Episodic memory in frontotemporal dementia: a critical review

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This review offers a critical appraisal of the literature on episodic memory performance in frontotemporal dementia. Historically, description of patients diagnosed with what was then known as Pick’s disease included the presence of memory deficits and an underlying amnestic syndrome was noted in some of these patients. Over the last 20 years, however, the clinical view has been that episodic memory processing is relatively intact in the frontotemporal dementia syndrome. In particular, patients with the subtypes of behavioural variant frontotemporal dementia and progressive non-fluent aphasia are reported to perform within normal limits on standard memory tests. In the third clinical presentation of frontotemporal dementia, semantic dementia, relatively intact episodic memory against a significantly impaired semantic memory was regarded as the hallmark. This position was instrumental in the development of clinical diagnostic criteria for frontotemporal dementia in which amnesia was explicitly listed as an exclusion criterion for the disease. The relative intactness of episodic memory, therefore, appeared to be a useful diagnostic marker to distinguish early frontotemporal dementia from Alzheimer’s disease, in which early episodic memory disturbance remains the most common clinical feature. We argue that recent evidence questions the validity of preserved episodic memory in frontotemporal dementia, particularly in behavioural variant frontotemporal dementia. In semantic dementia, a complex picture emerges with preservation of some components of episodic memory, notably recognition-based visual memory and recall of recent autobiographical events. We propose a critical synthesis of recent neuropsychological evidence on retrograde and anterograde memory in light of neuroimaging and neuropathological findings, demonstrating involvement of medial temporal structures in frontotemporal dementia, structures known to be critical for episodic memory processing. We further argue that the multifactorial nature of most memory tests commonly used clinically fail to capture the memory deficits in frontotemporal dementia and that sensitive assessment tools of memory are needed. Together, recent clinical and experimental findings and the historical evidence represent a strong case for a re-evaluation of the importance of memory disturbance in the clinical diagnosis of frontotemporal dementia.

Keywords: anterograde memory; retrograde memory; semantic dementia
Abbreviations: FTD = frontotemporal dementia; PNFA = progressive non-fluent aphasia
Introduction

Frontotemporal dementia (FTD) is a progressive neurodegenerative brain disorder characterized by deterioration of behaviour, personality and language abilities in association with prominent frontal and temporal lobar atrophy. Three major clinical variants are recognized: behavioural variant FTD, semantic dementia and progressive non-fluent aphasia (PNFA) (Neary et al., 1998; Hodges and Miller, 2001).

Neglected for over half of the 20th century following the original descriptions of the condition by Arnold Pick in the late 1890s and early 1900s, FTD has received renewed interest in the past 30 years. This rediscovery was stimulated in part by the increased awareness of patients presenting with focal neural degeneration associated with circumscribed cognitive deficits and behavioural changes, at least in the early disease stages of the disease. Investigations of patients with FTD have therefore provided invaluable insights into the nature of psychological processes such as language, semantic knowledge, emotion processing and social behaviour.

This review focuses on the cognitive processes related to episodic memory in FTD, which have been systematically investigated only recently. One reason for this neglect is that impaired episodic memory performance has been considered an exclusion criterion for a clinical diagnosis of FTD, more particularly behavioural variant FTD. We will argue that the notion of absence of episodic memory deficits in FTD is incorrect. Episodic memory deficits were documented in the historical reports and recent findings on episodic memory function in FTD reinforce this position. As such, the status of episodic memory in FTD deserves to be revisited. We will also argue that appraisal of the current literature on episodic memory in FTD has theoretical and clinical implications, in particular for distinguishing patients with early Alzheimer’s disease from FTD, a distinction which is largely based on the difference in episodic memory performance. We will first review the historical evidence for episodic memory performance in FTD before discussing contemporaneous findings.

Historical evidence

Arnold Pick: original cases

Between 1892 and 1904, Arnold Pick, a neurologist in Prague, meticulously described five patients with distinct language changes (Pick, 1892, 1901, 1904). The clinical presentation was characterized by loss of word despite preserved knowledge of action and usage and was labelled amnestic aphasia. Other language disturbances included impaired repetition, phonemic substitution and neologisms. Significant focal brain atrophy was present in all cases at post-mortem, being most pronounced in the left temporal region with involvement of the frontal regions. Pick’s reports demonstrated that specific language symptoms could result from focal degeneration rather than diffuse and generalized atrophy as previously believed. Despite an emphasis on language and behavioural changes, episodic memory disturbance was reported in three of these five patients. In particular, one patient, Josefa V., was described to have a ‘striking loss of memory’ with geographical and time disorientation and disturbance of autobiographical information. In other words, although not a central feature of the clinical phenomenology of this disease, evidence of anterograde and retrograde episodic memory disturbance was present in one, possibly three, of the five cases reported by Pick.

1920–1950: early case series of Pick’s disease

The next 50 years saw the publication of small series of clinical cases of Pick’s disease with or without pathological confirmation, with a majority of clinical descriptions focusing on language disturbance. Two types of Pick’s disease were described: with or without aphasia (Kahn and Thompson, 1934) and with the presence of behavioural changes (e.g. a loss of high-level social graces and behaviours). The presentation of Pick’s disease was reported to be uniform and predictable (‘monotonic de la présentation’) in contrast to Alzheimer’s disease (Caron, 1934).

In these case series, memory was generally reported to be impaired due to faulty retrieval strategies resulting in inefficient memory processes (i.e. ‘loss of memory as a tool’) (Kahn and Thompson, 1934) or a lack of attention (Schneider, 1929). Memory deficits could be present in later stages of the disease due to developing dementia (Caron, 1934), although some disputed the presence of true amnesic deficits in Pick’s disease (Nichols and Weigner, 1938). For these authors, the preserved memory was one of the chief features distinguishing Pick’s disease from other dementias, including Alzheimer’s disease.

Concurrently, evidence of anterograde memory deficit in cases of Pick’s disease with pathological confirmation emerged (Löwenberg, 1936; Urechia, 1940). Such anterograde memory deficits took the form of impaired memory for recent events, disorientation in time, with increased apathy and indifference (Urechia, 1940), preserved long-term autobiographical memory and absence of language disturbance at presentation (Löwenberg, 1936). Post-mortem investigations revealed significant anterior frontal and temporal atrophy that was asymmetric. Microscopic investigations revealed neuronal loss, spongiosis and the presence of Pick bodies and argyrophilic inclusions, involving subregions of the hippocampus. Importantly, none of these cases showed Alzheimer-related pathology (plaques or tangles).

1950–1975: systematic investigations

The 1950s see a more systematic approach to Pick’s disease: van Mansvelt (1954) published the first comprehensive and systematic clinicopathological review of all known cases of Pick’s disease. This exhaustive and painstaking work examined the clinical features and pathological findings of 196 cases. Disorientation was reported in 64 cases (~33%) accompanied by loss of memory in a majority of cases. For van Mansvelt, however, ‘the disturbances of memory are not the result of a loss in the function of memory (in the sense of imprinting, retention and reproduction), but a result of an incapacity to order
chronologically the material of memory which is related to their own experiences’ (p. 66).

In 1957, the first systematic neuropathological classification of Pick’s disease was published (Lüers and Spatz, 1957), which followed on the work by Grünthal (1936). This classification reported four main centres of atrophy: orbital, temporal-polar, frontal convexity/frontal insula and Ammon’s horn. Detailed description of the pathological changes (gliosis, inclusion, demyelination) showed that some regions of the hippocampus (dentate, subiculum) were more affected than others (CA 1–4). Despite the pathological changes noted in the hippocampal region, these authors did not specifically report on the presence of memory disturbance during clinical examination.

Delay and colleagues (1957a, b) contrasted the clinical presentations in 12 cases with Pick’s disease (seven with pathological confirmation) and 24 cases with Alzheimer’s disease (11 with pathological confirmation). The clinical presentation of Pick’s disease was described as ‘univocal, with a striking monotony’. Importantly, however, a disturbance of memory unrelated to attentional deficits was reported in 9 of their 12 cases with Pick’s disease, with five presenting with prominent memory deficits. Pathological investigations revealed bilateral frontotemporal atrophy localized frontally in three cases. In three other cases, neuronal loss was present in CA fields, accompanied by atrophy, neuronal loss and gliosis of the amygdala, as well as neuronal inclusions in the presubiculum in one case.

In the early 1970s, a group in Geneva, Switzerland, conducted painstaking and important work that has received limited attention but is highly germane to the issues under discussion here (Constantinidis et al., 1974; Tissot et al., 1975). These authors presented the clinicopathological correlations of 32 cases of Pick’s disease, grouped according to the location and type of underlying pathology. In 18 cases, behavioural changes (‘moria, bipolar humour’) were reported together with anterograde memory disorder (‘amnésie de fixation’), from early in the course of the disease. The memory deficit was described to be akin to that seen in Korsakoff’s and Alzheimer’s disease, and characterized by temporal and spatial disorientation, confabulations and poor recognition memory. In all these cases, atrophy was present in the middle temporal region, involving the hippocampus and other limbic structures, plus the anterior temporal lobe extending into the orbitofrontal regions. In over half of these cases, argyrophilic neuronal inclusions (Pick bodies) and neuronal swelling (Pick cells) were observed in the subiculum, Sommer’s sector of the hippocampus, and dentate gyrus with gliosis and demyelination of fornix. In addition, significant correlations were reported between severity of pathology and memory performance. Importantly, the authors state that the failure to recognize the memory deficit in Pick’s disease was often masked by language reduction and behavioural changes.

This presentation was contrasted with other cases where the atrophy and pathology was found predominantly in the prefrontal cortex and more particularly in the dorsolateral prefrontal region. In this group, clinical signs included memory inefficiency characterized clinically by preserved spatial orientation but impaired temporal orientation and inability to order events in the correct order (‘dyschronologic amnesia, frontal type’). This type of memory deficit was typically accompanied by severe atrophy of the frontal convexity. The authors finally note that 5 of their 32 cases did not show any memory disturbance, even in an advanced stage.

Taken together, the historical literature demonstrates that disturbance of episodic memory is an early clinical feature in a portion of patients with Pick’s disease. This memory deficit was reported in the very first cases described by Pick. Undoubtedly, memory deficits were less common than behavioural or language changes and, as indicated by Tissot and colleagues (1975), could be masked by other, more prominent, clinical features. In some series, memory deficit was not reported, potentially not recognized, or, in some instances, possibly even ignored (e.g. Caron, 1934). Pathologically, the presence of neuropathological changes (neuronal loss, intraneuronal deposition) in brain structures known to play a critical role in episodic formation and retrieval also provides strong support for the presence of episodic memory deficit in this disease. Importantly, the evidence reviewed suggests that the pathological evidence was not always taken into account.

In the subsequent years, further systematic investigations got under way, led by two research groups in Lund, Sweden and Manchester, UK (Brun, 1987; Neary et al., 1988). This research endeavoured to define the clinical characteristics of this non-Alzheimer disease pathology. This research paved the way for what is now known clinically as FTD and pathologically referred to as frontotemporal lobar degeneration. One major outcome was the publication of clinical diagnostic criteria, which for the first time proposed sets of guidelines that would help with the diagnosis of the main subtypes of FTD: behavioural variant FTD or simply FTD, semantic dementia and PNFA (Brun et al., 1994; Neary et al., 1998). At that time, the prominence of Alzheimer’s disease in dementia research, and the high prevalence of that disease compared with that of FTD, probably played a role in defining episodic memory deficit as an exclusion criterion for a diagnosis of FTD; in other words, defining FTD as not Alzheimer’s disease. These clinical diagnostic criteria guidelines have been recently revisited in two separate publications, the first focussing on behavioural variant FTD (Rascovsky et al., 2011) and the second proposing a classification of the language presentations of FTD within the umbrella of primary progressive aphasias (Gorno-Tempini et al., 2011).

The neuropathological classification of FTD or frontotemporal lobar degeneration has also evolved considerably since the first description by Pick, but remains heterogeneous (Mackenzie et al., 2010). About 40% of cases with FTD exhibit the microtubule-binding protein tau inclusions. Most remaining cases are tau-negative but show the 43 kDa TAR DNA-binding protein (TDP-43) inclusions. Recently, a small proportion of cases that are negative for both tau and TDP-43 have been found to show the RNA-binding protein fused in sarcoma (FUS) inclusions (Neumann et al., 2009). Within the current nosology, Pick’s disease is now used to describe specifically cases with microtubule-binding protein tau inclusions exhibiting round argyrophilic intracytoplasmic inclusions (Pick bodies) and ballooned achromatic neurons (Pick cells).
Recent evidence

This section reviews the current evidence on episodic memory in FTD. Unlike the historical studies reviewed above, most recent investigations have been group studies. We start by reviewing the evidence on retrograde memory (i.e. personal memories from the past) before examining studies investigating anterograde memory (i.e. acquisition of novel episodic memories). The distinction between retrograde and anterograde memory is deliberate as different patterns of performance for both types of memory have been reported in FTD subtypes.

Retrograde memory

A large proportion of studies investigating episodic memory in FTD have focused on memory for past events and experiences. In clinical practice, enquiries about personal events in the patient’s life are often unsystematic. To address this issue, a number of investigators have devised autobiographical memory tests (e.g. Kopelman et al., 1989; Levine et al., 2002). These tests typically comprise a free recall procedure, which allows participants to generate events across different life periods, followed, in some instances, by a cued recall procedure to probe further for contextual-rich event information. Despite these systematic approaches, conflicting findings have emerged in FTD subtypes, particularly in semantic dementia where most of the studies have been conducted. Findings from each FTD subtype are reviewed in the following sections.

Semantic dementia

Early studies in semantic dementia reported significantly better recall for events from the recent than from the more distant past (Snowden et al., 1996; Graham and Hodges, 1997; Hodges and Graham, 1998; Graham et al., 1999; Nestor et al., 2002; Hou et al., 2005). This profile of preserved recent episodic memories is the reverse of the temporal gradient seen in amnesia and Alzheimer’s disease (Ribot, 1882; Greene et al., 1995) where memory for recent events is most vulnerable arguably because of the pathological changes in medial temporal lobe structures, notably the hippocampi and surrounding structures (Scoville and Milner, 1957). Detailed investigations have suggested that autobiographical memory in semantic dementia is characterized by a temporal ‘step-function’ whereby recall of memories for 18 months to 2 years prior to testing is maintained, but memories beyond this recent period show a flat, impaired retrieval function, most likely due to the progressive semanticization of the memory traces (Graham and Hodges, 1997; Hodges and Graham, 1998).

The finding of a step-function is, however, not universal with some reports of a relative intact episodic memory across all life periods in semantic dementia (Westmacott et al., 2001; Moss et al., 2003; McKinnon et al., 2006; Maguire et al., 2010). One potential reason for these discrepant findings is that the integrity of remote memory in semantic dementia may have been underestimated in some studies because of these patients’ pervasive comprehension and language production difficulties. This position implies that such language problems will be overcome when patients are provided with specific cueing or probing of event information compared with free recall. Evidence of autobiographical memory performance in semantic dementia matching that of healthy controls following the provision of additional cueing or probing corroborates this view (Moss et al., 2003; McKinnon et al., 2006).

A recent study that used the same methodology as McKinnon and colleagues (2006), however, again found evidence for a ‘step-function’ and no additional benefit from cueing in a large group of patients with semantic dementia (n = 25) (Irish et al., 2011). It remains unclear whether these conflicting results may be due to different sample sizes [case studies (Moss et al., 2003; McKinnon et al., 2006) versus group study (Irish et al., 2011)] and associated statistical power, or reflect other variables, such as disease severity effects (Matuszewski et al., 2009; Maguire et al., 2010) (Fig. 1).

The finding of preserved recent autobiographical memory certainly accords with clinical experience in that patients with semantic dementia appear much more aware of recent events in their life than those with Alzheimer’s disease (Hodges, 2001; Rosen et al., 2004). In contrast, when questioned about more distant life events, responses appear reasonable but are stereotyped and lack specific content. At a theoretical level, the temporal step-function reported by some studies has implications for the debate between competing theories of the neural mechanisms underlying long-term memory storage. Hodges and Graham (2001) argue that the reverse temporal step-function seen in semantic dementia lends support to the hypothesis that the hippocampus and related structures may play a time-limited role in encoding and storage of episodic memories. The greater impairment to recall distant, as opposed to recent, memories suggests that neocortical areas of the temporal lobes may be the critical location for our enduring stores of autobiographical and semantic memory, independent of the hippocampal complex (Graham and Hodges, 1997; Hodges and Graham, 1998; Graham, 1999).

Proponents of the multiple-trace theory of memory storage (Nadel and Moscovitch, 1997; Moscovitch and Nadal, 1998; Winocur et al., 2010), which advocate that the hippocampal complex is involved in the storage of a memory for the whole of its lifetime, dispute Graham’s (1999) interpretation of the evidence arising from studies on semantic dementia. They argue that the impairment to distant memories may be attributable to dysfunctional strategic retrieval processes due to frontal cortical damage, which would affect distant memories more so than those from the recent past (Nadel and Moscovitch, 1997). It is not clear, however, how defective strategic retrieval processes would result in the reverse temporal ‘step-function’ documented in semantic dementia (Graham, 1999). This debate remains unresolved (Moscovitch and Nadal, 1999), although recent functional imaging findings (Maguire et al., 2010), which are discussed below, shed some new light on this issue.

Both theories of episodic long-term memory agree that the hippocampus and related structures are heavily involved in the acquisition and, at least temporary, storage of novel episodic memories. Patients with semantic dementia typically show severe temporal lobe atrophy including the perirhinal cortex and temporal pole (Chan et al., 2001; Galton et al., 2001; Rosen et al., 2002a; Davies et al., 2004; Du et al., 2007; Mion et al., 2010).

Episodic memory in FTD
Although earlier studies (e.g., Galton et al., 2001) suggested a selective sparing of the hippocampus, more recent objective measures have shown that the hippocampus and the entorhinal cortex are substantially involved in the pathological process (Chan et al., 2001; Davies et al., 2004, 2005; Williams et al., 2005). Surprisingly, despite such pervasive hippocampal involvement, patients with semantic dementia show partial or complete autobiographical memories in comparison to patients with Alzheimer's disease presenting with a comparable degree of hippocampal atrophy. One plausible explanation for this finding is the differential atrophy severity within the hippocampus between the two patient groups: patients with semantic dementia show a rostral-caudal atrophy gradient in the hippocampus, with anterior parts most affected, while patients with Alzheimer's disease show equivalent atrophy across all hippocampal parts (Chan et al., 2001; Davies et al., 2005). Another possible explanation is that patients with Alzheimer's disease exhibit dysfunction in additional brain areas relevant for supporting autobiographical memory processing, such as posterior cingulate and precuneus cortices (Nestor et al., 2003). Importantly, these brain regions have been implicated in episodic memory disturbance in neurodegenerative diseases (Nestor et al., 2006) and shown to be consistently activated in autobiographical memory functional MRI studies in healthy volunteers (e.g., Maguire et al., 2001; Svoboda et al., 2006). A critical study by Nestor et al. (2006) compared structural and metabolic changes in key limbic structures across semantic dementia and Alzheimer's disease groups. Although the degree of hippocampal atrophy on quantitative MRI and hypometabolism on FDG-PET was equivalent in the two groups, patients with semantic dementia showed sparing of the precuneus, which was severely hypometabolic in patients with Alzheimer's disease.

A recent case study further explored the neural correlates of autobiographical memory retrieval in semantic dementia using functional MRI (Maguire et al., 2010). In this patient, autobiographical memories were relatively intact initially but deteriorated over time with no evidence of a temporal gradient. The overall autobiographical performance remained relatively robust with increasing disease severity, which was corroborated by residual hippocampal and temporal lobe activation during recollection of autobiographical information. Interestingly, Maguire and colleagues (2010) also reported activation in the precuneus, which appears upregulated after the hippocampal activation was compromised by atrophy. Involvement of the precuneus confirms the importance of extra-hippocampal regions in autobiographical memory recall (Fig. 2). It is therefore not surprising that patients with Alzheimer's disease, who show atrophy and dysfunction in both regions, will exhibit the greatest deficits in autobiographical memory from an early disease stage.

### Progressive non-fluent aphasia

To our knowledge, only one study systematically investigated autobiographical memory in PNFA (McKinnon et al., 2008), which may be due to the inherent language production deficits impacting on any verbal recall performance in these patients. A mild autobiographical memory impairment was reported, which was abolished by providing additional probing of event information. The authors concluded that the autobiographical memory deficits were secondary to pervasive expressive language difficulties in these patients. The relatively intact performance after probing further suggested that the memory retrieval processes and medial temporal lobe functions were not impaired in PNFA. This conclusion is corroborated by voxel-based morphometry studies which have demonstrated absence of medial temporal lobe atrophy.
atrophy in this group (e.g. Gorno-Tempini et al., 2004; Rohrer et al., 2009).

**Behavioural variant frontotemporal dementia**

Systematic investigations of episodic memory in behavioural variant FTD are sparse because the presence of amnesia remains a diagnostic exclusion criterion for the disease (Neary et al., 1998; Rascovsky et al., 2011). From a clinical perspective, however, growing evidence has shown that many patients with behavioural variant FTD present with complaints (either self- or carer-report) of memory problems. Around 10% of pathologically confirmed cases with behavioural variant FTD have marked episodic memory deficits in the initial stages of disease (Hodges et al., 2004), and occasional cases have severe amnesia (Caine et al., 2001; Graham et al., 2005). A clinicopathological study (Rosen et al., 2002b) confirmed that although the absence of severe amnesia markedly increased the odds for FTD, the converse was not true. Although patients with dementia with primary memory complaints are likely to have Alzheimer’s disease, the specificity of this complaint is low (Rascovsky et al., 2007, 2011).

Investigations of retrograde autobiographical memory in behavioural variant FTD have also yielded inconsistent results. An early investigation using the Autobiographical Memory Interview failed to find impairment (Nestor et al., 2002) but recent studies that distinguished specific from generic information found uniform impairment across all time periods with a loss of specific details but no temporal gradient (Thomas-Anterion et al., 2000; Piolino et al., 2003, 2007; Matuszewski et al., 2006). Similarly, Irish and colleagues (2011) showed impaired recall of specific and contextual-rich autobiographical memory across all time periods, regardless of how much cueing was provided. This pattern was interpreted as reflecting a disorder of strategic retrieval processes. Indeed, several studies have shown that autobiographical memory deficits in behavioural variant FTD are strongly correlated to executive dysfunction, which is a common neuropsychological feature of this group (Piolino et al., 2003, 2007; Matuszewski et al., 2006). This relation is further corroborated by findings of dorsolateral and ventromedial atrophy on structural MRI (Seeley, 2008), which would explain the dysexecutive deficits in these patients. Additional evidence of dysfunction in these regions and their importance for autobiographical memory processing comes from metabolic neuroimaging. Recall of specific autobiographical memories was associated with resting-state FDG-PET activation in the orbitofrontal cortex in a group of patients with behavioural variant FTD (Piolino et al., 2007). In contrast, generic or semantic event information was related to anterior temporal lobe activation. These findings further substantiate the contribution of prefrontal cortex regions, and in particular orbitofrontal cortex, to autobiographical memory performance. Disturbance in these regions leads to a retrieval access deficit for all autobiographical memories regardless of their time of acquisition.

In summary, retrograde memory performance differs across FTD subtypes. It is in semantic dementia that evidence is most variable and complex. While some studies have reported impairment for most recent retrograde memories with more remote memories being relatively intact, others show relative intact performance across all time periods tested in the early disease stages and an overall impairment later on in the disease. It is currently not clear which factors cause these discrepant findings. One potential explanation is that most of the studies used only single cases with semantic dementia or small samples, while the only large semantic dementia group study (Irish et al., 2011) shows a temporal gradient. The limited data suggest that patients with PNFA are mostly intact for this type of episodic memory. In contrast, patients with behavioural variant FTD show an overall impairment of retrograde memories regardless of the time of acquisition. Recent findings suggest that the retrograde memory deficits in patients with behavioural variant FTD are strongly related to their executive deficits. In turn, this finding supports the view that retrograde memory deficits in this group are due to a failure in strategic

![Figure 2 Longitudinal changes in the pattern of brain activation during autobiographical memory retrieval in a patient with semantic dementia >3 years. Top: Loss of activation in the hippocampal region over time. Bottom: Increased activation in posterior brain regions with disease progression. Autobiographical memory was relatively intact in this patient until late in the disease with no evidence of temporal gradient. Adapted from Maguire et al. (2010) with permission from Elsevier.](image-url)
retrieval processes, which are mainly mediated by prefrontal cortex, brain regions showing the most severe atrophy in behavioral variant FTD.

Anterograde memory

Semantic dementia

The first systematic neuropsychological assessment of anterograde episodic memory in FTD involved three patients with semantic dementia who demonstrated impaired recall of the Wechsler Memory Scale short story and a virtually complete failure in free recall of 10-word lists (Warrington, 1975). In addition, these patients with semantic dementia performed as poorly as four amnesic patients on word and face stimuli on forced-choice recognition memory tests. When recognition memory for paintings was tested, however, all patients with semantic dementia scored in the normal range, in contrast to the amnesic patients. Warrington speculated that the patients with semantic dementia might have utilized perceptual features, such as colours, to remember the paintings, whereas memory for words relies essentially on semantic information. As Warrington indicated: ‘the patients reported here are by no means as amnesic as a patient with a severe amnesic syndrome, although their verbal memory is far from normal’ (Warrington, 1975, p. 653).

This classic description still best summarizes the distinction between verbal and visual anterograde memory performance in semantic dementia, in particular for recall-based tests. Verbal recall tests have the inherent confound of requiring spoken output from the participant that is affected by the semantic knowledge loss and pervasive anoma in semantic dementia. Not surprisingly, performance on word-list learning, such as the Rey Auditory Verbal Learning Test, or recall of a story (e.g. Wechsler short story passages) can be particularly impaired in semantic dementia and can make a distinction from Alzheimer’s disease difficult (e.g. Perry and Hodges, 2000). Patients perform in general better on tests using non-verbal material, such as the Rey complex figure test, and show overall better performance on recognition tests.

From the late 1990s, a series of studies investigated systematically aspects of anterograde memory in semantic dementia. One of the first studies used black and white line drawings of real and fictitious animals (Graham et al., 1997). While no significant difference between a group of patients with semantic dementia and healthy controls was found on a test of recognition memory for these drawings, patients with semantic dementia were significantly impaired when asked to indicate during the study task whether the animals were real or not. This observation was confirmed using colour pictures of objects (Graham et al., 2000) and photographs of people (Simons et al., 2001). Scahill and colleagues (2005) went on to address the issue of laterality of atrophy and episodic memory processing in semantic dementia. Anatomical distinctions in semantic dementia are important in that predominant left-versus right-sided patients with semantic dementia can present with varying degrees of anoma. Patients with predominant left-sided atrophy are assumed to perform worse on verbal tasks than non-verbal tasks, whereas the opposite should be true for patients with semantic dementia with predominant right-sided atrophy. Such a pattern was indeed observed, whereby patients with semantic dementia with predominant left-sided atrophy performed normally on non-verbal memory tasks, whereas those with predominant right-sided atrophy performed poorly on unfamiliar face memory tasks, such as the Warrington Recognition Memory Test. Thus, examination of anterograde memory in semantic dementia needs to take into account the laterality of greatest brain atrophy, given its influence on test performance.

As Warrington (1975) suggested, patients with semantic dementia appear to rely on perceptual information from the studied stimuli to assist their recognition memory. To follow-up on this observation, Graham and colleagues (2000) investigated recognition memory in patients with semantic dementia using colour pictures. Crucially, while some target items were perceptually identical at study and test (e.g. the same telephone), others were perceptually different (e.g. telephones of different colours or shapes). Despite their profound semantic memory problems, the patients with semantic dementia showed relatively preserved episodic memory for perceptually identical pictures. In contrast, recognition performance was much poorer for the items that were perceptually different at study and test, some patients performing at chance level. These findings demonstrate that patients with semantic dementia rely, therefore, heavily on perceptual inputs whereas in healthy people both semantic and perceptual features can be used to encode new information. Not surprisingly, patients with semantic dementia show high rates of false recognition when perceptually similar objects are used for episodic memory testing (Simons et al., 2005). Further experimentation demonstrated that most perceptual aspects (colour, viewpoint, exemplar types) are important for object recognition memory performance in semantic dementia, with the exception of size (Ikeda et al., 2006). Patients with semantic dementia made false recognitions in all conditions, except the size change condition. These findings also explain the impaired recognition memory for words found in semantic dementia, given the little distinctive perceptual features written words have in comparison to pictures.

The perirhinal cortex, which is consistently affected in semantic dementia (Davies et al., 2004), emerges as the critical neuroanatomical region supporting episodic memory under perceptually difficult conditions. The role of perirhinal cortex in memory has been known for quite some time, with experimentally induced lesions of this region leading to severe recognition memory deficits in monkeys (e.g. Buckley and Gaffan, 1997). Recent evidence, however, suggests that such perirhinal cortex damage may cause a higher perceptual deficit, rather than a memory deficit per se (Bussey and Sakida, 2007). The perirhinal cortex appears critically involved in analysing and representing complex conjunctions of the features that comprise an individual object, which in turn affects the recognition of an object in a memory test. This position could explain the change in memory performance following perceptual manipulations (Graham et al., 2000; Simons et al., 2001). Indeed, perceptual tasks with virtually no memory load that use concurrent visual discrimination or object oddity judgements have been shown to be severely impaired in semantic dementia (Barense et al., 2005; Lee et al., 2005a, b, but see Levy et al., 2005; Shrager et al., 2006). These findings provide further evidence that visual memory problems in semantic dementia may be related
to perception rather than to memory per se. This finding could further explain the difficulty patients with semantic dementia experience with face recognition, as a more thorough ‘feature conjunction analysis’ is necessary to discriminate among similar faces successfully.

Importantly, however, anterograde memory deficits in semantic dementia are unlikely to be due solely to higher perceptual deficits caused by perirhinal damage but rather to a combined perirhinal and hippocampal atrophy. Performance on memory tests that are highly sensitive to hippocampal damage, such as associative memory or source memory, is impaired in semantic dementia (Simons et al., 2002; Clague et al., 2005). Tests of high percep-
tual/perirhinal functioning may potentially be helpful in discrimi-
nating semantic dementia from Alzheimer’s disease, as this function is relatively intact in Alzheimer’s disease, while both pa-
tient groups are impaired on hippocampal-dependent tests. Another promising avenue to discriminate patients with semantic dementia and Alzheimer’s disease is the use of ‘naturalistic’ episodic memory tasks with incidental encoding of information. An elegant study demonstrated that patients with semantic dementia remembered most spatial (e.g. ‘Did I sit in this chair?’), temporal (e.g. ‘How long did I stay?’) and event (e.g. ‘Did I wear a brooch yesterday?’) details from the examiner’s visit to their home, even after a 24-h delay in contrast to patients with Alzheimer’s disease (Adlam et al., 2009). Similarly, topographical memory was found to be relatively intact in semantic dementia but very impaired in Alzheimer’s disease using a virtual reality task (Pengas et al., 2010). Importantly, in this study, performance on a virtual route learning task in combination with naming performance resulted in a complete discrimination of patients with semantic dementia and Alzheimer’s disease.

Progressive non-fluent aphasia

To our knowledge, only one study has examined performance of patients with PNFA on neuropsychological memory tests (Libon et al., 2007). This study showed that patients with PNFA performed significantly better than patients with Alzheimer’s disease on the Verbal Serial List Learning Test. In contrast, patients with PNFA experienced working memory deficits, which are dependent on prefrontal cortex integrity. Clearly, future investigations of PNFA memory performance are needed, in particular in light of recent findings indicating that a subset of patients with PNFA have underlying Alzheimer pathology (Hu et al., 2010).

Behavioural variant frontotemporal dementia

Anterograde episodic memory function in behavioural variant FTD has been investigated systematically only recently. As mentioned before, the scarcity of such studies arises from the fact that amnesia is an exclusion criterion for behavioural variant FTD (Neary et al., 1998). While patients with behavioural variant FTD are often impaired on memory tasks compared with healthy controls (e.g. Pachana et al. 1996; Giovagnoli et al. 2008), these deficits are variable and tend to be overshadowed by the predominant behavioural changes. Compared with Alzheimer’s disease, patients with behavioural variant FTD are generally reported to perform better on verbal and visuospatial anterograde memory tasks (Elfgren et al., 1994; Frisoni et al., 1995; Pachana et al., 1996; Lindau et al., 1998; Thomas-Anterion et al., 2000; Rascovsky et al., 2002; Kramer et al., 2003; Lee et al., 2003; Rosen et al., 2004; Perri et al., 2005; Heidler-Gary et al., 2007; Libon et al., 2007; Giovagnoli et al., 2008) and do not normally show the accelerated forgetting under delayed free recall conditions typically found in Alzheimer’s disease (Hodges et al., 1999; Perry and Hodges, 2000; Glosser et al., 2002; Wicklund et al., 2006; Hutchinson and Mathias, 2007). Importantly, however, exceptions exist and patients with behavioural variant FTD with neuropsychological confirmation at post-mortem have presented with severe amnesia in some cases (Caine et al., 2001; Graham et al., 2005).

Relatively intact memory performance, at least in the early stages of behavioural variant FTD, has also been reported on complex associative memory tasks, such as the computerized Paired Associate Learning Test from the CANTAB (Cambridge Neuropsychological Testing Automated Battery). This task, in which subjects are required to learn the association between coloured patterns and spatial locations, is very sensitive to early Alzheimer’s disease (Swainson et al., 2001; Blackwell et al., 2004), whereas patients with early behavioural variant FTD tend to perform within the normal range (Lee et al., 2003). A similar dissociation between Alzheimer’s disease and behavioural variant FTD has been reported on a face-location association task (Clague et al., 2005). In contrast, no reliable difference between Alzheimer’s disease and behavioural variant FTD has been found on forced-choice recognition and free recall for verbal and non-verbal material (Glosser et al., 2002). A selective retrieval disorder, potentially caused by the known attention problems, was postulated for the impaired memory in behavioural variant FTD (Glosser et al., 2002). In addition, a dissociation has been reported in patients with behavioural variant FTD with a relatively preserved recognition memory but impaired temporal source memory (remembering whether an item was shown in list A or list B) (Simons et al., 2002), in contrast to patients with Alzheimer’s disease who are typically impaired on both recognition and source memory tasks (Multhaup and Balota, 1997).

Source memory performance is generally attributed to prefrontal cortex function (e.g. Duarte et al., 2011). Whether the variable memory performance observed in behavioural variant FTD is due to the prefrontal cortex atrophy or, like Alzheimer’s disease, due to hippocampal atrophy is unknown. Evidence regarding the severity of hippocampal atrophy in behavioural variant FTD is mixed.

At post-mortem, significant hippocampal atrophy has been reported in patients with FTD, even early in the course of the disease (van Mansvelt, 1954; Broe et al., 2003; Kril and Halliday, 2004) (Fig. 3). Medial temporal atrophy has also been found on neuroimaging (Seeley, 2008; Seeley et al., 2008; Whitwell et al., 2009), although no hypoperfusion has been reported in this region in behavioural variant FTD (Kanda et al., 2008). Involvement of medial temporal regions in behavioural variant FTD remains somewhat contentious but a consensus exists on the early involvement of mesial and orbital prefrontal cortical regions (Rosen et al., 2002a; Seeley, 2008). Questions, however, remain regarding the variability in the pattern of change in behavioural variant FTD and whether the anterior temporal and/or parietal atrophy, which is found in addition to the frontal atrophy, is dependent on the underlying pathology (Whitwell et al., 2009, 2011). Whether
this pathological heterogeneity is also reflected in the memory performance of these patients remains unclear. Existing evidence would suggest that cases with severe memory disturbance at presentation appear to have pathological changes associated with TDP-43 protein deposition (Graham et al., 2005) (Fig. 3). A critical issue in the next few years will be the development of reliable biomarkers capable of detecting those with underlying tau versus TDP-43 or FUS pathology, recent studies showing promising results (Piguet et al., 2011; Schofield et al., 2011). It may then be possible to relate the clinical phenotype, including the degree and nature of episodic memory impairment to the pathological type in vivo.

The reported dissociation between intact implicit but impaired explicit anterograde memory in behavioural variant FTD (Pasquier et al., 2001) provides further support for a disturbance of prefrontal mediated memory function in these patients. Critically, this study demonstrated that retrieval cues provided greater benefit in the explicit memory condition for patients with behavioural variant FTD than for Alzheimer’s disease. This finding prompted the suggestion that memory dysfunction in behavioural variant FTD resulted from frontally dependent, defective cognitive (retrieval) control processes rather than true amnesia (e.g. Collette et al., 2010). Further support arises from neuroimaging investigations showing that disturbance in the strategic aspects of episodic memory recall and retrieval processes are associated with prefrontal cortex atrophy, in particular the orbitofrontal cortex (Kramer et al., 2005; Pennington et al., 2011) as well as reduced metabolism in prefrontal, parietal and posterior cingulate cortices in patients with behavioural variant FTD (Bastin et al., 2011). The failure of these prefrontally mediated retrieval control mechanisms also explains the increased false recognition rates (de Boysson et al., 2011) and confabulations found in behavioural variant FTD (Nedjam et al., 2004).

The inconsistent findings across studies regarding episodic memory in behavioural variant FTD are also likely to be due to the inclusion of patients who do not have a progressive neurodegenerative disease. Recent studies have identified a subset of patients who meet current clinical criteria for behavioural variant FTD, yet show little or no progression over a decade or more (Davies et al., 2006; Kipps et al., 2007b, 2010; Piguet et al., 2009). These patients with non-progressor or ‘phenocopy’ behavioural variant FTD mimic the clinical features of behavioural variant FTD but lack the typical brain atrophy found on MRI and demonstrate preserved glucose metabolism on PET (Davies et al., 2006; Kipps et al., 2007a, 2009) and the pathology of these cases remains unclear. The prevalence of these phenocopy cases in existing studies is unknown but their inclusion is likely to underplay the magnitude of the deficits in progressive, or patients with ‘real’, behavioural variant FTD. This position was confirmed in a recent study in which patients with behavioural variant FTD, who had been followed over many years, were grouped according to their disease progression status (real versus phenocopy behavioural variant FTD) and their anterograde episodic memory performance at presentation compared with Alzheimer’s disease (Hornberger et al., 2010a). Patients with progressive behavioural variant FTD were nearly as impaired as patients with Alzheimer’s disease on most verbal and visual neuropsychological memory measures, in contrast to the phenocopy cases who showed only mild deficits compared with control participants (Fig. 4). The same study also showed that patients with Alzheimer’s disease scored worse on delayed recall tests and

Figure 3 Patient presenting with severe amnesia and pathological confirmation of frontotemporal lobar degeneration pathology. Significant atrophy is present involving the hippocampus and the middle temporal region on coronal MRI (A). At post-mortem, significant neuronal loss was found in the CA1 field of the hippocampus (B) and ubiquitin-positive staining (C). Adapted from Graham et al. (2005) with permission from Oxford University Press.
on orientation scores of the Addenbrooke’s Cognitive Examination-Revised compared with the patients with behavioural variant FTD. Importantly, these findings were replicated in an independent prospective sample (Pennington et al., 2011) (Fig. 4), which further showed that prefrontal atrophy ratings in patients with real behavioural variant FTD correlated with the memory performance. Interestingly, patients with behavioural variant FTD and Alzheimer’s disease showed hippocampal atrophy of similar severity. The pattern of atrophy, however, differed between the two groups with behavioural variant FTD showing more pronounced anterior than posterior hippocampal atrophy compared with Alzheimer’s disease (see also Laakso et al. 2000). Disturbance in both prefrontal and medial temporal lobe regions are therefore likely to contribute to the memory impairments seen in patients with behavioural variant FTD, with the relative contribution varying across patients, possibly related to the site of underlying pathology or to the disease severity. Memory tests that are capable of differentiating between these anatomical contributions are required.

In summary, studies investigating anterograde memory in behavioural variant FTD report inconsistent results. Possible reasons for the discrepant findings are (i) the use of memory tests which place different demands on prefrontal versus medial temporal lobe functioning, such as recall versus recognition; and (ii) the potential admixture of real patients with behavioural variant FTD with phenocopy cases, resulting in some studies to an under-representation of anterograde memory deficits in this patient group. Taking all the evidence reviewed into account indicates that patients with true behavioural variant FTD can have memory deficits of the same magnitude as seen in Alzheimer’s disease. This finding poses a challenge to the widely used diagnostic criteria for behavioural variant FTD (Neary et al., 1998), which states severe memory deficits as an exclusion criterion, as well as for the recently revised criteria (Rascovsky et al., 2011).
which advocate a relative sparing of episodic memory on neuropsychological testing.

Conclusions and future directions

The evidence reviewed in this article demonstrates the relevance of episodic memory investigations in FTD with each subtype showing specific changes in retrograde and anterograde memory. In semantic dementia, the profile is one of significant retrograde memory deficits (with or without step-gradient) modulated by disease severity and of anterograde memory deficits that are affected by visuoperceptual aspects and the modality of the information to be remembered. In contrast, both retrograde and anterograde memory functions are mostly intact in PNFA, with the exception of a mild autobiographical memory deficit, which is abolished following the provision of retrieval cues. Finally, retrograde and anterograde memory performance is affected in behavioural variant FTD, and appears to be particularly sensitive to the co-occurrence of executive dysfunction.

Importantly, aspects of this review are relevant for clinical practice. Patients with semantic dementia and behavioural variant FTD experience episodic memory problems that have been under recognized so far, likely due to their pervasive language and behavioural deficits. The historical and current evidence shows that some patients with FTD can have episodic memory problems similar to Alzheimer’s disease, which can make a diagnostic distinction difficult, particularly early in the disease course. More specifically, patients with semantic dementia exhibit retrograde and anterograde memory deficits, the severity of which varies according to the tests used. For clinicians, impaired performance on verbal but not visuospatial memory tests combined with a loss of semantic knowledge should raise the strong possibility of semantic dementia. Other features supportive of this diagnosis include preservation of visual memory particularly under forced-choice recognition format and preserved memory for temporal information and for recent autobiographical events.

With regards to behavioural variant FTD, retrograde memory data demonstrate that behavioural variant FTD and Alzheimer’s disease group, and cast further doubt on the validity of amnesia as a diagnostic exclusion criterion for the disease (although this point has been rectified somewhat in the recent revision of the clinical diagnostic criteria for behavioural variant FTD). Nevertheless, delayed recall memory tests, in particular of verbal material (e.g. word lists), emerge as a good predictor of behavioural variant FTD and Alzheimer’s disease diagnosis (Hornberger et al., 2010a). In contrast, recognition memory scores appear the least predictive markers of episodic memory differences between the groups. Improved clinical diagnostic accuracy may also be achieved using executive function tests, such as the Hayling test of inhibition, which discriminate behavioural variant FTD from Alzheimer’s disease and from phenocopy cases to a high degree even in the early stages of the disease (Hornberger et al., 2008, 2010b).

As indicated above, accurate assessment of memory performance has crucial implications for the clinical diagnosis of patients with FTD. The importance of evaluating memory performance within the context of other cognitive abilities, however, cannot be overemphasized, as presence/absence of deficits in other cognitive domains will inform as to the relative severity of the memory impairment and help reach a clinical diagnosis. For example, comparing episodic memory and temporal orientation integrity appear useful, as disorientation is commonly observed in Alzheimer’s disease but rarely so in behavioural variant FTD. Complementing clinical tests with imaging investigations, imaging neural correlates, in particular of prefrontal cortex regions, such as in Pennington and colleagues (2011) appear very promising in dissociating patients with behavioural variant FTD and Alzheimer’s disease memory deficits.

Investigations of memory in FTD have improved our theoretical understanding of episodic memory processes. In particular, the retrograde memory findings in semantic dementia have informed and challenged memory consolidation theories. Further, results of anterograde memory investigations have addressed the interactions between memory (episodic and semantic) and high-level perceptual processes. The disentangling of these processes continues to advance our understanding of medial temporal lobe memory systems, which are critical to episodic memory functions. Similarly, studies examining anterograde memory in behavioural variant FTD have uncovered prefrontal cortex and/or medial temporal lobe contributions to memory deficits in this group. These contributions, however, remain difficult to tease apart with standard neuropsychological tests. Memory tests, such as within- and between-domain associative memory tasks, which are based on current experimental findings and can be easily applied in the clinics are needed. Such tests are capable of delineating between prefrontal cortex and medial temporal lobe, as well as among regions within the medial temporal lobe, specific memory processes. These new theoretical developments will inform clinical practice which will lead to improved diagnosis and improved patient management.

Acknowledgements

We thank Prof. J. Hodges for helpful comments on earlier versions of the article.

Funding

The Australian Research Council (ARC) Centre of Excellence in Cognition and its Disorders. ARC Research Fellowship
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