revealed that controls performed significantly higher than all patient groups (all p values < 0.001). Importantly, no significant differences were evident among the patient groups (all p values > 0.1).

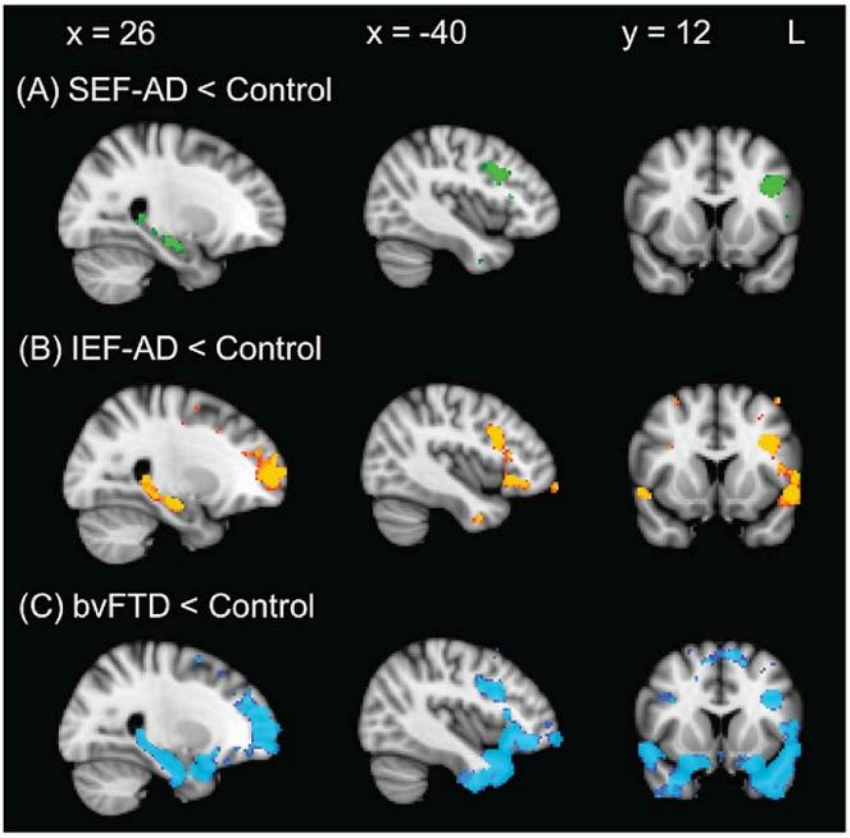

Fig. 2. VBM analyses showing brain regions of decreased grey matter intensity in (A) SEF-AD patients in comparison with controls, (B) IEF-AD patients in comparison with controls, and (C) bvFTD patients in comparison with controls. Colored voxels show regions that were significant in the analyses with $p < 0.001$, uncorrected for all contrasts, with a cluster threshold of 100 contiguous voxels. Clusters are overlaid on the MNI standard brain.

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 (Fig. 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 (Fig. 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 (Fig. 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

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					
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					
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 $p < 0.001$; only clusters with at least 100 contiguous voxels included. All clusters reported $t > 3.87$. MNI, Montreal Neurological Institute.

(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 $p < 0.001$ and cluster threshold of 100 contiguous voxels (Fig. 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 (Fig. 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 (Fig. 3C, Table 2).

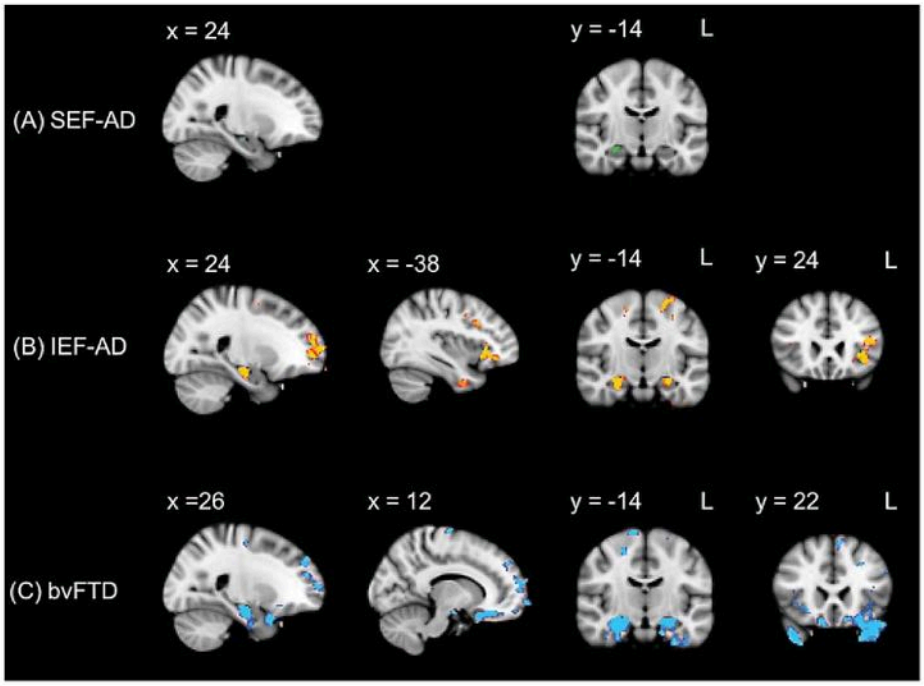

Fig. 3. VBM analyses showing brain regions in which grey matter intensity correlates significantly with memory recall performance in (A) SEF-AD compared with controls, (B) IEF-AD compared with controls, and (C) bvFTD compared with controls. Colored voxels show regions that were significant in the analysis with $p < 0.001$ uncorrected, with a cluster threshold of 100 contiguous voxels in (B) and (C). Clusters are overlaid on the MNI standard brain.

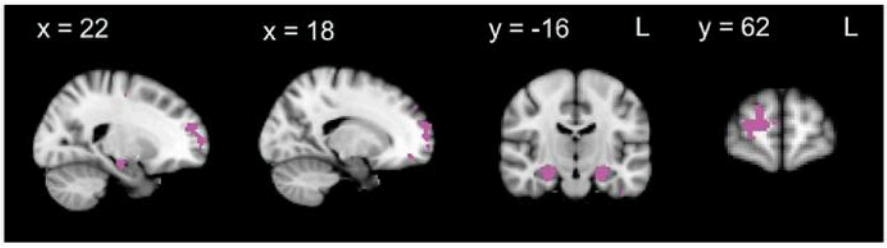

Fig. 4. VBM analyses showing brain regions in which grey matter intensity correlates significantly with memory recall performance in both IEF-AD and bvFTD. Colored voxels show regions that were significant in the analysis with $p < 0.001$ uncorrected, with a cluster threshold of 100 contiguous voxels. Clusters are overlaid on the MNI standard brain.

Next, we conducted an overlap analysis to investigate common regions of atrophy that underlie memory performance in IEF-AD and bvFTD (Fig. 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 ($p < 0.001$) 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 ($p < 0.05$) 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

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 behavioural-variant frontotemporal dementia (bvFTD) patients

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

All results uncorrected at $p < 0.001$; only clusters with at least 100 contiguous voxels included. All clusters reported $t > 4.53$. MNI, Montreal Neurological Institute.

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, 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 organization of information, monitoring and inhibition of responses, and contextual memory [53]. Hence, this dichotomous view does not take into 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. 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 behavioral 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 behavioral symptoms on the CBI-R, including abnormal behavior, stereotypic and motor behaviors, 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 behavioral 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 organization 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.

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SUPPLEMENTARY MATERIAL

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2.2. Concluding remarks

The findings reported in this chapter provide further support against the dichotomous view that memory impairments in AD and bvFTD are solely driven by MTL and PFC dysfunction, respectively. Very little is understood, however, regarding the contributions of different PFC subdivisions to episodic memory impairment in these patient groups. As outlined in Chapter 1, the lateral PFC purportedly mediates strategic and organisational aspects of memory, whereas the medial PFC appears to be crucial for attaching subjective value to memory. While this chapter provided insights into the influence of lateral PFC functions in memory, it is unclear how medial PFC functions relate to episodic memory recall in AD and bvFTD. To address this gap in the literature, the next chapter contrasts the relative contributions of the lateral and medial PFC to episodic memory dysfunction in AD and bvFTD.

Chapter 3
Lateral and medial prefrontal cortex contributions to episodic memory in AD and bvFTD

The lateral and medial subdivisions of the PFC are proposed to mediate different aspects of episodic memory, though it is unclear how the functions of these subdivisions relate to episodic memory impairments in AD and bvFTD. This chapter focuses on contrasting these PFC subdivisions in AD and bvFTD using standardised neuropsychological measures that assess dlPFC and vmPFC functions, and explores associations between episodic memory recall performance and PFC atrophy.

3.1. Publication II

Wong, S., Flanagan, E., Savage, G., Hodges, J. R., & Hornberger, M. (2014). Contrasting prefrontal cortex contributions to episodic memory dysfunction in behavioural variant frontotemporal dementia and Alzheimer's disease. *PLoS ONE*, *9*(2), e87778–13. http://doi.org/10.1371/journal.pone.0087778

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Contrasting Prefrontal Cortex Contributions to Episodic Memory Dysfunction in Behavioural Variant Frontotemporal Dementia and Alzheimer's Disease

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Abstract

Recent evidence has questioned the integrity of episodic memory in behavioural variant frontotemporal dementia (bvFTD), where recall performance is impaired to the same extent as in Alzheimer's disease (AD). While these deficits appear to be mediated by divergent patterns of brain atrophy, there is evidence to suggest that certain prefrontal regions are implicated across both patient groups. In this study we sought to further elucidate the dorsolateral (DLPFC) and ventromedial (VMPFC) prefrontal contributions to episodic memory impairment in bvFTD and AD. Performance on episodic memory tasks and neuropsychological measures typically tapping into either DLPFC or VMPFC functions was assessed in 22 bvFTD, 32 AD patients and 35 age- and education-matched controls. Behaviourally, patient groups did not differ on measures of episodic memory recall or DLPFC-mediated executive functions. BvFTD patients were significantly more impaired on measures of VMPFC-mediated executive functions. Composite measures of the recall, DLPFC and VMPFC task scores were covaried against the T1 MRI scans of all participants to identify regions of atrophy correlating with performance on these tasks. Imaging analysis showed that impaired recall performance is associated with divergent patterns of PFC atrophy in bvFTD and AD. Whereas in bvFTD, PFC atrophy covariates for recall encompassed both DLPFC and VMPFC regions, only the DLPFC was implicated in AD. Our results suggest that episodic memory deficits in bvFTD and AD are underpinned by divergent prefrontal mechanisms. Moreover, we argue that these differences are not adequately captured by existing neuropsychological measures.

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Introduction

Behavioural variant frontotemporal dementia (bvFTD) is the second leading cause of early-onset dementia, after Alzheimer's disease (AD) [1,2]. Patients with bvFTD present with a range of symptoms, notably decline in social behaviour and personal conduct, ritualized activity, loss of empathy, emotional blunting and executive dysfunction [3]. While episodic memory deficits are a well-established early feature of AD [4], the diagnostic criteria for bvFTD mandate a predominantly dysexecutive cognitive profile, with relative sparing of episodic memory and visuospatial skills [3]. Indeed, an amnestic presentation still remains an exclusion criterion for diagnosis of bvFTD [3,5].

Increasing evidence, however, shows that a proportion of bvFTD cases, including those with pathological confirmation, can present with marked episodic memory deficits [6–9], and are generally impaired on standard recall based memory tasks [10], despite relatively intact recognition memory compared to age-matched controls [11–13]. While some studies report greater impairment on measures of memory recall in AD compared to bvFTD [14–16], others have demonstrated that patients with bvFTD show comparable deficits [17–20]. The reason for these discrepant results is currently unclear, but may be due to various factors, such as disease progression, types of memory measures and the inclusion of the recently recognised non-progressive bvFTD 'phenocopy' patients [17].

Investigations into the underlying neural correlates of episodic memory deficits usually focus on medial temporal lobe (MTL) damage, particularly in the hippocampus. Episodic memory impairments in AD have largely been attributed to hippocampal atrophy [18,21]. Not surprisingly, in light of the recent memory findings, bvFTD patients show similar degrees of hippocampal atrophy during earlier disease stages compared to AD [18,22], and this can be even more severe in bvFTD at post mortem [23]. Nevertheless, the extent to which the pervasive prefrontal cortex atrophy in bvFTD contributes to their amnesia is unclear. Indeed, evidence from visual atrophy rating [18], whole-brain voxel-based morphometry (VBM) [24] and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) [19] studies, in which the degree of episodic memory deficits was covaried with brain dysfunction, show that not only MTL but also prefrontal atrophy contribute to the episodic memory deficits in bvFTD.

The role of the prefrontal cortex (PFC) in episodic memory is still controversial [25]. Current evidence from neuroimaging and lesion studies suggests that the strategic aspects of episodic memory recall are mediated by PFC structures [26,27], in particular the dorsolateral PFC (DLPFC) [28,29]. Accordingly, it has been proposed that episodic memory deficits in bvFTD may be related to failure of strategic retrieval processes due to difficulties with planning and organisation of information during encoding and/or retrieval [30]. Further support for this arises from studies that have demonstrated associations between impaired autobiographical memory retrieval and executive dysfunction in bvFTD [31]. Executive dysfunction is also a prominent component of AD [4,32], however, and is associated with memory deficits [33] and PFC atrophy [34]. DLPFC atrophy is evident in both AD and bvFTD and does not serve as a reliable marker to distinguish between the two diseases [35]. This raises the question as to whether other PFC regions might contribute to the memory deficits seen in bvFTD.

The ventromedial prefrontal cortex (VMPFC) emerges as the region which most likely influences episodic memory performance in bvFTD because it is affected very early in the illness [35–37] and shows strong connections with the MTL [38]. Very few studies, however, have investigated the relative contribution of VMPFC dysfunction to episodic memory recall in bvFTD. For example, Pennington and colleagues [18] revealed that correlations between PFC atrophy and episodic memory deficits were strongest for the VMPFC and not DLPFC. Similarly, impaired autobiographical memory recall appears to be related to VMPFC dysfunction [39]. This is corroborated by functional imaging studies in healthy participants, which have shown that contextual information retrieval is associated with MTL-VMPFC interaction [40,41]. Still, to date no study has directly contrasted the DLPFC and VMPFC contributions to episodic memory deficits in bvFTD and AD to reveal such a dissociation.

The current study set out to address this issue by directly contrasting DLPFC and VMPFC functions and their contributions to episodic memory in bvFTD and AD. In particular, we employed neuropsychological measures typically tapping into either DLPFC or VMPFC functions, to quantify the relationship between performance on these tasks and measures of episodic memory recall. We further sought to elucidate the prefrontal neural substrates of these relationships using VBM covariate analyses. Based on previous evidence we predicted that episodic memory dysfunction in both patient groups would relate to divergent patterns of prefrontally mediated task performance and grey matter atrophy. Specifically, in bvFTD we hypothesised that episodic memory impairment would be mainly related to VMPFC-mediated tasks and atrophy. In contrast, we predicted that episodic memory impairment in AD would be more correlated with DLPFC-mediated tasks and atrophy.

Methods

Case Selection

A sample of 22 bvFTD and 32 AD patients and 35 age- and education-matched controls were selected from the FRONTIER database, resulting in a total of 89 participants. All bvFTD patients fulfilled proposed criteria for possible bvFTD [3] as well as consensus criteria for FTD [5], with insidious onset, decline in social behaviour and personal conduct, emotional blunting and loss of insight. All AD patients met NINCDS-ADRDA diagnostic criteria for probable AD [4]. Disease duration was estimated as the number of years elapsed since onset of symptoms. The age- and education-matched healthy control group consisted of volunteers or spouses/carers of patients (see Table 1 for demographic details). To determine their overall level of cognitive functioning, all participants underwent general cognitive screening using the Addenbrooke's Cognitive Examination-Revised (ACE-R) [42]. The Frontotemporal Dementia Rating Scale (FRS) [43] and Clinical Dementia Rating Scale (CDR) [44] were used to determine the disease severity in bvFTD and AD patients. In addition, the Cambridge Behavioural Inventory revised (CBI-R) [45] was used to quantify symptoms of behavioural disturbance reported by the family or carer, with higher scores indicative of more behavioural disturbance.

Ethics Statement

All participants provided written informed consent, and dual consent was obtained from the carer for some participants. This study was approved by the South Eastern Sydney and Illawarra Area Health Service and the University of New South Wales ethics committees.

Neuropsychological Measures

The Rey Auditory Verbal Learning Test (RAVLT) [46] was administered as a measure of episodic memory recall 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 of those words. Following a 30-minute delay, recall of List A is re-assessed, followed by a recognition test, containing all items from List A as well as words from List B and 20 new words. The immediate recall following interference trial (A6) score was included in our analyses.

Episodic memory recall for visual information was assessed using the Rey-Osterrieth Complex Figure (RCF) test [47]. Three minutes after copying a complex figure as accurately as possible, participants were instructed to reproduce the figure from memory. The 3-minute recall score was included in our analyses.

The following measures of prefrontal function were administered: the Controlled Oral Word Association Test (COWAT) [48], the Backwards Digit Span test [49], the Brixton Spatial Anticipation Test and the Hayling Sentence Completion Test [50], the Iowa Gambling Task (IGT) [51] and The Awareness of Social Inference Test (TASIT) [52].

The COWAT is a timed task that involves generating a list of words that begin with a specified letter (over 3 trials, for F, A or S). The Backwards Digit Span is measure of working memory, where participants are required to repeat series of numbers (which increase in length over trials) in backwards order. In healthy adults, performance on the COWAT is associated with DLPFC grey matter volume [53] and activation of the DLPFC has been demonstrated during the Backwards Digit Span task [54]. The total correct scores were recorded for both the COWAT and Backwards Digit Span tests.

The Brixton Spatial Anticipation Task involves rule attainment and the use of feedback to guide future actions. In this task, participants view several pages with an array of ten circles. In each array, one of the ten circles is coloured blue and the position of the blue circle varies from page to page in accordance with simple rules. The participant is required to predict the location of the blue circle on subsequent pages, based on its location in previous pages. Although few studies have systematically examined the neural correlates that underpin performance on the Brixton Test, one study has found significantly impaired performance in patients

Table 1. Demographic characteristics and experimental composite scores across participant groups[a].

	Controls	*bvFTD*	*AD*	*Group effect*	*bvFTD vs. Control*	*AD vs. Control*	*bvFTD vs. AD*
N	35	22	32				
Sex (M/F)	19/16	14/8	20/12	n.s.	.	.	.
Mean age (years)	64.20 (5.38)	61.23 (7.45)	63.53 (6.98)	n.s.	.	.	.
Education (years)	12.79 (2.60)	11.33 (2.51)	12.41 (3.28)	n.s.	.	.	.
Disease duration (years)	.	3.82 (2.44)	3.20 (2.09)	.	.	.	n.s.
FRS Rasch score [b]	.	−0.37 (1.02)	0.25 (0.96)	.	.	.	n.s.
CDR sum of boxes [18][b]	0.32 (0.46)	7.08 (2.86)	5.05 (2.68)	***	***	***	**
ACE-R [100]	95.00 (3.3)	76.00 (10.47)	67.84 (17.75)	***	***	***	n.s.
CBI-R total frequency score [180]	3.77 (4.57)	67.36 (34.72)	40.33 (26.48)	***	***	***	n.s.
CBI-R selected subscores:							
Memory/Orientation [32]	1.50 (2.68)	16.18 (6.95)	16.00 (7.27)	***	***	***	n.s.
Everyday skills [20]	0.17 (0.389)	7.09 (5.49)	7.25 (5.599)	***	***	***	n.s.
Abnormal behaviour [24]	0.25 (0.45)	9.18 (6.74)	2.08 (2.31)	***	***	n.s.	**
Stereotypic/motor behaviours [16]	0.58 (0.79)	7 (5.33)	1.5 (2.15)	**	***	n.s.	**
Recall composite	99.56 (21.1)	37.86 (28.76)	20.55 (18.69)	***	***	***	n.s.
DLPFC task composite	99.53 (18.88)	54.60 (26.03)	57.39 (21.73)	***	***	***	n.s.
VMPFC task composite	99.81 (7.95)	69.26 (17.19)	82.88 (15.03)	***	***	***	***

[a]Standard deviations in parentheses, maximum score for tests shown in brackets.
[b]All patients had either FRS or CDR disease severity measures.
**$p<.01$, ***$p<.001$, n.s. = non-significant.
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with focal left lateral PFC lesions [55]. To allow comparison between neuropsychological measures, the Brixton total error score was converted to a total correct score.

The Hayling Test assesses the ability to inhibit prepotent verbal responses on a sentence completion task. An initial baseline phase requires completion of a sentence with a logical word as quickly as possible; the second phase involves inhibition of an automatic logical response, and rather, completion of the sentence with a word that is semantically unrelated. Performance on the Hayling Test is correlated with orbitofrontal cortex (OFC) atrophy in bvFTD [56]. The total number of errors scored by each participant on Section 2 of the test was subtracted from the maximum possible error score to allow comparison between neuropsychological measures, such that lower values indicate greater impairment.

The IGT is a computer-administered task, which involves selecting cards from four decks, each of which is associated with varying degrees of monetary profit or loss. Overall, selecting cards from decks A and B results in larger net loss, whereas selecting cards from decks C and D leads to greater net profit. The total number of cards chosen from each of the four decks was recorded, from which a modified total net score (decks D – A) was calculated. Positive scores indicate a dominance of advantageous deck choices, whereas negative scores indicate a dominance of disadvantageous deck choices. IGT task performance in bvFTD is correlated with VMPFC atrophy [57]. To allow conversion of IGT scores into percentages of the control mean for calculation of composite scores, scores were linearly transformed to ensure all scores were positive.

The Emotion Evaluation subtest from the TASIT evaluates comprehension of basic emotion through 28 professionally enacted video vignettes, portraying positive (happiness, surprise or neutral) or negative (sadness, anger, anxiety or revulsion) emotions. Participants are shown a response card listing each of the emotions in a random order, and are required to state the emotion that is being portrayed by the actor. In bvFTD patients, poor negative emotion recognition is associated with OFC atrophy [58]. The total number of correct responses was recorded.

Composite Scores

All neuropsychological test scores were converted into percentage of the control mean, before averaging to yield composite scores. RAVLT and RCF recall scores were averaged to produce a recall composite. Based on previous studies that demonstrate associations between task performance and regional atrophy or activation, prefrontal tasks were subdivided into DLPFC task and VMPFC task composite scores. The DLPFC task composite included scores from the COWAT, Backwards Digit Span and Brixton Spatial Anticipation tasks. Scores from the Hayling Sentence Completion Task, IGT and TASIT were included in the VMPFC task composite score.

Statistics

Data were analysed using SPSS20.0 (SPSS Inc., Chicago, Ill., USA). Kolmogorov-Smirnov tests were used to check for normality of distribution in the demographic data, neuropsychological measures and composite scores. Where the data were normally distributed, scores were compared across the three groups (bvFTD, AD and controls) using ANOVAs followed by Bonferroni *post-hoc* tests. Data that were not normally distributed were analysed using Kruskal-Wallis tests followed by *post-hoc* Mann-Whitney U tests with Bonferroni correction for multiple comparisons. A chi-square test was used to check for significant gender differences across groups.

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 256×256, 200 slices, 1×1 mm^2 in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 ms. 3D T1-weighted sequences were analysed using FSL-VBM, a voxel-based morphometry analysis [59,60], which is part of the FLS software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html [61]. Following brain extraction from the images, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) [62]. The resulting gray matter partial volume maps were aligned to the Montreal Neurological Institute standard space (MNI52) using the nonlinear registration approach with FNIRT [63,64], which uses a b-spline representation of the registration warp field [65]. 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: 8 mm). Next, a voxelwise general linear model (GLM) was applied and permutation-based non-parametric testing (with 500 permutations per contrast) was used to form clusters with the Threshold Free Cluster Enhancement (TFCE) method [66]. Given our focus on the PFC and MTL involvement in memory recall, the VBM analysis was limited to the temporal and frontal lobes by creating a mask using the Montreal Neurological Institute standard space (MNI152) atlas. Based on the a priori hypothesis that performance on tasks included in the DLPFC task composite is related to the integrity of the DLPFC, VBM analysis of this composite score was performed using a mask including this region. Similarly, VBM analysis of the VMPFC task composite was limited to the VMPFC by using a mask for this region.

Group comparisons and covariate analyses of the composite data were tested for significance at $p<.05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space. Within patient groups, covariate analyses were conducted at significance levels of $p<.05$, False Discovery Rate (FDR) corrected. This increases sensitivity by controlling the expected proportion of false positives among suprathreshold voxels only, rather than all false positives across all voxels. Regions of significant atrophy were superimposed on T1-weighted standard brain images for spatial normalization and visual comparison with a brain atlas, allowing localisation of areas of significant grey matter loss. A cluster threshold of 50 contiguous voxels for significant atrophy clusters was applied and regions of atrophy are reported in MNI coordinates. To increase sensitivity, the cluster threshold was lowered to 20 contiguous voxels for within patient group analyses.

Results

Demographics and Global Cognitive Functioning

Demographics and general cognitive scores can be seen in Table 1. As a Bonferroni correction was applied, all *post hoc* group comparisons are reported at a.0167 level of significance. Participant groups did not differ in terms of age, sex or education ($p's>.1$). The bvFTD and AD patient groups were matched for disease duration ($p>.1$). While disease severity did not differ between patient groups on the FRS ($p>.05$), the mean CDR sum of boxes score was higher in bvFTD compared to AD patients ($p=.008$). On the cognitive screening test (ACE-R), both patient groups were significantly impaired in comparison to controls ($p<.001$) but did not differ ($p>.1$). Based on CBI-R scores, both patient groups showed significantly more symptoms of overall behavioural disturbance compared to age-matched controls ($p's<.001$), with a trend towards more severe symptoms in bvFTD compared to AD patients, though this did not survive correction for multiple comparisons ($p=.039$). Further analysis of selected CBI-R subscales showed that although memory/orientation and everyday skills ($p's>.05$) were equally impaired in both patient groups, bvFTD patients showed more severe symptoms of abnormal behaviour and stereotypic/motor behaviours ($p's<.01$).

Neuropsychological Measures

The results of the neuropsychological measures are shown in Table S1. Distributions across all measures were non-normal, except for the COWAT. On measures of memory recall, both patient groups were significantly impaired compared to controls ($p's<.001$). While RAVLT scores did not differ between patient groups ($p=.238$), there was a trend for better RCF recall performance in bvFTD compared to AD patients ($p=.032$), though this did not survive correction for multiple comparisons. On all measures of prefrontal function, both patient groups were significantly impaired in comparison to controls ($p's<.0167$). However, bvFTD and AD patients only differed significantly on the Hayling AB error score ($p=.008$), with bvFTD patients making overall more errors.

Composite Scores

Results for the composite scores are shown in Table 1. Distributions were normal for the DLPFC task and VMPFC task composites but non-normal for the recall composite. Both patient groups were significantly impaired across all composite scores, in comparison to controls ($p's<.001$). Although there was a trend for worse recall performance in AD compared to bvFTD patients, this did not survive correction for multiple comparisons ($p=.025$). There were no significant differences between bvFTD and AD patients in terms of DLPFC task composite scores ($p>.1$). In contrast, VMPFC task composite scores were significantly lower in bvFTD patients compared to AD patients ($p=.001$).

Correlations between Composite Scores

Spearman rank correlations were used to quantify relationships between the composite scores. Across all groups, the recall composite was significantly correlated with both the DLPFC task ($r_s=.589$, $p<.001$) and VMPFC task ($r_s=.558$, $p<.001$) composites. Correlations between composite scores failed to reach statistical significance in either patient group, separately.

VBM Results

Group analysis. Participant groups were contrasted to reveal patterns of brain atrophy in the frontal and temporal mask. In comparison to controls, bvFTD patients showed widespread atrophy in frontal polar, orbitofrontal, anterior temporal, hippocampal, paracingulate and insular regions (Figure S1A). For AD patients, significant atrophy was found in comparison to controls, encompassing hippocampal, temporal, paracingulate and frontal regions (Figure S1B). Direct comparison of patient groups revealed significantly greater atrophy of the prefrontal and anterior temporal regions in bvFTD (Figure S1C). The reverse contrast did not reveal any regions of significantly greater atrophy in AD compared to bvFTD (Figure S1D).

Correlations with composite scores across all participants. Composite scores were entered as covariates in the design matrix of the VBM analysis. FWE corrected

significance levels of $p<.05$ and a cluster threshold of 50 contiguous voxels was used for all significant atrophy clusters. Across all participants, regions of atrophy that correlated with the recall composite included the insular cortex, frontal operculum cortex, middle and inferior temporal gyri, parahippocampal gyrus, hippocampus, frontal pole and temporal fusiform gyrus (Figure 1A, Table 2). The DLPFC task composite correlated with atrophy in the pre- and post-central gyri and the inferior and middle frontal gyri (Figure 1B, Table 2), whereas the VMPFC task composite was correlated with frontal pole, frontal operculum cortex, orbitofrontal cortex, paracingulate gyrus and insular cortex atrophy (Figure 1C, Table 2).

Correlations with composite scores within patient groups. In further analyses, we investigated the correlations between the composite scores and regions of atrophy for each patient group. FDR corrected significance levels of $p<.05$ and a cluster threshold of 20 contiguous voxels were used for all significant atrophy clusters. In bvFTD patients, recall measures were associated with atrophy in regions including the parahippocampal gyrus, hippocampus, temporal pole, paracingulate gyrus, frontal pole, orbitofrontal gyrus, and superior and middle frontal gyri (Figure 2A, Table 3). Scores on the DLPFC task composite were related to atrophy in the middle and superior frontal gyrus, precentral gyrus, supplementary motor cortex, postcentral gyrus and posterior cingulate gyrus (Figure 2B, Table 3). In contrast, the VMPFC task composite was associated with atrophy in the orbitofrontal cortex, medial frontal cortex, anterior and paracingulate gyri, frontal pole and frontal operculum cortex (Figure 2C, Table 3).

In AD patients, recall measures were correlated with atrophy in the pre- and post-central gyri, middle temporal gyrus, supplementary motor cortex, middle and superior frontal gyrus, temporal pole and frontal pole (Figure 3A, Table 4). Whereas the DLPFC task composite scores were related to atrophy in the precentral gyrus and inferior, middle and superior frontal gyri (Figure 3B, Table 4), the VMPFC task composite was associated with atrophy in the orbitofrontal cortex, frontal pole, supplementary motor

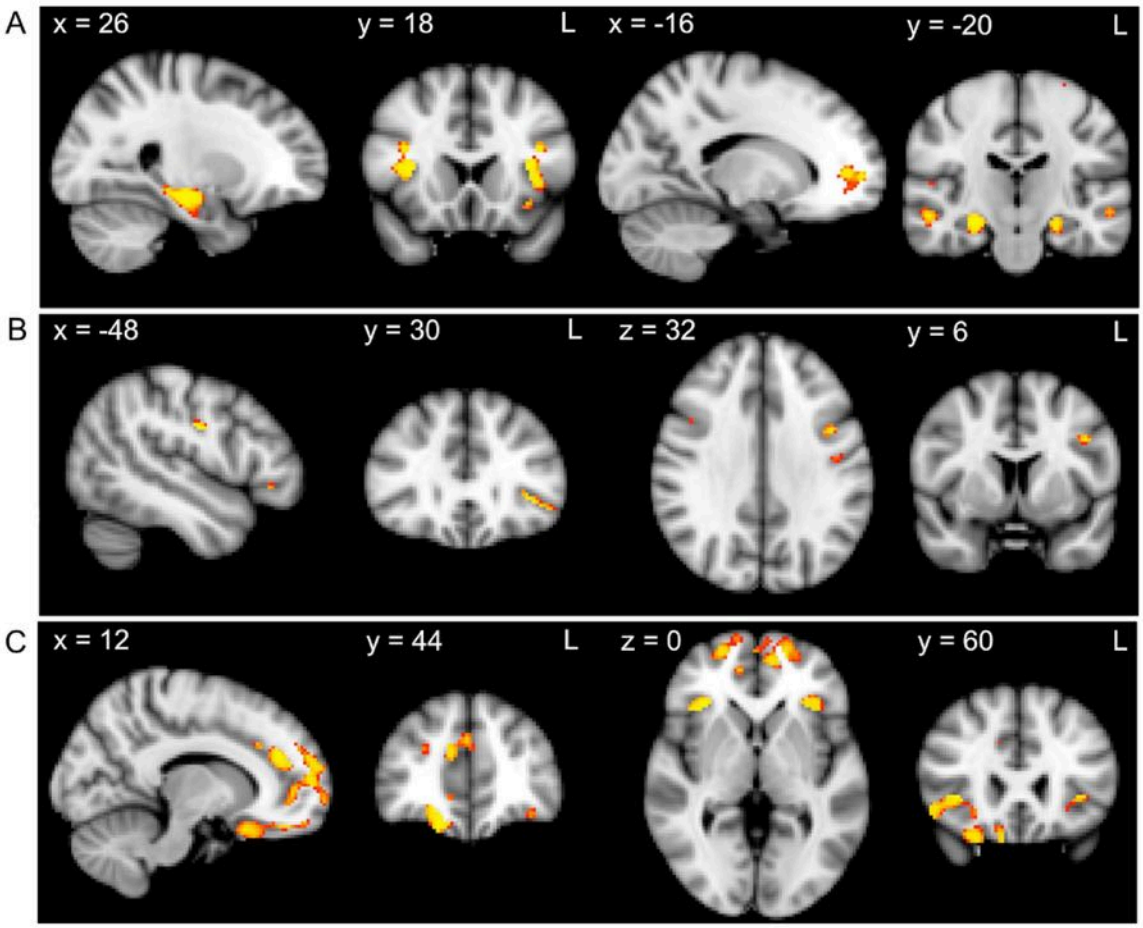

Figure 1. Grey matter atrophy correlates for recall, DLPFC task and VMPFC task performance across all participants. VBM analysis showing brain regions in which grey matter intensity correlates with the A) recall composite, B) DLPFC task composite and C) VMPFC task composite. Clusters are overlaid on the MNI standard brain. Coloured voxels show regions that were significant in the analysis for $p<.05$, corrected for multiple comparisons via Family-wise Error correction across space, and a cluster threshold of 50 contiguous voxels.
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Table 2. Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with composite scores across all groups.

Regions	Hemisphere (L/R/B)	MNI Coordinates			Number of voxels	T-score (peak voxel)
		X	Y	Z		
Recall						
Insula cortex/frontal operculum cortex	L	−38	20	0	395	2.96
Middle temporal gyrus	R	58	−32	−4	292	2.96
Parahippocampal gyrus	R	26	−20	−18	285	2.96
Hippocampus	L	−24	−14	−20	268	2.96
Frontal operculum cortex/insula cortex	R	36	18	8	220	2.96
Frontal pole	L	−16	56	2	172	2.96
Temporal fusiform cortex/parahippocampal gyrus	L	−30	−14	−36	99	2.96
Inferior temporal gyrus	R	50	−42	−18	58	2.46
DLPFC tasks						
Postcentral gyrus/precentral gyrus	L	−48	−10	30	52	2.96
Postcentral gyrus	L	−30	−28	62	27	2.96
Middle frontal gyrus	L	−42	6	32	23	2.71
Inferior frontal gyrus	L	−42	30	−2	22	2.71
VMPFC tasks						
Frontal pole	R	18	44	−22	1260	2.96
Frontal operculum cortex/orbitofrontal cortex	R	36	24	0	726	2.96
Paracingulate gyrus	L	−10	54	6	486	2.71
Paracingulate gyrus	R	12	38	22	176	2.96
Insular cortex/orbitofrontal cortex	L	−32	26	2	102	2.71
Frontal pole/orbitofrontal cortex	L	−34	40	−16	73	2.57

All results corrected at $p<.05$; only clusters with at least 50 contiguous voxels included.
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cortex, paracingulate gyrus and cingulate gyrus (Figure 3C, Table 4).

Prefrontal contributions to recall composite scores. A partial correlation analysis further explored whether damage to prefrontal regions could have explained the significant correlations with the recall composite score. In bvFTD patients, both DLPFC and VMPFC regions still correlated significantly (p's$<.01$) with the recall composite score when temporal lobe atrophy was taken into account. In AD patients however, only DLPFC regions remained significantly correlated ($p<.05$) with the recall composite score once temporal lobe atrophy was taken into account.

Overlap in recall, DLPFC and VMPFC task atrophy covariate regions. Finally, we explored whether atrophy covariates of the memory recall composite overlapped with the atrophy covariates of the DLPFC task and VMPFC task composites. For all participants combined, atrophy patterns showed significant overlap between the recall and VMPFC task measures in the orbitofrontal cortex/insular cortex, paracingulate gyrus and frontal pole (Figure 4 Table 5). Although a small region of atrophy correlating with both recall and DLPFC task composites was identified in the inferior frontal gyrus, this failed to reach statistical significance (Table 5). Within bvFTD patients, no regions of overlap were identified for the recall and DLPFC task composites. Within AD patients however, a significant region of overlap for recall and DLPFC task composites was identified in the precentral gyrus (peak voxel: $X=-36$, $Y=-24$, $Z=58$). While small regions of overlap for recall and VMPFC task composites were identified within each patient group, these failed to reach statistical significance.

Discussion

The current study investigated the PFC contributions to episodic memory recall performance in bvFTD and AD. Behaviourally, our results confirm that episodic memory recall performance is strongly correlated with DLPFC and VMPFC task performances. However, imaging analysis showed that impaired recall performance is associated with divergent patterns of PFC atrophy in bvFTD and AD. Whereas in bvFTD, PFC atrophy correlates for recall encompassed DLPFC, VMPFC and frontal pole regions, only the DLPFC and frontal pole were implicated in AD. Importantly, after controlling for temporal lobe atrophy, both DLPFC and VMPFC regions remained significantly correlated with recall performance in bvFTD, whereas only DLPFC atrophy remained correlated with recall performance in AD.

On a behavioural level, the current findings provide further support to a growing body of evidence, which suggests that bvFTD and AD patients are impaired to a similar degree on standard neuropsychological measures of episodic memory recall [17–19,24]. Successful memory recall is multifaceted, however, and poor performance may be due to the disturbance of different underlying mechanisms. The current study aimed to compare the contribution of DLPFC- and VMPFC-mediated processes to episodic memory recall impairments in bvFTD and AD. Consistent with previous findings [14,32,33], our results demon-

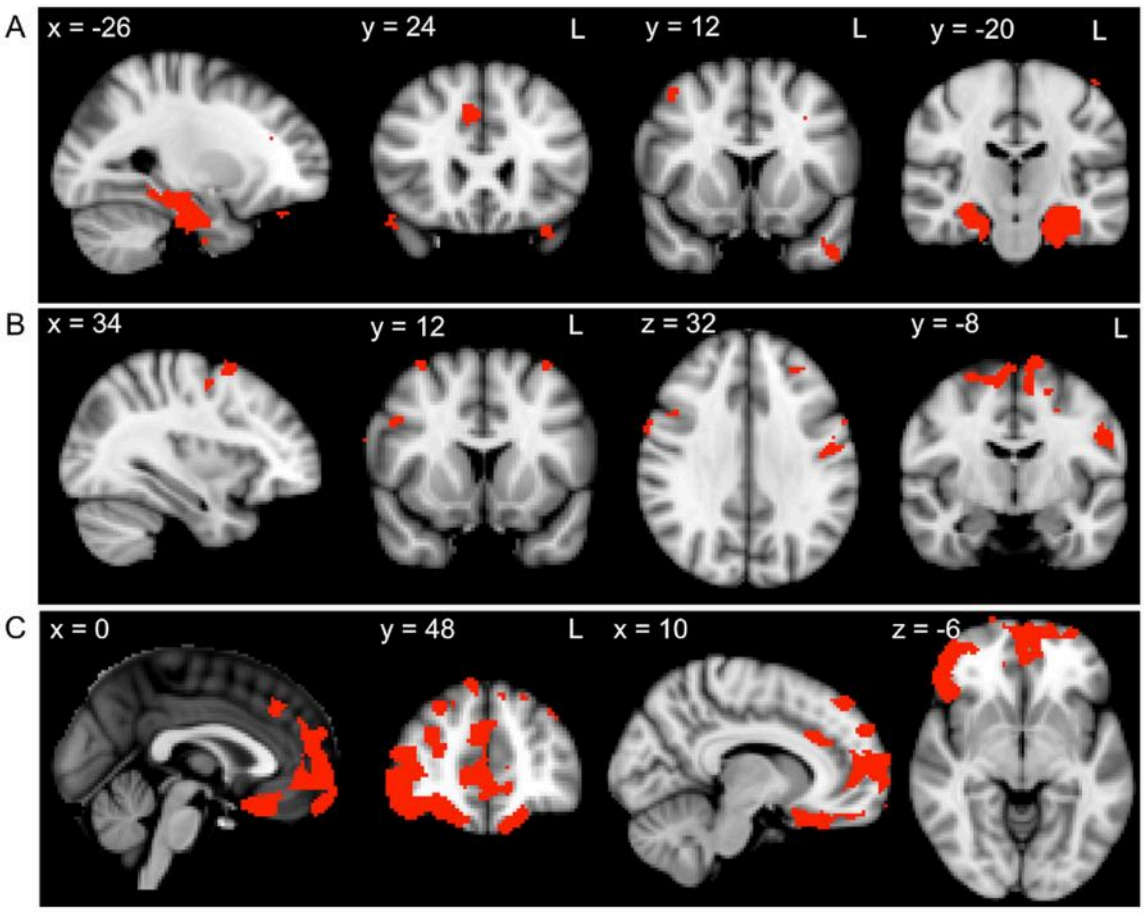

Figure 2. Grey matter atrophy correlates for recall, DLPFC task and VMPFC task performance within the bvFTD group. VBM analyses showing brain regions in which grey matter intensity correlates with the A) recall composite, B) DLPFC task composite and C) VMPFC task composite in bvFTD patients. Clusters are overlaid on the MNI standard brain. Coloured voxels show regions that were significant in the analyses for $p<.05$ FDR corrected and a cluster threshold of 20 contiguous voxels.
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strate that both patient groups are impaired on standard neuropsychological measures that tap into DLPFC function. This likely reflects the comparable severity of DLPFC atrophy found in both patient groups [35]. In contrast, performance on VMPFC tasks was significantly worse in bvFTD compared to AD patients, consistent with the typical pattern of atrophy evident early in bvFTD [35–37]. Correlations between the recall composite and DLPFC or VMPFC task composite scores were significant across all groups, however, this did not reach significance within patient groups, likely due to a lack of statistical power. Another possible explanation is the heterogeneity of DLPFC- and VMPFC-mediated functions targeted by the measures included in our composite scores. The use of composite scores did not allow disentangling specific aspects of these prefrontal functions, which may differentially contribute to recall performance and needs to be addressed in future studies.

Our imaging findings support the notion that episodic memory deficits in bvFTD and AD are mediated by different neural mechanisms. Previous studies have demonstrated that divergent patterns of atrophy and hypometabolism underlie the memory deficits evident in both AD and bvFTD [19,24]. Whereas medio-parietal and temporal regions are implicated in AD, neural correlates of memory impairment in bvFTD include lateral and medial frontal, frontal-subcortical and anterior temporal regions [19,24]. Our imaging results support these previous findings by showing that both frontal and temporal regions are correlated with episodic memory recall across patient groups. Whilst previous studies have contrasted the neural correlates of episodic memory using whole brain approaches [19,24], we sought to further elucidate specific prefrontal contributions to memory recall using a combination of region-of-interest analyses and partial correlations, which showed that divergent patterns of PFC atrophy are associated with recall performance in bvFTD and AD. Crucially, VMPFC regions were implicated in bvFTD only, whereas DLPFC and frontal pole atrophy was correlated with recall performance in both patient groups. These results are in line with earlier findings that these regions are implicated in episodic memory deficits in bvFTD [18,19,24]. Furthermore, the prefrontal regions remained significantly correlated with recall performance even after controlling for temporal lobe atrophy. This suggests that DLPFC

Table 3. Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with composite scores within the bvFTD group.

Regions	Hemisphere (L/R/B)	MNI Coordinates			Number of voxels	T-score (peak voxel)
		X	Y	Z		
Recall						
Parahippocampal gyrus/hippocampus	L	−24	−20	−34	1068	3.23
Parahippocampal gyrus/hippocampus	R	22	−20	−32	813	3.23
Temporal pole	L	−48	18	−44	80	3.23
Paracingulate gyrus	R	6	24	34	53	3.23
Frontal pole	R	8	42	−28	48	3.23
Orbitofrontal cortex	L	−32	22	−26	38	3.23
Paracingulate gyrus	R	18	50	4	31	3.23
Frontal pole	R	42	60	6	29	3.23
Superior frontal gyrus	L	−22	8	72	27	3.23
Middle frontal gyrus	R	32	30	22	24	3.23
Frontal pole/Orbitofrontal cortex	L	−28	36	−24	24	3.23
DLPFC tasks						
Precentral gyrus/Supplementary cortex	R	6	−14	58	502	3.23
Precentral gyrus/Postcentral gyrus	L	−48	−10	28	108	3.23
Middle frontal gyrus	R	34	8	58	69	3.23
Precentral gyrus	R	16	−28	40	43	2.93
Middle frontal gyrus	L	−34	14	62	33	2.93
Frontal pole/Middle frontal gyrus	L	−28	38	30	31	3.23
Precentral gyrus/Superior frontal gyrus	L	−20	−14	56	29	3.23
Precentral gyrus	L	−45	−10	32	28	2.52
Precentral gyrus/Middle frontal gyrus	R	34	−6	52	27	3.23
Precentral gyrus	L	−57	4	38	25	2.75
Precentral gyrus	R	62	6	32	23	2.52
Superior frontal gyrus	R	12	4	72	22	2.75
Cingulate gyrus (posterior)	L	−14	−32	40	21	2.93
VMPFC tasks						
Orbitofrontal cortex/Medial prefrontal cortex/Frontal pole	B	12	24	−26	5589	3.23
Frontal pole	R	8	46	46	96	3.23
Anterior cingulate gyrus	R	10	24	28	86	2.93
Paracingulate gyrus	B	2	32	44	69	3.23
Frontal pole	R	24	46	38	62	2.75
Frontal pole	L	−52	42	12	57	3.23
Frontal pole	L	−38	44	36	46	3.23
Frontal pole/Superior frontal gyrus	L	−24	38	48	40	2.3
Frontal operculum cortex/Orbitofrontal cortex	L	−34	26	2	33	2.36
Anterior cingulate gyrus	L	−8	−14	38	28	2.93
Frontal pole	L	−12	52	44	25	2.52
Frontal pole	L	−26	38	28	24	2.3
Frontal pole	L	−18	64	26	22	2.3
Orbitofrontal cortex	R	26	24	−26	21	2.1

Results FDR corrected at $p<.05$; only clusters with at least 20 contiguous voxels included.
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atrophy independently contributes to the memory impairments in both patient groups, with additional involvement of the VMPFC in bvFTD only.

Previous studies have highlighted the role of the DLPFC in the strategic aspects of episodic memory recall [28,29]. Together with previous reports that bvFTD and AD patients show comparable levels of DLPFC atrophy [35], our findings suggest that episodic

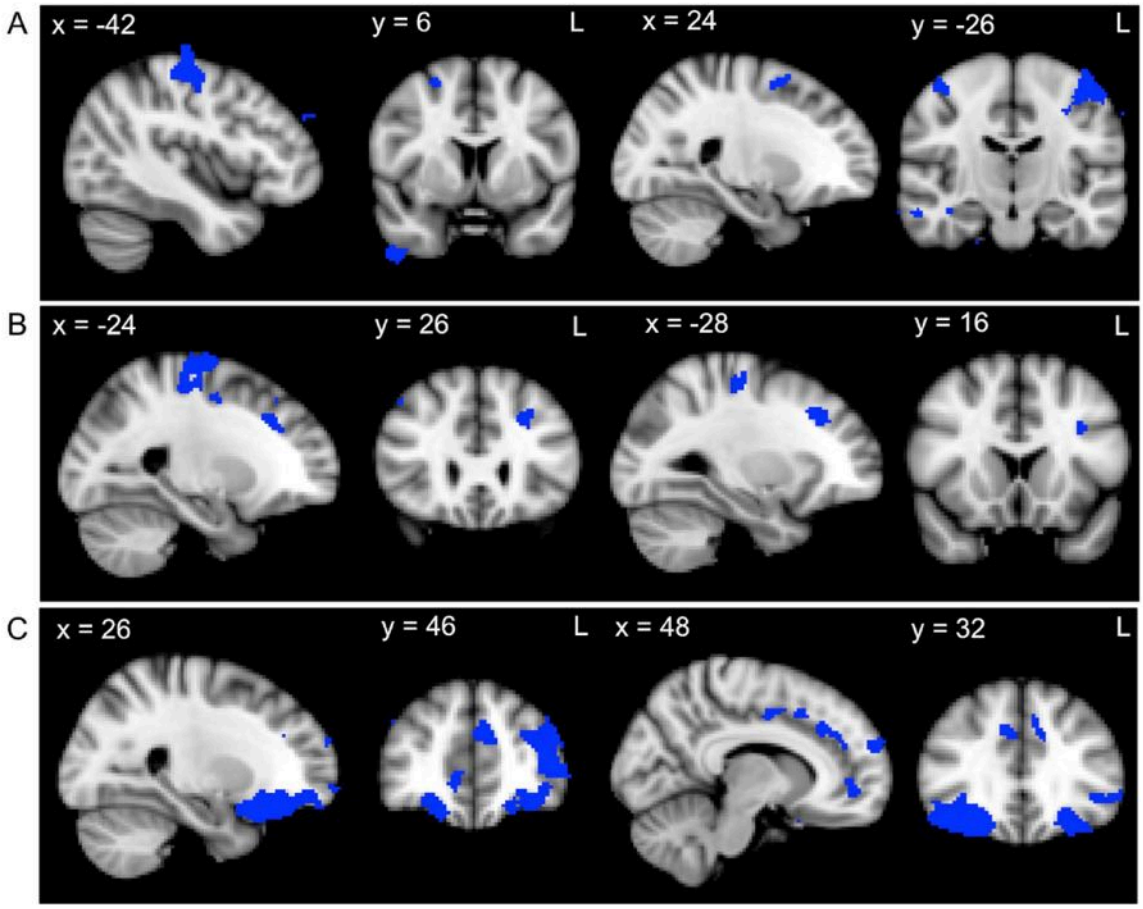

Figure 3. Grey matter atrophy correlates for recall, DLPFC task and VMPFC task performance within the AD group. VBM analyses showing brain regions in which grey matter intensity correlates with the A) recall composite, B) DLPFC task composite and C) VMPFC task composite in AD patients. Clusters are overlaid on the MNI standard brain. Coloured voxels show regions that were significant in the analyses for $p<.05$ FDR corrected and a cluster threshold of 20 contiguous voxels.
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memory deficits in both patient groups are related to the disruption of DLPFC-mediated strategic retrieval processes. Previous studies investigating these processes using conventional measures of executive function (e.g. COWAT and digit span backwards) suggest that impaired performance on these tasks is not specific to bvFTD, with AD patients also showing deficits [33,67]. Another potential explanation for the DLPFC involvement is that it reflects an inherent bias towards the use of strategic retrieval processes in standard neuropsychological measures of episodic memory recall. It is therefore possible that current measures of episodic memory recall lack sufficient specificity to distinguish between the two patient groups because they target memory processes that require the DLPFC, a region which is similarly affected in bvFTD and AD [35]. By contrast, an association between episodic memory performance and VMPFC integrity was found in bvFTD patients only. The VMPFC has been shown to be involved in various social-executive cognitive processes, including theory of mind [68], self-referential processing and perspective taking [69], emotion processing [70] and inhibition [71]. Not surprisingly, bvFTD patients are known to be impaired on tasks tapping into VMPFC functions [72,73]. We confirm this notion by showing more impairment on VMPFC-mediated tasks in bvFTD when compared to AD. Findings from our overlap analyses, however, suggest that the atrophy correlates for recall, DLPFC and VMPFC task performance show only minimal similarities. This is likely due to the heterogeneity of measures included within our prefrontal composite scores. It is also possible that these measures quantify individual prefrontal mechanisms rather than their contributions to episodic memory recall per se.

Taken together, our results indicate that performance on measures tapping into VMPFC function can distinguish between bvFTD and AD patients, and that there is greater involvement of VMPFC regions in episodic memory recall in bvFTD. It may therefore be worthwhile employing episodic memory tasks that tap into VMPFC functions. One potential approach could involve the self-reference effect on memory, where information that is evaluated in reference to one's self is better remembered than information that is evaluated external to one's self [74]. For example, items that have been subjectively rated for pleasantness are better remembered than items rated for similarity to

Table 4. Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with composite scores within the AD group.

Regions	Hemisphere (L/R/B)	MNI Coordinates			Number of voxels	T-score (peak voxel)
		X	Y	Z		
Recall						
Precentral gyrus	L	−42	−14	46	559	3.11
Precentral gyrus/postcentral gyrus	R	40	−24	58	182	3.11
Middle temporal gyrus (temporo-occipital part)	R	66	−58	6	120	3.11
Supplementary motor cortex	B	2	0	54	116	3.11
Middle temporal gyrus (posterior)	R	70	−6	−26	108	3.11
Superior frontal gyrus	R	22	−2	52	89	3.11
Temporal pole	R	48	8	−52	69	3.11
Postcentral gyrus	L	−64	−20	38	52	3.11
Frontal pole	L	−10	76	12	44	3.11
Frontal pole	R	60	42	−2	44	3.11
Middle frontal gyrus	L	−52	22	30	42	3.11
Frontal pole	R	44	60	−18	35	3.11
Frontal pole	L	−16	62	38	33	3.11
Middle frontal gyrus	R	32	24	26	33	3.11
Supramarginal gyrus/Middle temporal gyrus (temporo-occipital part)	L	−52	−50	12	32	3.11
DLPFC tasks						
Precentral gyrus/Superior frontal gyrus	L	−24	−28	52	480	3.11
Middle frontal gyrus	L	−28	24	38	113	2.83
Precentral gyrus	R	12	−16	72	27	2.55
Precentral gyrus	R	22	−16	64	26	2.83
Superior frontal gyrus	L	−18	−6	56	26	2.67
Inferior frontal gyrus	L	−32	14	26	23	3.11
VMPFC tasks						
Orbitofrontal cortex/Frontal pole	L	−24	22	−26	2130	3.11
Orbitofrontal cortex/Frontal pole	R	24	20	−26	2101	3.11
Paracingulate gyrus/Cingulate gyrus	B	−12	50	18	621	3.11
Frontal pole	R	12	62	22	124	3.11
Frontal pole	R	38	56	10	63	3.11
Paracingulate gyrus	R	12	48	−4	51	2.55
Frontal pole	L	−22	68	−2	47	2.67
Supplementary motor cortex	R	10	2	46	41	2.83
Frontal pole	L	−4	70	2	31	2.67
Paracingulate gyrus	R	12	16	44	26	2.67

Results FDR corrected at $p<.05$; only clusters with at least 20 contiguous voxels included.
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background colour [41]. Importantly, retrieval of self-relevant information is associated with the integrity [75] and activity [76] of the medial PFC (MPFC). Similarly, Leshikar and Duarte [41] demonstrated that activation of the MPFC during the self-referential encoding of information is predictive of subsequent accuracy in source memory retrieval. The incorporation of such measures may therefore provide important insights into the role of VMPFC regions in episodic memory retrieval in bvFTD.

From a clinical perspective, identifying differences in the underlying mechanisms of episodic memory deficits in bvFTD and AD may support differential diagnosis of these cohorts. Our findings confirm that performance on verbal and visual episodic memory recall tasks do not reliably distinguish between bvFTD and AD patients. Given that memory impairment remains an exclusion criterion, this may limit the sensitivity of current diagnostic criteria for bvFTD [3]. One potential reason for the limited sensitivity of current neuropsychological measures of episodic memory recall is their reliance on DLPFC-mediated strategic retrieval processes. Importantly, our findings also demonstrate that both bvFTD and AD patients are impaired on executive measures that tap into DLPFC function. While current diagnostic criteria for bvFTD describes a predominantly dysexecutive profile [3], revised criteria for AD also allow for nonamnestic presentations, with prominent executive dysfunction

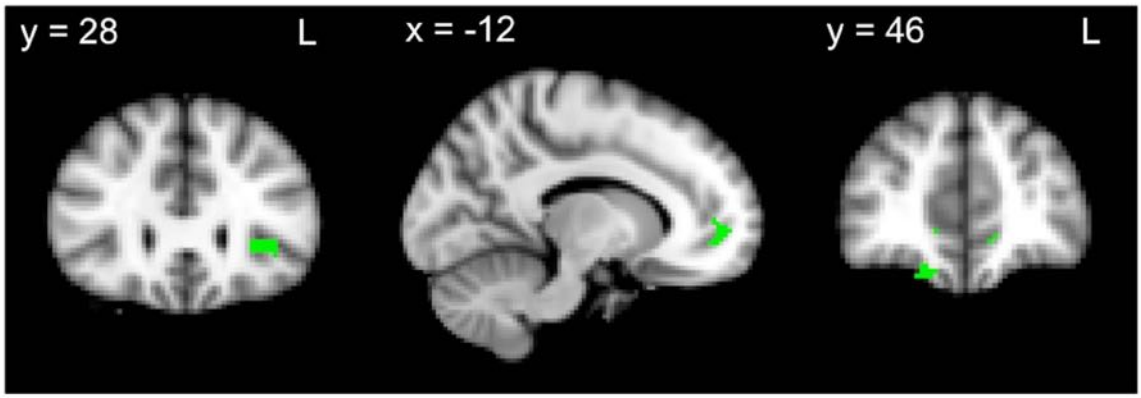

Figure 4. Overlapping regions of grey matter atrophy for the recall and VMPFC task composites across all participants. VBM analyses showing overlap in brain regions in which grey matter intensity correlates with recall and VMPFC task composites across all participants. Coloured voxels show regions that were significant in the analyses for $p<.05$ FDR corrected and a cluster threshold of 20 contiguous voxels.
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[77]. As such, the inclusion of measures that tap into VMPFC-mediated social-executive functions appears to be a promising approach. Accordingly, previous studies that have compared DLPFC- and VMPFC-mediated executive functions in low and high functioning bvFTD patients showed that VMPFC-mediated functions were affected in both the low and high functioning patient groups, whereas impairments on DLPFC-mediated tasks were evident in low functioning patients only [72,73]. This supports the notion that VMPFC- rather than DLPFC-mediated tasks are more sensitive to the earliest neuropathological changes in bvFTD, which occur in the VMPFC before progressing to the DLPFC [37,72,73]. Therefore, incorporation of these measures into standard clinical assessments would likely contribute to earlier diagnosis and treatment. Nonetheless further exploration of the divergent neural mechanisms underlying episodic memory deficits in bvFTD and AD is warranted.

There are a number of caveats to consider. Firstly, despite the significant hippocampal atrophy identified in AD patients compared to controls, hippocampal atrophy correlates for recall performance failed to meet our criteria for statistical significance. While it is possible that regions not included in our frontal and temporal lobe mask show stronger correlations with recall performance in AD, this finding is difficult to explain. Similarly, the involvement of pre- and postcentral gyrus and supplementary motor cortex atrophy in recall performance in AD was an unexpected finding. However, precentral gyrus atrophy [35] and correlations between recall performance and pre- and post-central gyrus atrophy [24] have previously been reported. There is also some evidence to suggest that these motor and premotor regions are involved in the maintenance of verbal or visual information in working memory [78,79]. Given that atrophy in these regions were also correlated with DLPFC task performance, it is likely that deficits in working memory contribute to poor episodic memory recall. Nevertheless, replication of our results using specific measures of working memory rather than a composite of DLPFC-mediated tasks represents an important area of future inquiry. Finally, the impact of prefrontal grey matter atrophy on underlying white matter tracts remains to be elucidated. Given that the hippocampus shares reciprocal connections with both the DLPFC and VMPFC [38,80], future studies should explore the prefrontal white matter contributions to episodic memory deficits.

A number of methodological issues warrant discussion. Firstly, neuropathological confirmation of the patients' clinical diagnoses were not available, given that the majority of our sample had not

Table 5. Voxel-based morphometry results showing regions of significant grey matter intensity decrease that correlate with recall performance and overlap with those which correlate with DLPFC or VMPFC task performance (across all groups).

		MNI Coordinates				
Regions	**Hemisphere (L/R/B)**	**X**	**Y**	**Z**	**Number of voxels**	**T-score (peak voxel)**
Recall and DLPFC task						
Inferior frontal gyrus	L	−34	30	0	1*	1.67
Recall and VMPFC task						
Insular cortex/Orbitofrontal cortex	L	−32	26	2	43	2.49
Paracingulate gyrus	L	−12	52	−4	25	2.15
Frontal pole	R	16	46	−20	21	2.15

All results FDR corrected at $p<.05$; only clusters with at least 20 contiguous voxels included.
*Non-significant.
doi:10.1371/journal.pone.0087778.t005

yet come to autopsy. Although we cannot exclude the possibility that some bvFTD patients had underlying AD pathology, our findings are consistent with previous reports of memory impairment in pathologically confirmed bvFTD cases [8,9,17]. Secondly, the patient groups were matched on the FRS but not CDR sum of boxes. This is unsurprising, given that the two measures emphasize different aspects of disease severity. The FRS encompasses everyday cognition and functional dependence, whereas the CDR is more cognitive and memory oriented. Nonetheless, the use of dementia-specific clinical disease severity staging tools to compare across dementia types remains controversial. Furthermore, the use of composite measures to probe episodic memory recall and DLPFC- or VMPFC-mediated functions did not allow the dissection of specific aspects of these functions. Heterogeneity in memory recall test administration should also be taken into account, given that the RAVLT involves incremental and explicit learning, whereas the RCF test is based on one-trial incidental learning. Nonetheless, our findings help elucidate the PFC correlates of general episodic memory recall dysfunction in different neurodegenerative conditions.

To our knowledge, this is the first study to explore specifically the prefrontal neural correlates of episodic memory recall deficits in bvFTD and AD. The behavioural results of our study call into question the specificity of memory recall impairment in discriminating between the neurodegenerative conditions. Taken together, our behavioural and imaging findings suggest that although divergent prefrontal mechanisms may underlie episodic memory deficits in bvFTD and AD, these are not adequately captured by existing neuropsychological measures. Thus, development of tests that specifically target VMPFC contributions to memory recall would likely further elucidate differences in the nature of memory impairment in bvFTD and AD.

Supporting Information

Figure S1 Grey matter atrophy comparisons between groups. VBM analyses showing brain areas of decreased grey matter intensity in A) bvFTD patients in comparison with Controls, B) AD patients in comparison with Controls, C) bvFTD patients in comparison with AD patients, and D) AD patients in comparison with bvFTD patients. Patient and control group comparisons corrected for multiple comparisons (FWE) with voxel-based thresholding at $p<.05$. Comparisons between patient groups corrected for multiple comparisons (FWE) with threshold-free cluster enhancement at $p<.025$. Clusters are overlaid on the MNI standard brain.
(TIF)

Table S1 Mean raw scores for bvFTD, AD patients and controls on neuropsychological measures.
(DOCX)

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Author Contributions

Conceived and designed the experiments: SW MH GS. Performed the experiments: SW EF MH. Analyzed the data: SW EF MH. Contributed reagents/materials/analysis tools: JRH MH. Wrote the paper: SW MH GS JRH.

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3.2. Concluding remarks

Collectively, findings from Chapters 2 and 3 demonstrate that existing measures of executive function and episodic memory recall lack sufficient specificity to distinguish between AD and bvFTD, as both patient groups show overlapping profiles of dlPFC and MTL atrophy. By capitalising on the disproportionate impairments on measures of vmPFC and dmPFC functions in bvFTD, measures that assess the contributions of these medial PFC regions to episodic memory may therefore provide a novel means of disentangling the memory profiles of bvFTD and AD patients. As discussed in Chapter 1, the medial PFC appears to be involved in attaching subjective value to incoming stimuli, thereby augmenting the encoding of elaborated memory traces that are more amenable to storage and retrieval. This value-based enhancement of episodic memory remains underexplored in bvFTD and AD, and will be the focus of the following three chapters.

Chapter 4
The self-reference effect on memory in AD and bvFTD

The medial PFC is proposed to play a crucial role in attaching subjective value to personally relevant memories. The current and following chapters explore memory for different types of highly valued information, including those that are self-relevant (current chapter), socially-relevant (Chapter 5) and reward-related (Chapter 6), using novel memory measures that have been adapted from experimental tasks previously employed in healthy adults. Considerations for task adaptation, as well as the rationale for assessment and analysis of source memory are discussed in the following sections. To minimise repetition, points discussed here are applicable across Chapters 4–6, unless otherwise stated within those chapters.

4.1. Considerations for task adaptation

In healthy adult participants, investigations of memory encoding effects typically involve exposure to stimuli under certain experimental conditions (encoding phase), followed by assessment of memory for the studied stimuli (test phase). While this general procedure was preserved when adapting experimental tasks for dementia patients and healthy older adults, several issues were taken into consideration. Firstly, the number of stimuli were reduced to adjust for lower attention span and memory capacity, while stimulus exposure time was increased to account for slower processing speed. Although equal stimulus exposure times

were maintained across conditions and participants during the encoding phase, procedures during the test phase were conducted in a self-paced manner. To reduce the effects of fatigue, the total time for each experimental task was minimised as much as possible (< 30 min per task), and regular rest breaks were taken between tasks. Furthermore, instructions were simplified and practice procedures were conducted, to ensure adequate comprehension of the task requirements prior to commencing the main experimental task. The novel memory tasks employed in Chapters 4–6 were initially piloted in samples of healthy younger adults (18–30 years) and healthy older adults (> 65 years), before testing in patient cohorts. This was to ensure that the task parameters and instructions were age-appropriate. Pilot data from the healthy older adults were not included in the final study samples of age-matched controls.

4.2. Assessment of source memory

To examine the effects of medial PFC-driven encoding processes on episodic memory retrieval, item and source recognition memory tests were employed in the current and following two chapters. Source memory refers to memory for the contextual details of an item or event, such as perceptual, temporal, spatial, emotional and social features (Johnson, Hashtroudi, & Lindsay, 1993). These source details distinguish one item/event from another, and are therefore essential in giving memories their 'episodic' nature (Mitchell & Johnson, 2009).

In clinical settings, responses on standardised neuropsychological measures of episodic memory recall and recognition can provide an indirect measure of source memory retrieval accuracy. On word list learning tests, such as the Rey Auditory Verbal Learning Test (Schmidt, 1996), immediate and delayed free recall involve correctly retrieving words associated with the target source (i.e. presented by the experimenter in List A), while recognition requires correctly attributing words to this source. Failures in source memory

may result in intrusions or false positives, where the word is incorrectly attributed to the target source (e.g. incorrectly endorsing a distractor item as belonging to List A) (Mitchell & Johnson, 2009). While such measures are useful in quantifying errors in source memory however, they do not allow us to objectively compare memory for specific contextual details between participants.

In experimental settings, a common method for investigating memory for source details is the Remember/Know/Guess procedure (Yonelinas, 2002). Originally developed by Tulving (1985), the procedure involves asking participants to distinguish between the recognition of items on the basis of 'remembering' or 'knowing'. 'Remember' responses are presumed to involve recollection of specific episodic details, including source memory, whereas 'know' responses reflect a 'feeling of knowing' in the absence of recollection. Although this procedure allows distinction between contextually-rich episodic memory recollection versus mere item recognition, this does not control for variability in the remembered contextual details for each item, thereby rendering it difficult to compare retrieval of source details between different encoding conditions or between participants. Furthermore, this procedure can be difficult to implement in cognitively impaired patients, due to the complexity in eliciting distinct 'remember' and 'know' responses.

A source memory experimental paradigm (or 'source monitoring paradigm') enables the objective assessment of memory for specific contextual details (Johnson et al., 1993). As illustrated in Figure 4.1, this typically involves an initial encoding phase, where items are presented in association with an experimentally manipulated context or source (e.g. different coloured backgrounds). Subsequently, memory for the item (e.g. 'Did you see this item?') and source (e.g. 'Was this item seen on a blue or red background?') are tested using a recognition format. The advantage of this method is that it allows us to compare memory for

specific contextual details across different encoding conditions, as well as across participants. The procedure is also relatively straightforward to implement in patients with dementia (see for example, Irish, Graham, Graham, Hodges, & Hornberger, 2012), as the recognition format provides limited response options. Importantly, the inclusion of both item recognition and source memory measures provides an index of the *quality* of episodic memory, which involves retrieval of not only the item or event itself, but also its contextual details. The novel memory tasks in the current and following two chapters therefore employ a source memory experimental paradigm to investigate the impact of medial PFC encoding processes on item and source memory retrieval.

It is important to note that source memory retrieval inherently involves strategic aspects of memory retrieval. As discussed in Chapter 1, the lateral PFC is involved in selecting retrieval cues that are used to reactivate the stored memory trace, which is monitored and evaluated before a responding on a source memory test (Dobbins, Foley, Schacter, & Wagner, 2002; Rugg et al., 2012; Simons & Spiers, 2003). Patients with damage to the lateral PFC show impairments in source memory, often in the context of intact memory for the item/event itself (Duarte, Ranganath, & Knight, 2005; Schacter, Harbluk, & McLachlan, 1984; Shimamura, Janowsky, & Squire, 1990). Given that the focus of this thesis is on episodic memory—rather than familiarity-based recognition memory, which does not include recollection of contextual details—the use of memory measures that rely on lateral PFC functions is unavoidable. As demonstrated in Chapters 2 and 3, AD and bvFTD patients cannot be reliably distinguished on the basis of lateral PFC mediated memory functions. The novel memory measures in the current and following two chapters therefore aim to contrast the impact of medial PFC mediated encoding processes on episodic memory retrieval, which invariably involves the lateral PFC.

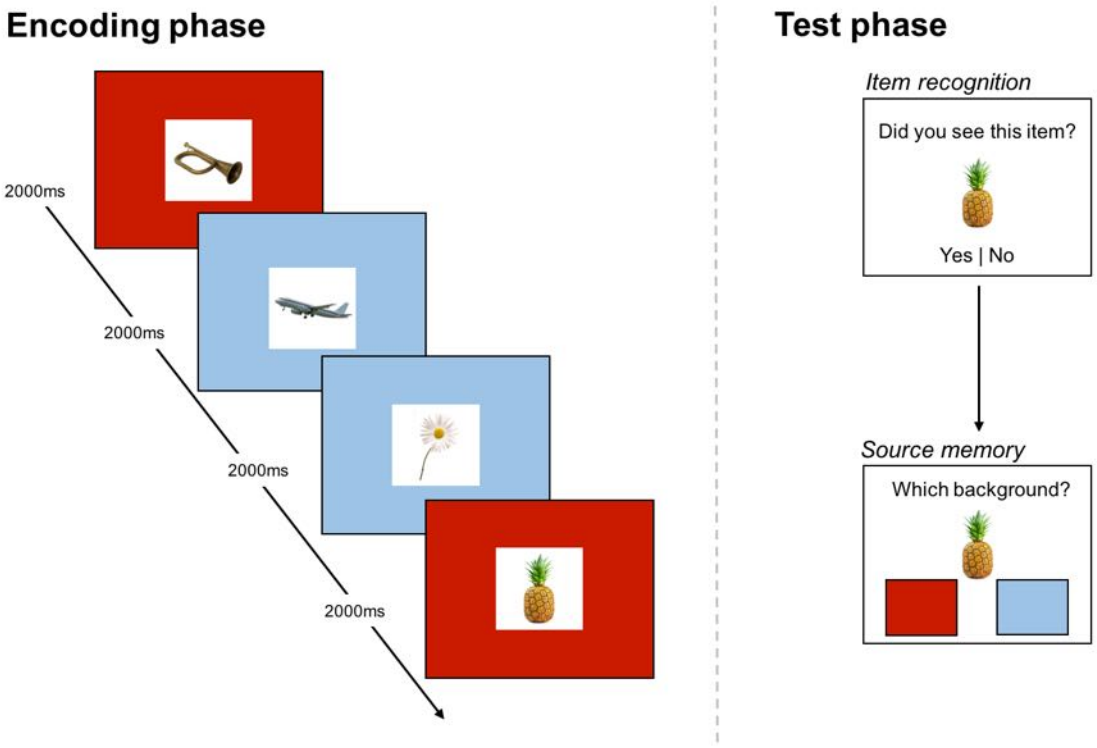

Figure 4.1. Example of encoding and test phase procedures in a source memory experimental paradigm.

Table 4.1. Categories of item and source recognition responses on a source memory experimental paradigm.

		Item recognition	
		Hit	**Miss**
Source recognition	**Hit**	Item-hit/source-hit	Item-miss
	Miss	Item-hit/source-miss	

4.3. Analysis of source memory data

From a source memory experimental design, responses for each item-source association are categorised as one of the following: item-hit/source-hit, item-hit/source-miss or item-miss. Source recognition is presumed to be incorrect for all item-miss responses, as source recognition is only assessed following a 'yes' response on item recognition. This is represented in Table 4.1.

In the source memory literature, empirical measures of source memory data may be calculated using different methods, which affect the types of conclusions that may be drawn from the measure. The first is known as the source identification measure (SIM), which is calculated as the number of item-hit/source-hit responses divided by the total number of items tested (Murnane & Bayen, 1996). As such, the SIM collapses item-hit/source-miss and item-miss responses into one overarching response category (i.e. source unrecollected). As noted by Leshikar & Duarte (2013), this method allows conclusions to be drawn about source memory effects only (and not item memory effects). Item memory effects are instead, assessed separately, typically by subtracting the proportion of item false positives from the proportion of item-hits. The second measure is the conditional source identification measure (CSIM), which is calculated as the number of item-hit/source-hit responses divided by the total number of item-hit responses. As such, source memory decisions are only considered after correct item recognition responses.

While the CSIM avoids confounding item and source memory, this approach can artificially inflate source memory accuracy when item accuracy is low (Bröder & Meiser, 2007; Murnane & Bayen, 1996). For this reason, the CSIM is problematic when analysing source memory in patients with memory impairment. As an alternative to these empirical measures, source memory data may also be analysed using a two-high-threshold multinomial model

(Bayen, Murnane, & Erdfelder, 1996; Simons et al., 2002). As such modeling methods require large numbers of responses, however, this was not feasible in our novel memory measures, which had greatly reduced numbers of stimuli to suit testing in dementia patients. In keeping with previously reported procedures in dementia patients (Rosa, Deason, Budson, & Gutchess, 2014), analyses of source memory data in Chapters 4–6 were therefore conducted using the SIM. This chapter continues with the first study employing these novel methods.

4.4. Publication III

Wong, S., Irish, M., Leshikar, E. D., Duarte, A., Bertoux, M., Savage, G., et al. (2016). The self-reference effect in dementia: Differential involvement of cortical midline structures in Alzheimer's disease and behavioural-variant frontotemporal dementia. *Cortex*, 1–17. http://doi.org/10.1016/j.cortex.2016.09.013

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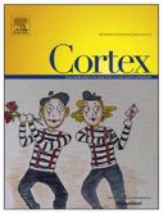

Special issue: Research report

The self-reference effect in dementia: Differential involvement of cortical midline structures in Alzheimer's disease and behavioural-variant frontotemporal dementia

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ABSTRACT

Encoding information in reference to the self enhances subsequent memory for the source of this information. In healthy adults, self-referential processing has been proposed to be mediated by the cortical midline structures (CMS), with functional differentiation between anterior-ventral, anterior-dorsal and posterior regions. While both Alzheimer's disease (AD) and behavioural-variant frontotemporal dementia (bvFTD) patients show source memory impairment, it remains unclear whether they show a typical memory advantage for self-referenced materials. We also sought to identify the neural correlates of this so-called 'self-reference effect' (SRE) in these patient groups. The SRE paradigm was tested in AD ($n = 16$) and bvFTD ($n = 22$) patients and age-matched healthy controls ($n = 17$). In this task, participants studied pictures of common objects paired with one of two background scenes (sources) under self-reference or other-reference encoding instructions, followed by an item and source recognition memory test. Voxel-based morphometry was used to investigate correlations between SRE measures and regions of grey matter atrophy in the CMS. The behavioural results indicated that self-referential encoding did not ameliorate the significant source memory impairments in AD and bvFTD patients. Furthermore, the reduced benefit of self-referential relative to other-referential encoding was not related to general episodic memory deficits. Our imaging findings revealed that reductions in the SRE

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were associated with atrophy in the anterior-dorsal CMS across both patient groups, with additional involvement of the posterior CMS in AD and anterior-ventral CMS in bvFTD. These findings suggest that although the SRE is comparably reduced in AD and bvFTD, this arises due to impairments in different subcomponents of self-referential processing.

1. Introduction

For many years, the concept of self has intrigued philosophers, psychologists and, more recently, neuroscientists. While a number of different theoretical notions and definitions of the self exist, it is accepted that the self plays an important role in memory consolidation (Northoff et al., 2006; Rogers, 1977; Symons & Johnson, 1997). According to Rogers, Kuiper, and Kirker (1977), evaluating new information in relation to the self promotes deeper and more elaborate memory encoding. This so-called self-reference effect (SRE) on memory has since been demonstrated in numerous studies, where self-referentially encoded information is retrieved more accurately on a subsequent memory task, relative to information that has been encoded in relation to another person (other-reference) or based on its physical or semantic features (Rogers et al., 1977; Symons & Johnson, 1997). While the SRE paradigm typically involves encoding and retrieval of trait adjectives (Bower & Gilligan, 1979; Gutchess, Kensinger, & Schacter, 2010), the effect has also been replicated with memory for objects (Hamami, Serbun, & Gutchess, 2011; Leshikar & Duarte, 2013), actions (Rosa & Gutchess, 2011) and specific contextual details (Hamami et al., 2011; Leshikar & Duarte, 2012; Serbun, Shih, & Gutchess, 2011). As such, self-referential encoding promotes episodic memory retrieval by enhancing not only item memory, but also source memory.

The robustness of the SRE has been demonstrated across the lifespan in healthy individuals (Glisky & Marquine, 2009; Gutchess, Kensinger, Yoon, & Schacter, 2007; Gutchess et al., 2015; Leshikar, Dulas, & Duarte, 2015). Importantly, while older individuals typically show age-related decline in source memory accuracy (Johnson, Hashtroudi, & Lindsay, 1993; Yonelinas, 2002), recent work has found that these deficits are ameliorated for source information that has been encoded with reference to the self (Leshikar & Duarte, 2013; Leshikar et al., 2015). Nevertheless, it remains to be established whether self-referencing may benefit source memory retrieval in dementia patients presenting with episodic memory impairment.

Patients with Alzheimer's disease (AD) show marked impairments in episodic memory (McKhann et al., 2011) and perform poorly on source memory tests (Haj & Kessels, 2013; Multhaup & Balota, 1997). While retrieval of self-referential episodic memories from the past are adversely affected in AD (Irish, Lawlor, O'Mara, & Coen, 2011), notably, concept of self appears to be relatively preserved, as indexed on measures of trait self-knowledge (Klein, Cosmides, & Costabile, 2003; Rankin, 2005) and self-descriptive statements (Eustache et al., 2013). To date, evidence for the benefit of self-referential encoding on source memory retrieval in AD is mixed. Most existing studies have evaluated the self-reference *recollection* effect (SRRE) in AD using the Remember/Know/Guess paradigm, where 'remember' responses are presumed to involve episodic memory, with conscious recollection of contextual details, as opposed to 'know' responses, which reflect a 'feeling of knowing' without recollection (Tulving, 1985; 2002). While three studies in AD patients have demonstrated higher rates of 'remember' responses for self-referenced trait adjectives (Kalenzaga & Clarys, 2013; Kalenzaga, Bugaïska, & Clarys, 2013; Lalanne, Rozenberg, Grolleau, & Piolino, 2013), others have found no SRE for item recognition (Leblond et al., 2016) or both reduced SRE and SRRE (Genon et al., 2013). Nonetheless, the Remember/Know/Guess paradigm does not control for the variability of remembered contextual details for each item within and between participants. As such, a source memory experimental design would help objectively determine which, if any, specific contextual details are disproportionately enhanced by self-referencing in AD. While no prior research in AD has investigated the SRE on source memory, one study in patients with amnestic mild cognitive impairment (aMCI) showed a benefit of self-referencing in terms of reducing item and source memory errors (Rosa, Deason, Budson, & Gutchess, 2014).

Individuals diagnosed with behavioural-variant frontotemporal dementia (bvFTD) can also present with episodic memory dysfunction (Bertoux et al., 2014; Graham et al., 2005; Hornberger & Piguet, 2012; Hornberger, Piguet, Graham, Nestor, & Hodges, 2010) and show impaired performance on tests of source memory (Irish, Graham, Graham, Hodges, & Hornberger, 2012; Simons et al., 2002). In contrast to AD however, the core clinical features of bvFTD include marked changes to personality and interpersonal conduct (Piguet, Hornberger, Mioshi, & Hodges, 2011), with declines in social cognition and empathy (Eslinger, Moore, Anderson, & Grossman, 2011; Rascovsky et al., 2011) and lack of insight (Mendez & Shapira, 2011; O'Keeffe et al., 2007). Not surprisingly, bvFTD patients show alterations in their self concept, as reflected in the striking discrepancies between patient and carer ratings of personality traits (Rankin, 2005; Ruby et al., 2007), as well as reports of dramatic changes in social, political or religious values (Miller et al., 2001). To the best of our knowledge, no study to date has explored the impact of self-referential processing on source memory in bvFTD, nor has this been directly contrasted in AD and bvFTD.

Evidence from neuroimaging studies points overwhelmingly to the involvement of cortical midline structures

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(CMS) in self-referential processing (Craik et al., 1999; Gutchess, Kensinger, & Schacter, 2007; Northoff & Bermpohl, 2004; Northoff et al., 2006; Qin & Northoff, 2011). Drawing from this vast body of literature, Northoff et al. (2006) proposed a model in which three distinct CMS subregions (anterior-ventral, anterior-dorsal and posterior CMS) are associated with subfunctions of self-referential processing, including representation, reappraisal and evaluation, and integration (see also Northoff & Bermpohl, 2004). Specifically, the anterior-ventral CMS encompasses the medial orbitofrontal cortex (MOFC), the ventromedial prefrontal cortex (VMPFC) and the sub- and pregenual parts of the anterior cingulate cortex (PACC). This region is proposed to be involved in coding the self-relatedness of stimuli, thereby forming a self-related representation. Evaluation and appraisal of self-referenced stimuli is associated with the anterior-dorsal CMS, which includes the dorsomedial prefrontal cortex (DMPFC) and the supragenual anterior cingulate cortex (SACC). Finally, the posterior CMS comprises the posterior cingulate cortex (PCC), the retrosplenial cortex (RSC), and the medial parietal cortex (MPC). These posterior regions are proposed to be involved in the integration of new self-referential information within the temporal context of one's emotional and autobiographical self. While each of these CMS subregions purportedly mediate specific aspects of self-referential processing, no study to date has directly contrasted the differential contributions of these subregions. One way to address this is by comparing the SRE in AD versus bvFTD patients, as these neurodegenerative disorders are characterised by predominantly posterior and anterior burdens of CMS pathology, respectively (Rabinovici et al., 2007).

To our knowledge, only one study has investigated the neural correlates of self-referential processing in dementia patients (Genon et al., 2013). In this study, AD patients did not show a significant SRE, despite showing similar activation of the VMPFC compared to controls when encoding stimuli with reference to the self. A follow-up investigation revealed a wider functional network of brain regions associated with the accurate recognition of self-referenced information, including the PCC and hippocampus in AD patients (Genon et al., 2014). In the context of Northoff et al. (2006) model, these findings (Genon et al., 2013, 2014) suggest that the absence of SRE in AD may not be related to impairments in the representation of stimuli as self-related by the anterior-ventral CMS, but rather, to a broader deficit in the retrieval of self-related memories, mediated by posterior CMS subregions known to be affected early in the course of the disease (Chételat et al., 2007; Irish, Addis, Hodges, & Piguet, 2012; Nestor, Fryer, Ikeda, & Hodges, 2003; Scahill, Schott, Stevens, Rossor, & Fox, 2002). This dovetails with previous reports of intact concept of self in AD (Eustache et al., 2013; Klein et al., 2003; Rankin, 2005).

Of particular relevance to this study is the pattern of neurodegenerative changes typically seen in bvFTD. Given that the MPFC is one of the earliest affected regions (Kipps, Hodges, Fryer, & Nestor, 2009; Rabinovici et al., 2007; Seeley et al., 2008), this neurodegenerative condition offers an excellent opportunity to examine the impact of MPFC damage on self-referenced memories. While no previous research has explored the SRE in bvFTD, evidence from studies of autobiographical memory in these patients suggests a link between MPFC atrophy and impairments in their retrieval of personally relevant memories from the past (Irish, Hodges, & Piguet, 2013; Irish, Hornberger, et al., 2014). Furthermore, the MPFC represents a site of particular interest, as atrophy in this region has been associated with episodic memory dysfunction in bvFTD, which contrasts with the predominantly posterior pattern of atrophy implicated in AD (Frisch et al., 2013; Irish, Piguet, Hodges, & Hornberger, 2014; Wong, Flanagan, Savage, Hodges, & Hornberger, 2014). Nevertheless, it remains unclear how this anterior-posterior dissociation between bvFTD and AD potentially disrupts the SRE for source memory in these patient groups.

The objectives of this study were twofold: i) to explore whether self-referential encoding would enhance source memory retrieval differentially in bvFTD and AD, and ii) to identify the CMS correlates of the SRE in these patient groups using region-of-interest voxel-based morphometry (VBM). We hypothesised that the SRE for source memory would be comparably attenuated in bvFTD and AD, but that these deficits would be associated with an anterior-posterior dissociation of CMS atrophy. Specifically, we proposed that atrophy of anterior-ventral CMS subregions would relate to the limited benefit of self-referential encoding on source memory retrieval in bvFTD. On the other hand, we predicted that the reduced SRE in AD would be associated with atrophy in the posterior CMS subregions.

2. Material and methods

2.1. Participants

Thirty-eight dementia patients (bvFTD = 22; AD = 16) and 17 age-matched healthy controls were recruited through FRONTIER at Neuroscience Research Australia, Sydney. All bvFTD patients fulfilled clinical diagnostic criteria for probable bvFTD (Rascovsky et al., 2011), with insidious onset, progressive decline in social behaviour and personal conduct, apathy, emotional blunting and loss of insight. To exclude potential phenocopy cases in the bvFTD cohort (Kipps, Hodges, & Hornberger, 2010), only those who showed evidence of progressive decline and atrophy on structural MRI brain scans were included. All AD patients met clinical diagnostic criteria for probable AD (McKhann et al., 2011), with worsening episodic memory impairment in the context of preserved personality and behaviour. Disease duration was estimated as the number of years elapsed since the reported onset of symptoms. The Frontotemporal Dementia Rating Scale (FRS) (Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010) and Clinical Dementia Rating Scale (CDR) (Morris, 1997) were used to determine the disease severity in bvFTD and AD patients. In addition, the Cambridge Behavioural Inventory Revised (CBI-R) (Wear et al., 2008) was completed by the family or carer, to quantify symptoms of behavioural disturbance, with higher scores indicative of more severe behavioural disturbance. To determine their overall level of cognitive functioning, all participants underwent general cognitive screening using the Addenbrooke's Cognitive Examination-III (ACE-III) (Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013). Age-matched healthy controls were recruited from the FRONTIER research

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volunteer panel and scored >88 on the ACE-III (Hsieh et al., 2013).

Exclusion criteria for all participants included current or prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease (stroke, transient ischaemic attacks), alcohol and other drug abuse and limited English proficiency. Exclusion criteria for MRI scanning procedures included presence of metal fragments in the eyes, cardiac pacemaker, brain aneurysm clips, cochlear implants, other ferromagnetic implants or severe claustrophobia.

2.2. Ethics statement

All participants provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethics Committee of the South Eastern Sydney Local Health District and the University of New South Wales.

2.3. Neuropsychological assessment of episodic memory

Following previously reported procedures (Irish, Piguet, et al., 2014; Pennington, Hodges, & Hornberger, 2011), standardised neuropsychological measures of verbal (Rey Auditory Verbal Learning Test; RAVLT) (Schmidt, 1996) and visuospatial (Rey-Osterrieth Complex Figure Test; RCFT) (Rey, 1941) episodic memory were administered to all participants. The following scores were included in our correlational analyses between episodic memory and SRE task performance: RAVLT immediate recall following interference trial (maximum score = 15); RAVLT delayed recall following 30 min (maximum score = 15); and RCFT 3-minute delayed recall (maximum score = 36).

2.4. Experimental self-reference source memory task

The self-reference source memory task was adapted from previous studies (Leshikar & Duarte, 2013; Leshikar et al., 2015). The current version assessed source memory recognition following self-reference and other-reference encoding conditions. A perceptual condition was included as a control condition.

2.4.1. Stimuli

The stimuli consisted of 40 objects and 2 background scenes. During encoding, 30 objects were presented superimposed on 1 of the 2 background scenes. A further 10 objects were presented as novel items at the subsequent recognition memory test. The objects were colour images of common objects (e.g., saxophone, spoon, notebook, etc.) taken from the Hemera Technologies Photo-Objects DVDs (Hemera Technologies, Inc.). The 2 background scenes were colour images of landscapes (a mountain or a beach). The word frequency and familiarity of each object was determined using the MRC Psycholinguistic Database (http://www.psych.rl.ac.uk). Ten objects were allocated to each of the 4 stimulus sets (self-reference, other-reference, perceptual and novel), which were matched for total word frequency and familiarity. Sets assigned per condition were counterbalanced across participants.

2.4.2. Procedure

Participants were first trained on a short version of the encoding and recognition tasks. Training included 12 practice encoding trials (4 trials per encoding task) and 16 practice recognition test trials, containing stimuli from the 12 practice items plus 4 novel items. Participant's understanding of the task instructions was checked before progressing from training to the experimental task. The procedures for the encoding and test phases are illustrated in Fig. 1.

During the training and experimental encoding phases of the study, participants performed encoding tasks under three conditions (self-reference, other-reference and perceptual). Encoding task instructions emphasized that there were no correct answers, as judgements made during the encoding tasks were intended to be subjective.

Self-reference condition: Participants judged whether they liked the object-background pairing (yes/no).

Other-reference condition: Participants judged whether the Queen of England, Elizabeth II, would like the object-background pairing (yes/no). Importantly, a well-known but not close-other person was selected for this condition, as brain regions activated during close-other processing (e.g., one's best friend) have been shown to overlap with those activated during self-referential processing (Grigg & Grady, 2010). As previously described (Leshikar & Duarte, 2013), Queen Elizabeth II was selected as the *other* referent, under the assumption that she was well-known but not personally acquainted with any of the participants. A photograph of Queen Elizabeth II was displayed with the encoding instructions that preceded the other-reference condition. All participants demonstrated intact recognition of Queen Elizabeth II.

Perceptual condition: Participants judged whether the object and background contained similar colours (yes/no).

The encoding phase of the study included a total of 30 trials (10 in each encoding condition). Each encoding trial lasted 4000 msec, including presentation of the object-scene pair for 3500 msec, followed by a 500 msec central fixation. To minimize task-switching costs, trials were presented in blocks of 10 trials per encoding condition. At the beginning of each block, an instruction prompt ("Get ready for the [*self/queen/colour*] task.") was displayed. The order of the blocks was counterbalanced across participants.

The test phase of the experiment was conducted immediately following encoding. The test phase consisted of 40 test trials, where all 30 of the objects from the encoding phase were individually displayed, intermixed with 10 novel objects. Trials were self-paced and presented in a random order. For each trial, participants first made an item recognition decision by judging whether the object was "old" or "new", or whether they didn't know ("don't know"). The prompt "Old|New|Don't know" was written below the object. This was followed by a source recognition decision for those objects judged to be "old". During the source decision, the two background scenes were displayed above the object, with the prompt "Mountain|Beach|Don't know" written below the object. Following previously reported procedures (Leshikar & Duarte, 2013), the "don't know" response option was offered in order to reduce potential contamination of guessing. No feedback regarding response accuracy was provided throughout the task.

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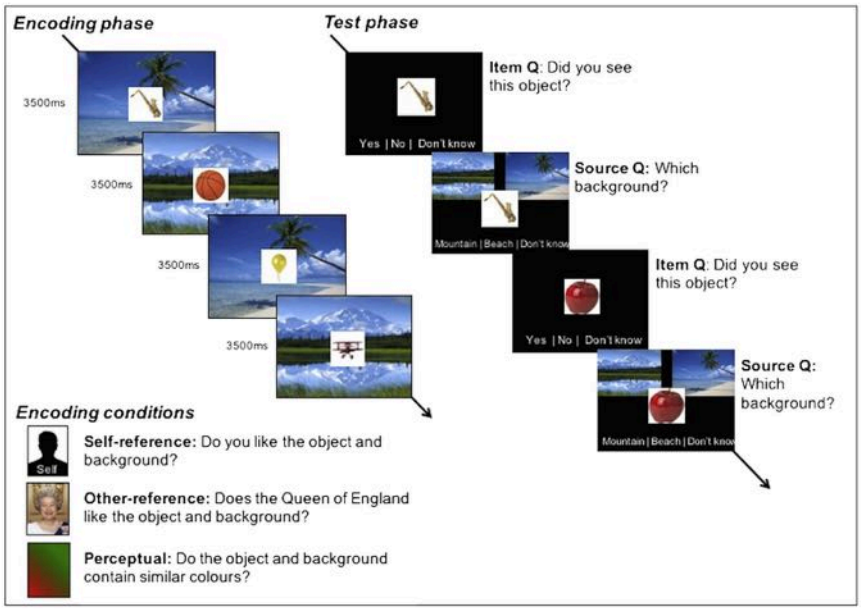

Fig. 1 – Encoding and test phase procedures for the SRE task. Screens were separated by a fixation cross (500 msec) not represented here.

The self-reference source memory task was programmed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), and testing was conducted on a laptop with a 14-inch LED-backlit display. During testing, participants provided verbal responses, which were recorded by the experimenter using the programmed response keys.

2.5. *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. Where the data were normally distributed, scores were compared across groups 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, using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. A chi-squared test was used to compare sex distribution across groups. Demographic variables that differed significantly across groups were included as covariates in between-group analyses of SRE task variables. Item and source recognition accuracy measures from the SRE task were analysed using ANCOVAs. Pairwise comparisons of the main effects were adjusted for multiple comparisons using the Sidak method. To examine differences between encoding conditions within each participant group, *post hoc* paired-samples *t*-tests were conducted for each group separately.

Responses from the test phase of the SRE task were converted into percentages of total items in each condition (self-reference, other-reference, perceptual, novel). Item recognition responses were classified as *studied* 'item hit' (correct recognition), *studied* 'item miss' (incorrect rejection) and *studied* "don't know" for objects previously seen during the encoding phase; and *unstudied* 'item hit' (correct rejection), *unstudied* 'item miss' (false alarm) and *unstudied* "don't know" for novel objects presented in the test phase only. Corrected item recognition was calculated by subtracting the percentage of *unstudied* 'item misses' (false alarms) from the percentage of *studied* 'item hits' (correct recognition) in each condition. Source recognition responses were classified as 'source correct', 'source incorrect' and 'source "don't know"'. Given that the source recognition question was not asked following incorrect item responses (i.e., *studied* 'item miss' and *studied* "don't know" responses), source recognition for incorrect item responses was classified as 'source incorrect'. As such, source recognition responses were assumed to be incorrect for incorrect item responses.

To investigate the source memory advantage of self-reference over other-reference encoding, a SRE magnitude score was computed for source recognition accuracy by subtracting the other-reference percentage 'source correct' scores from the self-reference percentage 'source correct' scores. Thus, larger SRE magnitude scores indicated better memory for self-reference compared to other-reference encoded source information. Within each participant group, independent samples *t*-tests were conducted to determine whether SRE magnitude for source recognition was significantly greater than 0. SRE magnitude scores comparing source recognition accuracy for "self-reference" and "perceptual" encoding conditions were also computed (see Supplementary Material).

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2.6. Image acquisition and VBM analysis

Structural MRI brain scans were available for a subset of participants (19/22 bvFTD and 15/16 AD patients and 15/17 controls). 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 × 256, 200 slices, 1 × 1 mm in-plane resolution, slice thickness 1 mm, TE/TR = 2.6/5.8 msec. 3D T1-weighted sequences were analysed using FSL-VBM, a VBM analysis (Ashburner & Friston, 2000; Good et al., 2001), which is part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html (Smith et al., 2004). Following brain extraction, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang, Brady, & Smith, 2001). The resulting grey matter partial volume maps were aligned to the Montreal Neurological Institute standard space (MNI52) using the nonlinear registration approach with FNIRT (Anderson, Jenkinson, & Smith, 2007a, 2007b) which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). To correct for local expansion or contraction, the registered partial volume maps were modulated by dividing them by the Jacobian of the warp field. Importantly, the Jacobian modulation step did not include the affine part of the registration, which means that the data was normalized for head size as a scaling effect. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8 mm).

Given our strong *a priori* predictions, a single region of interest mask of CMS regions was created by combining individual masks of the relevant Harvard-Oxford cortical structural atlas regions included in the FSL software package. As the regional masks for the frontal pole, orbitofrontal cortex and superior frontal gyri include both medial and lateral portions, masks containing only the medial portions were manually traced. In accordance with Northoff et al. (2006), medial regions were defined as those falling within MNI coordinates $x < 25$ or $x > -25$ (see Fig. 2). The following regions were included in the CMS mask: medial frontal pole, MOFC, medial superior frontal gyrus, medial prefrontal cortex, subcallosal cortex, paracingulate cortex, anterior cingulate cortex, PCC and precuneus. These regions broadly correspond to the CMS subdivisions proposed by Northoff et al. (2006), such that the anterior-ventral CMS includes the medial frontal pole, MOFC, medial prefrontal cortex and subcallosal cortex; the anterior-dorsal CMS includes the medial superior frontal gyrus, paracingulate and anterior cingulate cortices; and the posterior CMS includes the PCC and precuneus.

A voxel-wise general linear model (GLM) was applied to investigate differences in grey matter intensity via permutation-based non-parametric testing (Nichols & Holmes, 2002) with 5000 permutations per contrast. Age and total years of education were included as nuisance variables in all imaging analyses. As a first step, differences in grey matter intensity between patients (bvFTD and AD) and controls were assessed. Group comparisons between patients and controls were tested for significance at $p < .05$, corrected for multiple comparisons via Family-wise Error (FWE) correction across space. A cluster extent threshold of 100 contiguous voxels was applied for group comparisons. Next, correlations between SRE magnitude and regions of grey matter atrophy were investigated separately in each patient group (bvFTD, AD) combined with controls. This procedure has previously been used in similar studies including AD and bvFTD patients (Irish, Piguet, et al., 2014) and serves to achieve greater variance in behavioural scores, thereby increasing the statistical power to detect brain-behaviour relationships. To check for potential co-atrophy effects, diagnostic group membership was entered as an additional nuisance variable in the design matrix of the SRE magnitude covariate analyses, as per the method reported in Sollberger et al. (2009). For this co-atrophy check, we accepted a level of significance of $p < .05$ uncorrected for multiple comparisons for clusters of CMS atrophy previously identified in the SRE magnitude covariate analysis, and $p < .01$ for clusters outside these regions. Finally, inclusive and exclusive masking procedures were employed to identify regions commonly associated with SRE magnitude across both patient groups, as well as regions uniquely associated with SRE magnitude in bvFTD and AD. SRE magnitude covariate analyses and masking procedures were conducted at significance levels of $p < .01$, uncorrected for multiple comparisons. To reduce the potential for false positives, we applied a stringent cluster extent threshold of 50 contiguous voxels for the covariate analyses. Regions of significant atrophy were superimposed on T1-weighted standard brain images, and regions of significant grey matter intensity decrease were localised with reference to the Harvard-Oxford probabilistic cortical atlas. Maximum coordinates for the anatomical locations of significant results are reported in MNI coordinates.

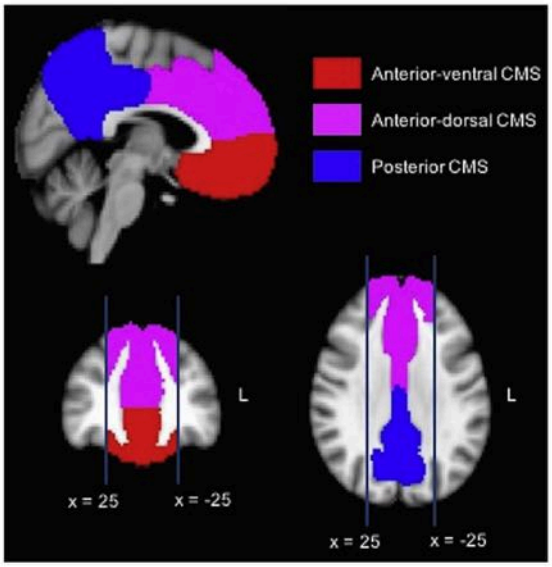

Fig. 2 – Representation of brain regions included in the CMS mask used in VBM analyses.

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3. Results

3.1. Demographics

Demographic and clinical characteristics of the participants are detailed in Table 1. Participant groups were matched for age ($p = .111$) and sex distribution ($p = .281$). An overall group difference was evident for total years of education ($p = .015$), driven by the fact that controls were more highly educated than both bvFTD ($p = .023$) and AD ($p = .039$) patients. The total years of education were subsequently included as a covariate in between-group comparisons of cognitive, episodic memory and SRE task measures.

Importantly, the patient groups were matched for disease duration ($p = .871$) and severity of dementia symptoms on the CDR ($p = .976$). As expected, bvFTD patients were more impaired in comparison to AD patients on a FTD-specific measure of functional impairment (FRS; $p = .016$). Based on CBI-R scores, both patient groups showed significantly more symptoms of overall behavioural disturbance compared to controls (p values $< .001$), with more severe symptoms in bvFTD compared to AD patients ($p = .006$).

3.2. General cognition and episodic memory assessment

Both patient groups were significantly impaired on the ACE-III cognitive screening measure, relative to controls (bvFTD, $p < .001$; AD, $p < .001$). However, performance on the ACE-III was comparable between AD and bvFTD patients ($p = .202$). In comparison to controls, both patient groups demonstrated significant episodic memory impairment across all measures of verbal and visual recall (p values $< .01$). Comparisons between patient groups revealed lower episodic memory performance in AD compared to bvFTD on the RAVLT immediate recall ($p = .004$), RAVLT delayed recall ($p = .015$) and RCFT 3-minute delayed recall ($p = .003$) scores.

3.3. SRE task performance

Supplementary Table 1 shows the mean percentages of each response type (hit, miss, "don't know") for items and sources from the self-reference, other-reference and perceptual encoding conditions, as well as for unstudied items.

3.3.1. Item recognition task

Supplementary Fig. 1 depicts corrected item recognition accuracy for each encoding condition across the three participant groups. A three (group) by three (condition) repeated measures ANCOVA with years of education included as a covariate revealed a significant group effect [$F(2,51) = 10.702$, $p < .001$] for overall corrected item recognition accuracy. This group effect reflected the fact that corrected item recognition accuracy was significantly lower in AD patients relative to controls ($p < .001$), irrespective of condition. Similarly, corrected item recognition accuracy was significantly lower in bvFTD patients compared to controls ($p = .003$). No significant condition effect ($p = .465$) or group × condition interaction ($p = .857$) was evident.

Post hoc paired-samples t-tests were conducted separately for each participant group, to explore differences in corrected item recognition for each encoding condition. In the control group, as expected, corrected item recognition accuracy was higher for the self-reference compared to perceptual condition [$t(16) = 3.913$, $p = .001$] and higher for the other-reference relative to perceptual condition [$t(16) = 3.118$, $p = .007$]. However, corrected item recognition accuracy did not differ across self-reference and other-reference conditions [$t(16) = 1.231$, $p = .236$] in this group. In the bvFTD group, corrected item recognition accuracy was lower for the self-reference compared to other-reference condition [$t(21) = -2.085$, $p = .049$]. While corrected item recognition accuracy was comparable for the self-reference and perceptual conditions in bvFTD [$t(21) = .756$, $p = .458$], this was significantly higher for the other-reference relative to perceptual condition [$t(21) = 2.795$, $p = .011$]. In AD patients, no significant difference in corrected item recognition accuracy was observed between the self-reference and other-reference conditions [$t(15) = .659$, $p = .520$], or between the other-reference and perceptual conditions [$t(15) = .768$, $p = .455$]. Nonetheless, a trend was present for higher corrected item recognition accuracy in the self-reference compared to perceptual condition [$t(15) = 2.085$, $p = .055$].

Table 1 – Demographic and clinical characteristics of the study cohort.[a]

	Control	bvFTD	AD	Group effect	Post hoc test
Sex (M:F)	9:8	14:8	6:10	n.s.	
Age (y)	67.21 (6.35)	62.10 (6.78)	64.81 (9.13)	n.s.	
Education (y)	14.38 (2.38)	11.90 (2.64)	11.91 (3.42)	*	Controls > bvFTD, AD
Disease duration (y)	–	5.54 (3.80)	5.51 (4.67)	n.s.	
CDR sum of boxes [18]	.25 (.38)	5.45 (2.83)	4.10 (1.79)	***	Controls < bvFTD, AD
FRS Rasch score	–	−1.06 (.99)	.06 (1.48)	*	bvFTD < AD
CBI-R total frequency score [100]	3.06 (3.06)	39.57 (13.44)	27.08 (13.36)	***	Controls < AD < bvFTD
ACE-III [100]	96.31 (2.87)	75.82 (12.14)	67.50 (7.67)	***	Controls > bvFTD, AD
RAVLT immediate recall [15]	10.8 (2.48)	5.69 (4.01)	2.07 (1.98)	***	Controls > bvFTD > AD
RAVLT delayed recall [15]	10.67 (2.99)	5.63 (3.26)	1.27 (1.33)	***	Controls > bvFTD > AD
RCFT 3-min recall [36]	22.21 (6.86)	9.80 (6.15)	4.32 (4.99)	***	Controls > bvFTD > AD

Clinical Dementia Rating Scale (CDR); Frontotemporal Dementia Rating Scale (FRS); Cambridge Behavioural Inventory-Revised (CBI-R); Addenbrooke's Cognitive Examination-III (ACE-III); Rey Auditory Verbal Learning Test (RAVLT); Rey-Osterrieth Complex Figure Test (RCFT).
*$p < .05$, **$p < .01$, ***$p < .001$, n.s. = non-significant.
[a] Standard deviations in parentheses, maximum score for tests shown in brackets.

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3.3.2. *Source recognition task*

Fig. 3A depicts source recognition accuracy for each encoding condition across the three participant groups. A three (group) by three (condition) repeated measures ANCOVA with years of education included as a covariate revealed a significant group effect [$F(2,51) = 25.372$, $p < .001$] for overall source recognition accuracy. This group effect indicated that source recognition accuracy was significantly higher in controls compared to both bvFTD ($p < .001$) and AD ($p < .001$) patients, irrespective of condition. Furthermore, AD patients scored significantly lower than bvFTD patients ($p = .003$) on overall source recognition accuracy, regardless of condition. No significant condition effect ($p = .937$) or group × condition interaction ($p = .977$) was detected.

To explore differences in source recognition for each encoding condition, *post hoc* paired-samples *t*-tests were conducted separately for each participant group. In controls, source memory recognition accuracy was significantly higher for the self-reference compared to the other-reference condition [$t(16) = 3.357$, $p = .004$], and higher for the self-reference compared to the perceptual condition [$t(16) = 3.067$, $p = .007$]. In contrast, source memory accuracy did not differ between the other-reference and perceptual conditions in controls [$t(16) = .803$, $p = .434$]. That is, controls showed a significant SRE for source recognition accuracy. In the patient groups however, none of the pairwise comparisons between self-reference, other-reference and perceptual conditions reached significance (all *p* values > .1). Therefore, only control participants showed a significant source memory benefit for self-referenced compared to other-referenced and perceptually encoded stimuli.

3.3.3. *SRE magnitude for source recognition*

Fig. 3B shows the mean SRE magnitude for source recognition accuracy across participant groups. Independent samples *t*-tests were conducted to determine whether SRE magnitude for source recognition was significantly greater than 0, indicating a positive memory advantage for self-referenced information. While SRE magnitude was significantly greater than 0 in the control group [$t(16) = 3.357$, $p = .004$], this did not reach statistical significance in either bvFTD [$t(21) = -.576$, $p = .571$] or AD [$t(15) = .496$, $p = .627$]. As such, only control participants showed a significant SRE, whereas both AD and bvFTD patients showed no source memory enhancement effect for self-referenced information.

3.4. *Correlations between SRE magnitude and episodic memory impairment*

Spearman rank correlations were used to examine the relationship between SRE magnitude and performance on neuropsychological tests of episodic memory. Across all participants, SRE magnitude scores did not correlate significantly with the RAVLT immediate recall ($R = .114$, $p = .449$), RAVLT delayed recall ($R = .178$, $p = .238$) or RCFT 3-min recall ($R = .238$, $p = .097$) scores. Similarly, correlations between SRE magnitude scores and episodic memory scores within each participant group did not reach statistical significance (all *p* values > .1). This suggests that the benefit of self-reference over other-reference encoding was not related to episodic memory performance per se.

3.5. *VBM results*

3.5.1. *CMS grey matter atrophy profiles across patient groups*

Fig. 4 displays the patterns of CMS grey matter atrophy evident in each patient group relative to controls. BvFTD patients showed a predominantly anterior profile of CMS atrophy, encompassing the bilateral subcallosal cortex, orbitofrontal cortex, medial prefrontal cortex, frontal pole, anterior cingulate cortex, paracingulate cortex and superior frontal gyrus, as well as bilateral regions of the PCC (see Fig. 4A, Table 2). In contrast, the AD group showed a predominantly posterior profile of grey matter atrophy, including the bilateral PCC and precuneus. To a lesser extent, bilateral anterior cingulate and paracingulate and right frontal polar

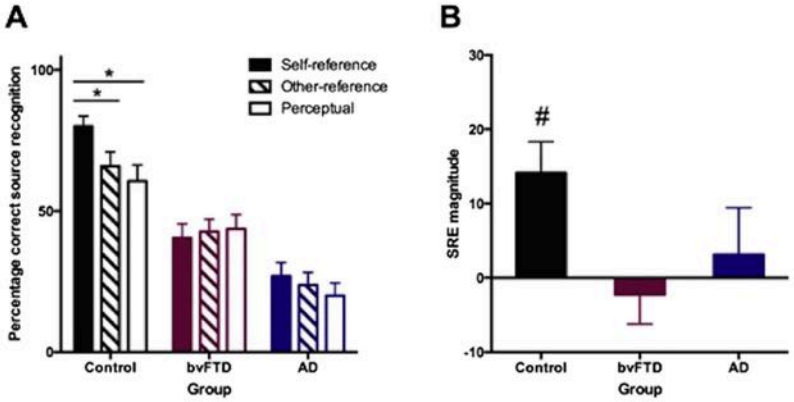

Fig. 3 – A) Mean percentage correct source recognition responses for self-reference, other-reference and perceptual encoding conditions across participant groups. (B) SRE magnitude (self-reference source accuracy – other-reference source accuracy) across groups. * = significant difference between encoding conditions. # = SRE magnitude significantly different from 0. Error bars represent standard error of the mean.

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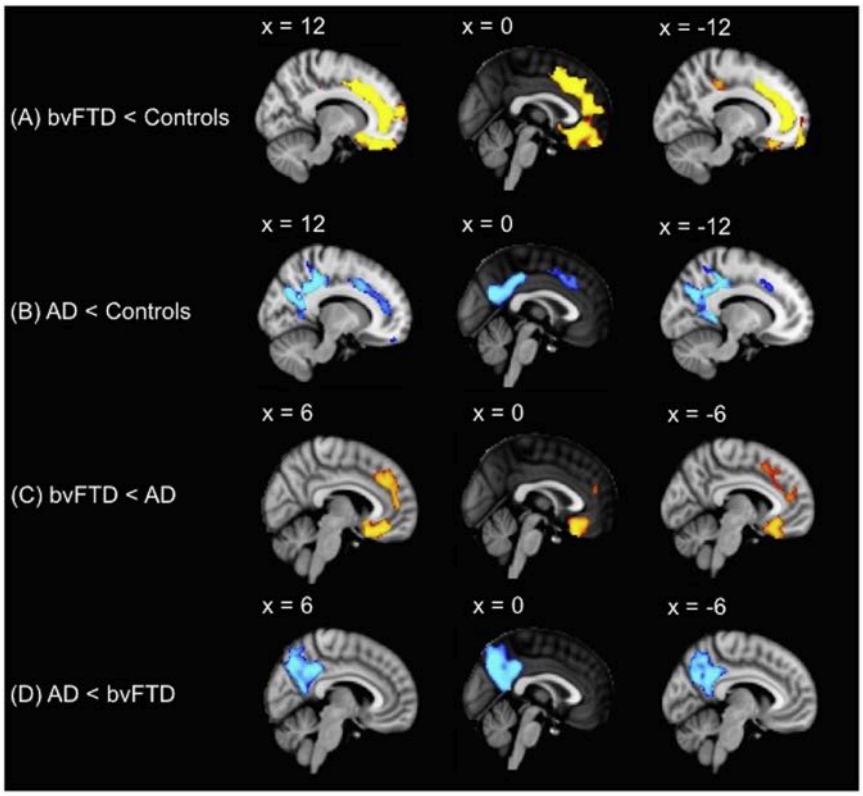

Fig. 4 – VBM analyses showing CMS regions of greater reduction in (A) bvFTD patients in comparison with controls (B) AD patients in comparison with controls (C) bvFTD patients in comparison with AD patients and (D) AD patients in comparison with bvFTD patients. Coloured voxels show regions that were significant in the analysis with $p < .05$, Family-wise Error corrected, and a cluster threshold of 100 contiguous voxels. Clusters are overlaid on the MNI standard brain.

Table 2 – Voxel-based morphometry results showing regions of significant grey matter intensity decrease for bvFTD and AD groups compared to controls.

Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels
		X	Y	Z	
bvFTD < controls					
Medial prefrontal cortex, subcallosal cortex, orbitofrontal cortex, frontal pole, anterior cingulate cortex, paracingulate cortex, superior frontal gyrus	B	6	32	−16	7462
Posterior cingulate cortex	L	−14	−34	38	104
AD < controls					
Posterior cingulate cortex, precuneus	B	−8	−46	2	3669
Anterior cingulate cortex, paracingulate cortex	B	12	14	34	699
Frontal pole	R	16	50	−22	113
bvFTD < AD					
Subcallosal cortex, orbitofrontal cortex, medial prefrontal cortex	B	10	14	−20	1426
Paracingulate cortex, anterior cingulate cortex	B	6	34	32	867
AD < bvFTD					
Precuneus, posterior cingulate cortex	B	2	−68	40	3196

All results FWE-corrected at $p < .05$; only clusters with at least 100 contiguous voxels included. All clusters reported $t > 1.99$. Age and years of education were included as covariates in all contrasts. L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.

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grey matter atrophy was also evident in AD patients (see Fig. 4B, Table 2).

Direct comparison of the two patient groups revealed a predominantly anterior burden of atrophy in bvFTD, in contrast to a predominantly posterior burden of atrophy in AD. Bilateral regions in the subcallosal cortex, orbitofrontal cortex, medial prefrontal cortex, anterior cingulate cortex and paracingulate cortex showed greater atrophy in bvFTD compared to AD (see Fig. 4C, Table 2). The reverse contrast revealed significantly greater atrophy in the bilateral PCC and precuneus in the AD group (see Fig. 4D, Table 2). These grey matter atrophy profiles are consistent with previously reported patterns of atrophy in bvFTD (Seeley et al., 2008) and AD (Karas et al., 2004; Rabinovici et al., 2007).

3.5.2. *Grey matter correlates of SRE magnitude*

SRE magnitude (indicating source memory advantage of self *vs* other-referencing) scores were entered into two separate GLMs, to investigate correlations between SRE magnitude and regions of grey matter atrophy in each patient group (bvFTD, AD) combined with controls. In bvFTD, SRE magnitude covaried with grey matter intensity decrease in predominantly anterior CMS regions including the anterior cingulate cortex, paracingulate cortex, medial prefrontal cortex and subcallosal cortex, bilaterally (see Fig. 5A, Table 3). In AD, SRE magnitude covaried with grey matter intensity decrease in bilateral anterior cingulate and paracingulate cortices, right PCC and precuneus, and right frontal pole and orbitofrontal and medial prefrontal cortices (see Fig. 5B, Table 3). Analysis of potential co-atrophy effects revealed that these regions remained significant ($p < .05$, uncorrected) when controlling for diagnostic group effects (see Table 3), and no significant clusters outside the regions of CMS atrophy identified in the SRE magnitude analyses emerged ($p < .01$, uncorrected). As a final check, mean cluster intensity values were extracted for each significant cluster in the anterior-dorsal CMS, anterior-ventral CMS and posterior CMS and plotted against SRE magnitude scores for bvFTD patients and controls (see Supplementary Fig. 3A) and AD patients and controls (see Supplementary Fig. 3B).

To identify the regions significantly associated with SRE magnitude in both bvFTD and AD, we conducted an overlap analysis (see Fig. 6, Supplementary Table 2). This analysis revealed the bilateral anterior cingulate and paracingulate cortices to be commonly implicated across both patient groups. Next, exclusive masking was used to identify the regions that uniquely contributed to SRE magnitude in each patient group (see Fig. 6, Supplementary Table 2). In bvFTD, integrity of the right medial prefrontal and subcallosal cortices, as well as left anterior cingulate cortices correlated exclusively with SRE magnitude. In contrast, SRE magnitude in AD patients was exclusively associated with integrity of the right PCC, as well as regions in the right frontal pole and orbitofrontal cortex and right anterior cingulate cortex. Thus, in relation to the three CMS subregions proposed by Northoff et al. (2006), anterior-dorsal CMS atrophy was associated with reduced SRE magnitude across both bvFTD and AD. In bvFTD, there was additional involvement of anterior-ventral CMS atrophy only. By contrast, SRE magnitude was exclusively associated with posterior CMS atrophy in AD patients, as well as atrophy in an OFC/frontal polar region within the anterior-ventral CMS.

Table 3 – Voxel-based morphometry results showing regions of significant grey matter intensity decrease that covary with SRE magnitude scores.

Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels
		X	Y	Z	
bvFTD combined with controls					
Anterior cingulate cortex, paracingulate cortex[a]	B	0	32	28	152
Medial prefrontal cortex, subcallosal cortex[a]	R	4	38	−14	122
AD combined with controls					
Anterior cingulate cortex[a]	B	2	28	26	311
Frontal pole, orbitofrontal cortex, medial prefrontal cortex[a]	R	12	42	−20	240
Posterior cingulate cortex[a]	R	16	−36	38	68

All results uncorrected at $p < .01$; only clusters with at least 50 contiguous voxels included. All clusters reported $t > 3.36$. Age and years of education were included as covariates in all contrasts. L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.

[a] Clusters significant ($p < .05$) when diagnostic group included as an additional covariate for co-atrophy check.

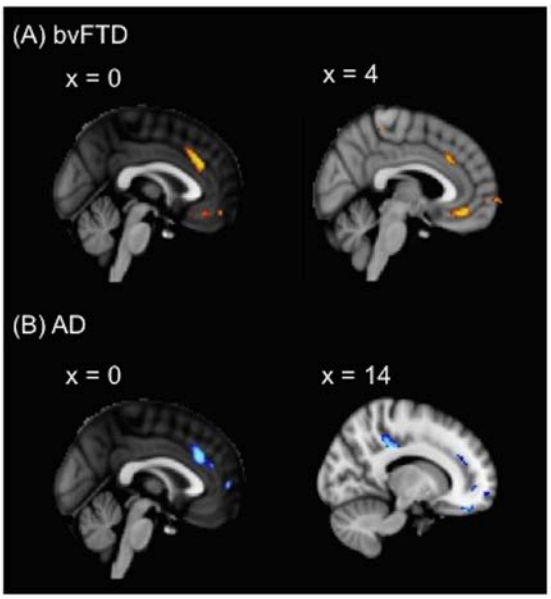

Fig. 5 – Regions of CMS grey matter atrophy correlating with self-other SRE magnitude in (A) bvFTD patients and (B) AD patients. Coloured voxels show regions that were significant in the analysis with $p < .01$, uncorrected and a cluster threshold of 50 contiguous voxels. Clusters are overlaid on the MNI standard brain.

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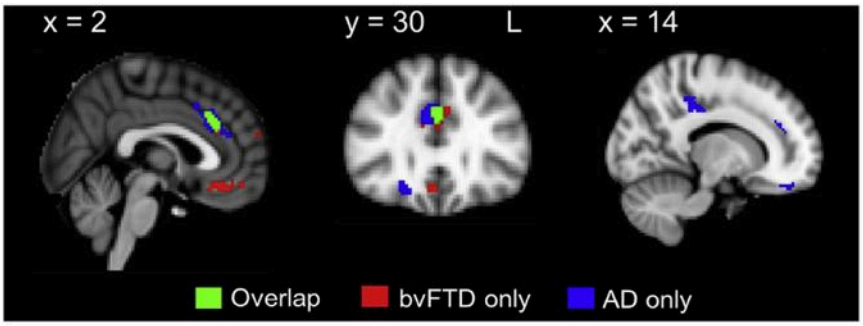

Fig. 6 – Regions of CMS grey matter atrophy that correlate with SRE magnitude scores across both bvFTD and AD (overlap shown in green), and regions that correlate exclusively in bvFTD patients (red) and exclusively in AD patients (blue). Coloured voxels show regions that were significant in the analysis with $p < .01$, uncorrected and a cluster threshold of 50 contiguous voxels. Clusters are overlaid on the MNI standard brain.

4. Discussion

A vast body of work highlights the preferential encoding of information related to the self. In the current study, we investigated how damage to regions in the CMS, crucial for self-referential processing, impact the SRE in neurodegenerative disorders with divergent anterior versus posterior CMS pathology. In bvFTD, where the burden of pathology is overwhelmingly anterior, we found that the reduced SRE was related to atrophy in the anterior-ventral CMS. In contrast, atrophy in the posterior CMS was uniquely associated with the attenuated SRE in AD, consistent with the predominantly posterior burden of atrophy in this patient group. Furthermore, atrophy in the anterior-dorsal CMS was implicated across both patient groups. Our findings therefore highlight important similarities and differences in the contribution of these CMS subregions and corresponding subcomponents of self-referential processing, in mediating the SRE in bvFTD and AD.

This is the first study, to our knowledge, to explore the mechanisms underpinning SRE disruption in AD and bvFTD. In line with our predictions, bvFTD patients did not show an enhancement effect of self-referential processing. Our findings mesh well with previous work showing impaired retrieval of autobiographical memory, which is inherently self-referential, in these patients (Irish, Hornberger, et al., 2011; Piolino et al., 2003). Importantly, the reduced benefit of self- versus other-referential encoding did not correlate with performance on standardised tests of episodic memory, suggesting that the absence of SRE in these patients could not be explained by a general memory deficit per se. Rather, our results indicate that self-referencing has no appreciable influence on source memory retrieval in bvFTD. One potential explanation is that alterations in self concept influence the degree to which self-related information is preferentially encoded in this syndrome. In his original study, Rogers (1977) described the self as a cognitive structure that plays an active role in memory, such that new information that is consistent with one's self is organised and remembered more easily than information that is incompatible with one's self. This raises the possibility that alterations to the self, as documented by changes in personality (Rankin, 2005; Ruby et al., 2007) and personal values (Miller et al., 2001) in bvFTD, impact on its stability and reliability as a cognitive structure that facilitates the encoding of self-related information. Nonetheless, the precise mechanisms underlying this effect require further investigation.

On a behavioural level, our findings in AD are comparable with bvFTD, where there was no self-referential enhancement of source memory. The absence of SRE in our AD group corroborates results from previous reports of attenuated SRE and SRRE in AD (Genon et al., 2013; Leblond et al., 2016), but extend these findings by using a source memory experimental design, showing neither item nor source memory enhancement. While a number of existing studies have demonstrated significant SRE and SRRE in AD (Kalenzaga & Clarys, 2013; Kalenzaga et al., 2013; Lalanne et al., 2013), the apparent disparity in results may be related to differences in methodological approaches. Whereas all previous self-referential encoding tasks conducted in AD patients have involved making judgements regarding the self-relevance of trait adjectives, reports of significant SRE or SRRE appear to be driven by the effect in positive (Lalanne et al., 2013) or negative (Kalenzaga & Clarys, 2013; Kalenzaga et al., 2013) trait adjectives only. Thus, it is plausible that self-referencing alone is not sufficient to provide a memory advantage in AD, unless the to-be-remembered stimuli are emotional in nature. Indeed, evidence suggests that a significant emotional enhancement effect persists in AD patients, despite their profound episodic memory impairments (Kalenzaga, Piolino, & Clarys, 2014; Kumfor, Irish, Hodges, & Piguet, 2013, 2014). Given that we included relatively neutral objects and background stimuli in our SRE paradigm, it is unlikely that emotional valence had any appreciable impact on memory performance. Taken together, our findings contribute to a growing body of research which indicates that self-referential processing alone is insufficient to enhance memory retrieval in AD.

Importantly, while the absence of source memory enhancement for self-referential information was comparable in bvFTD and AD, the neural correlates differed markedly

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between groups. In line with evidence from neuroimaging studies that have highlighted the importance of the MPFC for SRE (D'Argembeau et al., 2005; Moran, Heatherton, & Kelley, 2009; Northoff et al., 2006; Philippi, Duff, Denburg, Tranel, & Rudrauf, 2012), atrophy in this region was associated with reductions in SRE magnitude in bvFTD. In the context of Northoff et al. (2006) model, damage to this anterior-ventral CMS region disrupts the initial coding of stimuli as self-related, thus compromising downstream self-referential processes in more posteriorly located CMS regions. In conjunction with findings from MPFC lesion patients, who do not show any significant SRE (Philippi et al., 2012), our results support the notion that disruption to the initial stages of self-referential processing in the anterior-ventral CMS may impact the extent to which memory for self-related information is enhanced. On a broader level however, the anterior-ventral CMS has also been proposed to function as a 'valuation' centre, where subjective value is assigned to incoming stimuli (D'Argembeau, 2013; Northoff & Hayes, 2011). As such, this region appears to be involved in processing and integrating features that contribute to the subjective value of a stimulus, such as self-relatedness (D'Argembeau, 2013; Northoff & Hayes, 2011), reward value (Kringelbach, 2005; Levy & Glimcher, 2012) and emotional value (Winecoff et al., 2013), which determines whether it is preferentially encoded. Of particular relevance, bvFTD patients do not show the typical memory advantage for emotional information, and this has been associated with atrophy in the OFC, which forms the most ventral part of the anterior-ventral CMS (Kumfor et al., 2013, 2014). In the same vein, the reduced memory enhancement effect for personally 'valuable' information was related to anterior-ventral CMS atrophy in our bvFTD patients. Damage to this anterior-ventral CMS region in bvFTD may therefore be particularly disruptive to the early processing of self-referential information, during which personal value is assigned.

In contrast, integrity of the posterior CMS regions (including the PCC and precuneus) was exclusively associated with the degree of self-referential enhancement of memory in AD. This contrasts with results from Genon et al. (2013, 2014), where PCC activity was associated with the accurate recognition of self-referentially encoded information, rather than the SRE magnitude per se. Instead, SRE magnitude was associated with lateral PFC atrophy, which presumably mediates the interaction between self-referential and higher order cognitive processes (Genon et al., 2013; Northoff et al., 2006). Nonetheless, our results extend existing findings by using a targeted region-of-interest approach to identify specific CMS correlates of the SRE in AD, primarily involving the posterior CMS but also an OFC/frontal polar region in the anterior-ventral CMS. Notably however, this anterior-ventral CMS subregion implicated in AD was located more laterally and did not overlap with the anterior-ventral CMS subregion implicated in bvFTD. Whether this lateral-ventral distinction reflects further functional subdivisions within the anterior-ventral CMS, requires further investigation. Nonetheless, our results in AD are compatible with previous reports of both posterior and anterior-ventral CMS activity during the retrieval of self-referenced relative to non-self-referenced stimuli in healthy adults (Fossati et al., 2004; Leshikar & Duarte, 2013; Yaoi, Osaka, & Osaka, 2015). On a broader level, the involvement of both posterior and anterior-ventral CMS subregions is also consistent with the pattern of CMS activity during inherently self-related memory processes such as autobiographical memory retrieval (Addis, McIntosh, Moscovitch, Crawley, & McAndrews, 2004; Maguire, 2001; Svoboda, McKinnon, & Levine, 2006). In the context of Northoff et al. (2006) model, involvement of the posterior CMS in AD, but not bvFTD, suggests that the reduced SRE in AD may be further impacted by specific deficits in the ability to integrate newly coded self-referential information within the context of existing autobiographical memories (Cavanna & Trimble, 2006). Our findings therefore point to the unique contribution of posterior CMS atrophy to self-referential memory processes in AD, corroborating previous work emphasizing the role of the posterior CMS regions in the retrieval of past, and simulation of future, self-referential events in this patient group (Irish, Addis, et al., 2012; Irish et al., 2013).

While we identified divergent CMS contributions to the SRE specific to each patient group, our analyses also implicated the anterior-dorsal CMS, particularly the anterior cingulate cortex, as a common neural correlate of SRE magnitude in bvFTD and AD. With respect to its role in self-referential processing, Northoff et al. (2006) proposed that the anterior-dorsal CMS is involved in the reappraisal and evaluation of self-related information. Indeed, a recent meta-analysis of functional neuroimaging studies contrasting self- and other-judgements revealed a spatial gradient in MPFC activation, such that self-referential judgements were associated with greater ventral MPFC activity, whereas other-referential judgements were related to greater activity in the dorsal MPFC (Denny, Kober, Wager, & Ochsner, 2012). The finding that dorsal MPFC supports judgements about others is unsurprising, given its role in perspective taking tasks, such as those involving theory of mind (ToM) (D'Argembeau et al., 2007; Gallagher & Frith, 2003). Crucially, bvFTD patients show impairments in perspective taking and empathy (Cerami et al., 2014; Dermody et al., 2016; Eslinger et al., 2011), which have been proposed to be associated with underlying difficulties in inhibiting their own perspective when required to adopt another person's perspective (Le Bouc et al., 2012). It is therefore possible that bvFTD patients tended to encode all stimuli in relation to the self, thereby reducing the SRE magnitude. Importantly however, our findings from the perceptual encoding condition do not support this position, as we did not find enhanced source memory retrieval for both the self- and other-reference conditions compared to the perceptual condition. Furthermore, while perspective taking and ToM deficits have been widely reported in bvFTD patients (Adenzato, Cavallo, & Enrici, 2010; Bertoux, Funkiewiez, O'Callaghan, Dubois, & Hornberger, 2013; Kipps & Hodges, 2006), recent work has delineated between cognitive (attribution of intention) and affective (attribution of emotion) ToM, showing comparable deficits in cognitive ToM across both bvFTD and AD patients (Dermody et al., 2016; Dodich et al., 2016). Against this background, the anterior-dorsal CMS involvement in SRE magnitude across both bvFTD and AD patients may be related to deficits in their ability to evaluate information from the perspective of another person. Nonetheless, the relationship between perspective taking ability

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and self-referential enhancement of memory in these patient groups remains to be established, and represents an important area for future research.

From a theoretical viewpoint, the current findings suggest that attenuation of the self-referential enhancement effect in bvFTD and AD may reflect the breakdown of discrete facets of self-referential processing, which in turn rely upon the integrity of different subregions of the CMS. Our results in bvFTD confirm the importance of prefrontal cortex contributions to episodic memory function (Simons & Spiers, 2003; Wong et al., 2014) and complement a growing body of literature, which views the anterior-ventral CMS as a core 'valuation' hub by assigning subjective value to personally-, affectively- and motivationally-salient information (D'Argembeau, 2013; Northoff & Hayes, 2011). On the other hand, our findings in AD confirm the prominence of the PCC in mediating all aspects of self-related memory impairments in this syndrome (reviewed by Irish & Piolino, 2015). While our findings are in line with the notion that different CMS subregions mediate discrete aspects of self-referential processing, functional neuroimaging studies employing targeted experimental paradigms that directly contrast the different aspects of self-referential processing are necessary to support this proposal.

A number of methodological issues warrant consideration. Firstly, as our SRE task only assessed source memory accuracy for background images, it is unclear how this compares to accurate retrieval of other source details (e.g., encoding context). Nonetheless, our findings demonstrate that self-referential processing in AD and bvFTD does not ameliorate impairments on an objective measure of source memory. A second point to consider is the use of background image, rather than encoding context, as the source recognition question, as this precluded us from distinguishing between false alarms for 'new' items incorrectly assigned as self, other or perceptually referenced. Of particular relevance, recent studies (Rosa & Gutchess, 2013; Rosa, Deason, Budson, & Gutchess, 2015) have indicated that the SRE may also impact false alarm rates, such that 'new' items that are subsequently judged to be highly self-relevant are more likely to be falsely recognized as 'old'. Given that false recognition rates on clinical measures of episodic memory are elevated in both bvFTD and AD patients (Flanagan et al., 2016), future studies should investigate the potential impact of self-referential processing on false alarm rates in these patient groups. Thirdly, due to time constraints and patient fatigue, it was necessary to limit the number of trials in our SRE encoding task. Given the small number of responses, item-only hits and item misses were collapsed into the same response category (i.e., source-unrecollected) to contrast against item-and-source hits (i.e., source-recollected). Hence, our source memory recognition accuracy measure only allowed us to draw conclusions regarding source memory effects, which were not conditionalised based on item memory effects. Similarly, the small number of responses also precluded us from correcting for lucky guesses in source recognition performance, as per previously reported procedures in healthy adults (Leshikar & Duarte, 2013). As such, the impact of such response biases on source recognition memory following self-referential encoding in these patient groups represents an important area of future enquiry. Additionally, we were not able to contrast subsequent item and source recognition accuracy for items positively or negatively judged for pleasantness during encoding. Given that greater MPFC activation is observed in relation to stimuli judged to be self-relevant (D'Argembeau et al., 2005; Moran et al., 2009), comparison of memory for stimuli according to degree of self-relevance may further elucidate mechanisms underlying the reduced SRE in bvFTD and AD. Likewise, the relationship between the SRE and alterations in concept of self represents an important area of future enquiry, especially considering the marked changes to personality and interpersonal conduct in bvFTD (Piguet et al., 2011). While previous studies in AD have used self-rated measures of identity valence and certainty (Lalanne et al., 2013; Leblond et al., 2016), inclusion of measures that allow comparison between self and informant responses is necessary, as loss of insight is a prominent clinical characteristic in bvFTD (Piguet et al., 2011). Furthermore, given that we employed a region-of-interest approach in our VBM analyses, we could not exclude the possibility that atrophy of regions beyond the CMS may have also contributed to the reduced SRE in bvFTD and AD. In particular, the lateral prefrontal cortex has been proposed to support interactions between self-referential and higher-order processes, especially during tasks with a strong cognitive component (Northoff et al., 2006). Comparison of the SRE on tasks with a low versus high cognitive load may help further elucidate the role of the lateral prefrontal cortex in self-referential processing in these patient groups. Nonetheless, given that the lateral prefrontal cortex shows a similar degree of atrophy (Rabinovici et al., 2007) and contributes to episodic memory deficits (Wong et al., 2014) in both bvFTD and AD, it is unlikely that this region differentially contributes to the reduced SRE in these patient groups. Finally, future investigations of self-referential processing in bvFTD and AD would benefit from incorporating resting-state functional connectivity metrics to clarify the impact of CMS pathology on the SRE, in the context of large-scale network dysfunction characteristic of these disorders.

In summary, this study reveals the differential involvement of CMS subregions in facilitating the SRE, by contrasting neurodegenerative disorders with a predominantly anterior versus predominantly posterior burden of pathology. Absence of the SRE in bvFTD is associated with underlying pathology in the anterior-ventral CMS, which potentially mediates the early stages of self-referential processing, during which personal value is assigned to stimuli. In contrast, pathology in the posterior CMS uniquely contributes to the attenuated SRE in AD, likely reflecting breakdown in integrative processes that link newly encoded self-related information with existing self-referential, autobiographical memories. In addition, anterior-dorsal atrophy appears to contribute to reductions in SRE across both bvFTD and AD, pointing to deficits in the evaluative aspects of self-referential processing in both syndromes. Our results provide important insights into the mechanisms underlying self-referential memory and point to clinically relevant similarities and differences in the interaction between self and memory in bvFTD and AD. Exploring the relationship between alterations in self concept and the memory benefit conferred by self-referential processing will be an important next step for future studies to address.

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Supplementary data

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4.5. Concluding remarks

The findings reported here highlight the importance of medial PFC regions in adding personal significance to support memory for self-relevant information. Nonetheless, as proposed by Northoff and colleagues (2004; 2006), the medial PFC is not a unitary structure, and works in concert with other cortical midline structures (CMS), which mediate distinct aspects of the self-referential processing framework. The finding that the anterior-ventral CMS (i.e., vmPFC), which is important for the initial flagging of information as self-relevant, is particularly affected in bvFTD, is consistent with increasing evidence of deficits in processing value or rewards in these patients (Kloeters, Bertoux, O'Callaghan, Hodges, & Hornberger, 2013; Perry & Kramer, 2013). Indeed, an overarching valuation system comprised of vmPFC and striatal structures has been proposed to be involved in coding the self-relevance and reward value of incoming stimuli, with the notion that self-relevant stimuli are essentially those that are assigned a high value (Enzi, de Greck, Prösch, Tempelmann, & Northoff, 2009; Northoff & Hayes, 2011). The findings in this chapter therefore raise the question of whether memory for other types of value-related information is differentially affected in bvFTD and AD. The following chapter addresses this by exploring memory for socially rewarding information in these patient groups.

Chapter 5
Learning and memory of social interactions in AD and bvFTD

This chapter further explores the notion that the medial PFC engages in valuation processes that enhance memory for information that is of high subjective value. Here, the focus is placed on memory for social interactions, which are of higher value than non-social interactions. The emphasis on memory for this socially relevant information is particularly fitting in bvFTD patients, as they show widespread deficits in social cognition, including abnormal social reward processing and decision-making (Grossman et al., 2010; Perry, Sturm, Wood, Miller, & Kramer, 2015). Methodologically, this study differs from the previous chapter, in that it assesses learning in response to socially relevant feedback across repeated trials during the encoding phase, in addition to item and source memory measures during the test phase. This study also employed a carer-rated questionnaire measure, to examine the relationship between memory for social interactions and susceptibility to financial exploitation in these patient groups.

5.1. Manuscript IV

"Should I trust you? Learning and memory of social interactions in dementia"

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Abstract

Social relevance has an enhancing effect on learning and subsequent memory retrieval. Neuroimaging evidence from healthy adults implicates frontostriatal and medial temporal lobe regions in learning and memory of socially relevant information. While deficits in learning and memory are well established in Alzheimer's disease (AD) and behavioural-variant frontotemporal dementia (bvFTD), the latter show disproportionate impairments in social cognition and frontostriatal atrophy. It is unclear, however, if these patient groups show a typical memory advantage for socially relevant information, and how this relates to financial vulnerability in everyday life. Fourteen patients with AD, 20 patients with bvFTD and 20 age-matched healthy controls were assessed using a novel neuroeconomic task based on the "trust game" paradigm. Here, participants invested virtual money with partners who acted either in a trustworthy or untrustworthy manner over repeated interactions. A non-social "lottery" condition was also included. Participants' memory for the partners and trust game interactions were assessed using face and source recognition memory tests, respectively. Carer-rated profiles of financial vulnerability were collected and voxel-based morphometry was used to investigate patterns of grey matter atrophy associated with social learning and memory performance. Relative to controls, both patient groups showed attenuated learning of trust/distrust responses, and lower overall face and source memory. Despite poor learning performance, AD patients showed enhanced face memory for trustworthy partners, as well as enhanced source memory for trustworthy and untrustworthy, relative to non-social partners. Importantly, social learning and memory performance in AD was associated with medial temporal lobe atrophy, and greater memory accuracy correlated with lower informant ratings of financial vulnerability. In contrast, although bvFTD patients showed similar face memory across conditions, source memory appeared to be modulated by social information (i.e., recognition of the condition in which partners were encountered). Importantly, social learning and memory performance was predominantly associated with

frontostriatal atrophy. Furthermore, social memory accuracy was not related to financial vulnerability in bvFTD. Our findings suggest that although social relevance influences memory to an extent in both dementia syndromes, these are associated with divergent neural correlates, and are associated with vulnerability to financial exploitation in AD only. Theoretically, these findings provide novel insights into potential mechanisms that give rise to vulnerability in people with dementia, and open avenues for possible interventions.

Keywords: Alzheimer's disease; frontotemporal dementia; memory; social cognition; trust game

1. Introduction

In everyday life, we draw upon memories of past social experiences to guide current or future social interactions. These include memories of the people with whom we have interacted, and whether these interactions led to socially rewarding outcomes, such as approval, acceptance and reciprocity (Fareri & Delgado, 2014). Converging evidence from neuroimaging studies implicates a network of frontostriatal and medial temporal lobe (MTL) regions, pointing to the involvement of both social reward processing and memory functions to support socially relevant memories (Delgado, Frank, & Phelps, 2005; Tsukiura & Cabeza, 2008; Vrtička, Andersson, Sander, & Vuilleumier, 2009). In healthy older adults, increased susceptibility to financial exploitation is associated with memory decline (James, Boyle, & Bennett, 2014). Although such mistreatment is commonly reported across a range of neurodegenerative conditions, it is unclear whether this is related to impaired memory for social interactions.

Here, we focus on Alzheimer's disease (AD) and behavioural-variant frontotemporal dementia (bvFTD). Patients with bvFTD show progressive changes in personality and social interactions, with disturbance in emotion processing (Kumfor, Irish, Hodges, & Piguet, 2013a), empathy (Dermody *et al.*, 2016), Theory of Mind (Le Bouc *et al.*, 2012), social reward processing and decision making (Grossman et al., 2010; Perry, Sturm, Wood, Miller, & Kramer, 2015), compliance with social norms (O'Callaghan *et al.*, 2016) and strategic social bargaining (Melloni *et al.*, 2016). Of particular relevance, overly friendly or gullible behaviours are frequently reported in bvFTD (Pressman & Miller, 2014), suggesting distinct alterations in processing socially relevant information. While episodic memory impairments in bvFTD can be commensurate with those seen in AD (Hornberger, Piguet, Graham, Nestor, & Hodges, 2010; Pennington, Hodges, & Hornberger, 2011), socio-emotional functions remain relatively intact in AD, particularly during the mild-moderate stages of the disease

(Bertoux, de Souza LC, et al., 2015a; Shany-Ur & Rankin, 2011). The divergent patterns of social-emotional dysfunction in bvFTD and AD are thought to reflect underlying differences in brain regions that are affected in each syndrome, with selective vulnerability of frontostriatal and insular regions in bvFTD, versus MTL and parietal regions in AD (Irish, Piguet, & Hodges, 2012; Seeley et al., 2007). Nevertheless, it remains unclear how this frontostriatal-insular versus MTL-parietal dissociation potentially disrupts learning and memory of social interactions in these syndromes.

The trust game, an experimental paradigm drawn from the neuroeconomics literature, offers a means of assessing learning and memory for social reciprocity (Johnson & Mislin, 2011; Tzieropoulos, 2013). Originally developed by Berg, Dickhaut and McCabe (1995), the trust game involves an exchange where the participant may choose to transfer a sum of money to another player, who will either reciprocate or violate their trust. Across multiple rounds of the trust game, participants typically learn whether to trust or distrust players based on their previous experience of social reciprocity (Anderhub, Engelmann, & Güth, 2002; King-Casas et al., 2005). On subsequent memory tests, healthy adults show enhanced face recognition and source memory for the associated behaviours of trustworthy and untrustworthy players encountered during the trust game (Bell, Buchner, & Musch, 2010), in keeping with evidence which suggests a distinct memory advantage for socially relevant information (Cassidy & Gutchess, 2014; Mitchell, Macrae, & Banaji, 2004; Rule, Slepian, & Ambady, 2012).

The current study sought to assess learning and memory of trust behaviour in AD and bvFTD patients using a trust game paradigm. We hypothesized that the use of social reciprocity as a form of feedback would improve learning over trials in AD patients but not bvFTD patients, in line with the well-documented impairments in social and monetary reward

processing in bvFTD (Melloni et al., 2016; Perry et al., 2015; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009). Secondly, we aimed to explore whether memory for social information would be differentially enhanced in AD and bvFTD. We hypothesised that in bvFTD, the capacity for social enhancement of memory may be reduced, whereas the relative preservation of social cognition in patients with AD may facilitate their memory of social interactions. While no previous research has explored social memory enhancement in these patient groups, evidence of successful emotional memory enhancement in AD, but not bvFTD, supports this prediction (Kumfor, Irish, Hodges, & Piguet, 2013b; 2014). We anticipated that learning and memory of social interactions would correlate with atrophy in frontostriatal regions in bvFTD, reflecting the predominant social reward processing deficits in this patient group. In contrast, we expected that social learning and memory would correlate with the degeneration of predominantly MTL regions in AD, consistent with the primary deficit in memory mechanisms underpinning performance in this group. The final aim of this study was to examine the relationships between learning and memory for socially relevant information and carer-rated profiles of day-to-day financial vulnerability in AD and bvFTD patients.

2. Materials and methods

2.1 Participants

Thirty-four dementia patients (bvFTD=20; AD=14) and 20 age-matched healthy controls were recruited through FRONTIER at Neuroscience Research Australia, Sydney. All bvFTD and AD patients fulfilled clinical diagnostic criteria for probable bvFTD (Rascovsky *et al.*, 2011) or probable AD (McKhann *et al.*, 2011), respectively. Disease duration was estimated as the number of years elapsed since the reported onset of symptoms. The Frontotemporal Dementia Rating Scale (FRS; Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010) and Clinical Dementia Rating Scale (CDR; Morris, 1997) were used to determine disease

severity in bvFTD and AD patients. All participants underwent general cognitive screening using the Addenbrooke's Cognitive Examination-III (ACE-III; Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013) to determine their overall level of cognitive functioning. Age-matched healthy controls were recruited from the FRONTIER research volunteer panel and scored >88 on the ACE-III (Hsieh *et al.*, 2013).

All participants provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethics Committee of the South Eastern Sydney Local Health District and the University of New South Wales.

2.2 Background neuropsychology

All participants underwent a comprehensive neuropsychological assessment, including measures of attention (Castel, Balota, & McCabe, 2009; Castel, Balota, McCabe, & Castel, 2008), psychomotor speed (Trail Making Test (TMT), A time; Reitan & Wolfson, 1985), working memory (Digit Span Backward, total score; Wechsler, 1997) and cognitive flexibility (TMT, B − A time; Reitan & Wolfson, 1985). Verbal episodic memory learning, recall and recognition were assessed using the Rey Auditory Verbal Learning Test (RAVLT, sum of Trials 1–5, 30-minute recall score and corrected recognition (hits − false positives) score; Schmidt, 1996) and short-term visuospatial recall was assessed using the Rey Complex Figure Test (RCFT, 3-minute recall score; Rey, 1941).

2.3 Assessment of Social Vulnerability

The Social Vulnerability Scale (SVS; Pinsker, McFarland, & Stone, 2011) is a 15-item informant-rated questionnaire used to measure vulnerability to financial exploitation in older adults. The SVS comprises two subscales: credulity, the propensity to believe things that are

unproven or unlikely to be true; and gullibility, the tendency to act upon these beliefs, usually in relation to outcomes of a financial nature. As such, the credulity and gullibility subscales tap into cognitive and behavioural aspects of financial vulnerability, respectively. Each item is rated on a 5-point Likert scale, ranging from 0 (never) to 4 (always), with higher scores indicative of greater vulnerability. The SVS was completed by a relevant informant and was available for 16 bvFTD and 10 AD patients and 16 controls.

2.4 Trust game memory task

2.4.1 Stimuli and materials

To serve as trust game partners, images of 24 individuals (12 males, 12 females, age range 20–30 years) showing neutral facial expressions were selected from the Karolinska Directed Emotional Faces (KDEF) set (Lundqvist, Flykt, & Öhman, 1998). Twelve faces were randomly allocated as target stimuli, with four faces (two males, two females) in each learning condition (trustworthy, untrustworthy, lottery). The remaining 12 faces were presented as distractor stimuli during the face recognition memory test. Stimuli assigned per condition were counterbalanced across participants.

2.4.2 Practice phase

The trust game payoff structure and procedures for the learning and test phases are illustrated in Fig. 1. Following presentation of instructions, participants were shown examples of payoff outcomes for each possible response combination on the trust game (you 'keep', partner 'shares'; you 'keep', partner 'steals'; you 'invest', partner 'shares'; you 'invest', partner 'steals'). Participants only proceeded to the learning phase of the experimental task if they could correctly indicate the amount of money they would receive in each payoff outcome.

Fig. 1. (A) Example of trials and possible outcomes across trustworthy, untrustworthy and lottery conditions in the learning phase of the trust game memory task. (B) Example of face and source recognition questions in the test phase of the trust game memory task.

Each round of the trust game began with a screen displaying the image of a partner with the written instructions 'You have $10. Keep or invest?'. If the participant decided to 'keep' (i.e. distrust), they retained the $10 in their account and the partner received $0, regardless of whether they chose to 'share' or 'steal'. If the participant decided to 'invest' (i.e. trust), their $10 was transferred to the partner's account and quadrupled in value ($40). Then, if the partner chose to 'share' (i.e. reciprocate trust), the $40 was divided evenly, resulting in $20 for each player. Alternatively, if the partner chose to 'steal' (i.e. violate trust), they retained the $40 in their account and the participant received $0. Participants did not make any trust-related responses on the lottery game.

2.4.3 Learning phase

To investigate learning of trust behaviour we adapted a multi-round trust game (see for example, Fouragnan et al., 2013; van den Bos, van Dijk, & Crone, 2012), whereby participants always played the role of the investor and played multiple trust games with computerised partners. Social reciprocity strategies were kept consistent within each partner, such that trustworthy partners shared on 100% of trials and untrustworthy partners stole on 100% of trials (see Fig. 1A).

The following crucial manipulations were incorporated into our multi-round trust game:

1. Participants were told that their partners would make each 'share'/'steal' decision simultaneously. Both the participant's and partner's decisions were revealed, so that all participants received the same feedback about the trustworthiness of each partner, regardless of whether they chose to 'keep' or 'invest'. The trust game was self-paced but once a 'keep'/'invest' decision was made, outcome presentation was kept consistent across trials (6000 ms).
2. In order to contrast subsequent recognition memory for social versus non-social interactions, we adapted a lottery condition from Delgado, Frank and Phelps (2005). On these trials, there was a 50% probability of winning on each lottery round, and winnings were shared equally ($10 each; see Fig. 1A). The presentation and timing of lottery outcomes was consistent with trust game outcomes (6000 ms).
3. To limit working memory demands in patients, trials were divided into four blocks, with three different partners per block. Within each block, participants played six trust games with a trustworthy partner, six trust games with an untrustworthy partner and six lottery games with a lottery partner, in a randomised order (total trials = 72). The order of the blocks was counterbalanced across participants.

Participants were instructed to maximise their earnings throughout the learning phase but did not receive actual monetary payouts contingent on their performance, and they were not financially compensated for their involvement in the study. Feedback was provided at the end of each block regarding the total amount earned.

At the end of the learning phase, participants completed a brief affect rating task, to indicate how they felt following each of the 2 partner outcomes (share/steal) and 2 lottery outcomes (win/lose) on a 10 point Likert scale, ranging from 1 (very unhappy) to 10 (very happy). See Supplementary Materials.

For the learning phase, trial-by-trial outcome measures were percentage 'invest' responses on each of the six learning trials in the trustworthy and untrustworthy conditions. As such, higher percentage 'invest' responses reflected better learning in the trustworthy condition but poorer learning in the untrustworthy condition. To compare learning accuracy across all trials in the trustworthy and untrustworthy conditions, the number of 'correct' responses in each condition was summed (i.e. 'invest' responses towards trustworthy partners and 'keep' responses towards untrustworthy partners; maximum score = 24). As responses and outcomes on lottery rounds were consistent across participants, these were not analysed.

2.4.4 Test phase

A surprise recognition memory test was administered following a 20-minute delay, to assess face and source recognition memory (Bell et al., 2010) (see Fig. 1B).

Face recognition memory was assessed using a two-alternative forced choice format with 12 trials. For faces correctly recognized, participants then made a source decision i.e., "What did this person do during the game?" ('share', 'steal', 'lottery' and 'don't know'). The 'don't

know' response option was included to reduce potential contamination of guessing (Wong *et al.*, 2016). No feedback regarding response accuracy was provided throughout the task. Recognition trials were self-paced and presented in a random order.

For the test phase, outcome measures were percentage correct face recognition responses and percentage source recognition responses, which were classified as 'source-recollected' (i.e. source-correct) or 'source-unrecollected' (i.e. 'source-incorrect' or 'source-don't know'). Given that source recognition was only relevant following correct face recognition responses, trials were classified as 'source-unrecollected' when face recognition was incorrect. Source recognition accuracy was calculated as the percentage of source-correct responses out of the total number of items in each condition (e.g. percentage source-correct $_{\text{trustworthy}}$ = (source-correct $_{\text{trustworthy}}$ / 4) × 100) (Rosa, Deason, Budson, & Gutchess, 2014).

2.5 Behavioural analyses

Data were analysed using SPSS 20.0 (SPSS Inc., Chicago, Ill., USA). Normally distributed variables, as determined by Shapiro-Wilks tests, were compared across groups 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, using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. A chi-squared test was used to compare sex distribution across groups.

Learning performance across the six trials was analysed using separate repeated measures ANOVAs for the trustworthy and untrustworthy conditions. To contrast trust game memory task conditions across groups, measures of overall learning accuracy, post learning phase affect ratings, face recognition accuracy and source recognition accuracy were analysed using repeated measures ANOVAs. *Post hoc* simple-effects tests were conducted to examine

differences between conditions within each participant group. All pairwise comparisons of the main effects and simple-effects were adjusted for multiple comparisons using the Sidak method.

Spearman rank correlations were used to examine relationships between learning, face recognition and source recognition performance and SVS variables. To contrast these associations across social (i.e. trustworthy and untrustworthy) and non-social (i.e. lottery) conditions, regardless of social reciprocity valence, we collapsed face and source recognition accuracy for trustworthy and untrustworthy partners. A one-tailed significance level of $p<.05$ was applied for all correlational analyses.

2.6 Voxel-based morphometry analysis

Structural MRI brain scans were available for a subset of participants (18 bvFTD and 13 AD patients and 20 controls). Patients and controls underwent the same imaging protocol in accordance with previously reported standardised procedures (Irish, Piguet, Hodges, & Hornberger, 2014). A detailed description of image acquisition and pre-processing procedures is reported in Supplementary Material.

Voxel-wise general linear models (GLM) were applied to investigate differences in grey matter intensity via permutation-based non-parametric testing (Nichols & Holmes, 2002) with 5000 permutations per contrast. As a first step, group differences in grey matter intensity were tested for significance at $p <.005$, corrected for multiple comparisons via Family-Wise Error (FWE) correction across space. A cluster extent threshold of 200 contiguous voxels was applied for group comparisons. Relative to controls, bvFTD and AD patients showed characteristic patterns of atrophy in keeping with their diagnoses (see Supplementary Table 1).

To identify the neural correlates of social learning and memory performance in AD and bvFTD, correlations between trust game performance and grey matter intensity were conducted in each patient group separately, using the total learning, social face recognition and social source recognition accuracy scores. In accordance with previously reported procedures (Irish *et al.*, 2014; Sollberger *et al.*, 2009), patients and controls were included in the analyses to achieve greater variance in behavioural scores, thereby increasing the statistical power to detect brain-behaviour relationships. Trust game covariate analyses were conducted at significance levels of $p<.001$, uncorrected for multiple comparisons, with a cluster extent threshold of 200 contiguous voxels. Regions of significant atrophy were superimposed on T1-weighted standard brain images, and regions of significant grey matter intensity decrease were localised with reference to the Harvard-Oxford probabilistic cortical atlas. Maximum coordinates for the anatomical locations of significant results are reported in MNI space.

3. Results

3.1 Demographics and background neuropsychology

Demographics and clinical characteristics of the participants are detailed in Table 1. Participant groups were matched for age ($p=.085$) and sex distribution ($p=.155$). An overall group difference was evident for total years of education ($p=.029$), with controls more educated than bvFTD patients (bvFTD vs. controls $p=.021$; AD vs. bvFTD $p=.377$). Importantly, the patient groups were matched for disease duration ($p=.372$) and disease severity (CDR, $p=1.0$). As expected, bvFTD patients were more functionally impaired relative to AD patients (FRS; $p=.016$).

On the ACE-III cognitive screening measure, both patient groups were significantly impaired relative to controls (both p values $<.001$), with comparable performance in the

patient groups (p=.307). AD and bvFTD patients displayed characteristic cognitive profiles, with both patient groups showing deficits in attention (Digit span forwards; p values <.001), psychomotor speed (TMT A time; p values <.001), working memory (Digit span backwards; p values <.001) and cognitive flexibility (TMT B – A time; p values <.001) in relation to controls, with no significant differences between patient groups except for poorer attention in AD compared to bvFTD (p=.042). Verbal episodic memory was significantly compromised in both patient groups relative to controls across measures of learning (RAVLT learning total; p values <.001) and recall (RAVLT 30-minute recall; p values <.001). Notably, learning performance (p <.001) was disproportionately disrupted in AD versus bvFTD, with a trend towards lower recall performance (p=.058). Verbal episodic memory recognition was comparably impaired in the patient groups in relation to controls (p values <.001; bvFTD vs. AD, p=.318). Similarly, patients' nonverbal recall was significantly impaired relative to controls (RCFT recall, p values <0.001), with no significant differences between bvFTD and AD (p=.096).

3.2 Social Vulnerability Scale

The subscale scores from the SVS are detailed in Table 1. Patients with bvFTD showed global difficulties on both credulity and gullibility subscales relative to controls (p <.001) and AD patients (credulity, p=.047; gullibility p=.038). While AD patients did not differ from controls on the gullibility subscale (p=.533), a trend towards higher credulity was present (p=.051), indicating a greater tendency to believe things that are unproven or unlikely to be true.

Table 1. Demographic and clinical characteristics of the study cohort[a]

	Control	bvFTD	AD	Group effect	Post hoc test
Sex (M:F)	8:12	14:6	7:7	n.s.	
Age (years)	63.29 (6.53)	62.23 (8.03)	68.06 (8.52)	n.s.	
Education (years)	13.18 (1.99)	11.14 (2.19)	12.23 (2.93)	*	Con > bvFTD
Disease duration (years)	-	5.96 (3.16)	5.58 (4.37)	n.s.	
CDR SoB [18]	0.10 (0.21)	5.82 (3.17)	4.73 (2.07)	***	Con < bvFTD, AD
FRS Rasch score	-	−0.84 (1.45)	0.50 (1.53)	*	bvFTD < AD
ACE-III [100]	95.75 (3.45)	75.60 (11.90)	64.29 (11.61)	***	Con < bvFTD, AD
Digit span forward [16]	12.20 (2.02)	9.10 (2.36)	7.36 (1.34)	***	Con > bvFTD > AD
Digit span backward [14]	8.35 (1.90)	5.15 (1.81)	4.21 (2.15)	***	Con > bvFTD, AD
TMT A time (seconds)	30.42 (7.34)	46.50 (17.36)	127.64 (153.04)	**	Con < bvFTD, AD
TMT B − A time (seconds)	35.89 (14.18)	106.35 (63.32)	249.70 (147.29)	***	Con < bvFTD, AD
RAVLT learning total [75]	54.25 (7.93)	36.69 (8.62)	21.36 7.53)	***	Con > bvFTD > AD
RAVLT 30-min recall [15]	10.65 (3.10)	5.19 (2.93)	1.93 (1.59)	***	Con > bvFTD, AD
RAVLT corrected recognition [15]	12.55 (2.48)	2.88 (6.34)	−3.14 (6.79)	***	Con > bvFTD, AD
RCFT 3-min recall [36]	19.83 (5.10)	8.63 (6.65)	2.77 (3.50)	***	Con > bvFTD, AD
SVS credulity [28]	3.88 (3.16)	13.00 (5.44)	8.40 (5.19)	***	Con, AD < bvFTD
SVS gullibility [32]	1.50 (1.46)	9.25 (7.52)	3.80 (4.83)	**	Con, AD < bvFTD

[a] Standard deviations in parentheses, maximum score for tests shown in brackets.
Clinical Dementia Rating Scale (CDR); Frontotemporal Dementia Rating Scale (FRS); Addenbrooke's Cognitive Examination (ACE-III); Trail Making Test (TMT); Rey Auditory Verbal Learning Test (RAVLT); Rey Complex Figure Test (RCFT); Social Vulnerability Scale (SVS).
*p<.05, **p<.01, ***p<.001, n.s. = non-significant

3.3 Trust game memory task results

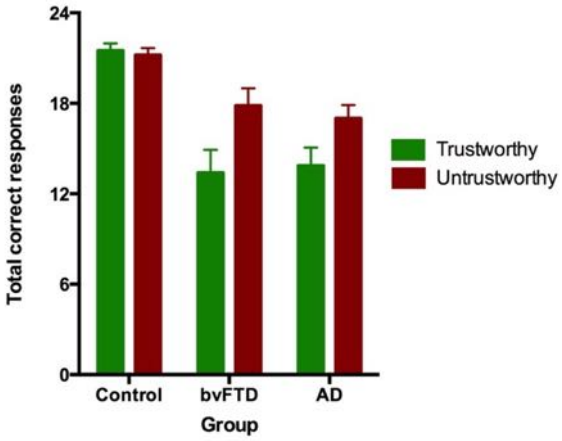
3.3.1 Learning

The total number of 'correct' responses, summed across learning trials according to condition is shown in Fig. 2. Comparisons of 'invest' responses across each of the six learning trials is included in Supplementary Material. A significant main effect of group was evident ($F_{2,51}$=25.493, p<.001), indicating that learning accuracy was lower in AD (p<.001) and bvFTD (p<.001) patients compared to controls, but did not differ between patient groups (p=.996). A significant condition effect was also evident ($F_{1,51}$=6.531, p=.014), with learning accuracy higher in the untrustworthy compared to trustworthy condition, across all groups. However, no significant group × condition interaction ($F_{2,51}$=2.399, p=.098) was observed.

3.3.2 Neural correlates of learning

Regions of grey matter intensity reduction associated with social learning accuracy (sum of correct trust/distrust responses) in each patient group are shown in Table 2 and Fig. 4A. In bvFTD, learning accuracy covaried with grey matter loss in the right orbitofrontal cortex and putamen, left temporo-parietal junction (TPJ), and right frontal pole, and middle frontal, middle temporal and angular gyri and lateral occipital cortex. Learning performance in AD was associated with grey matter intensity decrease in MTL regions including the amygdalae, hippocampi and parahippocampal gyri, bilaterally, as well as the left TPJ, right lateral occipital cortex and left cerebellum.

Fig. 2. Sum of total correct responses (i.e. 'invest' for trustworthy Partners and 'keep' for untrustworthy partners) in the trustworthy and untrustworthy conditions across groups. Error bars represent standard error of the mean



3.3.3 Face recognition

Fig. 3A depicts face recognition accuracy for each condition across AD, bvFTD and controls. Analyses revealed a significant group × condition interaction ($F_{4,102}$=3.243, p=.015), with *post hoc* analyses indicating AD patients had significantly greater recognition of trustworthy compared to lottery (p=.002) and untrustworthy (p=.001) faces. In contrast, no difference in recognition across conditions was seen in bvFTD patients (all p values >.741). Controls also showed no difference in performance across conditions, likely due to their ceiling performance on this task (all p values >.986). The group effect for face recognition accuracy was significant ($F_{2,51}$=10.744, p<.001), with lower performance in AD patients than controls (p<.001) and a trend for lower performance in bvFTD patients relative to controls (p=.055), irrespective of condition. AD also tended to show lower face recognition accuracy than bvFTD (p=.057). A significant main effect of condition was also evident ($F_{2,102}$=4.311, p=.016), such that averaged across groups, face recognition accuracy was higher in the trustworthy compared to lottery condition (p=.027). Face recognition

accuracy did not differ between the trustworthy and untrustworthy conditions (p=.121) or between the untrustworthy and lottery conditions (p=.598).

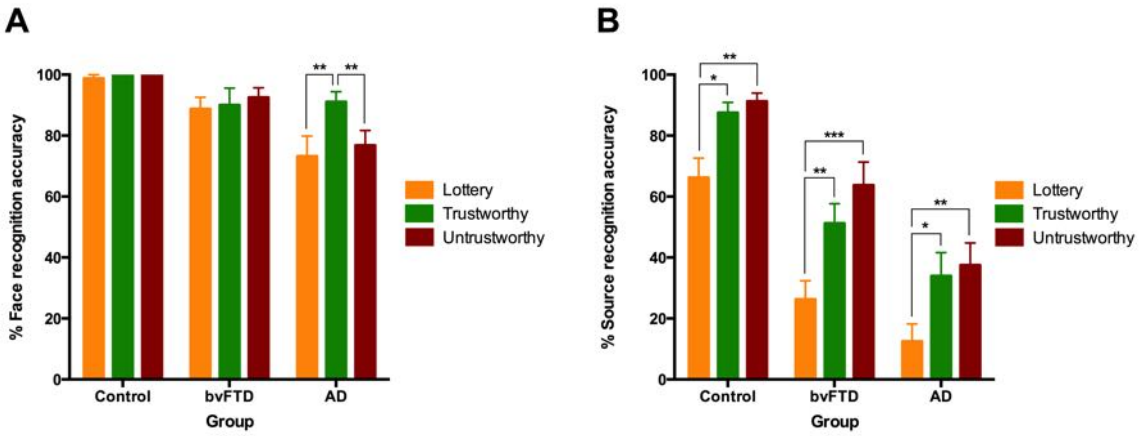
3.3.4 Neural correlates of social face recognition

Regions of grey matter intensity reduction associated with social (trustworthy and untrustworthy) face recognition accuracy in each patient group are shown in Table 3 and Fig. 4B. In bvFTD, social face recognition performance was associated with frontostriatal regions bilaterally (frontal pole, orbitofrontal cortex, subcallosal cortex, anterior cingulate and paracingulate cortices, caudate, putamen, and nucleus accumbens), as well as regions in the right TPJ, bilateral fusiform cortex, left parahippocampal and right inferior temporal gyri. In contrast, no regions of grey matter intensity covaried with social face recognition performance in AD.

3.3.5 Source recognition

Fig. 3B depicts source recognition accuracy for each condition across AD, bvFTD and controls. Analyses revealed a significant group effect for source recognition accuracy ($F_{2,51}$=35.886, p<.001), driven by lower accuracy in both bvFTD (p<.001) and AD (p<.001) patients compared to controls. Source recognition accuracy was also lower in AD relative to bvFTD patients (p=.016). A significant main effect of condition was also observed ($F_{2,102}$=27.26, p<.001) with higher source recognition accuracy in the trustworthy (p<.001) and untrustworthy (p<.001) conditions compared to the lottery condition. Surprisingly, the interaction between group and condition was not significant ($F_{4,102}$=.577, p=.68), with *post hoc* within group analyses confirming that all groups showed higher source recognition accuracy in the trustworthy and untrustworthy conditions, relative to the lottery condition (all p values <.05).

*Fig. 3. (A) Percentage face recognition accuracy across conditions and groups on the two-alternative forced-choice recognition test. (B) Percentage source recognition accuracy for each condition across groups. Error bars represent standard error of the mean. Brackets indicate significant post hoc simple effects, *p<.05, **p<.01, ***p<.001.*



3.3.6 Neural correlates of social source recognition

Regions of grey matter intensity associated with social (trustworthy and untrustworthy) source recognition accuracy in each patient group are shown in Table 3 and Fig. 4C. In bvFTD, social source recognition accuracy was associated with integrity of primarily frontostriatal regions (right orbitofrontal cortex, caudate, putamen, inferior and middle frontal gyri, left frontal pole, and paracingulate gyrus), as well as MTL regions (right amygdala, hippocampus, parahippocampal gyrus), bilateral TPJ regions extending to the insular cortex on the left, right posterior temporo-occipital regions (fusiform, inferior temporal and lateral occipital cortices), left fusiform cortex and right cerebellum. Regions of grey matter intensity reduction covarying with social source recognition performance in AD included bilateral MTL regions (amygdala, hippocampus, parahippocampal gyrus and temporal pole), as well as left TPJ, right temporo-occipital regions (inferior temporal, middle temporal cortices), and lateral occipital regions bilaterally.

Fig. 4. Voxel-based morphometry (VBM) results showing areas of significant grey matter intensity decrease correlating with (A) Social learning on the trust game; (B) Social face recognition; and (C) Social source recognition. Neural correlates for AD and bvFTD patients shown in blue and red, respectively. Results uncorrected at p<.001 and at a cluster threshold of >200 contiguous voxels.

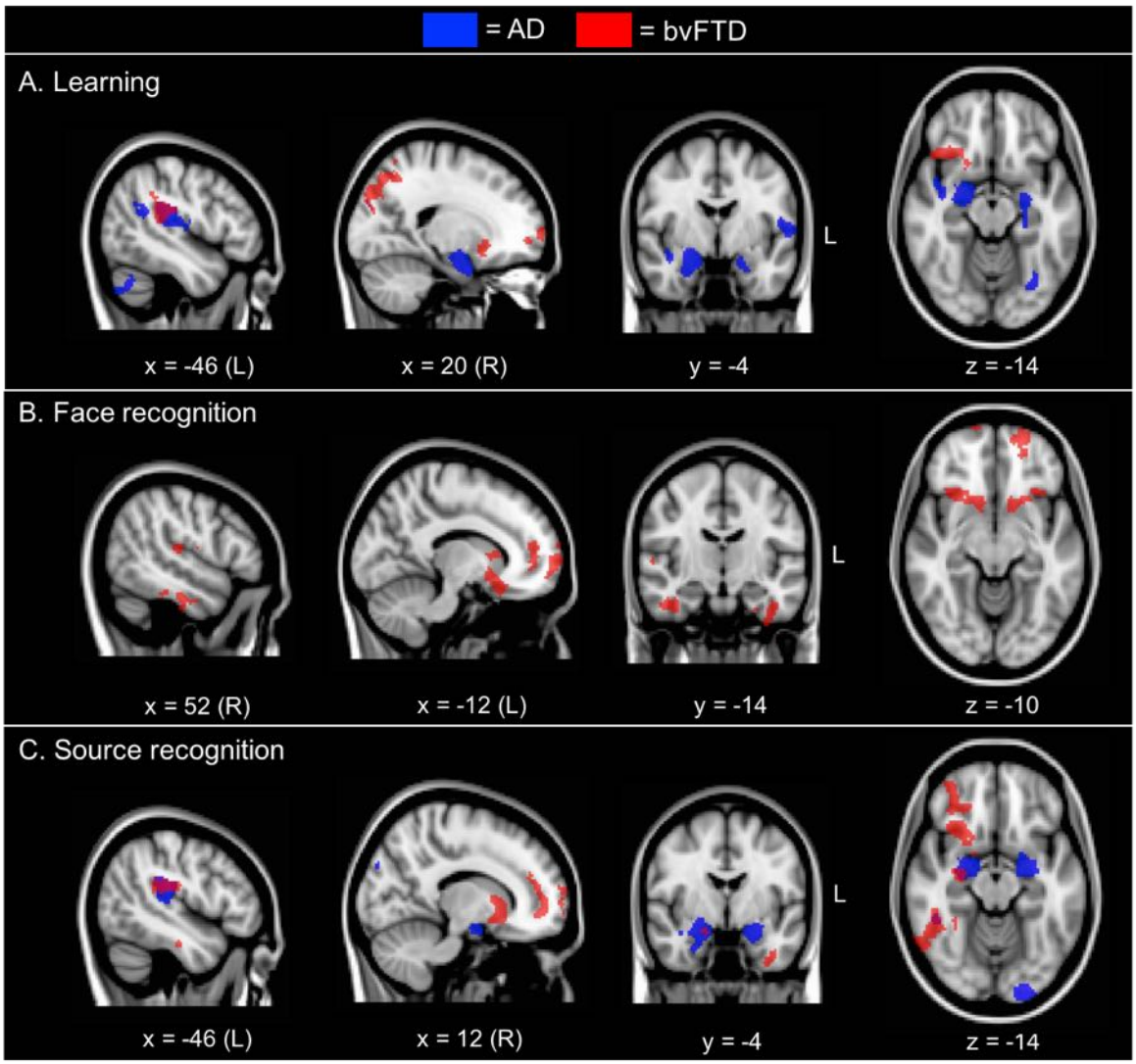


Table 2. Voxel-based morphometry results showing regions of grey matter intensity decrease that covary with trust game learning performance in bvFTD and AD.

Regions	Hemisphere (L/R/B)	MNI Coordinates			Number of voxels
		X	Y	Z	
bvFTD					
Lateral occipital cortex (superior)	R	24	-78	16	1213
Superior temporal gyrus (posterior), planum temporale, parietal operculum cortex	L	-54	-38	10	505
Middle temporal gyrus (temporo-occipital), angular gyrus, lateral occipital cortex (inferior)	R	50	-52	-4	442
Frontal pole	R	6	68	-6	289
Orbitofrontal cortex, putamen	R	36	20	-18	281
Middle frontal gyrus	R	34	28	26	229
AD					
Superior temporal gyrus (anterior), central opercular cortex, parietal operculum cortex, supramarginal gyrus (posterior), angular gyrus, insular cortex, Heschl's gyrus, planum temporale	L	-60	-2	0	1369
Cerebellum	L	-38	-44	-36	1066
Parahippocampal gyrus (anterior), hippocampus, amygdala	R	26	-2	-30	692
Hippocampus, amygdala, parahippocampal gyrus (anterior)	L	-20	-14	-24	406
Lateral occipital cortex (superior)	R	30	-86	24	301

Results uncorrected at $p < .001$ and at a cluster extent threshold of > 200 contiguous voxels and reported at $t > 4.89$.
L = left; R = right; B = bilateral.

Table 3. Voxel-based morphometry results showing regions of grey matter intensity decrease that covary with social face and source recognition in bvFTD and AD.

Contrast	Regions	Hemisphere (L/R/B)	MNI Coordinates			Number of voxels
			X	Y	Z	
Face recognition	**bvFTD**					
	Frontal pole, paracingulate cortex, anterior cingulate cortex	R	16	68	-10	721
	Frontal pole, paracingulate cortex	L	-24	62	-14	677
	Temporal pole, inferior temporal gyrus (anterior), temporal fusiform cortex (posterior)	R	36	6	-44	576
	Orbitofrontal cortex, subcallosal cortex, putamen, nucleus accumbens	L	-18	20	-22	564
	Orbitofrontal cortex, insular cortex, putamen, caudate, nucleus accumbens	R	36	24	-16	425
	Fusiform cortex (anterior), parahippocampal gyrus (anterior),	L	-34	-8	-44	370
	Supramarginal gyrus (anterior)	L	-44	-40	32	277
	Planum temporale, central opercular cortex	R	56	-18	2	217
	AD					
	None above threshold					
Source recognition	**bvFTD**					
	Orbitofrontal cortex, caudate, putamen, amygdala, hippocampus, parahippocampal gyrus	R	8	12	-24	1713
	Cerebellum, fusiform cortex (posterior), inferior temporal gyrus (temporo-occipital), lateral occipital cortex (inferior)	R	56	-62	-38	1166
	Frontal pole, paracingulate gyrus	L	-24	60	-10	596
	Insular cortex, central opercular cortex, parietal operculum cortex, planum temporale	L	-32	-20	14	587
	Inferior frontal gyrus, middle frontal gyrus	R	40	14	26	300
	Planum temporale, central opercular cortex	R	58	-18	4	292
	Fusiform cortex (anterior and posterior)	L	-36	-14	-44	220

AD					
Planum temporale, parietal operculum cortex, central opercular cortex	L	-48	-28	8	662
Parahippocampal gyrus (anterior), temporal pole, amygdala, hippocampus	R	28	-6	-34	650
Inferior temporal gyrus (temporo-occipital), middle temporal gyrus (temporo-occipital), lateral occipital cortex (inferior)	R	50	-44	-16	531
Amygdala, hippocampus, temporal pole	L	-28	0	-26	490
Lateral occipital cortex (superior), occipital pole	R	24	-88	22	419
Lateral occipital cortex (superior)	L	-12	-76	42	286
Lateral occipital cortex (superior)	L	-38	-70	10	270
Lingual gyrus	L	-20	-56	0	245
Occipital pole	L	-18	-98	-16	232

Results uncorrected at $p < .001$ and at a cluster extent threshold of > 200 contiguous voxels and reported at $t > 4.89$.
L = left; R = right; B = bilateral; MNI = Montreal Neurological Institute.

Table 4. Spearman rank correlation coefficients from analyses exploring associations between total learning, face recognition and source recognition accuracy for social and non-social partners and SVS variables.

		Social Vulnerability Scale	
		Credulity	**Gullibility**
bvFTD	**Learning**	-0.231	0.292
	Face recognition		
	Social	-0.005	0.249
	Non-social	0.177	0.283
	Source recognition		
	Social	-0.108	0.467
	Non-social	0.002	0.352
AD	**Learning**	-0.219	-0.379
	Face recognition		
	Social	-0.499	**-0.583***
	Non-social	0.332	-0.272
	Source recognition		
	Social	**-0.677***	**-0.603***
	Non-social	-0.317	-0.353

Correlation coefficients representing significant one-tailed correlations are shown in bold typeface (*p<.05). Higher scores on the Social Vulnerability Scale (SVS) denote greater impairment.

3.4 Relationships between trust game memory task performance and SVS variables

Finally, we examined whether learning and memory for socially relevant (trustworthy and untrustworthy) partners on the trust game was associated with susceptibility to financial mistreatment in AD and bvFTD (see Table 4). In AD patients, lower gullibility scores correlated with greater face (r=–.583, p=.039) and source (r=–.603, p=.033) recognition accuracy for socially relevant partners. Similarly, lower scores on the credulity subscale were associated with greater source recognition accuracy for socially relevant partners in AD (r=–.677, p=.016). No significant associations were identified between credulity, gullibility and memory for non-social (lottery) partners in AD (p values >.158). In contrast, credulity and gullibility scores did not correlate with memory for socially relevant or socially irrelevant partners in bvFTD (all p values >.072). No significant associations were identified between learning and SVS subscale scores in either patient group (all p values >.136).

4. Discussion

This is the first study to investigate learning and memory of social interactions using a novel neuroeconomic task across neurodegenerative brain disorders. Our results revealed a reduced capacity to learn socially relevant information on the trust game in both bvFTD and AD. Despite poor learning, however, a significant social enhancement effect for face and source memory was evident in AD. In contrast, face recognition did not differ across social and non-social conditions in bvFTD. Unexpectedly, however, source memory was better for socially relevant information in this patient group, reflecting a relatively preserved capacity to remember whether partners shared or stole during the task. Importantly, these behavioural findings were associated with everyday financial vulnerability in the AD group only. Our neuroimaging analyses revealed divergent neural correlates of social learning and memory contingent on dementia subtype, with primary involvement of MTL regions in AD, as opposed to a wider network of frontostriatal, insular, fusiform and MTL regions in bvFTD. The TPJ also emerged as a common neural substrate underpinning social learning and memory performance across both dementia syndromes, albeit with some differences in terms of laterality. Here, we discuss the implications of our findings in terms of how these memory profiles account for the similar and distinct disease features in bvFTD and AD, the potential neurocognitive mechanisms that underpin learning and memory of social interactions in these patient groups, as well as how the deficits uncovered here relate to susceptibility to financial exploitation in dementia.

4.1 Profile of performance in AD

On multi-round trust games, participants typically learn to trust or distrust partners based on their history of positive or negative social reciprocity on previous rounds. The use of social reciprocity as a form of feedback during the learning phase of our trust game memory task did not appear to benefit AD patients to the same extent as controls. Poor learning of trust-

related responses was associated with bilateral amygdala and hippocampal atrophy in AD, consistent with deficits in MTL-mediated memory encoding processes (Dickerson & Sperling, 2008; Rombouts et al., 2000), as well as the involvement of the amygdala in emotional memory in these patients (Mori et al., 1999).

Importantly, we found that social relevance significantly enhanced subsequent face and source memory in AD, despite marked episodic memory dysfunction. This social enhancement effect corroborates previous reports of preserved emotional memory enhancement in this patient group (Kalenzaga, Piolino, & Clarys, 2014; Kumfor et al., 2014; Kumfor, Irish, Hodges, & Piguet, 2013b). The specificity of the social enhancement effect for trustworthy but not untrustworthy faces is an intriguing result, and adds to an increasing number of studies that demonstrate a positivity memory bias in AD (Sava, Krolak-Salmon, Delphin-Combe, Cloarec, & Chainay, 2016; Sava et al., 2015; Werheid, McDonald, Simmons-Stern, Ally, & Budson, 2011; Zhang, Ho, & Fung, 2015). While the neural correlates of this effect have not been explored in AD, evidence from healthy adults suggests that the amygdala is engaged in memory for both positive and negative stimuli (Kensinger, 2006). Social face recognition for trustworthy and untrustworthy partners, however, was not found to associate with any regions of atrophy in AD. Nonetheless, our findings highlight the importance of understanding this positivity memory bias in face recognition, especially given the potential therapeutic implications in supporting memory for social interactions in AD patients.

For source memory, the behaviours of trustworthy and untrustworthy partners were more accurately recognised than behaviours of non-social partners, though a positivity effect was not observed in AD. It is possible that trustworthy partners are more memorable at an implicit level, but when provided with cues regarding specific behaviours, memory for both

trustworthy and untrustworthy partners is more accurately retrieved than for socially irrelevant partners. Notably, this pattern of performance is consistent with enhanced source memory for both trustworthy and untrustworthy partners in healthy adults (Bell *et al.*, 2010), demonstrating that social relevance facilitates source memory in AD patients. Our source memory imaging findings implicate atrophy in similar amygdala-hippocampal regions across both learning and source memory retrieval. This corroborates the notion that learning and memory of trust-related social interactions in AD is associated with atrophy in brain regions that have been demonstrated to be crucial for not only retrieval, but also preferential encoding of emotionally-arousing stimuli (Klein-Koerkamp, Baciu, & Hot, 2012; Mori et al., 1999). While social enhancement of source memory in our study was evident following both positive and negative social reciprocity, further investigation is required to determine whether mechanisms that underlie social memory differ according to valence.

Collectively, our findings in AD indicate that social relevance enhances face and source memory in AD, despite lower learning of trust-related responses during the trust game. The pattern of neural correlates in AD suggests the primary involvement of memory and emotion processing structures.

4.2 Profile of performance in bvFTD

In bvFTD, poor learning of trust-related responses was associated with orbitofrontal and ventral striatal atrophy. Previous studies in healthy adults demonstrate that positive and negative social reciprocity on multi-round trust games engages orbitofrontal and ventral striatal regions (Phan, Sripada, Angstadt, & McCabe, 2010), which play a central role in reward-processing (O'Doherty, 2004). As such, our findings in bvFTD suggest that poor learning performance may be related to deficits in reward processing, in line with previous

reports of reduced sensitivity to social and monetary gains and losses in this patient group (Perry *et al.*, 2015; Torralva *et al.*, 2009).

In terms of face recognition memory, our results in bvFTD do not provide evidence of a clear social enhancement effect. While overall memory for faces tended to be lower in bvFTD compared to controls, memory for socially relevant faces was not enhanced relative to socially irrelevant faces. Although it is possible that our recognition test format led to ceiling effects in bvFTD patients with less severe memory impairment, bvFTD patients showed clear impairments relative to controls on background neuropsychological tests of episodic memory. Interestingly, however, recognition of socially relevant faces was associated with atrophy in frontostriatal regions, as well as the bilateral fusiform cortices in bvFTD. Atrophy of the fusiform cortex is associated with poor identity discrimination between faces showing different emotional expressions in bvFTD patients (Kumfor *et al.*, 2015). Hence, our neuroimaging findings point to a possible role of facial identity discrimination deficits in memory for socially relevant faces in bvFTD.

Contrary to expectations, the source memory profile seen in bvFTD indicates that memory is enhanced by social relevance. As such, our results stand in contrast with previous reports of compromised emotional enhancement of memory for negative emotional stimuli in bvFTD (Kumfor et al., 2014; Kumfor, Irish, Hodges, & Piguet, 2013b). Notably, however, the profile of behavioural performance was not correlated with everyday financial vulnerability. While speculative, this profile suggests that while bvFTD patients may be able to remember social interactions, abnormal reward processing/motivation may lead to a failure to incorporate and modify decisions using this information in an appropriate way. Our imaging results implicate a distributed network of social cognition, reward processing, memory, and face processing regions including the caudate, putamen and orbitofrontal

cortex, together with the paracingulate cortex, insular cortex, frontal pole, amygdala, hippocampus and fusiform cortex. The involvement of the paracingulate and insular cortices suggests that in addition to altered social reward processing, broader deficits in understanding social intentionality (Baez *et al.*, 2016; Walter *et al.*, 2004) and processing socio-emotional interoceptive cues (e.g. heart rate, skin conductance, muscle tension) (Craig, 2009; Sturm *et al.*, 2013) may also influence memory for socially relevant source details in bvFTD. Clearly, the relationships between socioemotional processing and cognition are only beginning to be uncovered and further research is necessary to understand these complicated relationships.

4.3. Shared neural correlates of social learning and memory performance in AD and bvFTD

It is interesting to note that the TPJ was found to correlate with social learning and source memory performance, across both bvFTD and AD patients. The TPJ is a supramodal association area known to support a diverse array of cognitive functions, including Theory of Mind (Saxe & Kanwisher, 2003), reorienting of attention (Krall *et al.*, 2015), and attentional aspects of episodic memory retrieval (Cabeza, Ciaramelli, Olson, & Moscovitch, 2008). Notably, however, our results showed laterality effects across groups, such that the left TPJ was implicated in both AD and bvFTD, whereas the right TPJ was associated with face recognition and source memory performance in bvFTD only. Although functional lateralisation of the TPJ is still debated, both hemispheres are commonly activated during social tasks in healthy adults (Schurz, Radua, Aichhorn, Richlan, & Perner, 2014). Nonetheless, it has been proposed that the right TPJ plays a specific role in attributing mental states to others, whereas the left TPJ is more broadly involved in both mental and non-mental perspective taking (Perner, Aichhorn, Kronbichler, Staffen, & Ladurner, 2006; Saxe & Wexler, 2005). Intriguingly, recent evidence has also implicated the right TPJ in processing social motivations, in the context of altruistic behaviours (Morishima, Schunk, Bruhin, Ruff,

& Fehr, 2012), social win/loss outcomes (van den Bos, Talwar, & McClure, 2013) or competition against familiar others (Sugimoto, Shigemune, & Tsukiura, 2016). Taken together, the specific involvement of right TPJ in bvFTD suggests that deficits in attributing intentions in socially-motivated contexts may also contribute to memory for social interactions. On the other hand, the shared involvement of left TPJ across groups likely relates to broader deficits in perspective taking, consistent with previous findings in both bvFTD and AD patients (Dermody *et al.*, 2016).

4.4 Implications for financial vulnerability

Identifying the extent to which memory for socially relevant information is associated with financial vulnerabilities is an important area to consider, given recent reports of financial abuse in patients with dementia (Lichtenberg, 2016; Tronetti, 2014). In AD, attenuation of the social memory enhancement effect was associated with higher susceptibility to the cognitive (credulity) and behavioural (gullibility) aspects of financial exploitation. The finding that these relationships were specific to AD concurs with the notion that general cognitive and memory deficits underlie financial errors in this syndrome (Chiong, Hsu, Wudka, Miller, & Rosen, 2013). Our findings in AD have clear implications for the awareness and management of such vulnerabilities. In particular, families and carers should bear in mind that social and emotional significance may continue to support memory retrieval in AD patients, particularly during the earlier stages of the disease. Indeed, emotional experiences in AD appear to persist beyond the ability to recall specifics of the event which caused the emotion, thus reinforcing the importance of fostering positive emotional experiences in these patients (Guzmán-Vélez, Feinstein, & Tranel, 2014). With disease progression, however, and continuing worsening of memory impairment and emotion recognition abilities (Bertoux, de Souza, et al., 2015b), AD patients will be

increasingly susceptible to social and financial mistreatment, and require further support in navigating day-to-day social and financial interactions.

In contrast, despite the fact that susceptibility to financial exploitation was disproportionately higher in bvFTD patients, this was unrelated to learning and memory of social information on the trust game memory task. This lack of association suggests a mediating factor between social memory and credulity/gullibility exists. As such, impaired memory for socially relevant information in bvFTD does not seem to play a central role in their susceptibility to financial mistreatment. Instead, our neuroimaging findings support the notion that these susceptibilities may be related to deficits in socio-emotional functions and reward processing (Chiong et al., 2013; Perry & Kramer, 2013).

Furthermore, bvFTD patients did not rate experiences of positive or negative social reciprocity on the trust game differently to controls or AD patients, suggesting a disconnect between ostensibly intact affective reactions and the ability to modify behaviour accordingly. The veracity of these affective ratings should be interpreted with caution, however, given that bvFTD patients may fail to integrate socio-emotional interoceptive information in order to recognise their own emotions (Sturm, Ascher, Miller, & Levenson, 2008). Together, these findings suggest that while bvFTD patients appear to learn and remember aspects of socially relevant information, they do not apply this knowledge to modulate their behaviour. Of interest, failure to modify behaviour within specific social contexts has been proposed to underlie impaired social cognition in bvFTD (Ibanez & Manes, 2012). As such, examining the influence of contextual details, such as reputation for trustworthiness (Fouragnan *et al.*, 2013) or moral character (Delgado *et al.*, 2005), represents an important area of future enquiry, especially considering recent evidence of impaired

integration of social contextual information during normative decision-making (O'Callaghan *et al.*, 2016) and social bargaining (Melloni *et al.*, 2016) in bvFTD.

A number of methodological limitations warrant further discussion. Firstly, the nature of the participants' responses on the learning phase of the trust game (i.e. to 'keep' or 'invest') did not allow us to distinguish between learning about the partner's *trustworthiness* and learning how best to *respond* to the partner's trustworthiness, as the learning performance scores only reflect the latter. Given that feedback regarding the partner's trustworthiness was kept constant regardless of each participant's response, it is possible that some patients were able to learn about the partner's *trustworthiness* but lacked the cognitive capacity to *deploy this information* in order to maximise monetary profits on the trust game. Importantly, this may explain why both AD and bvFTD patients showed a social memory enhancement effect despite poor learning performance on the trust game. To address this limitation, future studies should directly contrast passive viewing versus interactive paradigms for learning of trust-related behaviour in these patient groups. In addition, given the potential dissociation between subjective ratings versus objective physiological measures of affective responses (Sturm *et al.*, 2008), future investigations of social learning using the trust game paradigm would also benefit from incorporating psychophysiological measures of arousal (e.g. heart rate, pupil dilation and skin conductance) to examine underlying mechanisms of reward sensitivity in these patient groups. Furthermore, to minimize patient fatigue and reduce the likelihood of floor effects in our patient groups, we used a two-alternative forced choice recognition test to assess face memory. While this allowed us to detect a significant social enhancement effect on face memory in AD, ceiling effects were evident in controls. Our face memory results should therefore be interpreted with this caveat in mind.

In summary, this study is the first to investigate learning and memory of social interactions in AD and bvFTD, using a neuroeconomic trust game paradigm. While patients with AD may harness socially relevant information to facilitate memory retrieval, learning and memory of social information is strongly associated with the degeneration of episodic memory and emotion processing structures in the MTL, and is therefore vulnerable to decay with increasing disease severity. Most strikingly, this effect is associated with susceptibility financial mistreatment in AD, raising important ethical implications for the care and treatment of individuals living with dementia. Conversely, the memory advantage for socially relevant information does not appear to mitigate the striking financial vulnerabilities reported in bvFTD. Instead, such vulnerabilities are likely exacerbated by widespread social cognitive deficits and altered reward processing. From a broader theoretical perspective, our findings provide important insights regarding the complex interplay between social cognition and memory, and the devastating effect caused by a breakdown in these processes.

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5.2. Concluding remarks

The findings in this chapter demonstrate that, contrary to expectations, bvFTD patients show a memory advantage for socially relevant information. However, there appears to be a mismatch between memory for socially rewarding information and the ability to apply this knowledge in relevant situations (i.e., to maximise winnings by trusting or distrusting partners on the trust game or to avoid financial exploitation in everyday life). Clarifying this link in bvFTD is an important future direction, as the neurocognitive mechanisms that distinguish the *attachment* of reward value to memory from the *application* of reward-related memory are not well established. Considering the complex social context embedded within the trust game task however, it is possible that performance in bvFTD was affected by impairment either in social cognition and/or reward valuation. As such, it is unclear whether bvFTD patients would be able to apply reward-related memory in non-social contexts. This point is addressed in the following chapter, by removing the social context and examining learning and memory for items that have clearly defined reward values.

Chapter 6
Strategic value-directed learning and memory in AD and bvFTD

This chapter continues to investigate the notion that the medial PFC engages in valuation processes that enhance memory for rewarding information. Here, the focus is placed on the ability to prioritise learning of information that has been assigned a clear reward value, and how this impacts on subsequent recall and recognition. Methodologically, the task adapted for this study resembles word list learning tests that are commonly used in the clinic. As such, immediate and delayed recall measures are included, in addition to item and source memory recognition measures that are similar to those reported in Chapters 4 and 5.

6.1. Manuscript V

"Strategic value-directed learning and memory in Alzheimer's disease and behavioural-variant frontotemporal dementia"

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Abstract

Evidence from healthy adults indicates that the ability to prioritize learning of highly valued information is supported by executive functions, and enhances subsequent memory retrieval for this information. In neurodegenerative disorders such as Alzheimer's disease (AD) and behavioural-variant frontotemporal dementia (bvFTD), marked deficits are evident in learning and memory, presenting in the context of executive dysfunction. It remains unclear, however, if these patients show a typical memory bias for higher valued stimuli. We administered a value-directed word-list learning task to AD (n=10) and bvFTD (n=21) patients and age-matched healthy controls (n=22). Each word was assigned a low, medium or high point value and participants were instructed to maximize the number of points earned across three learning trials. Subsequently, participants' memory for the words was assessed on a delayed recall trial, followed by a recognition memory test for the words and corresponding point values. Relative to controls, both patient groups showed poorer overall learning, delayed recall and recognition. Despite these impairments, AD patients preferentially recalled high-value words on learning trials, and showed significant value-directed enhancement of recognition memory for the words and points. Conversely, bvFTD patients did not prioritize recall of high-value words during learning trials, and this reduced selectivity was related to inhibitory dysfunction. Nonetheless, bvFTD patients showed value-directed enhancement of recognition memory for the point values, suggesting a mismatch between memory of high-value information and the ability to apply this in a motivationally salient context. Overall, our findings demonstrate that value-directed enhancement of memory may persist to some degree in patients with dementia, despite pronounced deficits in learning and memory.

Keywords: Alzheimer's disease; frontotemporal dementia; memory; executive function; reward

Introduction

Every day, we encounter enormous amounts of information, which vary in terms of relative value or importance. The ability to prioritise what we need to learn and remember for higher valued information is therefore critical for maximizing memory efficiency. Indeed, evidence suggests that reward value plays a key role in shaping episodic memory (Shohamy & Adcock, 2010). The cognitive mechanisms by which this effect is achieved, however, remain unclear.

Encoding selectivity has been examined in healthy adults using the value-directed remembering (VDR) paradigm (Castel, Benjamin, Craik, & Watkins, 2002), where participants are presented with lists of words, which are each assigned a point value to signify its relative importance. A consistent finding in studies of both young and older healthy adults is that the probability of immediate (short-term) word recall increases with point value (Castel et al., 2002; Castel, Farb, & Craik, 2007). Importantly, age-related differences in recall are observed for words with lower values but not those with higher values, indicating that the ability to prioritise memory for highly valued information persists with healthy aging, despite declines in memory for less valued information (Castel et al., 2002). Furthermore, higher selectivity in encoding is associated with greater working memory capacity (Castel, Balota, & McCabe, 2009; Hayes, Kelly, & Smith, 2013) and enhances subsequent recognition memory for the words and associated point values, such that higher valued words are more accurately retrieved (Castel et al., 2007; McDonough, Bui, Friedman, & Castel, 2015).

Value-directed remembering therefore has interventional potential in neurodegenerative syndromes in which marked episodic memory deficits are present. Behavioural-variant frontotemporal dementia (bvFTD) and Alzheimer's disease (AD) are two such syndromes

in which episodic memory impairments are well-established, but have been proposed to be driven by different neurocognitive mechanisms. Owing to the predominantly prefrontal burden of neuropathology and prominent executive dysfunction in bvFTD (Kipps, Hodges, Fryer, & Nestor, 2009; Kramer et al., 2005), it has been suggested that deficits in strategic encoding and retrieval mechanisms underlie episodic memory impairment in these patients (Pasquier, Grymonprez, & Lebert, 2001; Wicklund, Johnson, Rademaker, Weitner, & Weintraub, 2006). However, both prefrontal and medial temporal lobe regions have been implicated in episodic memory dysfunction in bvFTD (Irish, Piguet, Hodges, & Hornberger, 2014; Pennington, Hodges, & Hornberger, 2011). Conversely, episodic memory deficits in AD are considered to reflect deficits in memory encoding, storage and consolidation (Golby et al., 2005; Lekeu et al., 2010), attributable to atrophy predominantly in the medial temporal lobes and posteromedial cortices (Irish et al., 2016; Ranganath & Ritchey, 2012). Concomitant deficits in executive function, however, are also commonly reported in AD (Swanberg, Tractenberg, Mohs, Thal, & Cummings, 2004), particularly with progression of the disease (Ramanan et al., 2016). Nevertheless, the degree to which executive deficits differentially contribute to episodic memory dysfunction in bvFTD and AD remains largely underexplored.

To our knowledge, only one study has investigated value-directed memory selectivity in AD (Castel et al., 2009). Using the VDR paradigm, Castel et al. (2009) found that AD patients showed better immediate recall of high-value compared to low-value words. On the other hand, value-directed memory selectivity has not been investigated in bvFTD. Importantly, AD and bvFTD patients show similar impairments in working memory and cognitive flexibility (Giovagnoli, Erbetta, Reati, & Bugiani, 2008). In contrast, bvFTD patients show disproportionate impairments in inhibitory control and value-based decision-making, which are associated with degenerative changes in the ventromedial prefrontal cortex and striatum

(Hornberger et al., 2010; Kloeters, Bertoux, O'Callaghan, Hodges, & Hornberger, 2013; O'Callaghan, Naismith, Hodges, Lewis, & Hornberger, 2013). Nonetheless, it remains to be explored whether deficits in inhibitory control and value-based processing can impact on learning and memory. Of primary interest is whether value-directed memory selectivity is comparably affected across AD and bvFTD, and the underlying cognitive mechanisms driving any such deficits.

In addition to examining how memory selectivity is affected in AD and bvFTD, we were also interested in investigating the impact of value-directed encoding on subsequent memory retrieval. While healthy older adults show enhanced memory for rewarding stimuli (Castel, Balota, McCabe, & Castel, 2008; Spaniol, Schain, & Bowen, 2014), it is unclear whether reward value is sufficient to ameliorate memory impairments in neurodegenerative conditions. Whether a value-directed memory enhancement effect persists in patients with dementia is of clinical relevance, given the potential therapeutic implications in supporting memory for information that holds greater relative value.

The first aim of this study was to assess strategic value-directed encoding in AD and bvFTD using a simplified version of the VDR paradigm, where the same word-list is presented over three immediate recall learning trials, followed by a delayed recall trial and recognition test. Considering the widespread executive dysfunction and deficits in value-based decision making in bvFTD, we hypothesized that value would have no effect on immediate recall in bvFTD. In contrast, AD patients may learn to prioritise recall of higher valued words over repeated trials, in keeping with previous reports of greater recall of high-value versus low-value words in this patient group. Secondly, we aimed to examine the relationship between encoding selectivity and profiles of executive dysfunction, to investigate whether deficits in working memory, cognitive flexibility and inhibition differentially contribute to selectivity

in AD and bvFTD. The final aim of this study was to explore whether reward value would enhance memory for the words and associated point values following a time delay. We hypothesised that value-directed enhancement of memory would be evident in AD, but attenuated in bvFTD patients, in-line with their expected performance on the preceding immediate recall trials.

Material and methods

Participants

Thirty-one dementia patients (bvFTD=21; AD=10) and 22 age-matched healthy controls were recruited through FRONTIER at Neuroscience Research Australia, Sydney. All bvFTD patients fulfilled clinical diagnostic criteria for probable bvFTD (Rascovsky et al., 2011), with insidious onset, progressive decline in social behaviour and personal conduct, apathy, emotional blunting and loss of insight and presence of frontal atrophy on brain imaging. All AD patients met clinical diagnostic criteria for probable AD (McKhann et al., 2011), with worsening episodic memory impairment in the context of preserved personality and behaviour and evidence of medial temporal lobe atrophy on imaging. Disease duration was estimated as the number of years elapsed since the reported onset of symptoms. The Frontotemporal Dementia Rating Scale (FRS; Mioshi, Hsieh, Savage, Hornberger, & Hodges, 2010) and Clinical Dementia Rating Scale (CDR; Morris, 1997) were used to determine disease severity in bvFTD and AD patients. All participants underwent general cognitive screening using the Addenbrooke's Cognitive Examination-III (ACE-III; Hsieh, Schubert, Hoon, Mioshi, & Hodges, 2013) to determine their overall level of cognitive functioning. Age-matched healthy controls were recruited from the FRONTIER research volunteer panel and scored >88 on the ACE-III (Hsieh et al., 2013).

Exclusion criteria for all participants included current or prior history of mental illness, significant head injury, movement disorders, cerebrovascular disease (stroke, transient ischaemic attacks), alcohol or other drug abuse and limited English proficiency.

Ethics statement

All participants provided written informed consent and this study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethics Committee of the South Eastern Sydney Local Health District and the University of New South Wales.

Assessment of executive function and verbal episodic memory

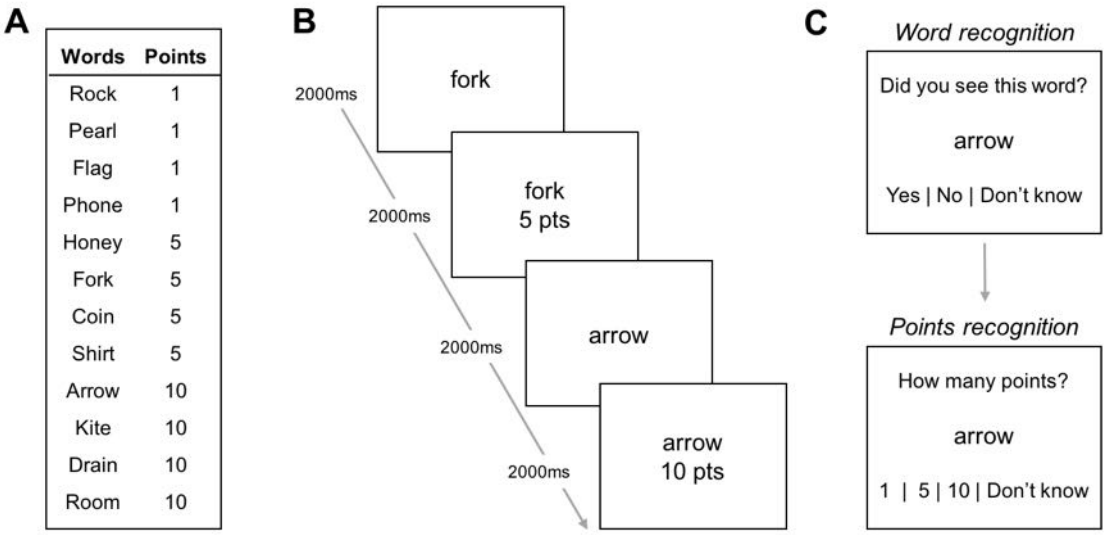
Assessment of executive function included measures of working memory (Digit Span Backward (DSB); total score; Wechsler, 1997), cognitive flexibility (Trail Making Test; B – A time; Reitan & Wolfson, 1985) and verbal inhibition (Hayling Sentence Completion Test; AB error score; Burgess & Shallice, 1997). Further details of the executive function tests are detailed in Appendix S1.

All participants underwent comprehensive neuropsychological assessment of verbal episodic memory in terms of immediate recall, delayed recall, and delayed recognition using the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941). Further details are provided in Appendix S1.

Value-directed memory task

The value-directed memory (VDM) task was adapted from previous studies (Castel et al., 2008; 2009). The current version assessed learning, recall and recognition of a list of 12 words, where each word was assigned a value of 1, 5 or 10 points.

Figure 1 (A) Example of words and associated points used in the VDM task. (B) Example of word presentation procedure during learning phase of the VDM task. (C) Example of word and points recognition questions in the test phase of the VDM task.



Stimuli and materials

The stimuli consisted of two lists of 12 words. Words from List 1 were presented during learning, while those in List 2 were presented as novel lures during the recognition memory test. Within List 1, 4 words were assigned to each of the low (1 point), medium (5 points) and high (10 points) value conditions. All words were concrete nouns containing either 4 or 5 letters. Words assigned to each condition were matched in terms of word frequency, familiarity, concreteness and imageability, determined using the MRC Psycholinguistic Database (http://www.psych.rl.ac.uk). Lists and words assigned per task phase and condition were counterbalanced across participants.

The VDM task was programmed using E-Prime 2.0 software (Psychology Software Tools, Pittsburgh, PA), and testing was conducted on a laptop with a 14-inch LED-backlit display. Participants responded verbally on the immediate recall learning trials, delayed recall trial and recognition tests.

Procedure

Following presentation of instructions, participants were presented with examples of the word and point stimuli. This included presentation of 3 words (worth 1, 5 and 10 points), followed by an immediate recall trial. After participants recalled the example words, feedback was provided regarding the total number of points earned and how this number was calculated. Participants were told that the aim of the task was to gain as many points as possible. Participants' understanding of the task instructions was checked before commencing the experimental task. Procedures for the learning and test phases are illustrated in Figure 1.

Learning phase

On each learning trial, participants viewed a list of 12 words, displayed one at a time on the computer screen. The order of presentation was randomised, with no more than 2 words from the same condition appearing consecutively. Each word was displayed for 2000 ms before the associated point value appeared below the word for an additional 2000 ms. Following presentation of the word list, participants were asked to recall as many words as possible from the list. Participants then received feedback regarding their total point score and were encouraged to beat their previous score on each upcoming trial. This procedure was repeated for trials 2 and 3 of the learning phase. To limit list-order effects, word-list presentation was randomised on each trial.

Following the learning phase, participants were asked to describe their encoding strategy throughout the 3 trials of the learning phase. Based on their responses, strategies were categorised as Type 1) 'focusing more on high-value words' or 2) 'ignoring value'.

Test phase

Delayed recall

A surprise recall test was administered following a 20-minute delay, where participants were asked to recall as many words as possible from the learning phase. No feedback was provided regarding the number of points earned.

Word and points recognition

Immediately after the delayed recall trial, recognition memory for the words and associated point values was assessed. The recognition phase consisted of 24 trials, where all 12 of the words from the learning phase were individually displayed, intermixed with the 12 novel lure words. On each trial, participants first made a word recognition decision by judging whether they had seen the word during the learning phase (yes/no) or whether they didn't know ("don't know"). The prompt "Yes | No | Don't know" was written below the word. Following each "yes" response, participants made a point recognition decision by responding whether that word had been worth 1, 5 or 10 points. The prompt "1 | 5 | 10 | Don't know" was displayed below the word. The point recognition question was not asked following "no" or "don't know" responses on the word recognition question. The "don't know" response option was offered in order to reduce potential contamination of guessing, in accordance with previously reported procedures (Leshikar & Duarte, 2013; Wong et al., 2016). Recognition trials were self-paced and presented in a random order. No feedback was provided regarding response accuracy.

Outcome measures

Learning phase

Outcome measures from the 3 immediate recall learning trials were the number of words recalled in each value condition. Participants' self-reported encoding strategies were also

included as a categorical outcome measure. Finally, to examine value-directed strategic encoding ability, a selectivity index was calculated using the following equation:

$$Selectivity\ index\ (SI) = \frac{[\,Total\ points\ earned + (chance\ score \times total\ words\ recalled)]}{[Ideal\ points\ earned + (chance\ score \times total\ words\ recalled)]}$$

As previously described (Ariel & Castel, 2013; Cohen, Rissman, Suthana, Castel, & Knowlton, 2016), the SI is a measure of a participant's point score, after taking into account the ideal point score and the chance point scores, which is weighted by the number of words recalled. The ideal point score is the maximum number of points that can be earned for recalling *n* number of words (e.g. the ideal point score for recalling 4 words is 10 + 10 + 10 + 10 = 40). The chance score represents the average points earned, and is calculated as the mean point value of the 12 words on each learning trial (i.e. 5.33). In line with previously reported procedures (Cohen et al., 2016), the weighting procedure was employed to account for low overall word recall performance in AD and bvFTD patients. SI scores range from -1 to 1, with values close to 1 indicating greater selectivity for high-value words. The trial 3 SI score was included in our analyses as a measure of participants' ability to develop value-directed strategic encoding by the end of the learning phase.

Test phase

Delayed recall

The number of words recalled on each value condition was included as the outcome measure on the delayed recall trial.

Word recognition

Word recognition responses were classified as 'studied word hit' (correct recognition), 'studied word miss' (incorrect rejection) and 'studied DK (don't know)' for words previously seen during the learning phase; and 'unstudied word hit' (correct rejection),

'unstudied word miss' (false alarm) and 'unstudied DK' for novel words presented in the test phase only. As the points recognition question was asked following each 'yes' response to the word recognition question, the point value subsequently ascribed to each false alarm was used to classify the response as a low-, medium- or high-value false alarm. To correct for false alarms per condition, corrected word recognition was calculated by subtracting the number of false alarms in each condition from the number of correct recognition responses in each condition.

Points recognition

Points recognition responses were classified as 'points-recollected' (i.e. points-correct) or 'points-unrecollected' (i.e. 'points-incorrect' or 'points-don't know'). Given that the points recognition question was not asked following incorrect word recognition responses, points recognition for such words were classified as 'points-unrecollected'. Following previously reported procedures (Rosa, Deason, Budson, & Gutchess, 2014), points recognition accuracy was calculated by taking the percentage of points-correct responses out of the total number of words in each condition (e.g. percentage points-correct $_{\text{low-value}}$ = (points-correct $_{\text{low-value}}$ / 4) × 100).

Statistical analyses

Data were analysed using SPSS 20.0 (SPSS Inc., Chicago, ILL., USA). Normally distributed variables, as determined by Shapiro-Wilks tests, were compared across groups 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, using Dunn's (1964) procedure with a Bonferroni correction for multiple comparisons. A chi-squared test was used to compare sex distribution across groups.

For each recall trial (Trials 1–3 immediate recall, delayed recall), a group (3) × condition (3) repeated measures ANOVAs was conducted to contrast the number of words recalled per condition across groups. Similarly, group (3) × condition (3) repeated measures ANOVAs were conducted to contrast corrected word and points recognition across conditions and groups. *Post hoc* simple-effects tests were conducted to examine differences between conditions within each participant group. All pairwise comparisons of the main effects and simple effects were adjusted for multiple comparisons using the Sidak method.

Due to the small numbers of participants reporting certain strategy types, Fisher's exact test was used to compare the distribution of participants' self-reported encoding strategies across groups. Independent samples t-tests were used to determine whether Trial 3 SI scores, delayed recall, word recognition or points recognition differed according to self-reported encoding strategy use.

Within each group, Spearman rank correlations were used to examine relationships between encoding selectivity on Trial 3 of the VDM task (SI scores) and background neuropsychological measures of executive function (DSB total, TMT B – A time and Hayling AB error score) and verbal episodic memory encoding (RAVLT learning trial 5 recall). A one-tailed significance level, corrected for multiple comparisons at of $p<.01$ was applied for all correlational analyses.

Results

Demographics

Demographics and clinical characteristics are detailed in Table 1. Participant groups were matched for age ($p=.091$) and sex distribution ($p=.363$). An overall group difference was evident for total years of education ($p=.007$), with controls being more educated than bvFTD

patients (p=.005). Total years of education did not differ between the two patient groups (p=.558) or between AD patients and controls (p=.264). Importantly, the patient groups were matched for disease duration (p=.751) and disease severity (CDR; p=.991). The bvFTD patients showed a trend towards higher levels of functional impairment relative to AD patients (FRS; p=.066). While both patient groups were significantly impaired relative to controls (all p values <.001) on the ACE-III cognitive screening measure, performance was comparable for bvFTD and AD patients (p=.353).

Assessment of executive function and verbal episodic memory

Patient groups displayed characteristic profiles of executive dysfunction relative to controls on tests of working memory (DSB; p values <.001), cognitive flexibility (TMT B – A time; p values <.001) and verbal inhibition (Hayling AB error score; p values <.014). No significant differences were evident between AD and bvFTD patients on any of the executive measures (p values >.47). Encoding, delayed recall and corrected recognition performance on the RAVLT are detailed in Table 1. Verbal episodic memory was significantly compromised in both patient groups relative to controls across all learning trials (RAVLT learning trials 1–5; p values <.001), delayed recall (RAVLT 30-minute recall; p values <.001) and corrected recognition (RAVLT corrected recognition; p values <.001). AD and bvFTD patients did not differ on any measures of verbal episodic memory performance (p values >.110).

Table 1. Demographic and clinical characteristics and performance on neuropsychological measures of executive function and episodic memory[a]

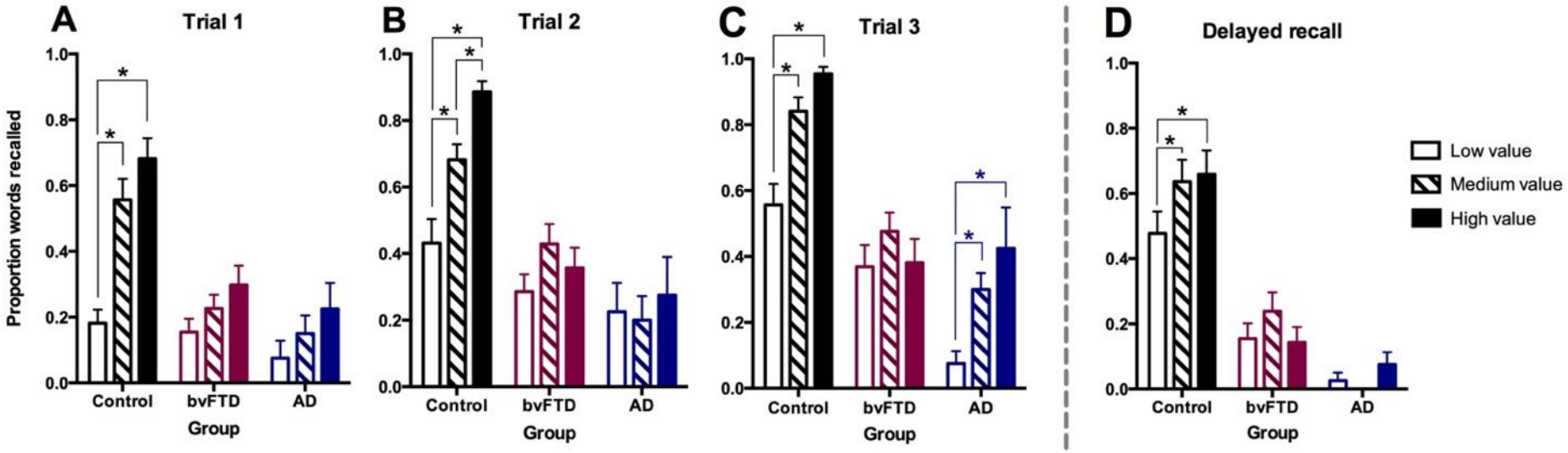
	Control	AD	bvFTD	Group effect	Post hoc test
Sex (M:F)	10:12	6:4	14:7	n.s.	
Age (years)	64.12 (6.82)	67.84 (9.12)	61.50 (7.13)	n.s.	
Education (years)	13.81 (2.43)	12.33 (2.86)	11.35 (2.29)	**	Con > bvFTD
Disease duration (years)		6.48 (4.99)	5.58 (3.22)	n.s.	
CDR SoB [18]		5.28 (1.39)	5.26 (3.22)	n.s.	
FRS Rasch score		0.27 (1.14)	−0.69 (1.31)	#	
ACE-III [100]	96.23 (3.58)	60.80 (12.14)	74.00 (13.05)	***	Con > AD, bvFTD
DSB [15]	8.68 (1.99)	4.5 (2.07)	4.52 (1.47)	***	Con > AD, bvFTD
TMT B − A time (seconds)	39.05 (16.66)	240.42 (149.04)	121.71 (103.78)	***	Con > AD, bvFTD
Hayling AB error score [128]	2.77 (4.92)	12.43 (6.80)	23.06 (18.66)	***	Con > AD, bvFTD
RAVLT learning trials					
Trial 1 [15]	6.73 (2.05)	2.78 (1.56)	4.25 (1.61)	***	Con > AD, bvFTD
Trial 2 [15]	9.91 (2.65)	3.89 (0.93)	5.75 (2.32)	***	Con > AD, bvFTD
Trial 3 [15]	11.68 (2.40)	5.33 (2.12)	7.44 (2.68)	***	Con > AD, bvFTD
Trial 4 [15]	12.73 (1.70)	4.89 (2.42)	7.69 (2.60)	***	Con > AD, bvFTD
Trial 5 [15]	13.14 (1.75)	4.44 (2.19)	8.31 (3.59)	***	Con > AD, bvFTD
RAVLT 30-minute recall [15]	10.32 (2.99)	1.56 (1.67)	4.94 (3.04)	***	Con > AD, bvFTD
RAVLT corrected recognition [15]	12.09 (2.81)	− 2.44 (7.25)	2.56 (5.75)	***	Con > AD, bvFTD

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

Clinical Dementia Rating Scale (CDR); Frontotemporal Dementia Rating Scale (FRS); Addenbrooke's Cognitive Examination (ACE-III); Digit Span Backwards (DSB); Trail Making Test (TMT); Rey Auditory Verbal Learning Test (RAVLT).

*p<.05, **p<.01, ***p<.001, n.s. = non-significant, #=trend, p=.066

*Figure 2 Number of low-, medium- and high-value words recalled across learning trials (A–C) and on the delayed recall trial (D) of the VDM task. Brackets indicate significant post hoc simple effects, *p<.05, **p<.01, ***p<.001.*



Value-directed memory task results

Learning phase

Words recalled per condition

The number of low-, medium- and high-value words recalled per learning trial are illustrated in Figure 2A–C. Separate group × condition repeated measures ANOVAs were conducted for each learning trial. The group × condition interaction was significant on trials 1, 2 and 3 (Trial 1: $F_{4,100}$=4.271, p=.003; Trial 2: $F_{4,100}$=3.901, p=.006; Trial 3: $F_{4,100}$=3.819, p=.006), indicating that differences in the recall of low-, medium- and high-value words varied across groups. *Post hoc* simple effects tests revealed that controls recalled significantly fewer low-value compared to medium-value (p values <.012) and high-value (p values <.001) across trials 1, 2 and 3. Furthermore, while controls recalled similar numbers of medium- and high-value words on Trials 1 and 3 (p values >.281), they recalled significantly more high-value compared to medium-value words on Trial 2 (p=.025). In AD patients, recall of low-, medium- and high-value words did not differ on trials 1 or 2. On trial 3 however, AD patients recalled significantly more high-value compared to low-value words (p=.023) and showed a trend towards recalling more medium-value compared to low-value words (p=.06). In contrast, bvFTD patients did not show any value-directed prioritisation of word recall, with similar numbers of low-, medium- and high-value words recalled across the 3 learning trials (p values >.159).

In addition, analyses for Trial 1, 2 and 3 each revealed significant main effects of group (Trial 1: $F_{2,50}$=26.091, p<.001; Trial 2: $F_{2,50}$=36.801, p<.001; Trial 3: $F_{2,50}$=43.393, p<.001), with controls outperforming AD (p<.001) and bvFTD (p<.001) patients. Significant condition effects were also observed on each learning trial (Trial 1: $F_{2,100}$=15.214, p<.001; Trial 2: $F_{2,100}$=6.241, p=.003; Trial 3: $F_{2,100}$=14.452, p<.001), reflecting the greater number of high-value versus low-value words recalled (p values <.004). Across all groups, more

medium-value versus low-value words were recalled on Trials 1 and 3 (p<.001) but not Trial 2 (p=.107). Recall of medium- and high-value words did not differ on any of the learning trials, averaged across all groups (p values >.311). Overall, results from the immediate recall learning trials indicate that controls showed a robust value-directed enhancement effect on encoding across all 3 trials. Whereas AD patients were able develop a value-directed encoding strategy by the 3rd learning trial, bvFTD patients did not appear to prioritise recall of higher value words across trials.

Self-reported encoding strategy

Participants' self-reported encoding strategies were categorised as 1) focusing more on high-value words or; 2) did not focus on the value of the words. Results from Fisher's exact test revealed that the distribution of encoding strategies was significantly different across groups (p=.004). The most commonly reported strategy in controls (86.4%) and AD patients (60%) was 'focusing more on high-value words'. In contrast, responses from bvFTD patients indicated that they had not implemented any specific encoding strategy, and when prompted with the two strategy types, the majority (61.9%) reported that they 'did not focus on the value of the words'.

Within AD patients, those who reported 'focusing more on high-value words' had significantly higher Trial 3 SI scores compared to those who 'did not focus on the value of the words' (t_8=3.375, p=.01). In contrast, Trial 3 SI scores did not differ according to self-reported encoding strategy use in bvFTD patients (t_{19}=0.432, p=.671). In other words, self-reported encoding selectivity did not appear to be related to *actual* encoding selectivity in bvFTD. Performance on subsequent word recall, word recognition and points recognition measures did not differ between these strategy-based subgroups in AD or bvFTD (p values >.05).

Selectivity index from immediate recall learning Trial 3

SI scores from the 3rd immediate recall learning trial provide a measure of value-directed strategic encoding ability at the end of the learning phase. Mean Trial 3 SI scores in both AD (*M*=.81; *SD*=.13, *p*=.014) and bvFTD (*M*=.74, *SD*=.23, *p*<.001) were significantly lower than controls (*M*=.94, *SD*=.12), though the two patient groups did not differ (*p*=1.0). Analyses of SI scores across all 3 immediate recall learning trials are included in Appendix S3.

Relationships between Trial 3 selectivity index, executive function and episodic memory

The ability to prioritise recall of high-value words by Trial 3 of the VDM task learning phase differentially associated with executive function across patient groups (see Table 2). In bvFTD, higher selectivity on Trial 3 was significantly associated with better performance on measures of verbal inhibition (*r*=–.560, *p*=.01). Weak associations between Trial 3 selectivity and working memory (DSB: r=.384, *p*=.044) and cognitive flexibility (*r*=–.416, *p*=.048) were also identified, but these did not reach significance after correcting for multiple comparisons. In contrast, no significant associations were identified between Trial 3 SI scores and performance on tests of executive function in AD patients (all *p* values >.119) or controls (all *p* values >.267). Furthermore, selectivity on Trial 3 of the VDM task was not significantly associated with verbal episodic memory encoding performance on the final learning trial of the RAVLT in any of the participant groups (*p* values >.104). Altogether, results from our correlational analyses indicate a specific association between value-directed strategic encoding and inhibitory dysfunction in bvFTD patients only. Conversely, correlational analyses within each group revealed that encoding selectivity on the final learning trial is not related to verbal episodic learning capacity, as indexed on the final learning trial of a separate word-list learning task (RAVLT Trial 5 total words recalled; all *p* values>.103)

Table 2. Spearman rank correlation coefficients from analyses exploring associations between selectivity index scores on Trial 3 of the VDM task and performance on neuropsychological measures of executive function and verbal episodic memory encoding.

	Executive function			Verbal episodic memory encoding
	DSB total	**TMT B-A time[a]**	**Hayling AB error score[a]**	**RAVLT Trial 5 total**
Controls	–0.140	–0.093	0.047	0.045
AD	0.387	–0.357	–0.019	0.355
bvFTD	0.382	–0.416	**–0.560***	0.334

[a]Higher scores denote greater impairment.
Values are Spearman correlation one-tailed *t* test. **p*=0.01.

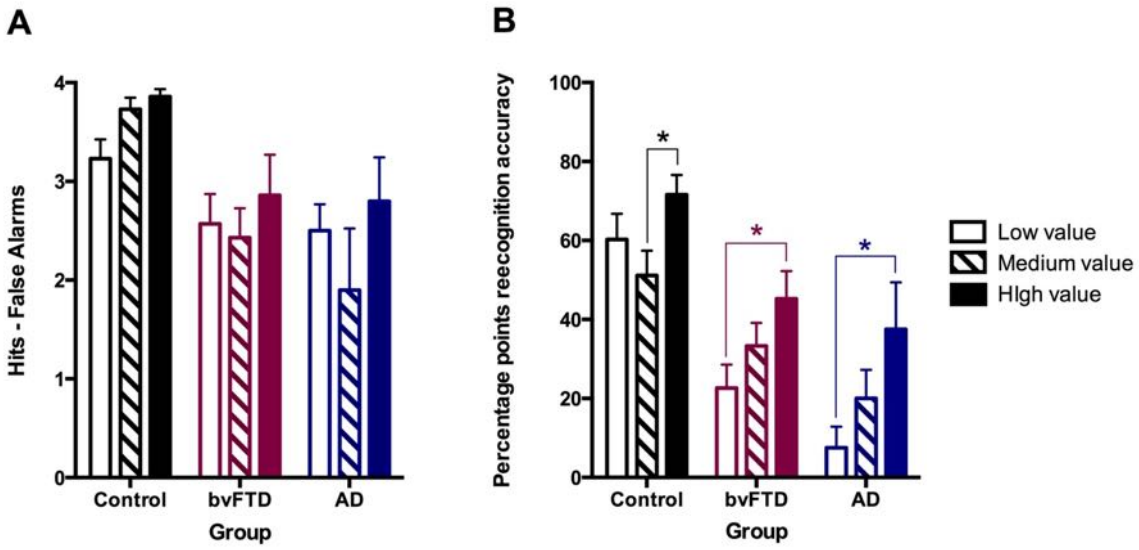
Test phase

Delayed recall

The number of low-, medium- and high-value words recalled on the delayed recall trial are shown in Figure 2D. Results from a repeated measures ANOVA revealed a trend towards a significant group × condition interaction ($F_{4,100}$=2.456, *p*=.051), suggesting that the condition effect varied across groups. *Post hoc* simple effects tests indicated that controls recalled significantly more high- and medium-value compared to low-value words (*p* values <.006), whereas recall of medium- and high-value words did not differ significantly (*p*=.959). In contrast, no such value-directed enhancement effect was observed in the delayed recall of low-, medium- and high-value words in AD (*p* values >.688) or bvFTD (*p* values <.199) patients. There was also a significant main effect of group ($F_{2,50}$=30.172, *p*<.001), where controls outperformed both AD (*p*<.001) and bvFTD (*p*<.001) patients. The overall effect of condition was not significant ($F_{2,100}$=2.706, *p*=.072). Overall, our results indicate that a value-directed enhancement effect on delayed recall memory was evident in controls but not AD or bvFTD patients. Analyses of the total number of words recalled and

points earned on the delayed recall trial, regardless of condition, are included in Appendix S2.

*Figure 3 (A) Corrected word recognition (hits – false alarms) across conditions and groups on the word recognition test. (B) Points recognition accuracy for each condition across groups. Error bars represent standard error of the mean. Brackets indicate significant post hoc simple effects, *p<.05, **p<.01, ***p<.001.*



Word recognition

Figure 3A depicts corrected word recognition accuracy (hits – false alarms) for each condition across AD, bvFTD and controls. A group (3) by condition (3) repeated measures ANOVA revealed a significant group effect for corrected word recognition accuracy ($F_{2,50}$=12.668, p<.001). This group effect was driven by significantly lower corrected word recognition accuracy in both AD (p<.001) and bvFTD (p<.001) patients relative to controls, though the two patient groups did not differ (p=.841). The main effect of condition was not significant ($F_{2,100}$=2.194, p=.117), and there was no significant interaction between group

and condition ($F_{4,100}$=0.861, p=.49). Thus, overall corrected word recognition accuracy was reduced in AD and bvFTD relative to controls, but did not appear to vary across the low-, medium- and high-value conditions. Analyses of uncorrected word recognition hits and false alarms are included in Appendix S4.

Points recognition

Figure 3B depicts points recognition accuracy for each condition across AD, bvFTD and controls. An overall group effect on points recognition accuracy was evident ($F_{2,50}$=14.96, p=<.001), driven by significantly lower accuracy in both AD (p<.001) and bvFTD (p<.001) compared to controls. There was also a significant main effect of condition ($F_{2,100}$=11.317, p<.001), where high-value words were recognised more accurately than low- (p<.001) and medium-value (p=.002) words. No significant difference was observed between low- and medium-value words (p=.613). The interaction between group and condition was not significant ($F_{4,100}$=1.438, p=.227). However, *post hoc* simple effects tests revealed that within controls, points recognition was significantly higher in the high-value compared to medium-value conditions (p=.012), with no significant differences between low- and medium-value (p=.377) or low- and high-value (p=.363) conditions. Conversely, only the difference between low- and high-value conditions was significant in AD (p=.03) and bvFTD (p=.016) patients. As such, both patient groups showed significant value-directed enhancement of memory for the points associated with high-value compared to low-value words, whereas this effect was most pronounced between high- and medium-value words in controls. Additional analyses exploring potential response biases on points recognition are included in Appendix S5.

Discussion

This is the first study to investigate preferential learning and retention of novel information that varies according to allocated value in two neurodegenerative syndromes. Our results in AD suggest that value-directed learning may support subsequent memory for high-value information where sufficient retrieval cues are provided. In contrast, bvFTD patients did not preferentially recall high-value information during the learning phase, and this reduction in value-directed selectivity was associated with inhibitory dysfunction. Here, we discuss the implications of our findings in terms of in the underlying cognitive mechanisms that contribute to value-directed learning and memory in these patient groups.

Value-directed learning

In AD, word-list learning was influenced by the value assigned to each word. With the opportunity to strategically encode high-value words across three immediate recall learning trials, AD patients learned to preferentially recall more high-value relative to low-value words. This is consistent with previous findings in AD (Castel et al., 2009). Importantly, when asked about their encoding strategy, the majority of AD patients reported having focused more on high-value words. Furthermore, those who reported prioritising encoding of high-value words showed higher selectivity on the final learning trial. Our findings in AD therefore demonstrate a relatively preserved capacity for value-directed learning over repeated trials, despite an overall reduction in the total number of words recalled.

In contrast, no clear evidence of preferential learning according to value was observed in bvFTD patients, where the number of low-, medium- and high-value words did not differ across trials. While this appeared to be corroborated by the encoding strategies reported by bvFTD patients—the majority of whom reported ignoring the value of the words—it is important to note that there was no clear relationship between *self-reported* selectivity and

actual selectivity as indexed on the final learning trial. This mismatch may be related to loss of insight, which is frequently reported in bvFTD (Banks & Weintraub, 2009; Hornberger et al., 2014). Nonetheless, our novel finding of impaired strategic value-directed learning in bvFTD align with previous findings which suggest that strategic encoding deficits impact on episodic memory impairment in bvFTD (Glosser, Gallo, Clark, & Grossman, 2002). Our findings therefore build upon research which indicates that memory impairment in bvFTD may be driven by deficits in strategic organisational processes at the encoding level (Pasquier et al., 2001; Wicklund et al., 2006).

Associations between value-directed selectivity and executive function

The second aim of this study was to examine the extent to which value-directed selectivity is associated with executive functions, including working memory, cognitive flexibility and verbal inhibition. The selectivity score was included as a measure of memory efficiency on the final learning trial, with higher scores indicating a bias towards recalling high-value words. Within bvFTD patients, lower selectivity on the final learning trial was strongly associated with poorer verbal inhibition. Inhibitory dysfunction is commonly reported in bvFTD (Bozeat, Gregory, Ralph, & Hodges, 2000; Hornberger, Piguet, Kipps, & Hodges, 2008; Krueger et al., 2009), and is associated with prefrontal cortex atrophy, particularly in the ventromedial regions (Hornberger, Geng, & Hodges, 2011; O'Callaghan et al., 2013). Atrophy in this region has also been associated with impaired episodic memory recall performance in bvFTD, though the mechanisms through which ventromedial prefrontal cortex functions impact on episodic memory remain to be established (Wong, Flanagan, Savage, Hodges, & Hornberger, 2014). Of relevance, studies of directed forgetting—where stimuli are presented with instructions to either 'remember' or 'forget'—also highlight the importance of prefrontally-mediated inhibitory functions for selective forgetting of 'to-be-forgotten' versus 'to-be-remembered' information (Anderson & Hanslmayr, 2014; Wylie,

Foxe, & Taylor, 2008). In the same vein, the significant association between inhibitory function and value-directed selectivity in our study suggests that bvFTD patients may have difficulty selectively inhibiting the encoding of low-value words, in order to prioritize encoding of the high-value words.

In contrast, value-directed selectivity did not correlate with executive function in AD. While it is possible that selectivity is related to other executive functions that are not captured on our tests, previous reports indicate that this is not significantly associated with working memory capacity in AD (Castel et al., 2009). Nonetheless, the adaptations made to reduce task complexity in our study (e.g., repeated learning trials using the same stimuli) may have restricted the range of selectivity scores on Trial 3. Consistent with their improvements across learning trials in terms of preferential recall of high-value words, AD patients also showed improvement in value-directed selectivity across the learning trials (see Appendix S3). Related to this point, encoding selectivity in our control group also appeared to be unrelated to performance on executive measures, though this was likely due to ceiling effects. Finally, it is important to note that across all participant groups, encoding selectivity on the value-directed learning task was not associated with general episodic encoding capacity per se. Taken together, whereas our findings in bvFTD demonstrate a clear link between reduced value-directed selectivity and inhibitory dysfunction, similar associations were not evident in AD patients or controls, nor were there any associations between selectivity and encoding capacity.

Value-directed enhancement of episodic memory recall and recognition

The final aim of this study was to examine the impact of value-directed learning on measures of delayed recall, as well as recognition for the words and associated point values. Our results on the delayed free recall trial indicated that value was not sufficient to reduce the significant

episodic memory recall deficits in either AD or bvFTD. Conversely, control participants showed a clear value-directed enhancement effect on delayed free recall, such that they recalled more medium- and high-value words relative to low-value words. While previous studies have shown this effect on recognition memory (Castel et al., 2007), we demonstrate, for the first time, that this enhancement effect also benefits recall of higher value information following a short delay in healthy adults.

Our corrected word recognition results (i.e. hits – false alarms) did not show a clear value-directed enhancement effect in any of the groups. In terms of raw word recognition and false positives however, AD patients were more likely to correctly endorse high-value words, and tended to attribute more medium point values to false positive word responses (see Appendix S4). This finding is in line with previous reports of increased susceptibility to false positives following value-directed encoding in healthy adults (Bui, Friedman, McDonough, & Castel, 2013). In contrast, although bvFTD patients endorsed more false positives and recognised fewer words relative to controls, this did not differ across conditions. Finally, although word recognition did not differ across conditions in controls, this appeared to be due to a ceiling effect. Taken together, our results suggest that value was not sufficient to enhance word recognition accuracy in bvFTD patients or controls. Conversely, value-directed encoding impacts on both word recognition and false positives in AD only.

On the other hand, both patient groups and controls showed value-directed enhancement of memory for the point values associated with each word. Our results in AD demonstrate, for the first time, that memory for episodic details, specifically those relating to point value, may be supported by value-directed learning. This suggests that memory for highly valued information may persist despite the profound memory impairment in AD, in circumstances where sufficient cues are provided to support retrieval. Conversely, although bvFTD patients

did not show preferential encoding of high-value words during the learning trials, a significant value-directed enhancement effect on points recognition accuracy was observed. Although this may initially seem counterintuitive given that value had no effect on learning performance, our results suggest that there may be a disconnection between the encoding and retention of high-value information and the ability to apply this information in order to maximise points during the immediate recall learning trials. While our correlational analyses indicated that reduced encoding selectivity was related to inhibitory dysfunction, an additional explanation may be that bvFTD patients were not sensitive to the motivational aspect of the reward values during the learning task. Indeed, reduced motivation is a diagnostic symptom of bvFTD (Rascovsky et al., 2011), and evidence indicates that these patients show altered sensitivity to primary and secondary rewards (Fletcher et al., 2015; Perry & Kramer, 2013; Perry, Sturm, Wood, Miller, & Kramer, 2015) and poor performance on value-based decision-making tasks (Kloeters et al., 2013; Strenziok et al., 2011). Conversely, symptoms of apathy are relatively less prevalent in AD compared to bvFTD (Chow et al., 2009), and these patient groups show divergent profiles of reward sensitivity (Perry et al., 2015). Nonetheless, as we did not include concurrent measures of reward sensitivity, whether motivation deficits differentially contribute to value-directed selective recall performance in bvFTD and AD requires confirmation in future studies.

Collectively, our results demonstrate that AD patients may have the capacity to learn and retain information that is associated with a high level of value or importance, providing there is adequate repetition when learning and support during retrieval. Importantly, this value-directed enhancement of learning and memory was observed despite the significant executive deficits present in this patient group. This has clinical implications for the implementation of memory retraining programs in AD, and highlights an important role for motivation in memory. Unlike laboratory settings where degrees of importance are clearly

assigned, however, in daily life one must initially determine the relative value of information encountered, before preferentially encoding highly valued information (Castel, McGillivray, & Friedman, 2012). As such, supporting the valuation process by emphasizing value or importance may benefit learning and memory for certain pieces of information in AD. Further investigations are required, however, to establish whether this value-directed enhancement effect persists over longer time delays.

In contrast, although bvFTD patients appear to learn and remember aspects of value-related information, they do not appear to apply this knowledge in a motivationally-salient context. As such, the provision of clear indicators of value or importance may not be sufficient to overcome the significant inhibitory deficits, which impact on preferential recall in these patients. Furthermore, encoding selectivity did not appear to be related to episodic memory encoding capacity in bvFTD. Additional research is needed in order to disentangle the contributions of altered reward sensitivity and inhibitory dysfunction on value-directed selectivity in bvFTD. One potential approach would be to contrast performance on a value-directed learning task against performance on a selective memory task without any value component, such as the item-method directed forgetting paradigm (Anderson & Hanslmayr, 2014). To circumvent the problem of impaired insight when eliciting self-reports of encoding strategy, future studies in bvFTD may also benefit from incorporating physiological measures of arousal, as evidence indicates that healthy adults show greater pupil dilation when studying words associated with higher point values (Ariel & Castel, 2013). From a broader clinical perspective, further characterisation of the impact of motivation on memory represents an important area of future inquiry, especially given the high prevalence of apathy in this patient group (Merrilees et al., 2013).

As discussed above, a potential limitation of our study design is that we did not include concurrent measures of sensitivity to value or motivation. In addition, while neuroimaging analysis was beyond the scope of this study, future investigations would benefit from incorporating structural and functional imaging metrics to further elucidate the neurocognitive mechanisms underpinning value-directed learning and memory in these patient groups. A final issue to note is the relatively small sample size of our patient groups. Our findings should therefore be interpreted with this caveat in mind, and future examination of value-directed learning and memory in bvFTD and AD will be important for confirmation of these novel findings.

Conclusions

In summary, we have adapted a selective memory task to provide insights into value-directed learning and memory in bvFTD and AD patients. In doing so, we have revealed a relatively preserved capacity to preferentially learn and recognise high-value information in AD patients. While reduced value-directed selectivity was distinctly associated with inhibitory deficits in bvFTD, our findings also uncovered a mismatch between memory for rewarding information and the ability to apply this knowledge in order to maximise rewards. From a broader theoretical viewpoint, our findings provide important insights regarding value-directed memory processes, and highlight the importance of interactions between motivation and memory.

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6.2. Concluding remarks

The findings reported in this chapter demonstrate the impact of assigning objective reward values to words that are to be remembered. While this benefited learning and subsequent item (i.e., words) and source (i.e., points) recognition in AD patients, bvFTD patients once again showed a pattern of performance which suggested a mismatch between memory for highly valued information and the ability to apply this knowledge in a motivationally salient context. As such, interesting parallels may be drawn between the bvFTD findings in the current and previous chapter. Collectively, these findings indicate a disruption to the medial PFC mediated valuation processes that augment encoding and retrieval of memory for rewarding aspects of items and events in certain contexts, though the precise mechanisms remain to be elucidated.

Chapter 7
General discussion

The aim of this thesis was to explore the PFC contributions to episodic memory in AD and bvFTD. Findings from five studies converge to indicate that episodic memory is impacted by PFC mediated memory processes, some of which are impaired across both neurodegenerative patient groups. Specifically, findings from Chapters 1 and 2 confirmed that performance on standardised neuropsychological measures of episodic memory recall relates to lateral PFC atrophy in AD and bvFTD, and this poses a particular challenge when differentiating between the cognitive profiles of dysexecutive AD and bvFTD patients. On the other hand, value-related memory processes that are mediated by the medial PFC appear to be disrupted in bvFTD only, although the influence of motivational context requires further elucidation. In particular, findings from novel measures of episodic memory retrieval in Chapters 4, 5 and 6 demonstrated, for the first time, that memory for self-relevant, socially relevant and reward-related information may be differentially affected in AD and bvFTD. Collectively, these studies indicate that the impact of lateral PFC dysfunction on memory is not specific to bvFTD, and propose that greater emphasis be placed on trying to understand the processes through which the medial PFC enhances episodic memory encoding and retrieval. Detailed implications of these findings and suggestions for future research have been addressed in the discussion sections of each chapter. The following sections integrate the main implications and future directions within a broader theoretical and clinical context.

7.1. Clarifying the lateral PFC contributions to memory in AD and bvFTD

Deficits in episodic memory have been attributed primarily to different underlying neurocognitive mechanisms in AD and bvFTD, with impairments relating to MTL-driven memory deficits in AD, as opposed to PFC-driven strategic retrieval deficits in bvFTD (Lemos, Duro, Simoes, & Santana, 2014; Pasquier, Grymonprez, & Lebert, 2001; Wicklund, Johnson, Rademaker, Weitner, & Weintraub, 2006). One of the goals of the thesis was to explore PFC atrophy and episodic memory in dysexecutive AD patients, who represent an exception to this AD-MTL versus bvFTD-PFC dichotomy. In doing so, findings from Chapter 2 challenged this dominant perspective by demonstrating that dysexecutive AD patients show both PFC and MTL atrophy, which correlated with episodic memory recall performance. This pattern of atrophy and neural correlates resembled that seen in bvFTD, highlighting the diagnostic difficulty that may be faced when differentiating between dysexecutive AD and bvFTD. In contrast, memory recall performance correlated with MTL atrophy in AD patients who did not present with significant executive deficits, suggesting that memory impairment in typical and dysexecutive AD patients are both underpinned by MTL atrophy, with additional PFC involvement in the latter group only. These findings therefore dovetail with those reported by Bertoux and colleagues (2014), where two distinct profiles of memory impairment were identified in bvFTD patients—one consistent with the MTL-driven amnestic profile characteristically seen in AD, and the other consistent with the PFC-driven dysexecutive profile typically associated with memory deficits in bvFTD. Collectively, these findings provide a strong argument against the dichotomous view that memory impairments in AD and bvFTD are solely driven by MTL and PFC dysfunction, respectively. Instead, heterogeneous memory profiles exist within both AD and bvFTD, likely mediated by the relative severity of PFC versus MTL atrophy.

From a clinical perspective, findings from Chapter 2 indicated that standardised neuropsychological measures of episodic memory and executive function lack sufficient specificity to reliably distinguish between bvFTD and AD, and especially atypical cases of AD with prominent executive dysfunction. Inclusion of social cognition measures has been suggested as a potential approach to resolving this diagnostic difficulty between dysexecutive AD and bvFTD. Recently, however, deficits on tests of Theory of Mind and social knowledge were reported in a single-case study of dysexecutive AD (Duclos et al., 2016). Future research in large cohorts of dysexecutive AD patients will be required to clarify whether dysexecutive AD patients show significant deficits in social cognition. This has particular clinical relevance, given that assessment of social cognition and other medial PFC-related functions is increasingly emphasised over tests of episodic memory and executive function for differential diagnosis of AD and bvFTD (Bertoux et al., 2015a; Torralva, Roca, Gleichgerrcht, Bekinschtein, & Manes, 2009).

7.2. Identifying the medial PFC as a region of interest

In line with the increasing emphasis on tests of medial PFC functions in bvFTD, Chapter 3 aimed to clarify the role of this PFC region to episodic memory in bvFTD and AD, and how this contrasts with lateral PFC contributions to memory in these patient groups. The findings confirmed that performance on standardised neuropsychological measures of episodic memory recall correlated with lateral PFC atrophy (specifically dlPFC) across both patient groups, whereas additional involvement of the medial PFC (specifically vmPFC) was found in bvFTD only. In keeping with the literature reviewed in Chapter 1, findings from this study also confirmed that AD and bvFTD patients show similar levels of impairments on commonly used clinical tests of executive function which were associated with dlPFC atrophy. On the other hand, only bvFTD patients showed impairments on tests that target vmPFC functions, such as inhibition, decision-making and emotion evaluation. As these

tests of vmPFC functions were not designed to assess the vmPFC contributions to episodic memory, however, further work is required to clarify its role in episodic memory, and how this may be disrupted in bvFTD. Taken together, the neuroimaging and behavioural findings identified the vmPFC as a feasible region of interest for the development of novel memory measures that target the role of this PFC subdivision in episodic memory.

These findings provide support for an important shift from examining components of episodic memory that show poor specificity across AD and bvFTD, towards exploring aspects that may be disproportionately affected in bvFTD. As the medial PFC is severely affected in bvFTD, these patients can serve as informative lesion models from which we can gain new insights regarding disruption to medial PFC-related memory processes. In contrast, AD patients represent an ideal comparison group, as they show significant episodic memory impairments, despite relative sparing of the medial PFC during the earlier disease stages. While the role of the medial PFC in episodic memory has been studied in healthy adults and patients with focal medial PFC lesions, investigation of these effects in neurodegenerative patient groups will extend current understanding of progressive damage to this region, and its related networks.

From a clinical perspective, identifying the medial PFC as a region of interest for future memory research provides a new approach that may help distinguish between episodic memory deficits in AD and bvFTD. Further insights into the breakdown of neurocognitive mechanisms that give rise to episodic memory impairment is crucial to better characterise the symptoms of each syndrome. Better understanding of these symptoms should also valuably inform the development of targeted interventions.

7.3. New insights into the role of the medial PFC in episodic memory

The studies presented in Chapters 4-6 represent the first steps in exploring the role of the medial PFC in episodic memory in AD and bvFTD. Collectively, these findings provide evidence that damage to the medial PFC, and particularly the vmPFC, impacts on the processes that augment learning and memory for highly valued information in bvFTD. The circumstances under which these effects manifest, however, require further elucidation. As such, the findings from Chapters 4-6 identify important issues to be addressed, thereby opening avenues for future research.

7.3.1. Summary of findings from novel memory measures

Findings from Chapter 4 indicated that both AD and bvFTD patients show a reduced effect of self-referential processing on episodic memory retrieval, such that memory for self-relevant information was not enhanced relative to memory for information related to another person. This reduction was, however, related to divergent patterns of atrophy across groups, with primary involvement of the vmPFC in bvFTD and posterior cingulate cortex in AD. In the context of the self-referential processing framework proposed by Northoff et al. (2004; 2006), the vmPFC involvement in bvFTD suggested that the reduced memory advantage for self-related information may be related to deficits in the processes that assign high value to this information. In contrast, deficits in AD were interpreted to be related primarily to downstream self-referential processes that integrate new self-related information with existing autobiographical memories.

A trust game paradigm was adapted in Chapter 5 to investigate learning and memory of socially relevant information from trust-related social interactions. Patients with bvFTD showed poor learning of trust/distrust responses following socially relevant feedback, and did not appear to remember the faces of socially relevant partners more accurately than non-

social partners. Contrary to expectations, however, bvFTD patients showed a memory enhancement effect for the contextual details of social (relative to non-social) interactions, although an overall reduction in retrieval of these source details was present. In AD, both item and source memory were enhanced for socially relevant information, despite poor learning of trust-related responses, and an overall reduction in item and source memory retrieval. Whereas learning and memory of socially relevant information was predominantly related to vmPFC and striatal atrophy in bvFTD, this correlated with MTL atrophy in AD. Importantly, better source memory for socially relevant information was associated with reduced susceptibility to financial mistreatment in AD, but did not appear to mitigate the striking financial vulnerabilities reported in bvFTD.

In Chapter 6, learning and memory of reward-related information was assessed using a strategic value-directed memory paradigm. Patients with bvFTD did not prioritise learning of high-value information during the encoding phase, and this reduced selectivity was related to deficits on tests of inhibitory control. While value did not appear to modulate learning performance, however, a value-directed enhancement effect on source memory was evident, with better memory for the points associated with words from the high-value condition compared to the low-value condition. In contrast, AD patients showed a relatively preserved capacity to preferentially learn and recognise high-value information, despite reduced learning and memory performance overall.

7.3.2. Methodological considerations across task paradigms

Enhancement effects on episodic memory retrieval were attenuated for self-relevant information, but not social or reward-related information across both patient groups. Direct comparison of these effects is difficult, given that they were demonstrated across three separate studies, but potential reasons for this discrepancy exist. At first glance, it seems

possible that the memory-enhancing effect of self-referential processing is simply more impaired in these patients, relative to the influence of socially relevant or reward-related information. However, this discrepancy likely stems from methodological differences across the three studies. Firstly, the self-reference effect paradigm included a large number of stimuli per encoding condition, and each stimulus was presented only once. In contrast, the trust game and value-directed memory paradigms included fewer stimuli, which were presented over multiple learning trials during the encoding phase. Secondly, the paradigms employed across studies also differed in terms of the level of active engagement in valuation processes (i.e., computing the subjective reward value of a stimulus) during the encoding phase. Arguably, the valuation of self-related information (i.e., "Do I like this object-background combination?") required deep engagement in self-directed valuation processes. In contrast, the value of socially relevant information (i.e., trustworthy, untrustworthy or neutral) and reward-related information (i.e., low, medium or high number of points) was essentially provided, although participants were not *explicitly* instructed to preferentially learn the socially relevant or higher valued stimuli. Furthermore, in contrast to the self-reference effect paradigm, the aims of the trust game and value-directed memory paradigms were inherently self-related and included a motivational element, as both tasks involved learning new information for personal benefit (i.e., fictional monetary gains or points). Despite these methodological differences, these studies are the first to explore the vmPFC contributions to episodic memory in AD and bvFTD, and each contributes important insights regarding the impact of value on memory encoding and retrieval. Direct comparison between memory for different types of value-related stimuli (e.g., social versus monetary rewards) in future studies is clearly warranted to establish whether this impacts on the memory-enhancing effect of value.

7.3.3. Mismatch between remembering and applying value-related information

Rather unexpectedly, findings from Chapters 5 and 6 demonstrated reduced learning of socially relevant and high valued information in bvFTD, despite better retrieval of this information—relative to non-social and low-valued information—on subsequent source memory tests. This contrasts with the expected pattern of results following poor learning on memory tests, which typically indicates limited encoding of memory traces, resulting in impaired memory retrieval. The pattern of source memory retrieval in bvFTD therefore suggests that a degree of value-related encoding has occurred during the learning phase, but this was insufficient to modulate their responses.

The finding that learning performance in bvFTD patients did not appear to benefit from socially relevant or reward-related feedback is consistent with previous reports of reward processing impairments in these patients, who show abnormal reaction times to social and monetary rewards (Perry, Sturm, Wood, Miller, & Kramer, 2015) and poor reward-related decision-making on gambling tasks that require learning from feedback in order to maximise rewards (Gleichgerrcht, Torralva, Roca, & Manes, 2010; Kloeters, Bertoux, O'Callaghan, Hodges, & Hornberger, 2013). However, the difference between reward valuation and the application of this value to decision-making and learning tasks requires further elucidation. Clarifying the component processes of valuation in memory is therefore an important future direction, as it is possible that the encoding of reward value does not automatically translate to applying this reward-related information in motivationally salient contexts, where such memories can be drawn upon to maximise rewards.

While speculative, it is possible that this mismatch results from a failure to integrate interoceptive cues that signal reward value. As such, bvFTD patients may learn and remember rewarding information to some extent, but lack the interoceptive "boost" required

to apply this in motivationally salient situations. This concurs with the *somatic marker hypothesis* which posits that decision-making is influenced by somatic signals of emotional processes (Bechara, Tranel, & Damasio, 2000; Damasio, 1996). These markers of autonomic arousal include elevations in skin conductance response and heart rate, and are processed by the vmPFC and amygdala. Importantly, these markers are closely related to performance on reward-related decision-making tasks, such as the Iowa Gambling Task (Bechara, Tranel, Damasio, & Damasio, 1996). Whereas healthy controls typically show elevated skin conductance responses both during and in anticipation of reward/punishment, patients with focal lesions to the vmPFC show variable responses to reward/punishment and do not develop an anticipatory response (Bechara et al., 1996; Bechara, Damasio, Damasio, & Lee, 1999). In healthy controls, the anticipatory responses help guide decisions based on previous experiences of reward/punishment, and may develop prior to explicit knowledge of the advantageous strategy (Bechara, Damasio, Tranel, & Damasio, 1997). In the absence of such anticipatory skin conductance responses, vmPFC patients continue to make disadvantageous choices on the task, despite demonstrating conscious knowledge of the advantageous strategy (Bechara et al., 1997). Furthermore, vmPFC damage is also linked with reduced activity in the ventral striatum, which typically increases in response to the anticipation of reward (Pujara, Philippi, Motzkin, Baskaya, & Koenigs, 2016). As such, damage to the vmPFC impairs reward-related anticipatory responses which, under normal circumstances, function as somatic markers that bias behaviour towards advantageous choices, even without explicit knowledge of the advantageous strategy.

In the same vein, knowledge or memory of reward-related information may not have been sufficient to guide responses during the learning trials of the trust game or value-directed memory tasks. As such, social relevance and reward value may indeed enhance encoding and retrieval, but in bvFTD there may be disruption to the somatic markers that guide

advantageous responses within the motivationally salient context of the learning phase. Future studies that incorporate measures of autonomic arousal will be crucial to exploring this tentative hypothesis. Encouragingly, studies of autonomic arousal in bvFTD and AD point to a specific deficit in bvFTD patients, who show reduced skin conductance responses to aversive stimuli (Hoefer et al., 2008) and moral dilemmas (Fong et al., 2016). In addition, further investigation of the structural and functional integrity of the vmPFC-ventral striatal circuit in bvFTD is warranted, to establish its involvement in reward processing, and its potential impact on value-based learning and memory. Importantly, atrophy of these ventral fronto-striatal regions is disproportionately higher in bvFTD compared to AD, and seems to clearly distinguish between the two patient groups (Bertoux, O'Callaghan, Flanagan, Hodges, & Hornberger, 2015b). Examining the autonomic and ventral fronto-striatal markers of reward processing and value-based memory therefore represents a promising future approach.

7.3.4. Clinical implications

Findings from these novel memory measures have raised important points regarding memory for valued information in everyday life. Although bvFTD patients may remember valued information, they appear unable to apply this knowledge in appropriate contexts. In particular, memory for socially relevant information, such as a person's trustworthiness, does not appear to be related to the strikingly high susceptibility to financial exploitation in bvFTD patients. Given that this is likely underpinned by alterations in reward sensitivity (Chiong, Hsu, Wudka, Miller, & Rosen, 2013; Perry & Kramer, 2013), memory-based interventions may have limited efficacy in reducing gullibility in this patient group.

In contrast, AD patients may benefit from memory interventions that support valuation processes by emphasizing the value or significance of certain pieces of information. With

regard to susceptibility to financial mistreatment, we have seen that this is lower in AD patients who show better memory for previous trust-related social interactions. This is supported by the finding that financial errors in AD tend to be underpinned by cognitive deficits such as memory impairment, rather than impaired reward processing (Chiong et al., 2013). Given the pervasive memory impairment in AD, the development of interventions that can support memory—if only for the most crucial and valued details—may be helpful in enhancing quality of life in these patients.

A final caveat is that the majority of studies comparing bvFTD and AD, including those included in this thesis, focus on young onset AD patients. This comparison is particularly relevant for differential diagnosis, as young onset AD patients tend to show greater overlap with bvFTD patients in terms of clinical, cognitive and neuroimaging features. Although younger and late onset sporadic AD cases share pathological disease processes (Atwood & Bowen, 2015), their rates of clinical and pathological progression (Frisoni et al., 2007; Migliaccio et al., 2015; Sá et al., 2012), prevalence of atypical presentations (Koedam et al., 2010) and age-related cognitive vulnerabilities (Licht, McMurtray, Saul, & Mendez, 2007) differ. The generalisability of results and implications from younger onset to late onset AD patients therefore requires confirmation in future research.

7.4. Final remarks

This thesis offered important new insights regarding PFC functions that contribute to episodic memory, and how these are impacted in AD and bvFTD. The findings challenged the prevailing notion that episodic memory impairments in AD and bvFTD are underpinned by MTL and lateral PFC dysfunction, respectively. Instead, these two patient groups display considerable heterogeneity in memory deficits, which may not necessarily conform to a purely amnestic or dysexecutive profile. The murky distinction between the memory profiles

of bvFTD and AD (particularly younger onset AD) adds to current difficulties in accurately diagnosing these patients, particularly during the earliest disease stages. This has significant ramifications for the development of disease-modifying pharmacotherapies and recruitment for clinical trials. The need for clinical tools that can improve differential diagnosis is therefore of paramount importance.

In this context, the thesis proposed a new approach, which capitalises on the disproportionate medial PFC dysfunction in bvFTD to examine how these deficits may influence episodic memory. Specifically, the studies examined the role of the medial PFC in representing the subjective value of information, which typically augments encoding and retrieval. In doing so, the findings provided novel insights regarding memory for self-relevant, socially relevant and reward-related information in AD and bvFTD, and highlighted critical areas for future research. In particular, further investigation of the component processes that underlie reward valuation, and its impact on episodic memory, is necessary to provide a fine-grained understanding of how these processes may break down in AD and bvFTD. Continued exploration of these processes, and their neural correlates, will arguably pave the way to the development of targeted interventions for the devastating symptoms of these neurodegenerative conditions.

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Appendix A
Structural neuroimaging techniques

The use of neuroimaging techniques in neuropsychological research has markedly advanced our understanding of the brain mechanisms that underpin cognitive and behavioural processes in health and disease. In the following experimental chapters, structural neuroimaging analyses were carried out in conjunction with standardised and novel neuropsychological tasks to identify the neural correlates of episodic memory processes. This section will provide a general overview of the relevant neuroimaging acquisition and analysis methodology.

T1-weighted images were acquired on a 3T Phillips MRI scanner, using established protocols that were standardised across patients and controls. Our research group has published extensively using these parameters, with robust and consistent neuroimaging findings in FTD patients, AD patients and healthy control participants (see for example, Hornberger et al., 2012; Irish, Piguet, Hodges, & Hornberger, 2014; Landin-Romero et al., 2016). The use of T1-weighted scans is appropriate for automated segmentations of grey matter that are carried out in structural neuroimaging analyses, as these provide the ideal contrast between grey and white matter (Bitar et al., 2006).

Structural neuroimaging analyses were conducted using FMRIB Software Library (FSL), which is a comprehensive neuroimaging software package (Smith et al., 2004). This software contains an optimised voxel-based morphometry (VBM) protocol, which is used to provide an unbiased, *in vivo* assessment of grey matter intensity at the voxel-by-voxel level on structural MRI scans (Ashburner & Friston, 2000; Good et al., 2001).

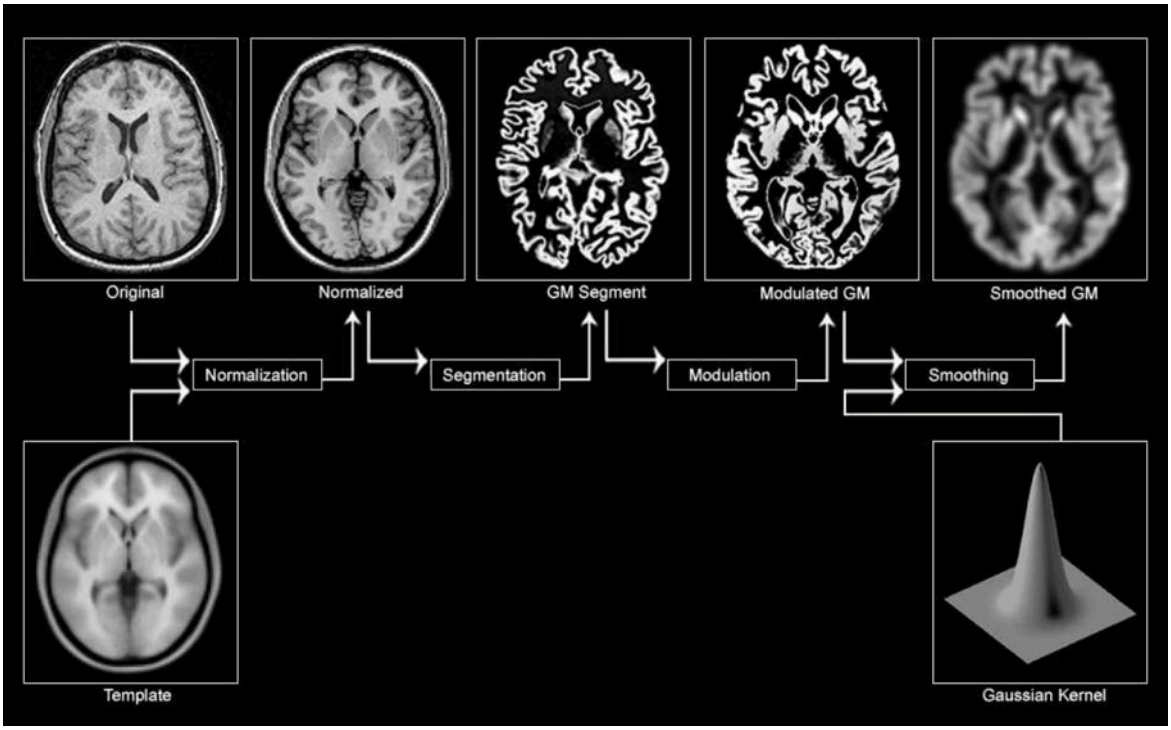

Figure A.1. Visualisation of neuroimaging pre-processing steps. Figure adapted from FSL Course online materials, FMRIB Analysis Group & MGH, 2015.

Firstly, skull and non-brain matter is removed from each individual's T1-weighted scan using the FSL brain extraction algorithm (Smith, 2002). Each scan is then manually inspected to ensure accurate delineation of brain and non-brain matter. Figure A.1. illustrates each stage of the neuroimaging pre-processing pipeline. A study specific brain template is generated by normalising and averaging each individual's scan. These template scans are aligned to the same stereotactic space—the Montreal Neurological Institute (MNI) standard brain template—thereby enabling comparisons of regional differences across studies using standardised x, y and z coordinates. This is followed by parcellation of the brain matter into individual voxels and segmentation of the grey matter, such that each voxel contains an intensity value for grey matter which corresponds to a specific location (Zhang, Brady, & Smith, 2001). Scans are then modulated by multiplying the spatially normalised grey matter by its relative volume before and after spatial normalisation. This step is taken to correct for changes in absolute brain volume caused by spatial normalisation, and also normalises the

data for head size as a scaling effect. As such, VBM analyses results are interpreted as differences in absolute volume, rather than differences in relative concentrations, of grey matter structures. Finally, the modulated scans are smoothed using an isotropic Gaussian filter (1mm, 2mm or 3mm) that is proportional to the expected inter-subject variability. This serves to increase the signal-to-noise ratio and allow comparison of residual differences after normalisation. Finally, parametric and non-parametric voxel-wise statistical tests are applied to identify significant regions of grey matter intensity change. This technique allows comparisons of regional grey matter intensity between groups (e.g. contrasting patterns of atrophy between AD and bvFTD patients), as well as correlations of grey matter intensity against clinical variables (e.g. exploring regions of grey matter intensity that correlate with episodic memory scores). Outcomes of these analyses are depicted as statistical parametric maps, showing areas that significantly differ across groups or significantly correlate with clinical variables. Furthermore, VBM analyses may be conducted across the whole brain or within masked regions of interest, in accordance with relevant *a priori* hypotheses.

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Appendix B
Supplementary material for publication I

Executive function

Results from the measures of executive function for all 4 groups are shown in Supplementary Table 1. Significant group effects were observed for all executive function scores. SEF-AD patients showed a significant impairment in relation to controls on the TMT only (p<.05), showing relatively intact performance on the COWAT (p=.443), DSB (p=.595) and Hayling (p>.1) tests. Conversely, the IEF-AD and bvFTD groups were significantly impaired in comparison to controls on all 4 executive measures (p's<.001). Importantly, the IEF-AD and bvFTD groups did not differ on all 4 measures of executive function (p's>.1). Moreover, while the IEF-AD patients were significantly more impaired than the SEF-AD group on the COWAT, DSB and Hayling Test (p's<.05), they did not differ on the TMT B-A time score (p=.407).

Episodic memory recall

Results from the measures of episodic memory recall (RAVLT trials A6 and A7, RCFT 3-minute recall) for all 4 groups are shown in Supplementary Table 2. Significant group effects were observed for all memory recall scores (p values <.001). All patient groups were significantly impaired relative to controls (p values <.01), with no significant differences between patient groups on all three memory recall measures (p values >.1).

Correlations between executive function and memory performance

Spearman rank correlations were used to quantify the relationship between performance on executive and memory measures. Across all groups, the memory composite was significantly correlated with all four executive measures (COWAT FAS: r_s=.571, p<.001;

DSB: r_s=.562, p<.001; TMT B-A time: r_s=-.566, p<.001; Hayling AB error: r_s=-.543, p<.001). Within the SEF-AD group, memory composite scores were correlated with TMT B-A time (r_s=.815, p=.002) scores. In the IEF-AD group, memory composite scores significantly correlated with Hayling AB error scores (r_s=-.498, p<.018). Within the bvFTD group, correlations between memory and executive scores failed to reach statistical significance.

Supplementary Table 1. Mean scores on executive tasks used to classify AD patients into spared (SEF-AD) and impaired (IEF-AD) executive functioning groups[a].

	Control	*SEF-AD*	*IEF-AD*	*bvFTD*	*F*	*Control vs. SEF-AD*	*Control vs. IEF-AD*	*Control vs. bvFTD*	*SEF-AD vs. bvFTD*	*IEF-AD vs. bvFTD*	*IEF-AD vs. SEF-AD*
COWAT total correct	44.79 (12.81)	38.82 (13.14)	27.05 (9.01)	21.75 (10.40)	***	n.s.	***	***	**	n.s.	*
DSB total correct	7.76 (2.44)	6.25 (1.22)	4.17 (1.23)	5.00 (2.18)	***	n.s.	***	***	n.s.	n.s.	*
TMT B-A time [seconds]	41.16 (25.89)	90.18 (59.07)	164.23 (66.20)	131.38 (76.56)	***	*	***	***	n.s.	n.s.	n.s.
Hayling AB error score	1.89 (3.31)	2.36 (2.66)	20.70 (17.09)	41.00 (27.14)	***	n.s.	***	***	***	n.s.	**

[a] Standard deviations in parentheses.
Controlled Oral Word Association Test (COWAT); Digit Span Backwards (DSB); Trail Making Test (TMT).
*p<.05, **p<.01, ***p<.001, n.s. = non-significant

Supplementary Table 2. Mean scores on episodic memory tests for participant groups[ab].

	Control	*SEF-AD*	*IEF-AD*	*bvFTD*	*F*	*Control vs. SEF-AD*	*Control vs. IEF-AD*	*Control vs. bvFTD*	*SEF-AD vs. bvFTD*	*IEF-AD vs. bvFTD*	*SEF-AD vs. IEF-AD*
RAVLT A6 recall [15]	10.21 (2.76)	4.73 (3.58)	2.8 (2.26)	3.72 (3.56)	***	**	***	***	n.s.	n.s.	n.s.
RAVLT A7 recall [15]	10.42 (2.96)	3.09 (3.88)	2.20 (2.98)	3.33 (3.60)	***	***	***	***	n.s.	n.s.	n.s.
RCFT 3 min recall [36]	17.41 (5.67)	5.54 (4.56)	3.43 (3.52)	8.76 (7.22)	***	***	***	**	n.s.	n.s.	n.s.

[a] Standard deviations in parentheses.
[b]Maximum test scores in brackets.
Rey Auditory Verbal Learning Test (RAVLT); Rey-Osterrieth Complex Figure Test (RCFT).
*p<.05, **p<.01, ***p<.001, n.s. = non-significant

Supplementary Table 3. Voxel-based morphometry results showing regions of significant grey matter intensity decrease for SEF-AD, IEF-AD and bvFTD groups compared to controls.

Regions	Hemisphere (L/R/B)	MNI Coordinates X	Y	Z	Number of voxels
SEF-AD < controls					
Inferior frontal gyrus, middle frontal gyrus,	L	-38	12	22	292
Hippocampus	R	30	-8	-26	251
IEF-AD < controls					
Temporal pole, inferior frontal gyrus, middle frontal gyrus, orbitofrontal cortex, frontal pole	L	-56	2	-16	1663
Frontal pole	R	14	68	-6	1262
Hippocampus	R	32	-10	-26	483
Hippocampus	L	-24	-18	-20	396
Superior frontal gyrus, middle frontal gyrus, precentral gyrus	L	-32	-12	46	328
Temporal pole	R	54	10	-10	143
Fusiform cortex (anterior), temporal pole	L	-36	-4	-42	112
bvFTD < controls					
Fusiform cortex (anterior and posterior), parahippocampal gyrus (anterior), hippocampus, temporal pole, orbitofrontal cortex, subcallosal cortex, medial prefrontal cortex, paracingulate cortex, anterior cingulate cortex, inferior frontal gyrus, frontal pole	B	-36	-6	-50	21236
Superior frontal gyrus	B	-18	18	46	979
Inferior frontal gyrus, middle frontal gyrus, precentral gyrus	L	-40	18	20	527
Inferior frontal gyrus, middle frontal gyrus, precentral gyrus	R	36	8	26	236
Superior frontal gyrus, precentral gyrus	R	22	-12	48	153
Hippocampus	L	-36	-32	-8	115

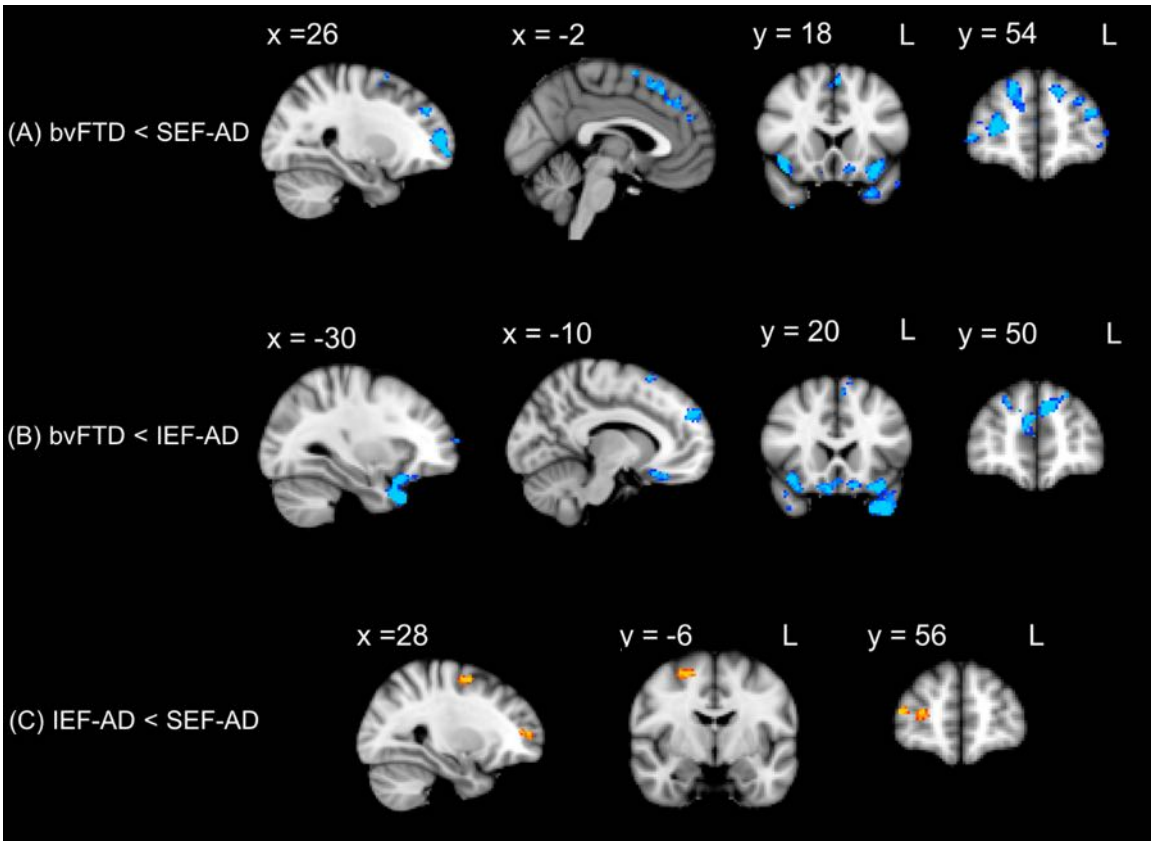
All results uncorrected at $p<.001$; only clusters with at least 100 contiguous voxels included. All clusters reported $t>3.97$. MNI = Montreal Neurological Institute.

Supplementary Table 4. Voxel-based morphometry results showing regions of significant grey matter intensity decrease for the contrasts between patient groups.

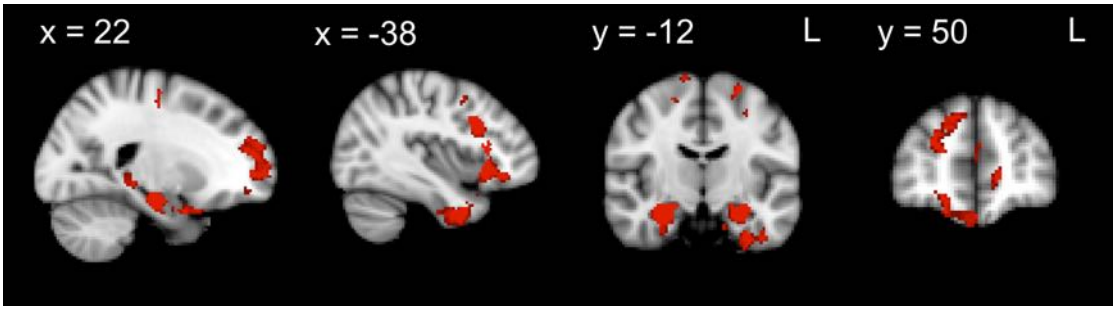
Regions	Hemisphere (L/R/B)	MNI Coordinates X	Y	Z	Number of voxels
IEF-AD < SEF-AD					
Superior frontal gyrus	R	24	-6	56	118
Frontal pole	R	26	48	8	77
SEF-AD < IEF-AD					
None					
SEF-AD < bvFTD					
None					
bvFTD < SEF-AD					
Frontal pole	R	20	62	-6	993
Temporal pole, orbitofrontal cortex	L	-36	20	-38	350
Orbitofrontal cortex	R	38	18	-18	331
Paracingulate gyrus, superior frontal gyrus	B	0	40	36	265
Frontal pole	L	-12	68	18	198
Frontal pole	L	-34	56	14	167
Orbitofrontal cortex, frontal pole	R	50	34	-20	135
Frontal pole	L	-46	44	-8	122
Subcallosal cortex	L	-12	24	-18	81
IEF-AD < bvFTD					
None					
bvFTD < IEF-AD					
Temporal pole, orbitofrontal cortex, subcallosal cortex	B	-40	16	-42	1170
Paracingulate cortex, superior frontal gyrus, frontal pole	B	10	50	14	500
Orbitofrontal cortex	R	32	18	-22	115

All results uncorrected at $p<.001$; only clusters with at least 75 contiguous voxels included. All clusters reported $t>4.06$. MNI = Montreal Neurological Institute.

Supplementary Figure 1. VBM analyses showing brain regions of greater reduction in grey matter intensity in (A) bvFTD patients in comparison with SEF-AD patients (B) bvFTD patients in comparison with IEF-AD patients and (C) IEF-AD patients in comparison with SEF-AD patients. 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.



Supplementary Figure 2. VBM analyses showing brain regions in which grey matter intensity correlates significantly with memory recall performance across all participant groups. 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.



Appendix C
Supplementary material for publication II

Figure S1. Grey matter atrophy comparisons between groups. VBM analyses showing brain areas of decreased grey matter intensity in A) bvFTD patients in comparison with Controls, B) AD patients in comparison with Controls, C) bvFTD patients in comparison with AD patients, and D) AD patients in comparison with bvFTD patients. Patient and control group comparisons corrected for multiple comparisons (FWE) with voxel-based thresholding at $p<.05$. Comparisons between patient groups corrected for multiple comparisons (FWE) with threshold-free cluster enhancement at $p<.025$. Clusters are overlaid on the MNI standard brain.

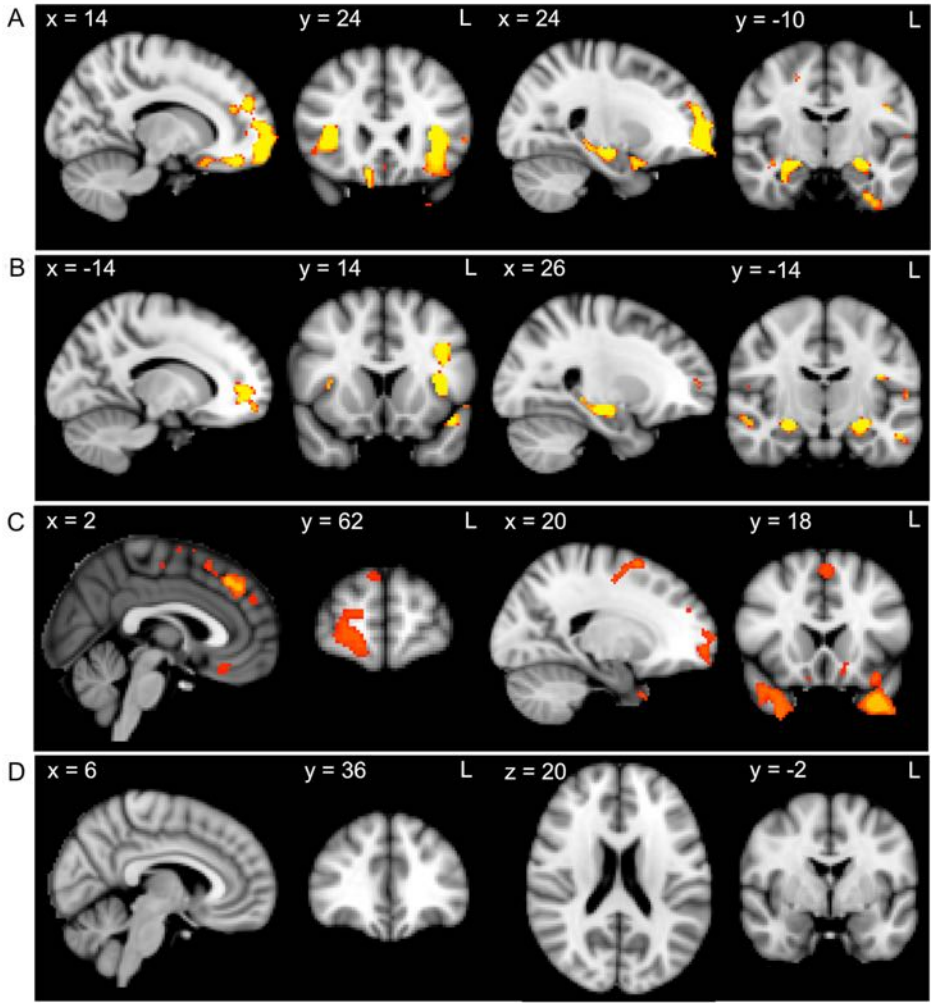


Table S1. Mean raw scores for bvFTD, AD patients and controls on neuropsychological measures [a]

	Control	***bvFTD***	***AD***	***Group effect***	***bvFTD vs Control***	***AD vs Control***	***bvFTD vs AD***
RAVLT A6 recall [15]	10.11 (2.71)	3.4 (3.07)	2.44 (2.92)	***	***	***	n.s.
RCF 3 min. recall [36]	17.35 (5.16)	6.55 (5.69)	3.13 (3.69)	***	***	***	n.s.
Digits Backwards raw score [14]	7.94 (2.63)	4.32 (2.21)	4.13 (1.75)	***	***	***	n.s.
FAS Verbal Fluency total correct	43.94 (12.05)	22.19 (11.55)	27.03 (11.47)	***	***	***	n.s.
Brixton total error [54]	16.09 (6.23)	25.89 (13.00)	26.25 (8.78)	**	*	**	n.s.
Hayling total AB score [128]	1.2 (1.76)	37.64 (28.12)	16.19 (17.80)	***	***	***	**
Iowa Gambling Task modified total net score (deck D- deck A)	27.72 (15.37)	4.8 (18.67)	8.33 (18.3)	***	***	**	n.s.
TASIT total correct [28]	23.87 (2.05)	15.61 (5.07)	18.10 (4.43)	***	***	***	n.s.

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

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

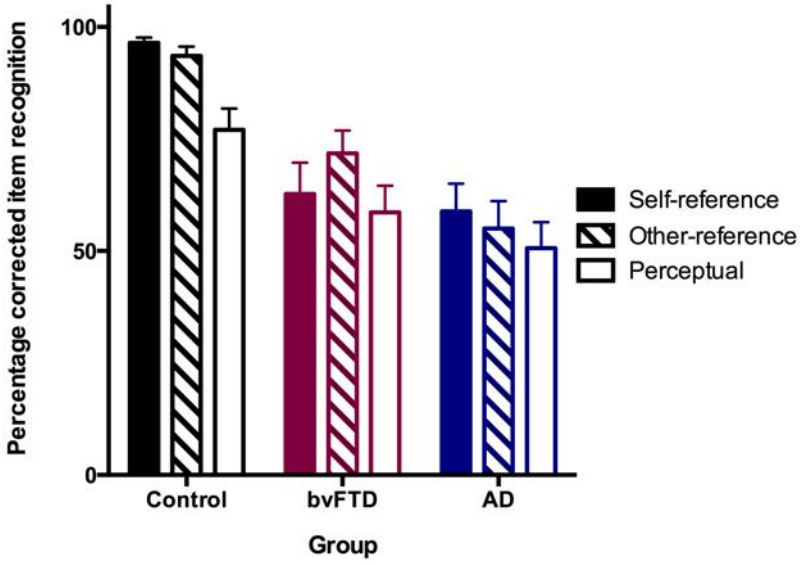
Appendix D
Supplementary material for publication III

Supplementary Table 1. Percentages of item and source recognition response types from the test phase of the SRE task in the control, bvFTD and AD groups.

	Control	bvFTD	AD
Studied in the Self-reference condition			
Item hit	96.47 (4.93)	71.36 (27.48)[a]	68.75 (21.87)[a]
Item miss	2.35 (4.37)	25.91 (26.49)[a]	26.25 (23.06)[a]
Item "don't know"	1.18 (3.32)	2.73 (6.31)	5.00 (7.30)
Source correct	80.00 (15.00)	40.45 (23.35)[a]	26.88 (19.23)[a]
Source incorrect	12.35 (12.52)	26.36 (15.90)[a]	23.13 (14.01)
Source "don't know"	4.12 (7.12)	4.55 (13.36)	18.75 (22.77)[a,b]
Studied in the Other-reference condition			
Item hit	93.53 (8.62)	80.45 (18.89)	65.00 (23.09)[a]
Item miss	5.29 (7.99)	19.09 (18.23)[a]	30.63 (24.89)[a]
Item "don't know"	1.18 (3.32)	0.45 (2.13)	5.00 (9.66)
Source correct	65.88 (20.93)	42.73 (20.51)[a]	23.75 (17.84)[a,b]
Source incorrect	25.88 (19.38)	32.73 (19.32)	26.25 (19.62)
Source "don't know"	1.76 (3.93)	5.00 (12.25)	14.38 (17.11)[a,b]
Studied in the Perceptual condition			
Item hit	77.06 (19.61)	67.27 (25.29)	60.63 (21.75)
Item miss	21.18 (19.65)	30.00 (23.50)	35.63 (25.81)
Item "don't know"	1.76 (5.29)	2.73 (6.31)	3.75 (8.85)
Source correct	60.58(23.59)	43.64 (23.81)	20.00 (17.89)[a,b]
Source incorrect	14.12 (13.26)	19.55 (13.97)[a]	25.63 (19.99)[a]
Source "don't know"	2.35 (4.37)	4.09 (9.59)	15.00 (17.51)[a,b]
Unstudied			
Item hit (Correct rejections)	100 (0)	89.55 (15.58)[a]	85.63 (16.72)[a]
Item miss (False alarms)	0 (0)	8.64 (13.56)[a]	10.00 (12.11)[a]
Item "Don't know"	0 (0)	1.82 (5.01)	4.38 (10.31)

Data are presented as means with standard deviations in parentheses. Scores are expressed as percentage of total items in each condition.
[a]The percentage is significantly different in the patient group than in the control group at $p < .05$.
[b]The percentage is significantly different between bvFTD and AD groups at $p < .05$.

Supplementary Figure 1. Mean percentage corrected item recognition responses (percentage item hits minus percentage false alarms) for self-reference, other reference and perceptual encoding conditions across participant groups. Error bars represent standard error of the mean.



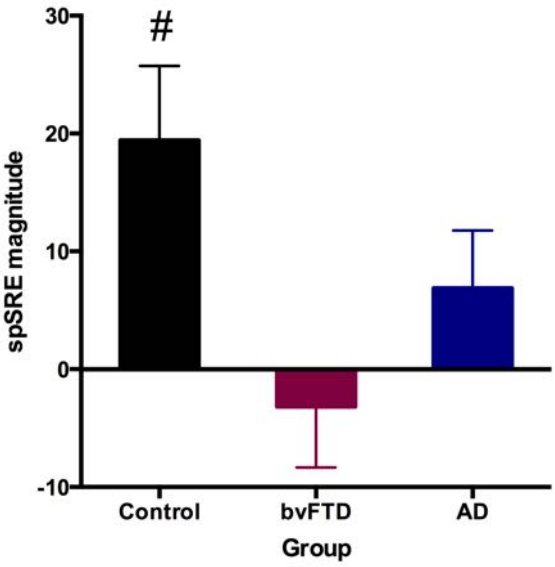
SRE magnitude for self-reference compared to perceptual encoding

A second SRE magnitude score was calculated to explore the source memory advantage of self-reference over perceptual encoding (spSRE magnitude = self-reference percentage 'source correct' – perceptual percentage 'source correct'). Larger spSRE magnitude scores therefore indicated larger biases for self-referenced compared to perceptually encoded source information. Within each participant group, independent samples t-tests were conducted to determine whether spSRE magnitude was significantly greater than 0.

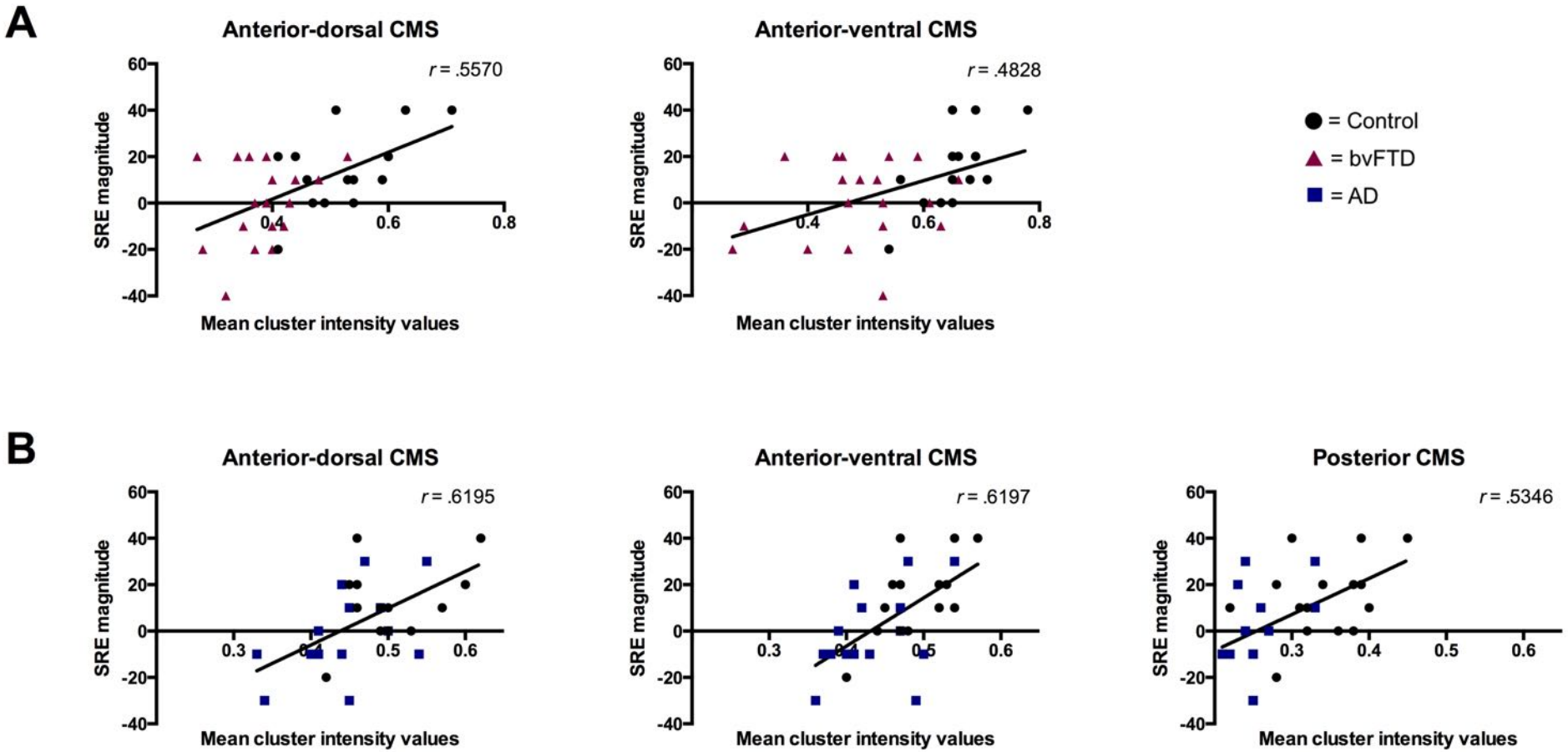
Supplementary Figure 2 shows the mean spSRE magnitudes for source recognition accuracy across patient groups. Independent samples t-tests were conducted to determine whether spSRE magnitude for source recognition was significantly greater than 0. Similar to the SRE magnitude findings, spSRE was significantly greater than 0 in the control group only ($t(16)=3.067$, $p=.007$), whereas this did not reach statistical significance in either bvFTD ($t(21)=-0.617$, $p=.544$) or AD ($t(15)=1.405$, $p=.18$).

Spearman rank correlations were used to examine the relationships between spSRE magnitude and performance on neuropsychological tests of episodic memory. Similar to SRE magnitude, spSRE magnitude did not correlate significantly with RAVLT immediate recall ($R=.048$, $p=.752$), RAVLT delayed recall ($R=.072$, $p=.634$) or RCFT 3-min recall ($R=.181$, $p=.209$) across all participants. Likewise, correlations between spSRE magnitude scores and episodic memory scores within each participant group did not reach statistical significance (p values >.1).

Supplementary Figure 2. spSRE magnitude across participant groups. Error bars represent standard error of the mean. #=spSRE magnitude significantly greater than 0 (p=.007).



Supplementary Figure 3. Relationship between mean cluster intensity values and SRE magnitude from voxel-based morphometry covariate analyses in A) bvFTD patients combined with controls and B) AD patients combined with controls. Plotted data depict a positive association between mean cluster intensity values and SRE magnitude, with the magnitude of this relationship calculated using Pearson's R correlations (r).



Supplementary Table 2. Voxel-based morphometry results showing regions of significant grey matter intensity that correlate with SRE magnitude scores across both bvFTD and AD, and regions that correlate exclusively in bvFTD patients and exclusively in AD patients.

Regions	Hemisphere (L/R/B)	MNI coordinates			Number of voxels
		X	Y	Z	
Overlap					
Anterior cingulate cortex, paracingulate cortex	B	2	28	32	77
bvFTD only					
Medial prefrontal cortex, subcallosal cortex	R	2	24	-16	90
Anterior cingulate cortex	L	0	30	20	57
AD only					
Anterior cingulate cortex	R	2	38	20	216
Frontal pole, orbitofrontal cortex	R	16	46	-26	177
Posterior cingulate cortex	R	14	-36	36	59

All results uncorrected at p<.01; only clusters with at least 50 contiguous voxels included. All clusters reported t>3.27. Age and years of education were included as covariates in all contrasts. L = Left; R = Right; B = Bilateral; MNI = Montreal Neurological Institute.

Appendix E
Supplementary material for publication IV

Materials and methods

Structural MRI image acquisition and data pre-processing

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, 1x 1 mm in-plane resolution, slice thickness 1mm, TE/TR=2.6/5.8ms.

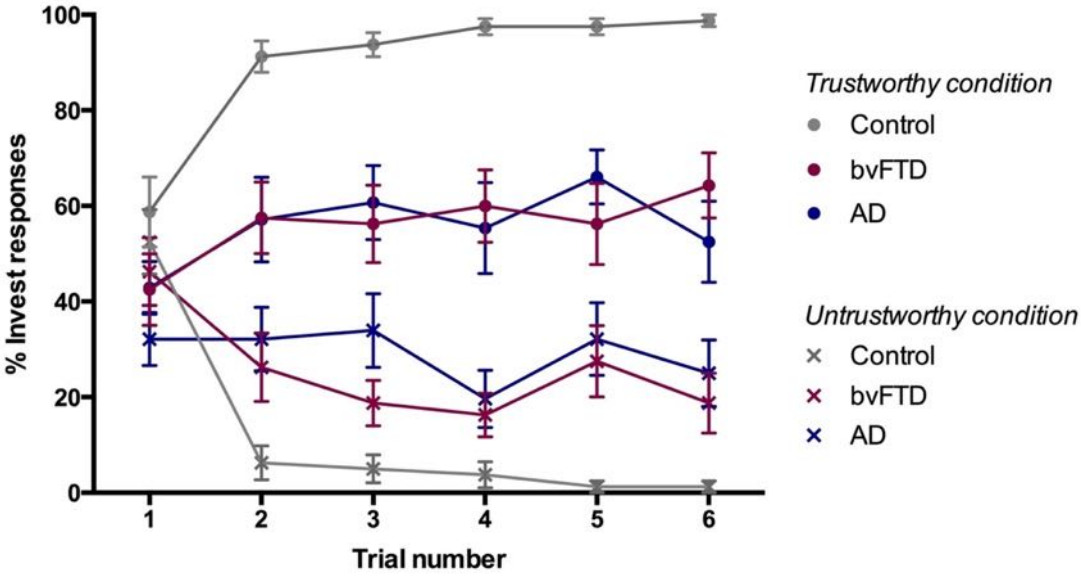
3D T1-weighted sequences were analysed using FSL-VBM, a voxel-based morphometry analysis (Ashburner & Friston, 2000; Good et al., 2001), which is part of the FSL software package http://www.fmrib.ox.ac.uk/fsl/fslvbm/index.html (Smith et al., 2004). Following brain extraction, tissue segmentation was carried out using FMRIB's Automatic Segmentation Tool (FAST) (Zhang, Brady, & Smith, 2001). The resulting grey matter partial volume maps were aligned to the Montreal Neurological Institute standard space (MNI52) using the nonlinear registration approach with FNIRT (Anderson, Jenkinson & Smith, 2007a; 2007b) which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). To correct for local expansion or contraction, the registered partial volume maps were modulated by dividing them by the Jacobian of the warp field. Importantly, the Jacobian modulation step did not include the affine part of the registration, which means that the data was normalized for head size as a scaling effect. The modulated images were then smoothed with an isotropic Gaussian kernel with a standard deviation of 3 mm (FWHM: 8mm).

Results

Learning to trust/distrust across trials

A repeated measures ANOVA was conducted to contrast groups across learning trials in the trustworthy condition, revealing a significant main effect of group ($F_{2,51}$=16.411, p<.001), where controls outperformed both AD (p<.001) and bvFTD (p<.001) patients. A significant main effect of trial ($F_{5,255}$=12.057, p<.001) was also evident, with fewer 'invest' responses on trial 1 compared to all subsequent trials (all p-values <.001). There was no significant difference between trials 2-6 (all p-values >.744). The group × trial interaction was not significant ($F_{10,255}$=1.284, p=.239), suggesting that the trial effect was similar within each group, though both patient groups showed consistently lower 'invest' responses towards trustworthy partners across all learning trials.

Figure S1. Mean percentage 'invest' responses towards trustworthy and untrustworthy partners on each trial (1-6) across groups



With regards to percentage 'invest' responses across learning trials in the untrustworthy condition, there was a significant group × trial interaction ($F_{10,255}$=5.044, p<.001), suggesting that differences across trials varied across groups. *Post hoc* simple effects tests revealed that within controls, percentage 'invest' responses for untrustworthy partners were significantly lower in trials 2-6 compared to trial 1 (all p-values <.001), with no significant differences between trials 2-6 (all p-values >.999). In contrast, percentage 'invest' responses for untrustworthy partners did not differ across trials in the AD group (all p-values >.286), except in trial 4, where responses were significantly lower than in those in trial 3 (p=.031). Similarly, bvFTD patients showed a varied pattern of performance, where percentage 'invest' responses for untrustworthy partners were significantly lower in trials 3, 4 and 6 compared to trial 1 (all p-values <.004), but did not differ across remaining trial comparisons (all p-values >.072). Main effects of group ($F_{2,51}$=5.455, p=.007) and trial ($F_{5,255}$=19.372, p<.001) were also significant. Relative to controls, bvFTD (p=.034) and AD (p=.013) patients showed more 'invest' responses towards untrustworthy partners. Across all groups, percentage of 'invest' responses were significantly higher on trial 1 compared to all subsequent trials (all p-values <.001), with no significant difference between trials 2-6 (all p-values >.152), though there was a trend towards fewer 'invest' responses on trial 4 compared to trial 2 (p=.054). Overall, only control participants showed evidence of a consistent improvement in learning to distrust untrustworthy partners, whereas learning was more variable in AD and bvFTD patients.

Post-learning affect ratings

We contrasted each group's affect ratings in relation to each of the 4 monetary outcomes ('share', 'steal', 'win lottery', 'lose lottery') from the learning phase using a group (3) by outcome (4) repeated measures ANOVA. There was no significant group effect ($F_{2,33}$=.99, p=.383), suggesting that overall affect ratings did not differ between groups. A significant

outcome effect was evident ($F_{3,99}$=103.074, p<.001), such that across all groups, ratings of happiness were significantly higher for the 'share' and 'win lottery' conditions, compared to the 'steal' and 'lose lottery' conditions (all p-values <.001). While ratings did not differ between 'share' and 'win lottery' outcomes (p=1.0), ratings were significantly lower for the 'steal' compared to 'lose lottery' outcome (p=.008) across all groups. Finally, a significant group x outcome interaction was also observed, indicating that the outcome effect differed across groups ($F_{6,99}$=3.012, p=.01). *Post hoc* simple effects tests revealed that this was driven by the fact that controls rated feeling significantly less unhappy in the 'lose lottery' compared to 'steal' outcome (p=.033), whereas both bvFTD and AD patients rated these two outcomes similarly (bvFTD p=.214; AD p=.909). Otherwise, all 3 groups rated feeling significantly happier in the 'share' and 'win lottery' outcomes compared to the 'steal' and 'lose lottery' outcomes (all p-values <.016). Again, ratings did not differ between 'share' and 'win lottery' outcomes in any of the groups (all p-values >.909). Overall, this suggests that affect ratings across all participant groups were sensitive to the outcome manipulation.

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Supplementary Table 1. Voxel-based morphometry results showing regions of significant grey matter intensity decrease for AD and bvFTD groups compared to controls. Results FWE-corrected at $p<.005$ and at a cluster extent threshold of > 200 contiguous voxels. All clusters reported $t>3.36$. L = left; R = right; B = bilateral; MNI = Montreal Neurological Institute.

Regions	Hemisphere (L/R/B)	MNI Coordinates			Number of voxels
		X	Y	Z	
AD < Controls					
Planum temporale, parietal operculum cortex, central opercular cortex, insular cortex, superior temporal gyrus (anterior and posterior), middle temporal gyrus (temporo-occipital), Heschl's gyrus, supramarginal gyrus (posterior), angular gyrus, lateral occipital cortex (inferior and superior)	L	-44	-30	10	3612
Lateral occipital cortex (inferior and superior), angular gyrus,	R	48	-64	6	1723
Parahippocampal gyrus (anterior), hippocampus, amygdala, fusiform cortex (anterior), temporal pole, orbitofrontal cortex	L	-20	0	-28	1652
Cerebellum	L	-48	-60	-40	1537
Amygdala, hippocampus, parahippocampal gyrus (anterior), temporal pole	R	22	-2	-26	760
Occipital pole, occipital fusiform gyrus	L	-20	-94	-14	236
bvFTD < Controls					
Orbitofrontal cortex, putamen, caudate, nucleus accumbens, paracingulate cortex, anterior cingulate cortex, insular cortex, temporal pole, frontal pole, frontal operculum cortex, central opercular cortex, parietal operculum cortex, Heschl's gyrus, planum temporale, middle temporal gyrus (posterior), superior temporal gyrus (posterior), inferior temporal gyrus (posterior and temporo-occipital), lateral occipital cortex (inferior), fusiform cortex (anterior and posterior), parahippocampal gyrus (anterior), hippocampus, amygdala, temporal pole, inferior frontal gyrus (pars opercularis), thalamus,	R	28	16	-24	11371
Fusiform cortex (anterior and posterior), inferior temporal gyrus (posterior), parahippocampal gyrus (anterior), hippocampus, amygdala, temporal pole, orbitofrontal cortex, putamen, nucleus accumbens, paracingulate cortex, anterior cingulate cortex, insular cortex, subcallosal cortex, frontal pole, central opercular cortex, superior temporal gyrus (anterior), precentral gyrus	L	-26	-6	52	6955
Cerebellum	B	-52	-66	-42	4059
Occipital pole, lateral occipital cortex (superior)	R	20	-88	34	1067
Occipital fusiform gyrus, occipital pole	R	26	-86	-10	705
Parietal operculum cortex	L	-44	-36	18	586
Middle frontal gyrus	R	38	6	6	484

Appendix F
Supplementary material for publication V

Appendix S1: Assessment of executive function and episodic memory

Digit Span Backwards

The Digit Span Backwards test (DSB) (Wechsler, 1997) is a measures of working memory, where participants are required to repeat series of numbers, which increase in length over trials, in the backward order. The total number of correct responses on the DSB was included in our analyses.

Trail Making Test

The Trail Making Test (TMT; Reitan & Wolfson, 1985) is a measure of 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 required to draw lines connecting numbers and letters in an alternating numerical and alphabetical sequence (1-A-2-B-3-C etc.). Participants are instructed to draw the lines 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 while accounting for psychomotor speed, Trails A time was subtracted from Trails B time (B − A time), with longer time indicative of greater impairment.

Hayling Sentence Completion Test

The Hayling Sentence Completion Test (Burgess & Shallice, 1997) assesses the ability to inhibit prepotent verbal responses on a sentence completion task. On an initial baseline phase, participants are required to complete a series of sentences using a logical word as quickly as possible. This is followed by a second phase, where participants must inhibit the

automatic logical response for a new set of sentences, and instead, complete each sentence with a word that is semantically unrelated. In accordance with 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, with higher scores indicative of greater impairment.

Verbal episodic memory

The Rey Auditory Verbal Learning Test (RAVLT; Rey, 1941) is a word-list learning test consisting of 15 words (List A), which are 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. The number of words recalled across Trials 1–5, words recalled on Trial A7 and corrected recognition score (hits – false positives) were included in our analyses as measures of verbal episodic memory encoding, delayed recall and recognition.

Encoding, delayed recall and corrected recognition performance on the RAVLT are detailed in Table 1. Verbal episodic memory was significantly compromised in both patient groups relative to controls across all learning trials (RAVLT learning Trials 1–5; p values <.001), delayed recall (RAVLT 30-minute recall; p values <.001) and corrected recognition (RAVLT corrected recognition; p values <.001). AD and bvFTD patients did not differ on any measures of verbal episodic memory performance (p values >.110).

Appendix S2: Overall word recall and points earned on learning and delayed recall trials of the VDM task

Learning phase

Total words recalled across learning trials

The total number of words recalled per learning trial in each group are depicted in Table S1. Results from a repeated measures ANOVA contrasting groups across learning trials for the total number of words recalled revealed a significant main effect of group ($F_{2,50}$=46.507, p<.001), where controls outperformed both AD (p<.001) and bvFTD (p<.001) patients. A significant main effect of trial ($F_{2,100}$=70.358, p<.001) was also evident, with significantly more words recalled with each successive learning trial (p values <.001). A significant group × trial interaction was also detected, suggesting that differences between trials varied across groups ($F_{4,100}$=5.395, p=.001). *Post hoc* simple effects tests revealed that both controls and bvFTD patients recalled more words on each successive learning trial (p values <.036). In AD patients however, the total number of words was significantly higher in Trial 3 compared to Trial 1 (p=.026), with no significant difference between Trials 1 and 2 (p=.077) or Trials 2 and 3 (p=.455). Thus, all 3 participant groups showed improvement across learning trials in terms of the number of words recalled.

Total points earned across learning trials

The total number of words recalled per learning trial for each group is depicted in Table S1. A repeated measures ANOVA contrasting groups across learning trials revealed a significant main effect of group ($F_{2,50}$=44.154, p<.001), where controls outperformed both AD (p<.001) and bvFTD (p<.001) patients. A significant effect of trial was also evident ($F_{2,100}$=19.624, p<.001), with significantly more points

earned with each successive learning trial (p values <.029). The group × trial interaction was not significant ($F_{4,100}$=.073, p=.573), indicating that differences across trials did not differ across groups. As such, all participant groups showed improvement across learning trials, in terms of the number of points earned.

Test phase

Overall word recall and points earned on the delayed recall trial were analysed separately from recall performance on the learning trials.

Total number of words recalled on delayed recall trial

Word recall following a 20-minute delay was significantly compromised in both AD and bvFTD patients relative to controls (p values <.001), with no significant difference between patient groups (p=.624) (see Table S1).

Total number of points earned on delayed recall trial

The number of points earned on the delayed recall trial was significantly lower in both patient groups compare to controls (p values <.001), with no significant difference between AD and bvFTD (p=.86) (see Table S1).

Table S1. Mean total number of words recalled and points earned on immediate recall learning trials and the delayed recall trial of the VDM across groups[a]

	Controls	AD	bvFTD
Total number of words recalled			
Immediate recall learning trials			
Trial 1 [12]	5.73 (1.86)	1.80 (1.55)	2.71 (1.42)
Trial 2 [12]	8.00 (1.80)	2.80 (1.40)	4.24 (2.00)
Trial 3 [12]	9.50 (1.63)	3.30 (1.89)	4.90 (1.63)
Delayed recall trial [12]	6.95 (3.37)	0.50 (0.71)	2.14 (2.17)
Total number of points earned			
Immediate recall learning trials			
Trial 1 [64]	40.05 (12.17)	12.30 (10.45)	16.86 (10.89)
Trial 2 [64]	49.18 (12.28)	15.90 (13.17)	24.00 (13.36)
Trial 3 [64]	54.82 (12.88)	23.40 (16.32)	26.38 (14.58)
Delayed recall trial [64]	40.27 (19.41)	4.10 (5.30)	11.10 (12.86)

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

Appendix S3: Encoding selectivity across immediate recall learning trials on the VDM task

Selectivity index (SI) scores from each of the immediate recall learning trials provide a measure of value-based strategic encoding performance on each trial (see Table S2). Results from a group (3) by trial (3) repeated measures ANOVA revealed a significant group effect ($F_{2,50}$=14.237, p<.001), with higher SI scores in controls compared to AD (p=.001) and bvFTD (p<.001). There was no significant difference between patient groups (p=.999). The main effect of trial showed a trend towards significance ($F_{2,100}$=2.798, p=.066), where SI scores were significantly higher on Trial 3 compared to Trial 2 (p=.04). While the group × trial interaction did not reach significance ($F_{4,100}$=.387, p=.817), the pattern of performance across trials appeared to differ across groups. To explore these differences within each group, *post hoc* simple effects tests were conducted. Within AD patients, SI scores were significantly higher in Trial 3 compared to Trial 2 (p=.038), suggesting that the ability to strategically encode words based on value improved across trials. In contrast, SI scores did not significantly improve across trials in either controls (p values >.85) or bvFTD patients (p values >.722). Thus, whereas controls showed similarly high levels of encoding selectivity across trials, bvFTD patients showed lower selectivity and did not improve across trials.

Table S2. Mean selectivity Index (SI) scores on Trials 1-3 from the learning phase of the VDM task across groups[a]

	Controls	AD	bvFTD
Trial 1	0.89 (0.1)	0.66 (0.38)	0.68 (0.27)
Trial 2	0.92 (0.11)	0.68 (0.20)	0.72 (0.22)
Trial 3	0.94 (0.12)	0.81 (0.13)	0.74 (0.23)

[a]*Standard deviations in parentheses.*

Appendix S4: Hits and false alarms on the VDM word recognition memory task

Word recognition hits

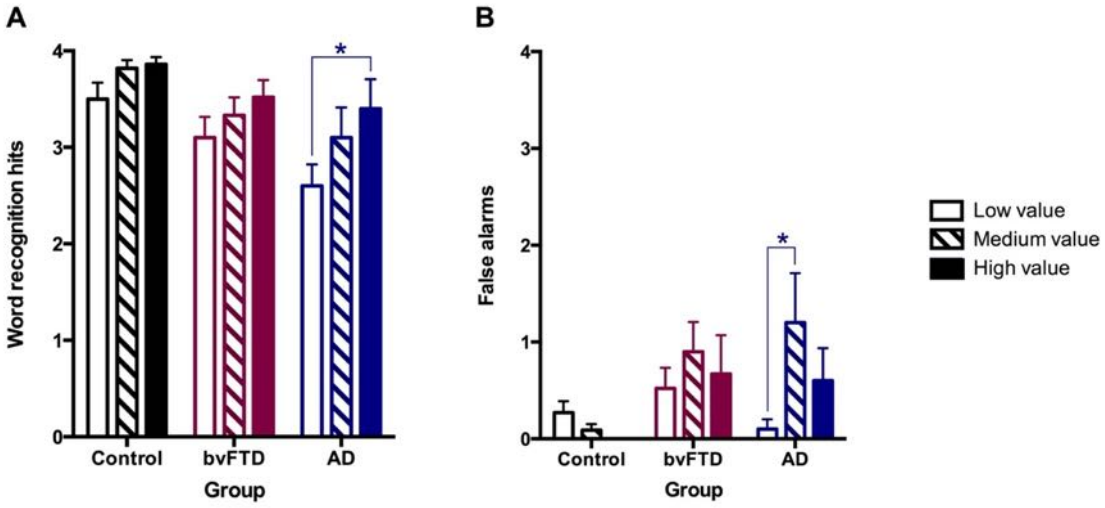
To determine whether patient and control groups show differences in uncorrected recognition hits for words that were associated with different point values, we contrasted raw word recognition hits for the low-, medium- and high-value conditions. Figure S1A depicts raw word recognition accuracy for each condition across AD, bvFTD and controls. A group (3) by condition (3) repeated measures ANOVA revealed a significant group effect for word recognition hits ($F_{2,50}$=6.299, p=.004). This group effect was driven by significantly lower word recognition hits in AD (p<.005) compared to controls and a trend for fewer hits in bvFTD (p=.052) relative to controls, though the two patient groups did not differ (p=.455). The main effect of condition was also significant ($F_{2,100}$=7.773, p=.001), with significantly greater word recognition hits in the high-value compared to low-value condition (p=.001) and a trend for more hits in the medium-value compared to low-value condition (p=.062). The interaction between group and condition was not significant ($F_{4,100}$=0.446, p=.775). To explore differences between conditions within each group, *post hoc* simple effects were conducted. Within controls and bvFTD patients, word recognition hits did not differ across conditions (p values >.094). In contrast, AD patients showed significantly greater word recognition hits in the high-value compared to low-value condition (p=.02).

Word recognition false alarms

To establish whether the tendency to ascribe low-, medium- or high-point values to word false alarms differed across groups, we contrasted false alarms across conditions and groups. Figure S1B depicts the number of false alarm responses that were subsequently attributed as belonging to the low-, medium- or high-value condition across AD, bvFTD and controls. A group (3) by condition (3) repeated measures ANOVA revealed a

significant group effect for false alarms ($F_{2,50}$=4.22, p=.02). This group effect was driven by significantly higher number of false alarms in bvFTD compared to controls (p=.025). The number of false alarm responses did not differ between AD patients and controls (p=.162) or bvFTD patients (p=.993). The main effect of condition was not significant ($F_{2,100}$=2.379, p=.098), and there was no significant interaction between group and condition ($F_{4,100}$=1.53, p=.199). *Post hoc* simple effects tests revealed differences across conditions within AD patients only, where the number of false alarm responses was significantly greater in the medium-value compared to low-value condition (p=.031). False alarm responses did not differ across conditions within the bvFTD or control group (p values >.463).

Figure S1. (A) Word recognition hits across conditions and groups on the word recognition test. (B) Word recognition false alarms across conditions and groups on the word recognition test. Error bars represent standard error of the mean. Brackets indicate significant post hoc simple effects, *p<.05, **p<.01, ***p<.001.



Appendix S5: Response bias in points recognition performance on the VDM task

As a proxy measure of response bias, we contrasted the number of points recognition responses where participants had incorrectly ascribed a low-, medium- or high-point value to a studied or unstudied word (see Table S3). To determine whether participant groups showed different response biases for low-, medium- and high-point values, we contrasted the number of incorrect point recognition responses across conditions and groups. A group (3) by condition (3) repeated measures ANOVA revealed a significant group effect ($F_{2,50}$=3.817, p=.029). This group effect was driven by significantly higher number of incorrectly ascribed point values in bvFTD compared to controls (p=.024). The number of incorrect point recognition responses did not differ between AD patients and controls (p=.713) or bvFTD patients (p=.529). The main effect of condition was significant ($F_{2,100}$=17.31, p=.008), where participants incorrectly ascribed medium-point values more often than low-point values (p=.002). However, the number of incorrectly ascribed high-point values did not differ significantly from medium- (p=.864) or low-point (p=.106) values. Furthermore, there was no significant interaction between group and condition ($F_{4,100}$=1.367, p=.251). Importantly, our results indicate that the significant value-based memory effect on points recognition in controls, AD and bvFTD patients was not driven by an indiscriminate assigning of high point values to all words.

Table S3. Mean number of points recognition responses for which low, medium and high point values were incorrectly ascribed across groups

	Controls	**AD**	**bvFTD**
Low value	1.09 (1.23)	0.50 (1.08)	1.19 (1.47)
Medium value	1.23 (0.97)	2.40 (2.59)	2.67 (2.35)
High value	1.05 (0.95)	1.80 (1.99)	2.57 (3.41)

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Appendix G
Ethics approval notification

From: **Ethics Secretariat** ethics.secretariat@mq.edu.au
Subject: Ethics Application REF 5201300764: External Approval Noted
Date: 18 November 2013 3:39 pm
To: A/Prof Greg Savage greg.savage@mq.edu.au
Cc: stephanie.wong@students.mq.edu.au

ES

Dear Ms Wong

Thank you for submitting the following externally approved ethics applications:

'Prefrontal contributions to learning and memory in behavioural variant frontotemporal dementia'

'Neuroimaging for ageing and neurodegeneration research'

As these applications have been submitted for one project, the Ethics Secretariat has placed both externally approved applications under one reference.

Your ethics reference number is 5201300764.

Please quote this number in all correspondence with the Ethics Secretariat.

The above applications were considered by the Executive of the Human Research Ethics Committee (Medical Sciences). In accordance with s 5.3 of the National Statement on Ethical Conduct in Human Research (2007) the Executive has accepted the approval from South Eastern Sydney Local Health District Human Research Ethics Committee and your right to proceed under their authority.

The Executive noted that the Macquarie University supervisor on this project, Associate Professor Greg Savage, was not listed on the original applications approved by South Eastern Sydney Local Health District Human Research Ethics Committee. Associate Professor Olivier Piguet, has granted permission for Associate Professor Savage to access de-identified data related to your PhD studies for the purposes of supervising the above projects.

Any modifications to the above studies must be made by South Eastern Sydney Local Health District Human Research Ethics Committee. A copy of the approved modification, progress reports or any new approved documents must be submitted to the Ethics Secretariat for the HREC's records.

Please retain a copy of this email as this is your official notification of external approval being noted.

The HREC (Medical Sciences) wishes you every success in your research.

Yours sincerely

Dr Karolyn White
Director of Research Ethics
Chair, HREC (Medical Sciences)

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