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# Episodic Memory and Regional Atrophy in Frontotemporal Lobar Degeneration

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## Abstract

It has been unclear to what extent memory is affected in frontotemporal lobar degeneration (FTLD). Since patients usually have atrophy in regions implicated in memory function, the frontal and/or temporal lobes, one would expect some memory impairment, and that the degree of atrophy in these regions would be inversely related to memory function. The purposes of this study were 1) to assess episodic memory function in FTLD, and more specifically patients' ability to episodically re-experience an event, and determine its source; 2) to examine whether memory performance is related to quantified regional brain atrophy. FTLD patients (n=18) and healthy comparison subjects (n=14) were assessed with cued recall, recognition, “remember/know” (self-reported re-experiencing) and source recall, at 30 min and 24 hr after encoding. Regional gray matter volumes were assessed with high resolution structural MRI concurrently to testing. Patients performed worse than comparison subjects on all memory measures. Gray matter volume in the left medial temporal lobe was positively correlated with recognition, re-experiencing, and source recall. Gray matter volume in the left posterior temporal lobe correlated significantly with recognition, at 30 min and 24 hr, and with source recall at 30 min. Estimated familiarity at 30 min was positively correlated with gray matter volume in the left inferior parietal lobe. In summary, episodic memory deficits in FTLD may be more common than previously thought, particularly in patients with left medial and posterior temporal atrophy.

### Keywords

episodic memory; recollection; familiarity; frontotemporal dementia; MRI; temporal lobe; parietal lobe; atrophy

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## Introduction

Frontotemporal lobar degeneration (FTLD) is a form of pre-senile dementia characterized by atrophy in the frontal and/or temporal lobes with associated changes in behavior and personality. Although the location of atrophy suggests that memory should be impaired, early reports noted relative sparing of everyday memory in FTLD, particularly in comparison to Alzheimer's disease (Hodges, Patterson, Oxbury, & Funnell, 1992; Neary et al., 1998). When directly assessed, however, memory has been shown to be affected in FTLD to varying degrees (Binetti, Locascio, Corkin, Vonsattel, & Growdon, 2000; Pasquier, Grymonprez, Lebert, & Van der Linden, 2001; Simons et al., 2002).

Assessment of memory in patients with brain disease requires consideration of distinct mnemonic processes that may be differentially affected by lesion type or location. Among the most important distinctions in this area is that between episodic memory (i.e., memory for events occurring at a specific time and place) and semantic memory (i.e., memory for factual information about oneself or the world that is not specific in time and place; (Tulving, 1983). More recent reformulations of episodic memory emphasize awareness of the self as a continuous entity across time, enabling a subjective conscious experience of “mental time travel” (Tulving, 2002; Wheeler, Stuss, & Tulving, 1997). Many patients with FTLD experience a disturbance in self-awareness (Miller et al., 2001), suggesting that mnemonic processes drawing upon this capacity may be especially affected.

The goal of the present study was to examine episodic memory in detail in patients with FTLD by supplementing measures of recognition and cued recall with the two more sensitive indices of episodic memory: remember/know judgments and source recall. We examined all measures at both short- and long-delay intervals (30 min and 24 hr). We also sought to relate performance to regional atrophy as measured by high resolution MRI.

Performance on standard memory tests such as those used in previous studies of FTLD can, in addition to episodic memory, be supported by non-episodic processes (e.g., perceptual priming, procedural memory, and familiarity). Familiarity is characteristic of semantic retrieval, which can be accomplished in the absence of re-experiencing an event. Remember/know (R/K) judgments (Gardiner, 1988; Tulving, 1985) are commonly used to assess the conscious mnemonic experience accompanying recognition of previously-studied items. In this technique, the subject indicates whether retrieval was accompanied by a phenomenological sense of re-experiencing of the encoding event (”remember”) or solely by a sense of familiarity (‘know”). To our knowledge, in FTLD this procedure has only been applied to the retrieval of autobiographical memories, for which patients do indeed have less re-experiencing than comparison subjects (Matuszewski et al., 2006; Piolino et al., 2003) Assessing patients' amount of re-experiencing during more common laboratory tests would shed light on previous findings where episodic memory in FTLD may have been overestimated.

Source recall involves recalling the encoding context of an event, such as an item's position in space or its modality of presentation. Source recall impairment is common in Alzheimer's disease (Multhaup & Balota, 1997) and aging (Spencer & Raz, 1995) , with memory for source being more impaired than item memory. We know of only one study that has investigated source recall in FTLD (Simons et al., 2002). In this study, source recall was more or less intact in semantic dementia, a subtype of FTLD affecting the temporal lobes, whereas it was impaired in a small sample of patients with the frontal variant of this disorder. As expected given the putative role of the frontal lobes in source monitoring (e.g., Janowsky, Shimamura, & Squire, 1989), source recall was related to performance on tests of executive functioning sensitive to prefrontal dysfunction. In the current study, items were presented either visually or auditorily

at study; source recall was assessed at test by asking patients to report recognized items' modality of presentation.

Finally, we investigated whether rate of forgetting is accelerated in FTLD. Such an acceleration would be indicative of what memory processes are affected in FTLD, such as encoding, retention, or retrieval. Patients with AD have a faster forgetting rate than those with FTLD (Pasquier et al., 2001; Wicklund, Johnson, Rademaker, Weitner, & Weintraub, 2006), which may suggest more impaired retention or consolidation in AD than FTLD. Although FTLD patients' forgetting rates are similar to controls (Pasquier et al., 2001), no study has had a longer retention interval than 30 min. It is possible that forgetting in FTLD is normal in the short term but accelerates in the long term (e.g., 24 hrs).

The nature of memory impairment in FTLD is likely to depend on the pattern of underlying atrophy. Episodic memory engages both frontal and temporal areas (Cabeza & Nyberg, 2000) , and it is possible that specific episodic memory tasks, such as remembering and source, are sensitive to damage in these areas. Although episodic memory in FTLD has been related to medial temporal lobe (MTL; Kramer et al., 2005; Simons et al., 2002) and frontal lobe volumes (Kramer et al., 2005), prior studies focused on these areas and either ignored or collapsed other areas of the brain, so the influence of atrophy of other areas cannot be ruled out. In this study, we related performance on episodic memory tasks to regional atrophy using all lobar brain regions as quantified on patients' high resolution structural MRI.

## Methods

### Participants

**Frontotemporal lobar degeneration patients—**Patients were identified from dementia clinics at three locations: Baycrest, Sunnybrook Health Sciences Centre (both in Toronto), and the University of California at San Francisco Medical Center based on their availability and ability to participate in ongoing studies of memory and executive function in FTLD. FTLD diagnosis followed the Neary et al. (Neary et al., 1998) criteria, including normal everyday memory function, delineating three subtypes: frontotemporal dementia (FTD), progressive non-fluent aphasia (PNFA), and semantic dementia (SD). Patients with significant aphasia, neglect or other focal neurological disturbance or severe cognitive or physical disability that interfered with testing were excluded. All patients had sufficient central semantic processing to understand the task instructions and to perform the cleverness rating encoding task (see below), as reinforced by normal or near-normal performance on the Pyramids and Palm Trees Test (Howard & Patterson, 1992) in the majority of patients for whom test data was available (see Table 1). In total, data were collected from 18 FTLD patients, seven of whom showed mixed features of FTD and SD. Of the remainder, seven met criteria for FTD, three for PNFA, and one SD. Because of the high degree of overlap across these clinical syndromes (e.g., Bozeat, Gregory, Ralph, & Hodges, 2000; Liu et al., 2004; Rosen, Kramer et al., 2002), the small N's per subgroup, and because we were able to analyze individual differences in atrophy patterns derived from high resolution structural MRI, we combined data across all three FTLD subtypes and analyzed patients as a single group. To date, eight patients in our sample have come to autopsy. These cases confirmed the presence of pathology consistent with FTLD, including ubiquitin-positive, tau-negative inclusions with or without degeneration of the motor neurons in some cases, tau-positive Pick bodies inclusions with or without α-synuclein inclusions, or progressive supranuclear palsy and cortical basal degeneration, which can also manifest tauopathy in other cases (see McKhann et al., 2001; Sha, Hou, Viskontas, & Miller, 2006 for a discussion of neuropathology in FTLD)

As seen in Table 1, gross mental status was intact on the MMSE, but the patients showed characteristic slowing and performance deficits on tests sensitive to frontal and temporal

dysfunction (Trail Making, Parts A and B, the Wisconsin Card Sorting Test, and phonemic word list generation). Of the 18 patients in our sample, 15 were assessed with structural MRI. Demographic and neuropsychological characteristics of this sub-sample were representative of the full sample. Regional brain atrophy (reduced gray matter volume; see below for methods) was assessed against a sample of 10 healthy comparison subjects (different from those described below), matched to the patients for age, education, and sex. Consistent with the diagnosis of FTLD, the patients had marked frontal and temporal atrophy (see Figure 1). One exception was the anterior temporal regions, where variability among the patients was high. With the exception of the right inferior parietal region, posterior regions were spared.

**Comparison subjects—**Fourteen healthy participants matched to the patients on age and education (see Table 1) were recruited from the Rotman Research Institute volunteer registry to serve as comparison subjects. Exclusion criteria were prior neurological or systemic disease that could affect cognition, prior psychiatric hospitalization or treatment with psychiatric medication for greater than six weeks, prior significant alcohol/drug abuse, and significant developmental disabilities. Subjects taking medication known to affect cognitive function were also excluded. As seen in Table 1, comparison subjects' neuropsychological test scores indicated intact cognitive functioning. These subjects also received the Hopkins Verbal Learning Test – Revised (HVLT-R; Benedict, Schretlen, Groninger, & Brandt, 1998) and the Symbol Digit Modalities Test (SDMT-O and SDMT-W, oral and written versions, respectively; Smith, 1978) as part of our assessment battery (these measures were not available for patients due to time constraints). Comparison participants' scores on these measures were within normal limits (HVLT-R total recall: 26.4 ± 3.9; SDMT-O: 57.6 ± 13.5; SDMT-W: 49.4 ± 11.1). All participants gave informed written consent, approved by the institutional review boards.

## Memory testing

**Materials and design—**A pool of 144 humorous definitions and the respective word they defined (e.g., “A drill artist – DENTIST”) were selected from items created by Tulving and Watkins (Tulving & Watkins, 1977). Definitions were randomly divided into 6 sets of 24 items and were counterbalanced across four test forms such that each definition set occurred equally often as an auditory target, a visual target, or a distracter across both delay intervals. The test forms were counterbalanced across participants and groups. Auditory targets were digitally recorded for presentation via laptop computer with external speakers.

**Procedure—**Participants were tested individually. Following orientation to the encoding task using 6 buffer items, the 72 targets (definition and word) were presented on a laptop computer at a fixed rate of 5 s per item. Targets were presented in four 18-item blocks alternating between auditory or visual presentation, with a rest between the second and third blocks. During presentation of the auditory items, a speaker icon appeared on the screen. To promote semantic processing of items during encoding, participants rated the cleverness of each definition on a scale of 1 (not clever at all) to 5 (very clever) after each target was presented.

Retrieval was assessed at two delays: 30 min and 24 hr. Each test session included 24 target items (half auditory, half visual) and 24 distracters, randomized. Four aspects of retrieval were tested: cued recall, recognition, source recall, and remember/know judgments. The examiner first read aloud the definitions as cues for participants to come up with the defined word (e.g., “A drill artist - ?”; *cued recall*). Participants were informed that some definitions would be ‘old’ ones that were presented earlier, while other definitions would be ‘new’ items not encountered before. Participants were thereafter asked if they recognized the item from the encoding list (*recognition*). If a participant had failed to recall a word in the cued recall part,

he/she was informed of the correct response and thereafter asked whether the item had been presented earlier or not.

For each definition recognized as 'old', participants were asked whether they heard the item on the speakers or read the item on the computer screen (*source recall*). They were next asked to make a decision about their subjective experience of remembering the item (*remember/know*; Gardiner, 1988; Tulving, 1985). The distinction between "remember" and "know" responses was explained to participants, defining "remember" (called "Type A") as the kind of recollection in which participants were able to think back and re-experience something from the presentation of that item during encoding, including re-experiencing of visual, auditory, or mental (thoughts or feelings) information. "Know" (called "Type B") was defined as familiarity-based recognition, where participants were not able to think back and re-experience anything specific from the presentation of that item during encoding. Participants were informed that both types of memories were completely normal and that there were no right or wrong answers to this part of the test.

Several steps were taken to ensure the validity of the Type A/B (remember/know) distinction. A written summary distinguishing the two types was available for participants to consult throughout the testing. Each test was preceded by six practice items with which the examiner clarified the testing procedure until participants appeared to correctly understand the classification system. The validity of Type A/B responses was further queried by asking participants to justify these responses throughout the testing. Responses were classified as either mental (e.g., based on a recollected mental association from encoding) or sensorial (e.g., recollection of a perceptual feature of the encoded stimulus). The vast majority (>90%) of these responses were mental. When patients had difficulty mapping the Type A/B distinction onto their subjective experience the examiner asked the patient how they knew the item was old, then coded the item as type "A" ("remember") if the patient reported recovery of specific details from the encoding of that item, such as mental associations or recollection of the item's physical properties (what it looked/sounded like). Two patients were unable to provide reliable responses for this aspect of the test; their remember/know data were therefore dropped from analysis.

Proportions of hits were assessed for cued recall, recognition and source, as well as the proportion of "remember" responses. All proportions were corrected for false alarms (i.e., when a participant qualified a new item as old). An estimate of familiarity was derived by adjusting "know" responses for the assumption of independence between recollection and familiarity according to the following formula: K/(1−R), where K is the proportion of "know" responses and "1−R" represents the opportunity a subject has to make a "know" response in the absence of recollection (Yonelinas & Jacoby, 1995). This familiarity estimate was used in place of raw "know" responses in the brain-behavior correlations involving patients. Many control subjects' proportion of "remember" responses was at or close to 1.0, resulting in a denominator of 0 for the estimate of familiarity. As familiarity estimates derived from such data are uninterpretable, we limit reporting of familiarity estimates to patients.

### MRI scan acquisition

Patients were scanned on 1.5 T scanners (Toronto: Signa, General Electric Medical Systems, Waukesha, WI; San Francisco: Magnetom VISION system, Siemens Inc., Iselin, N.J) with similar in-plane resolution. Scanning occurred concurrently with testing. The Toronto protocol involved axial acquisitions using spoiled gradient echo T1-weighted 3D volume imaging (TR/TE/flip angle = 35 ms/5ms/35°, 1.0 NEX, acquisition matrix = 256*256; 124 slices, slice thickness = 1.3mm; FOV=22 cm), as well as spin echo, proton density and T2-weighted images (TR/TE = 3000ms/30ms, 80ms, 0.5 NEX, acquisition matrix 256 × 192, slice thickness = 3 mm; FOV=20 cm). The San Francisco protocol also applied a double spin echo sequence (TR/

TE1/TE2 = 5000/20/85 ms, 51 contiguous 3 mm axial slices covering the entire brain and angulated −10 degrees from the AC-PC line). Volumetric T1-weighted gradient echo MRI were achieved using the MPRAGE sequence (TR/TE/TI = 10/4/300 ms, 15° flip angle, 1.5mm slab thickness) in coronal orientation perpendicular to the double spin echo sequence.

## Image processing

Brain MRI data were analyzed via an updated version of our previously reported image processing pipeline (Dade et al., 2004; Kovacevic et al., 2002). The main modification to this protocol involves template matching, allowing for comparison of individual images to a standard image and facilitating automation of previously semi-automated steps. The first step in the pipeline was to create an unbiased non-linear average of T1-weighted images from a set of 11 healthy age-matched comparison subjects (mean age = 65; SD = 11). The algorithm for constructing geometrically centered unbiased average images using a modification of an algorithm previously developed for mouse brain MRI (Kovacevic et al., 2005). Each participant's T1-weighted image was registered to the template brain (Woods, Grafton, Holmes, Cherry, & Mazziotta, 1998; Woods, Grafton, Watson, Sicotte, & Mazziotta, 1998), preserving the original size of the brain while standardizing the position and orientation. Images were resampled into template space using windowed sinc interpolation. Template matching was accomplished via non-linear registration of T1-weighted images to the template image (Collins & Evans, 1997). Removal of non-brain tissue from the image incorporated thresholding information derived from the PD- and T2-weighted images, facilitating the distinction between dura matter and gray matter (Kovacevic et al., 2002). This is contrasted to methods of brain extraction based on the T1-weighted image that emphasize the cortical surface, inconsistently preserving subdural CSF.

The voxels on the T1-image were then classified as representing gray matter, white matter, or CSF using an automated tissue classification method that corrects for radio-frequency inhomogeneity inherent to MR scanning (Kovacevic et al., 2002). For the purposes of this study, only gray matter volumes were analyzed.

A modified Semi-Automated Brain Region Extraction (SABRE; Dade et al., 2004) method was thereafter used to create ROIs on the template brain. This method involves manual identification of 15 landmarks (e.g. Sylvian fissure, central sulcus, interhemispheric fissure) and tracing of the cingulate gyrus on the template brain. Based on identification of the edges of the brain and the anterior and posterior commissures, a Talairach-like (Talairach & Tournoux, 1988) grid is automatically created. The algorithm uses this grid along with the landmark coordinates to divide the brain into 38 regions (19 per hemisphere). Non-linear deformation field matching of the template to individual images was used to customize these regions to fit each participant's brain anatomy (as opposed to transforming images to fit the template, which can distort inter-individual topographical variability). Regional gray matter volumes were adjusted for total intracranial capacity using a regression-based method (Arndt, Cohen, Alliger, Swayze, & Andreasen, 1991). As our segmentation protocol is flexible across different T1-weighted contrasts, no adjustment was necessary to accommodate images acquired from different scanners. All images were manually inspected, slice-by-slice, to confirm the accuracy of the pipeline steps. Our tissue compartment segmentation and SABRE software are particularly well-suited to analysis of brains with atrophy, as they do not require spatial transformation that can distort inter-individual topographical variability. These algorithms have been successfully applied with high reliability to normal aging (Dade et al., 2004), multiple sclerosis (Feinstein et al., 2004), and dementia (Bocti, Rockel, Roy, Gao, & Black, 2006; Gilboa et al., 2005) populations.

### Statistical analyses

Parametric tests were used to assess group differences between patients and comparison subjects. For most measures, these consisted of independent samples t-tests. Non-parametric tests were used to assess sex differences between groups (chi-square) and for neuropsychological tests that could not be transformed to meet the assumption of normality required for parametric tests (Mann-Whitney U). Forgetting rates between the two groups were assessed with a 2 (Group) × 4 (Test) × 2 (Retrieval Delay) repeated measures ANOVA, focusing on interaction terms involving Group and Retrieval Delay. This analysis was limited to 13 patients as 24 hr delayed recall were unavailable for six patients.

Because of the many brain variables derived from the structural measures, an attempt was made to reduce the number of comparisons to avoid Type II error. To this end, the analyses were performed in two steps. First subregions were collapsed to form right and left frontal, parietal, temporal, and occipital gray matter volumes that were correlated with recognition, source recall, and remember/know judgments. Correlations were not computed for cued recall, which was near the floor in patients. Second, lobes showing significant relationships to behavior were analyzed on a more local level, including all the subregions making up that lobe. The lobes and subregions analyzed in this study are displayed in Figure 2. Due to non-normality, brain-behavior relationships were assessed with Spearman's rho (rank order correlations).

## Results

### Memory performance

On average, patients performed significantly worse than comparison subjects on cued recall, recognition, source recall, and “remember” judgments (see Figure 3). Performance varied, however, and whereas some patients performed at the same level as comparison subjects, others were clearly impaired. All measures but cued recall were adjusted for false alarms, which were elevated in patients at both delays (0.23 ± 0.28 and 0.24 ± 0.25, respectively) but around zero in comparison subjects (0.0 ± 0.1 and 0.4 ± 0.8, respectively).

As seen in Figure 3, forgetting rates were similar across patients and comparison subjects; none of the interaction terms involving Retrieval Delay and Group were significant. In contrast to the other measures that declined across the retrieval delay intervals ($p$'s < .01), estimated familiarity in patients was stable at 30 min (0.32 ± 0.35), and 24 hrs (0.37 ± 0.25), $t(12) < 1$. As noted in the methods, comparison subjects' familiarity estimates could not be interpreted because their “remember” responses were at ceiling.

### Relationships between brain atrophy and performance

As can be seen in Table 2, significant positive correlations were observed between left temporal lobe gray matter volume and performance in recognition and source memory at 30 min, and recognition at 24 hrs. Left parietal lobe gray matter volume was positively correlated with estimated familiarity at both delays. Left occipital lobe gray matter volume was positively correlated with recognition and source memory at 30 min only.

As significant effects were noted for the temporal and parietal lobes, these regions were examined in more detail. The most robust effects were noted for the left MTL. Significant positive associations were found between left MTL gray matter volume and recognition and source at both delays, the strongest being with source at 24 hr delay. Left MTL gray matter volume was also positively correlated with the amount of “remember” responses at 30 min. Gray matter volume in the left posterior temporal lobe was positively correlated with recognition at both delays, and source at 30 min delay. Adjusted “know” responses (estimated familiarity) were positively correlated with gray matter volume in the left inferior parietal

cortex at 30 min. The occipital lobe did not consist of any subregions, so no further analysis was conducted on this measure.

To assess whether the apparent double association between recollection and the left medial temporal lobe on one hand, and estimated familiarity and the left inferior parietal lobe on the other hand, was significant, the four correlations at both time delays were compared to each other (Snedecor & Cochran, 1989). Although none of the comparisons reached significance due to low statistical power, there was a trend for recollection to be more strongly associated with left medial temporal gray matter volume than estimated familiarity ($Z = 1.37$, $p = .09$). Estimated familiarity was more strongly associated with left inferior parietal lobe gray matter volume than with left medial temporal lobe volume, but this comparison did not reach significance ($Z = 1.16$, $p = .12$).

## Discussion

While episodic memory in FTLD is considered preserved relative to AD, accumulating evidence suggests varying degrees of episodic memory impairment in this disorder. Nearly all laboratory studies on this topic, however, have employed standard tests of cued recall and recognition; very few have used measures of contextual recall considered central to the phenomenological experience of episodic memory (Tulving, 2002). To our knowledge, no published studies have assessed long-term forgetting rates and atrophy in all lobar brain regions in relation to episodic memory in FLTD.

In the present study, measures of contextual retrieval (source recall and “remember” responses) were sensitive to FTLD. Significant group differences, however, were not limited to these measures; effects were also noted for cued recall and recognition. We found that effects were similar at both short- and long-delay intervals, suggesting that forgetting rates do not differ between patients and comparison subjects. Finally, there were robust relationships between episodic memory performance and the integrity of the left temporal lobe, especially in the medial temporal region. Additional relationships were noted for the left posterior temporal, left inferior parietal, and occipital regions.

Previous studies of episodic memory in FTLD have mainly found relative preservation of recognition relative to recall (Mendez & Cummings, 2003), although impaired recognition has also been observed (Galton et al., 2001; Matuszewski et al., 2006). In this study, both cued recall and recognition were significantly impaired in patients with FTLD. This impairment may be partly attributable to the nature of our task, which consisted of the learning associations between humorous word definitions and their respective words (Tulving & Watkins, 1977). This task was originally developed to enhance encoding by engaging emotional and social processes. Although we did not assess these processes in detail, they are typically affected in patients with FTLD (Rosen, Perry et al., 2002). Patients may not have benefited as much as comparison subjects from deeper level processing at encoding. While effects of impaired basic central semantic processing on encoding cannot be ruled out, it is unlikely that such deficits alone could account for our findings as all patients had central semantic function sufficient to perform the encoding task.

The reduced “remember” responses among patients with FTLD suggests a deficit in the conscious re-experiencing of their initial encounter with that item relative to comparison subjects, who were more likely to have reported remembered something they thought or felt at the moment of encoding. The close association between episodic memory and the sense of self (Tulving, 2002; Wheeler et al., 1997) supports the notion that reduced episodic memory in FTLD can be accompanied by an altered sense of self. Indeed, the hallmark personality and behavioral changes of FTLD are considered to reflect altered self-awareness (Miller et al.,

2001). Our findings, combined with parallel results obtained in studies of FTLD and autobiographical memory (Piolino et al., 2003), suggest that this deficit affects patients' conscious experience of recollection. Although remember/know judgments may be suspect in FTLD patients with metacognitive impairment, we provided extensive instructions, collected confirmatory justification of responses, and excluded patients whose justifications did not match their remember/know judgments.

As with “remember” responses, source recall involves re-instatement of the encoding context. One advantage of source recall over “remember” responses is that the source of the item at encoding is verifiable, whereas self-reported of conscious experience as in remember/know judgments is not. Although source and “remember” responses can dissociate under certain conditions (Conway & Dewhurst, 1995; Levine, Freedman, Dawson, Black, & Stuss, 1999), they likely assess shared executive-mnemonic processes (Johnson, Hashtroudi, & Lindsay, 1993), a hypothesis further supported by the pattern of brain-behavior relationships in this study (see below). The FLTD patients' marked deficit in source memory provides further confirmation of their deficit in recollection of encoding context (see also Simons et al., 2002).

Although patients performed worse than comparison subjects in all measures at both delays, they had comparable forgetting rates, which were themselves consistent with previous studies of long-term forgetting in the elderly (e.g., Giambra & Arenberg, 1993; Tombaugh & Hubley, 2001). This finding is consistent with earlier studies using up to 30 min delay, and our study extends this finding to 24 hrs. Our results suggest that encoding may be deficient in FTLD, whereas retention is relatively preserved. One caveat to this conclusion was the poor performance of FTLD patients on “remember” responses and source recall at 24 hours, causing a floor effect that may have limited detection of accelerated forgetting for these measures. The initially low performance of patients complicates the interpretation of the findings for the same reason. In contrast to the delay effects on other measures, estimated familiarity (calculated only for FTLD patients because of ceiling effects in controls' “remember” responses) remained stable across the 30 min and 24 hr delay intervals, consistent with the notion that such delay intervals affect recollection more than familiarity (Gardiner & Java, 1991).

Episodic memory performance was related to gray matter integrity in functionally connected regions within the left posterior hemisphere. The effect was greatest for the left MTL, which was significantly related to nearly all indices of episodic memory across both delay periods. The greater memory impairment in AD relative to FLTD has been attributed to earlier temporal lobe atrophy in AD (Frisoni et al., 1996), although it has also been suggested that this difference is owing to additional damage throughout Papez's circuit in patients with AD (Nestor, Fryer, & Hodges, 2006). Our findings suggest that temporal lobe pathology may also be a determinant of memory deficits in FTLD. Previously reported lack of association between medial temporal lobe volumes and memory in FTLD (e.g., Nestor, Fryer, & Hodges, 2006) may be related to patient group, stage of disease progression, and test selection.

The MTL is classically associated with mnemonic processing (Scoville & Milner, 1957), with material-specific effects according to the side of damage (Milner, 1971) and greater mnemonic impairment associated with left-lateralized pathology (Spiers, 2001). In normal aging, hippocampal and MTL volume is related to memory function (O'Brien, Desmond, Ames, Schweitzer, & Tress, 1997). This is also the case for verbal and picture memory in amnestic disorders of varying etiology, including patients with both frontal and temporal lesions (Kopelman et al., 2001). This relationship is frequently observed in functional neuroimaging studies, where left MTL activation is associated with encoding and retrieval in verbal episodic memory tasks (Cabeza & Nyberg, 2000).

Turning to the advanced measures of episodic memory employed in this study, the MTL is associated with binding of features that is required for recall of contextual details (Eichenbaum, 2000). MTL damage has been consistently associated with deficits in associative memory, source recall, and “remember” responses (Giovanello, Verfaellie, & Keane, 2003; Yonelinas, Kroll, Dobbins, Lazzara, & Knight, 1998). In healthy adults, MTL activation is related to “remember” responses (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000) and source recall (Gold et al., 2006). The left MTL is also preferentially engaged by autobiographical recollection (Svoboda, McKinnon, & Levine, 2006), where it is thought to be related to recall of contextual details (Maguire, 2001). It is notable that that the correlation between MTL integrity and source memory increased from 30 minutes to 24 hr, suggesting that the MTL plays an increasing role in contextual retrieval at longer relative to shorter delay intervals. One limitation of our findings is that our MTL region encompassed the hippocampus, amygdala, parahippocampal, entorhinal, and perirhinal cortices. We are therefore unable to make any claims concerning the specificity of our findings to MTL substructures.

Posterior temporal gray matter was also significantly related to recognition and source recall performance. This brain-behavior relationship likely reflects encroachment of gray matter volume loss in regions involved in lexical-semantic processing and processing of non-spatial features in the ventral stream necessary for source discrimination. Similarly, the relationship of left occipital gray matter volumes to recognition and source recall may reflect the contribution of visual processing at encoding, or reinstatement of visual features at retrieval (Yonelinas, Hopfinger, Buonocore, Kroll, & Baynes, 2001). The MTL dynamically interacts with neocortical regions in mnemonic encoding and retrieval. Although network analysis is beyond the scope of this study, our data are consistent with the notion that decline in elements of this posterior network are functionally significant in FTLD, a hypotheses that could be pursued with more detailed structural or functional connectivity analyses.

The index of familiarity was associated with gray matter volume in the left parietal cortex, particularly the inferior parietal region. There has been recent interest in the role of the lateral parietal cortex in memory (for reviews, see Naghavi & Nyberg, 2005; Wagner, Shannon, Kahn, & Buckner, 2005), with evidence from functional neuroimaging data in support of a role for this region in both recollection and familiarity (for review, see Skinner & Fernandes). Densely amnesic patient K.C. can learn and retain the same paired associate stimuli as used in this study for up to 30 months in the absence of any recollection of the learning episode (Hayman, Macdonald, & Tulving, 1993). It is possible that the inferior parietal cortex (preserved in K.C.) may support non-conscious aspects of recognition memory. Accordingly, bilateral inferior parietal activation has been observed during encoding of items that are later recognized based on familiarity (Otten, 2006). The left inferior parietal lobe is also activated as a function of familiarity strength (Daselaar, Fleck, & Cabeza, 2006; Montaldi, Spencer, Roberts, & Mayes, 2006; Yonelinas, Otten, Shaw, & Rugg, 2005), although higher parietal activation has also been noted in association with familiarity (Wagner et al., 2005). On the other hand, “remember” responses were reduced among patients with focal lateral parietal lesions (mostly left-lateralized) tested with the same paradigm as used here (Davidson et al., submitted), which is in line with studies showing overlap between recollection and familiarity in inferior parietal areas (Montaldi, Spencer, Roberts, & Mayes, 2006; Wheeler & Buckner, 2004). These data underscore the complexity of the lateral parietal cortices' role in memory, especially when viewed across patient etiologies or experimental platforms (i.e., lesion, functional neuroimaging).

Source recall and “remember” responses have been associated with prefrontal cortical function (Janowsky et al., 1989; Rauchs et al., in press; Skinner & Fernandes, 2007; Wheeler & Stuss, 2003). In our sample of patients inter-individual variability in prefrontal gray matter volume was not related to these measures, notwithstanding substantial prefrontal gray matter volume

reduction. Contrary to our findings, Simons and colleagues (Simons et al., 2002) reported an association between source recall and prefrontal, but not temporal function in FTLD. However, this conclusion was drawn from small samples of patients using qualitatively rated measures of MTL integrity. Prefrontal function was assessed indirectly through measures of executive functioning. In the present study, sample-specific effects, such as stage of disease or degree of medial temporal atrophy, cannot be ruled out as contributing to the findings. Similarly, aspects of our task may draw more heavily upon associative mechanisms of the MTL than the retrieval processing mechanisms of the prefrontal cortex. We considered the possibility that our frontal ROI was too heterogeneous. However, no significant relationships emerged in exploratory investigation of the six prefrontal subregions per hemisphere as defined in our original SABRE protocol (Dade et al., 2004). In a separate study of lifespan autobiographical memory retrieval using an overlapping sample of patients (McKinnon et al., submitted), reductions in episodic autobiographical recollection were, as in this study, associated with left temporal regions and not prefrontal regions. Episodic recollection is a multimodal process reliant on interactivity between limbic and distributed neocortical regions, including the prefrontal cortex. Under the assumption that the temporal lobes, particularly the medial temporal regions, act as bottleneck structures in episodic recollection, performance in patients with combined frontal and temporal damage will more strongly covary with the integrity of temporal regions than with that of other neocortical regions. Finally, although we did not observe any structural brain-behavior correlations in frontal areas, we did not assess the functional integrity of these regions. Thus functional changes, possibly reflecting alternations in frontal-posterior networks, cannot be ruled out as contributing to patients' altered memory function.

In summary, even though memory impairment is not a typical characteristic of FTLD, it appears that two episodic features of memory that have been minimally explored in this disorder, source recall and re-experiencing, are distorted in addition to cued recall and recognition. These effects were consistent across two test delay intervals spanning 24 hours. Episodic impairment was associated with gray matter volume loss in left posterior regions, especially the medial temporal lobe, whereas familiarity was associated with left inferior parietal gray matter volume. Establishing the nature of episodic memory impairment in FTLD is informative not only about patients' memory function, but also about self-awareness in this disease.

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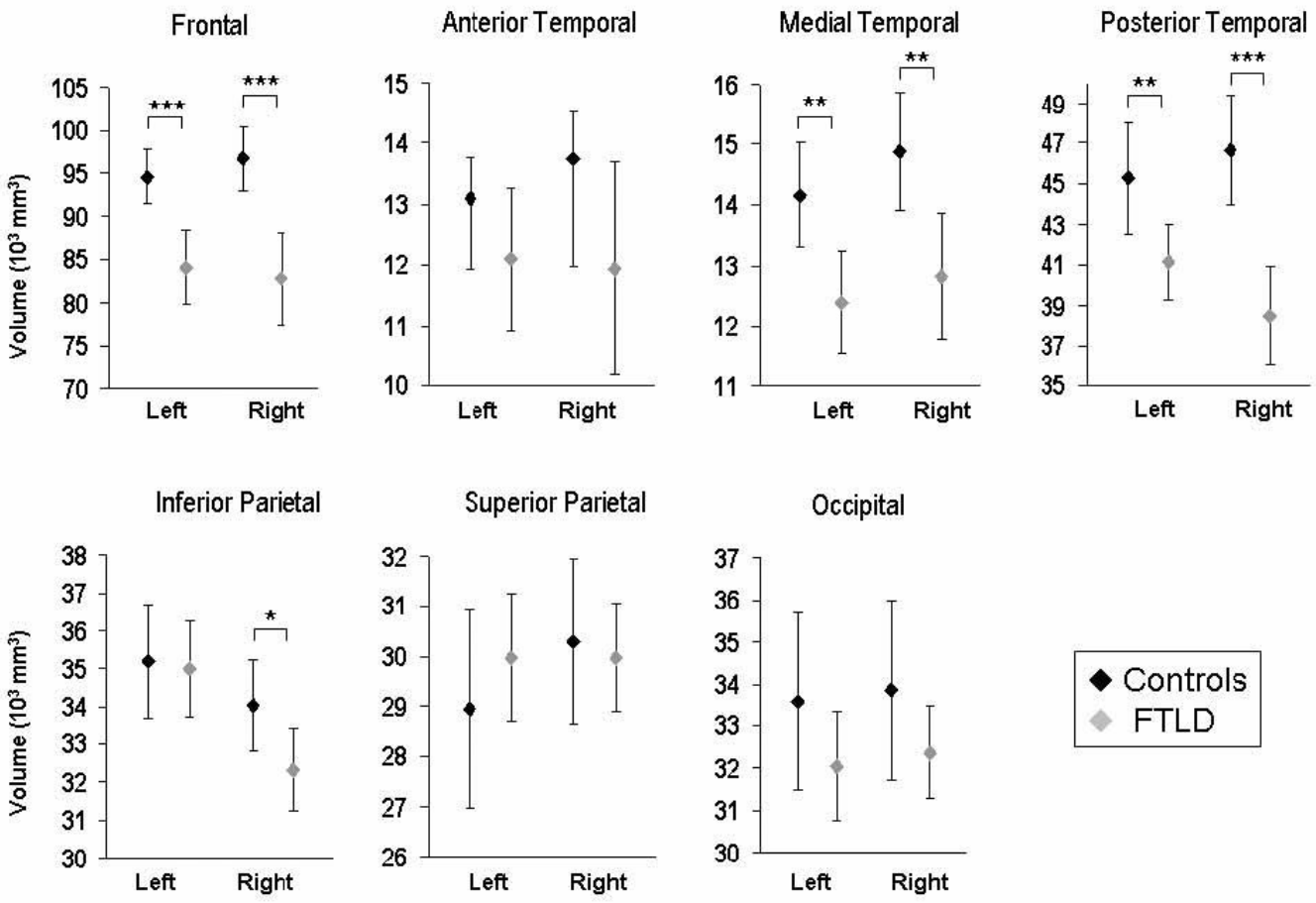


**Fig. 1.**

Regional gray matter volumes (means and 95% confidence intervals) in comparison subjects and patients, revealing smaller volumes in patients in all frontal and temporal areas except the anterior temporal lobe, and in the left inferior parietal lobe. Regional boundaries are depicted in Figure 2, and described in detail in Dade et al. (2004). FTLD different from comparison subjects at *<.05; **<.01; ***≤.001

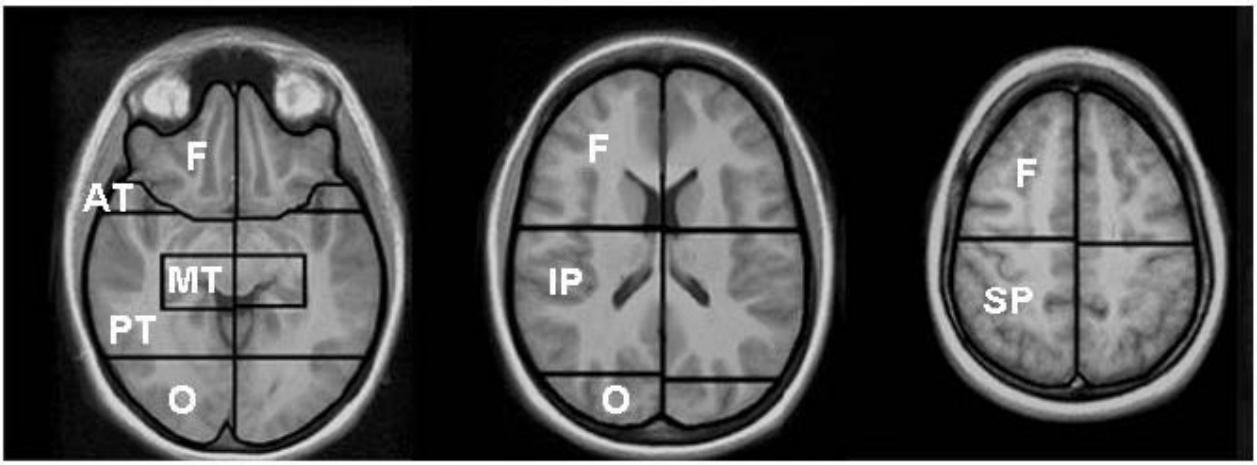


**Fig. 2.**

Parcellation of brain regions assessed in this study according to a modification of the Semi-Automated Brain Region Extraction (SABRE)(Dade et al., 2004; Kovacevic et al., 2002) method. Abbreviations: F = Frontal lobe, AT=anterior temporal lobe; MT=medial temporal lobe; PT=posterior temporal lobe; IP=inferior parietal lobe; SP=superior parietal lobe; O = Occipital lobe.

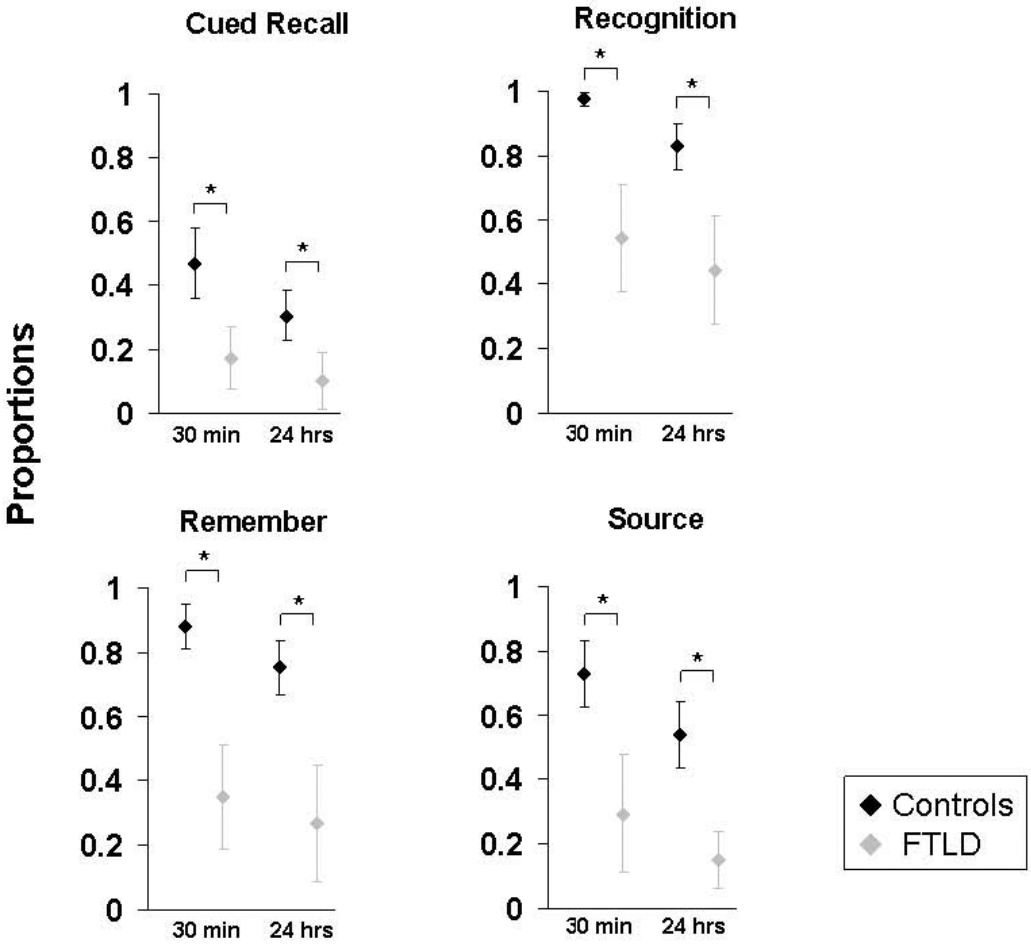


**Fig. 3.**

Memory performance (mean proportions and 95% confidence intervals) in comparison subjects and patients at 30 min and 24hrs, with patients being significantly worse in all measures, in spite of an equivalent rate of forgetting to comparison subjects. All measures except Cued Recall were adjusted by subtracting false alarms from hits. *FTLD different from comparison subjects at $p \leq .001$

**Table 1**

Demographic (means and S.D.'s) and neuropsychological characteristics (medians, 1st and 3rd quartiles) of patients and comparison subjects.

| | FTLD (n=18) | Comparison subjects (n=14) |
|---|---|---|
| Demographics | | |
| Age | 57.4 (6.5) | 57.5 (7.4) |
| Sex (% men) | 47 | 36 |
| Education | 16.0 (3.5) | 16.9 (2.9) |
| MMSE | 27.5 (1.8) | n.a. |
| Diagnosis (yrs)[1] | 3.2 (1.2) | n.a. |
| Cognitive scores | | |
| WCST, p.e.[2] | 41 (30; 61)** | 18 (9; 24) |
| Trails A, sec[3] | 40 (30; 57)** | 22 (21; 31) |
| Trails B, sec[3] | 111 (70; 165)* | 62 (57; 90) |
| FAS, total[2] | 22 (14; 34)** | 44 (33; 63) |
| PPT, total[4] | 50 (44; 51) | n.a. |

Abbreviations: MMSE=Mini-Mental State Examination; WCST=Wisconsin Card Sorting Test; p.e. = perseverative errors (tabulated according to the methods described in (Stuss et al., 2000); FAS= phonemic word list generation; PPT=Pyramids and Palm Trees Test.

[1] Estimated time since onset of symptoms. Data were unavailable for 1 FTLD patient.

[2] WCST and FAS data were unavailable 4 FTLD patients.

[3] Trails A, B data were unavailable for one comparison subject.

[4] PPT data were unavailable for 8 FTLD patients..

* p<.05 different from comparison subjects, tested with Mann-Whitney U

** p<.005 different from comparison subjects, tested with Mann-Whitney U

**Table 2**

Correlations between gray matter volumes and memory performance according to lobe (left) and subregions in the left temporal and parietal lobe (right) in FTLD patients.

| | Overall lobar correlations | | | | | | | | Local correlations | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | LF | RF | LT | RT | LP | RP | LO | RO | LAT | LMT | LPT | LIP | LSP |
| **30 min delay** | | | | | | | | | | | | | |
| Recognition | .08 | .02 | **.64**$^{**}$ | .36 | .41 | .44 | **.59**$^{*}$ | .08 | .30 | **.67**$^{**}$ | **.68**$^{**}$ | .10 | .41 |
| Hits | .37 | .13 | .13 | .10 | .18 | .23 | .11 | −.03 | .00 | −.12 | .01 | .25 | .12 |
| False alarms | .11 | .03 | .04 | .08 | .07 | .40 | −.13 | −.33 | .09 | −.12 | .07 | .43 | −.34 |
| Remember° | .14 | .10 | .32 | .13 | .23 | .04 | .34 | −.24 | .01 | **.75**$^{**}$ | .38 | .33 | −.10 |
| Adj. Know° | .19 | −.33 | .59 | .06 | **.73**$^{*}$ | .28 | .17 | −.07 | .21 | .11 | .49 | **.68**$^{*}$ | .47 |
| Source | .11 | −.03 | **.61**$^{*}$ | .10 | .46 | .32 | **.65**$^{**}$ | .04 | .19 | **.67**$^{**}$ | **.59**$^{*}$ | .45 | .04 |
| **24 hrs delay** | | | | | | | | | | | | | |
| Recognition | −.18 | −.06 | **.55**$^{*}$ | .36 | −.08 | .20 | .38 | .08 | .34 | **.65**$^{*}$ | **.60**$^{*}$ | .11 | .32 |
| Hits | .33 | .03 | .27 | −.04 | .24 | .37 | .40 | −.16 | .14 | .13 | .20 | .04 | .28 |
| False alarms | −.03 | −.20 | .04 | −.08 | .12 | .37 | −.25 | **−.57**$^{*}$ | .12 | −.11 | .24 | −.25 | .34 |
| Remember° | .19 | .20 | .24 | .09 | .06 | −.40 | .34 | −.07 | −.25 | .57 | .37 | .20 | −.40 |
| Adj. Know° | −.09 | −.37 | .29 | −.09 | **.64**$^{*}$ | .29 | .07 | −.28 | .08 | −.09 | .29 | .43 | .52 |
| Source | .06 | .15 | .54 | .19 | .26 | .22 | .21 | −.07 | .29 | **.83**$^{**}$ | .55 | .32 | −.20 |

*Note*. Because of the non-normal nature of the data, Spearman non-parametric correlations were used.

All memory measures were adjusted by subtracting false alarms from hits.

Left side abbreviations: L=left; R=right; F=frontal; T=temporal; P=parietal; O=occipital. Right side abbreviations: LAT=left anterior temporal; LMT=left medial temporal; LPT=left posterior temporal; LIP=left inferior parietal; LSP=left superior parietal.

$^{*}$ p<.05

$^{**}$ p<.01

° Two subjects were excluded that did not grasp the R/K distinction. “Know” responses were adjusted according to the independence assumption to yield and estimate of familiarity (Yonelinas & Jacoby, 1995; see methods)