Autobiographical Memory and Patterns of Brain Atrophy in Frontotemporal Lobar Degeneration

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Abstract

■ Autobiographical memory paradigms have been increasingly used to study the behavioral and neuroanatomical correlates of human remote memory. Although there are numerous functional neuroimaging studies on this topic, relatively few studies of patient samples exist, with heterogeneity of results owing to methodological variability. In this study, frontotemporal lobar degeneration (FTLD), a form of dementia affecting regions crucial to autobiographical memory, was used as a model of autobiographical memory loss. We emphasized the separation of episodic (recollection of specific event, perceptual, and mental state information) from semantic (factual information unspecific in time and place) autobiographical memory, derived from a reliable method for scoring transcribed autobiographical protocols, the Autobiographical Interview [Levine, B., Svoboda, E., Hay, J., Winocur, G., & Moscovitch, M. Aging and autobiographical memory: Dissociating episodic from semantic retrieval. *Psychology and Aging, 17,* 677–689, 2002]. Patients with the frontotemporal dementia (FTD) and mixed frontotemporal and semantic dementia (FTD/SD) variants of FTLD were impaired at reconstructing episodically rich autobiographical memories across the lifespan, with FTD/SD patients generating an excess of generic semantic autobiographical information. Patients with progressive nonfluent aphasia were mildly impaired for episodic autobiographical memory, but this impairment was eliminated with the provision of structured cueing, likely reflecting relatively intact medial temporal lobe function, whereas the same cueing failed to bolster the FTD and FTD/SD patients' performance relative to that of matched comparison subjects. The pattern of episodic, but not semantic, autobiographical impairment was enhanced with disease progression on 1- to 2-year follow-up testing in a subset of patients, supplementing the cross-sectional evidence for specificity of episodic autobiographical impairment with longitudinal data. This behavioral pattern covaried with volume loss in a distributed left-lateralized posterior network centered on the temporal lobe, consistent with evidence from other patient and functional neuroimaging studies of autobiographical memory. Frontal lobe volumes, however, did not significantly contribute to this network, suggesting that frontal contributions to autobiographical episodic memory may be more complex than previously appreciated. ■

INTRODUCTION

Frontotemporal lobar degeneration (FTLD) is a common form of dementia and a leading cause of early-onset dementia, along with Alzheimer's disease (Ratnavalli, Brayne, Dawson, & Hodges, 2002). Although everyday memory has been considered relatively spared in FTLD (Neary et al., 1998), there is evidence that this disease affects performance on laboratory tests of memory (Simons, Graham, & Hodges, 2002). An emerging literature suggests that this deficit extends to the autobiographical domain (Piolino et al., 2003; Nestor, Graham, Bozeat, Simons, & Hodges, 2002; Hodges & Gurd, 1994).

FTLD is uniquely positioned as a model for testing hypotheses concerning autobiographical memory. Generally speaking, memory impairments in FTLD follow from degeneration of the frontal and temporal cortex associated with this disease. The temporal lobes, particularly the medial temporal regions, are classically associated with mnemonic operations. The prefrontal cortex is involved in higher-order mnemonic retrieval operations (Fletcher & Henson, 2001; Stuss & Benson, 1986) including strategic retrieval and monitoring within autobiographical memory (McKinnon, Svoboda, & Levine, 2007; Conway & Pleydell-Pearce, 2000). More specifically, FTLD comprises three distinct subtypes: frontotemporal dementia (FTD), progressive nonfluent aphasia (PNFA), and semantic dementia (SD) (Neary et al., 1998). FTD is associated with unilateral or bilateral prefrontal degeneration with personality change, social comportment deficits, and impaired self-regulation. SD involves unilateral or bilateral degeneration of the anterior and inferior temporal cortex accompanied by a central semantic deficit and behavioral changes. PNFA involves left inferior

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prefrontal degeneration and insidious and progressive language abnormality, including reduced phrase length, agrammatism, and effortful and halting speech. Contrasting performance across these subtypes can illuminate the contribution of damage centered on different brain regions to autobiographical memory.

In contrast to standard laboratory testing of memory, assessment of autobiographical memory is affected by lack of control over encoding and the inherently personal nature of the memoranda. Autobiographical assessment methods, therefore, are more heterogeneous than laboratory memory tasks, confounding interpretation of autobiographical memory findings across studies. In the present study, we used advanced assessment methods to assess autobiographical memory in patients with FTLD. These allowed us to assess several hypotheses concerning the behavioral and neuroanatomical substrates of autobiographical memory.

The first hypothesis concerned the degree to which episodic versus semantic autobiographical memory is affected in FTLD. Episodic autobiographical memory refers to recollection for events specific in time and place, with accompanying mental and emotional information, including a subjective sense of personal continuity across time (Tulving, 2002). This latter element is of particular relevance in FTLD where behavioral disturbances suggest altered self-awareness (Miller et al., 2001). Semantic autobiographical memory refers to recall of personal information not specific in time or place, such as where one was born, or repeated events, such as yearly vacations at a particular location. Generally speaking, studies have shown that patients with FTLD are impaired on measures of episodic autobiographical memory while they are preserved on semantic autobiographical memory (Matuszewski et al., 2006; Piolino et al., 2003; Hodges & Gurd, 1994).

Although episodic and semantic autobiographical memory occur simultaneously during natural discourse (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002), instruments for the assessment of autobiographical memory assume that memories can be wholly classified as either ''episodic'' or ''semantic.'' Thus, these two elements of autobiographical memory are assessed separately using interviews unmatched for content, difficulty, and psychometric characteristics (e.g., Kopelman, Wilson, & Baddeley, 1990) or tallied by sorting memories into episodic or semantic categories (Piolino et al., 2007). Episodic memory is further quantified on the basis of ordinal scale ratings that encompass both generic (e.g., repeated or not temporally specific) and specific autobiographical events that are subject to contamination by semantic processing.

In this study, we used the Autobiographical Interview (Levine et al., 2002), which assumes that episodic and semantic memory reflect distinct information processing streams that can be simultaneously active during narrative recall. This instrument yields independent, parametric estimates of episodic and semantic autobiographical memory derived from within each memory at the time of scoring rather than with separate interviews at the time of testing or by wholesale assignment of recalled narrative events to episodic or semantic categories. This measure has proven useful in dissociating episodic from semantic memory in the elderly (St.-Jacques & Levine, 2007; Levine et al., 2002), in patients with medial temporal lobe damage (Rosenbaum et al., 2008; Addis, Moscovitch, & McAndrews, 2007; Steinvorth, Levine, & Corkin, 2005), and in patients with semantic dementia (McKinnon, Black, Miller, Moscovitch, & Levine, 2006). By quantifying independent categories of autobiographical details, the Autobiographical Interview permits the assessment of profiles of autobiographical content, including elevation of nonepisodic details extraneous to the central event as documented in aging (Levine et al., 2002), semantic dementia (McKinnon et al., 2006), and frontal dysfunction (Levine, 2004). Based on these studies, we predicted an elevation of nonepisodic autobiographical content (semantic and other extraneous details) in FTLD, in addition to a decrement of episodic content. As FTLD is a progressive disorder, we assessed this pattern not just cross-sectionally, but longitudinally, by retesting patients after 1 to 2 years. Decline in episodic, but not semantic, autobiographical memory over time would suggest that the former is specifically affected by progressive volume loss in regions affected by FTLD.

The second issue addressed in this study is the role of retrieval support in autobiographical memory. Retrieval support bolsters autobiographical memory recall in healthy adults (Levine et al., 2002) and in patients with FTLD (McKinnon et al., 2006; Moss, Kopelman, Cappelletti, De Mornay Davies, & Jaldow, 2003; Hodges & Gurd, 1994), possibly by compensating for executive deficits affecting strategic search and retrieval of remote information (e.g., Craik & McDowd, 1987). Methods of evoking autobiographical memories vary widely in the amount of retrieval support they provide, confounding comparison of findings across studies. In this study, we assessed autobiographical memory under both low and high levels of retrieval support to allow direct comparison of the effects of this manipulation. We also examined the relationship of neuropsychological test performance to autobiographical retrieval at these different levels of retrieval support.

To our knowledge, there are no studies of autobiographical memory in PNFA. Patients with PNFA compose an interesting comparison group as this condition is less likely to be associated with disturbances of the self such as loss of insight and social conduct disorder than are FTD or SD (Rosen et al., 2006). Given the relationship between self-related information processing and autobiographical memory (Tulving, 2002; Conway & Pleydell-Pearce, 2000), it was predicted that PNFA patients would show preservation of episodic autobiographical memory relative to the other FTLD patients. On the other hand, the left inferior frontal region affected in PNFA is part

of a core autobiographical network in the functional neuroimaging literature (Svoboda, McKinnon, & Levine, 2006). Given this region's association with strategic retrieval operations (Simons & Spiers, 2003), deficits in PNFA patients, if present, should be limited to the low retrieval support condition that places greater demands on strategic retrieval.

Finally, we investigated individual differences in autobiographical memory performance as a factor of regional atrophy quantified from patients' high-resolution structural magnetic resonance imaging (MRI) scans concurrent to testing. Such data can provide important adjunctive information to functional neuroimaging studies by identifying regions necessary for autobiographical memory, as opposed to those that are simply engaged by it. Few studies have assessed quantified cortical damage effects on remote autobiographical memory, with results implicating regions across the cortical mantle (e.g., McKinnon et al., 2007; Eustache et al., 2004; Kopelman et al., 2003; Eslinger, 1998; Rubin & Greenberg, 1998), including medial temporal lobe structures (Rosenbaum et al., 2008; Moscovitch et al., 2005), although this is disputed (Squire & Bayley, 2007).

In FTLD, the integrity of the medial temporal lobes has been related to mnemonic processing (Söderlund, Black, Miller, Freedman, & Levine, 2008; Simons, Graham, et al., 2002; Simons, Verfaellie, et al., 2002). Very general evidence in support of a role for the frontal lobes has been derived from neuropsychological test data and diagnostic grouping (Matuszewski et al., 2006; Simons, Verfaellie, et al., 2002). In a recent study of frontal-variant FTD patients, florodeoxyglucose (FDG) uptake in the left orbito-frontal and anterior temporal cortex was correlated with autobiographical specificity (Piolino et al., 2007).

In the present study, we used multivariate statistical analyses of quantitated regional volumes derived from structural MRI taken concurrent to testing to identify patterns of regional volume loss across the brain associated with indices of episodic and semantic autobiographical memory in FTLD. In line with evidence supporting a role for the medial temporal lobes and associated structures in episodic autobiographical memory retrieval (Svoboda et al., 2006; Moscovitch et al., 2005), we predicted that volume loss in these regions would be strongly and specifically associated with lifespan retrieval of episodic autobiographical details. We also predicted distributed involvement of other regions (particularly frontal and posterior regions given the strategic and visuospatial elements of autobiographical memory).

METHODS

Subjects

FTLD Patients

Patients were recruited from dementia clinics at Baycrest Centre and Sunnybrook Health Sciences Centre in Toronto and at the University of California at San Francisco Medical Center. FTLD diagnosis followed the consensus criteria set out by Neary et al. (1998), which delineates FTD, PNFA , and SD. Patients with significant aphasia, neglect, or other focal neurological disturbance or severe cognitive or physical disability that interfered with testing were excluded. PNFA patients were in the early stages of disease and, therefore, had sufficient residual speech capacity to participate.

We tested 22 patients. Eight met criteria for FTD and five met criteria for PNFA. Nine patients met criteria for both FTD and SD (Snowden, Neary, & Mann, 2007) and are therefore designated as FTD/SD. Two patients meeting criteria for SD have been reported as part of a separate study (McKinnon et al., 2006). To date, 10 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 as tauopathy in other cases (McKhann et al., 2001). There were no significant differences across groups for age, education, duration of illness, or Mini Mental State Examination (see Table 1). Seventeen of our patients (6 FTD, 7 FTD/SD, and 4 PNFA) received high-resolution structural MRI scans as part of the testing protocol. The background characteristics of these patients were similar to the full sample. Follow-up testing was conducted on eight patients (5 FTD, 1 FTD/SD, and 2 PNFA) 1 to 2 years after initial assessment. Seven of these eight patients received repeat MRI scans at the same time as their follow-up testing.

Comparison Groups

A comparison group for behavioral assessment was composed of 16 healthy adults with no history of neurological or psychiatric illness and free from medication known to affect cognitive functioning. They were matched to the FTLD patients in terms of age (M = 58, SD = 9.2) and education (M = 16.4, SD = 3.0). A separate scanning comparison group (n = 10), also matched to the FTLD patients in terms of age (M = 63, SD = 10.5) and education (M = 17, SD = 3.6), was used for the purposes of assessing volume reductions in our FTLD sample and for constructing an MRI template (see below). These subjects were not tested behaviorally and they were not included with the patients in the brain–behavior analyses. Exclusion criteria included prior neurological or systemic disease that could affect cognition, prior psychiatric hospitalization or treatment with psychiatric medication for greater than 6 weeks, prior significant alcohol/drug abuse, and significant developmental disabilities.

Table 1. Characteristics of FTLD Patients and Comparison Subjects

	Comparison	*FTD*	*FTD/SD*	*PNFA*	*Follow-up FTLD*[a]
n	16 (5 M)	8 (5 M)	9 (2 M)	5 (3 M)	8 (5 M)
Age[b]	58 (9.2)	59 (6.0)	59 (9.4)	66 (10.4)	61 (6.2)
Education (years)	16.4 (3.0)	15.5 (4.0)	16.5 (3.0)	17.3 (3.0)	15.1 (3.8)
Duration of illness (years)	N/A	3.0 (2–10)	4.0 (2–6)	2.5 (1–5)	3.0 (2–7)
MMSE	N/A	25.9 (3.3)	28.0 (1.9)	27.8 (1.5)	24.4 (3.4)

MMSE = Mini Mental State Examination.

[a]These patients comprise five FTD, one FTD/SD, and two PNFA patients that were retested 1 to 2 years after their initial assessment.

[b]Statistics are means and standard deviations, except for duration of illness, where median and range are reported.

Procedure

The Autobiographical Interview

Event selection and instructions. The Autobiographical Interview was administered as described by Levine et al. (2002), with slight modifications. Subjects were asked to provide a detailed description of a significant personal event from each of five life periods: early childhood (to age 11 years), teenage years (ages 11–17 years), early adulthood (ages 18–35 years), middle age (35–55 years), and the past year. Subjects were instructed to recall an event that occurred at a specific time and place. In cases where subjects were unable to generate a specific event independently, a list of typical life events (e.g., losing something important) was presented to assist in event retrieval.

Conditions of retrieval support. In order to examine facilitative effects of retrieval support on memory, we manipulated the level of structure available to subjects across three conditions: recall, general probe, and specific probe (Levine et al., 2002). At recall, subjects spoke about the event extemporaneously without any interruption from the examiner, continuing until it was evident that they had reached a natural ending point. After an event was recalled, general probes were used to clarify instructions and to encourage greater recall of details. If general probing did not elicit a specific event, the subject was given the option of selecting a different event that was more likely to result in successful recall. General probes were limited to nonspecific statements or repetitions of the instructions. At the specific probe phase, a structured interview was administered that was designed to elicit additional contextual details. In order to prevent the specific probe process from contaminating recall of subsequent memories, specific probing was administered after all five events were recounted under the recall and general probe conditions. Subjects' descriptions of the selected events were audio-recorded for later transcription and analysis.

Following probing, subjects were asked to rate the following on a 6-point scale: importance (both at the time of the event and at the time of testing), visualization, experienced emotion at the time of the event, and frequency of reactivation (thinking or talking about the event). These ratings were unavailable for five FTD patients. There were no significant group differences in ratings; these data will not be discussed further.

Text segmentation and categorization. Following transcription, each memory was segmented into informational bits or details. Each detail was then classified according to the procedure outlined in Levine et al. (2002). Briefly, details were defined as ''internal'' or episodic and assigned to one of five categories (event, place, time, perceptual, and emotion/thought) if they were related directly to the main event described, were specific to time and place, and conveyed a sense of episodic re-experiencing. Otherwise, details were considered ''external,'' and consisted of semantic facts (factual information or extended events that did not require recollection of a specific time and place), autobiographical events tangential or unrelated to the main event, repetitions, or other metacognitive statements (''I can't remember.'') or editorializing (''It was the best of times.'').

Details were tallied for each category and summed to form internal and external composites, which were the main variables of interest in the present study. Scoring was done separately for each condition (recall, general probe, specific probe), but scores were analyzed cumulatively across levels of recall with general probe and specific probe details added to details generated from the prior condition.

To avoid bias in scoring, subjects' memories were placed in a common pool and scored at random by seven experienced scorers who had achieved high interrater reliability (see Levine et al., 2002) and who were blind to group.

Neuropsychological test results are presented in Table 2. All neuropsychological tests showed a significant effect of group (Fs ranged from 4.1 to 11.3, ps ranged from $<.001$ to $<.05$). The pattern of group differences was consistent with expectation given the literature on neuropsychological differences across subgroups of patients with FTLD. Patients with FTD were impaired on tests of executive functioning and inventories of behavioral change due to frontal damage while being preserved on

Table 2. Neuropsychological Test Performance[a]

	FTD (n = 8)	*FTD/SD (n = 9)*	*PNFA (n = 5)*	*Comparison (n = 16)*
Trail Making Test, Part A[b]	11.4 (6.7)	5.4 (3.6)**	9.6 (3.7)	12.3 (2.2)
Trail Making Test, Part B	9.3 (2.4)	5 (2.5)*	9.8 (4.9)	10.4 (3.5)
Phonemic word list generation (FAS)	29 (11)*	24 (11)*	25 (13)*	46 (16)
WCST[c] perseverations	59 (48)*	49 (34)	26 (14)	21 (10)
WCST categories	2.8 (4.0)*	2.2 (2.5)*	6.2 (2.5)	6.9 (3.1)
Dysexecutive questionnaire[d]	23 (20)*	28 (22)*	−4.4 (10.7)***	−3.2 (7.8)
Frontal Behavior Inventory[e]	43 (10.8)	32 (13)	11 (1.8)***	N/A
Pyramids and Palm Trees[f]	47.3 (57.2)	39 (12)****	51 (1)	N/A
Boston Naming Test[g]	50 (9)	31 (14.5)****	54 (7)	N/A

[a]Means and standard deviations are reported.

[b]Four patients received the Trail Making Test from the Delis–Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001). The remaining patients and comparison subjects received the standard Trail Making Test (Army Individual Test Battery, 1944). All scores were converted to standard scores using the MOANS normative data (Ivnik, 1996) or the D-KEFS manual. Trails A: Control, $n = 15$. Trails B, FTD, $n = 7$.

[c]Wisconsin Card Sorting Test (Milner, 1963).

[d]Burgess et al., 1996. Other score minus self score (higher scores indicate greater executive problems with less insight).

[e]Frontal Behavior Inventory (Kertesz, Davidson, & Fox, 1997).

[f]Pyramids and Palm Trees—picture version. FTD/SD: $n = 4$.

[g]Boston Naming Test—when necessary, scores were prorated from 15- or 30-item version. FTD, $n = 5$. FTD/SD, $n = 6$. PNFA, $n = 4$.

*Significantly different from comparison group.

**Significantly different from comparison and FTD groups.

***Significantly different from FTD and FTD/SD groups.

****Significantly different from FTD and PNFA.

tasks of semantic retrieval and naming. FTD/SD patients were also impaired on executive tasks and behavioral inventories, with additional evidence of semantic and lexical retrieval deficits (although these data are limited by low *n*) and speeded information processing deficits. PNFA patients show low verbal fluency and preservation on executive tasks and behavioral inventories.

Statistical Analyses

FTLD patients' data for certain Autobiographical Interview indices were markedly positively skewed. This skewness could not be corrected through transformation. We therefore applied a Winsorization procedure to the data by which outliers (i.e., scores exceeding 1.5× the intraquartile range above the third quartile or below the first quartile) were rescaled to be ±2.5 *SD* from the mean (calculated excluding outliers), allowing the maintenance of extreme observations without unduly influencing statistical estimates or sample sizes.

We next examined detail composite production across each of the five time periods tested using a 4 × 2 × 5 mixed-design analysis of variance that treated group (FTD, FTD/SD, PNFA, and comparison) as a between-subjects factor and detail composite (internal, external) and lifetime period (early childhood, teenage years, early adulthood, middle age and past year) as within-subjects factors. There were no interactions involving the internal and external composites when these were incorporated into the lifetime period analyses. We found main effects of lifetime period reflecting a recency effect (i.e., greater recall from the past year; Rubin & Schulkind, 1997). As this effect did not interact with group, it will not be discussed further (for a similar finding, see Piolino et al., 2003).

A second analysis examined performance on the category-specific measures of autobiographical retrieval using a 4 × 9 mixed-design analysis of variance that treated group (FTD, FTD/SD, PNFA, and comparison) as a between-subjects factor and category (internal event, time, place, perceptual and emotion/thought details; external event, other, and semantic details and repetitions) as a within-subjects variable. To examine interval change in Autobiographical Interview performance among patients retested after 1 to 2 years, we used a 2 × 2 repeated measures design treating detail type (internal, external) and test session (Session 1, Session 2) as within-subjects factors.

Tukey's Honestly Significant Difference post hoc test was used for follow-up pairwise comparisons of between-subjects variables. Where required, the Greenhouse–Geisser correction was applied to effects involving repeated measures. All analyses were performed with alpha set at .05.

Correlations between neuropsychological assessment test scores and performance on the internal and external detail composites were assessed nonparametrically (Spearman's ρ [rho]) due to nonnormality of the data.

MRI Scan Acquisition

Patients and comparison subjects were scanned on 1.5-T scanners (Toronto: Signa, General Electric Medical Systems, Waukesha, WI; San Francisco: Magnetom VISION system, Siemens, Iselin, NJ) with similar in-plane resolution. The Toronto protocol involved axial acquisitions using spoiled gradient-echo T1-weighted 3-D volume imaging (TR/TE/flip angle = 35 msec/5 msec/35°, 1.0 NEX, acquisition matrix = 256 * 256; 124 slices, slice thickness = 1.3 mm; FOV = 22 cm), as well as spin echo, proton density, and T2-weighted images (TR/TE = 3000 msec/30 msec, 80 msec, 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 msec, 51 contiguous 3 mm axial slices covering the entire brain and angulated −10° from the AC–PC line). Volumetric T1-weighted gradient-echo MRI were achieved using the MP-RAGE sequence (TR/TE/TI = 10/4/300 msec, 15° flip angle, 1.5 mm 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 nonlinear average of T1-weighted images from the age- and education-matched scanning comparison group using a modification of an algorithm previously developed for mouse brain MRI (Kovacevic et al., 2005). Each subject's T1-weighted image was then 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 nonlinear registration of T1-weighted images to the template image (Collins & Evans, 1997). Removal of nonbrain tissue from the image incorporated thresholding information derived from the PD- and T2-weighted images, facilitating the distinction between the dura mater and the gray matter (Kovacevic et al., 2002). This is contrasted to methods of brain extraction on the basis of the T1-weighted image that emphasize the cortical surface, inconsistently preserving subdural cerebrospinal fluid (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).

A modified Semi-Automated Brain Region Extraction (SABRE) (Dade et al., 2004) method was then used to create ROIs on the template brain. This method involves manual identification of 15 landmarks 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; see Figure 1). Nonlinear deformation field matching of the template to individual images was used to customize these regions to fit each subject's brain anatomy (as opposed to transforming images to fit the template, which can distort interindividual topographical variability). Regional gray matter, white matter, and CSF 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.

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 interindividual topographical variability. They have thus been successfully applied across a variety of patient samples (e.g., Levine et al., 2008; Bocti, Rockel, Roy, Gao, & Black, 2006; Gilboa et al., 2005; Feinstein et al., 2004).

Image Analysis

Partial least squares (PLS) is a flexible multivariate technique that has been extensively applied to brain imaging data (McIntosh, Chau, & Protzner, 2004; McIntosh, Bookstein, Haxby, & Grady, 1996). In general terms, PLS is a multivariate analysis technique for relating two sets of variables to each other. In the present application, it was used to identify patients' patterns of volume loss related to measures derived from the Autobiographical Interview. It is unbiased in that there are no a priori assumptions about structure–function correlations. Because PLS considers the brain as a whole, it is well suited to the detection of distributed patterns of volume loss that covary with test performance.

In the first step of the PLS analyses, correlations were computed between the brain imaging data (i.e., regional gray matter, white matter, and CSF volumes) for the full sample of patients (without respect to diagnosis) and Autobiographical Interview category scores (i.e., five internal detail categories and four external detail catego-

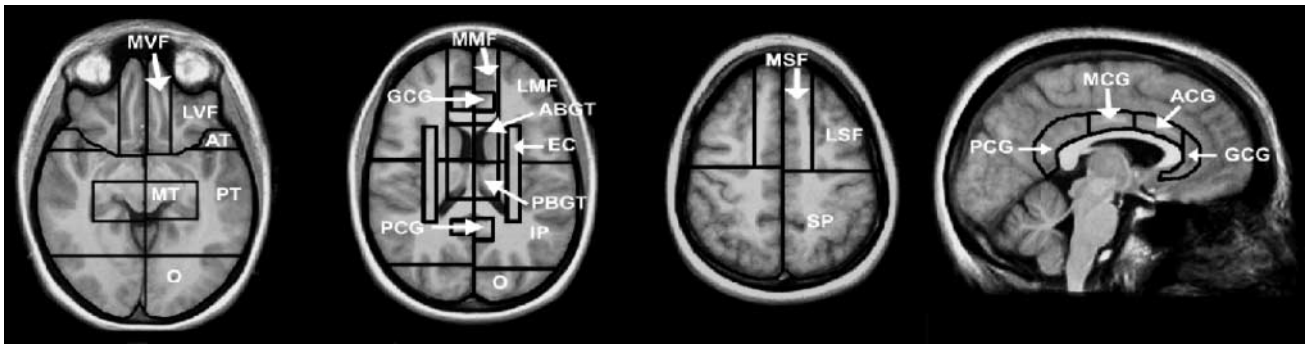

Figure 1. SABRE regional cortical divisions in axial and sagittal views. LSF = lateral superior frontal; MSF = medial superior frontal; LMF = lateral middle frontal; MMF = medial middle frontal; LVF = lateral ventral frontal; MVF = medial ventral frontal; GCG = genual cingulate gyrus; ACG = anterior cingulate; MCG = middle cingulate gyrus; PCG = posterior cingulate gyrus/retrosplenial; AT = anterior temporal; MT = medial temporal; PT = posterior temporal; O = occipital; ABGT = anterior basal ganglia/thalamus; PBGT = posterior basal ganglia/thalamus; EC = external capsule/corona radiata; IP = inferior parietal; SP = superior parietal.

ries) for both recall and specific probe, collapsed across time period. The goal of this analysis was to assess brain–behavior correlations in FTLD by treating quantified regional brain atrophy as an independent variable, rather than diagnosis, which is an imprecise proxy for regional brain changes.

Singular value decomposition was then applied to the correlation matrix to identify latent variables [LVs] that indicated optimal relations between patterns of regional brain volume loss and test performance. Saliences (similar to factor loadings in factor analyses) reflected the contribution of individual brain volumes and behavioral measures to the LV (McIntosh et al., 1996, 2004). Multiplication of each region's salience with its volume and summing over all volumes gives a ''brain score'' for each patient on a given LV that indicates the degree to which the pattern of volumetric changes identified by the LV is expressed in each patient. Similarly, each patient's contribution to the behavioral aspect of the LV (''behavior score'') is derived by multiplying the salience for each test by the patient's test score. The relationship between the two aspects of the LV (patterns of regional brain volume loss and test performance) can be examined by plotting the brain scores against the behavior scores on a patient-by-patient basis, allowing us to examine the contribution of diagnosis to the pattern of brain–behavior relationships (see Figure 5C).

The statistical significance of each LV was assessed by 1500 permutation tests (Edgington, 1980), in which the observations are randomly reordered without replacement to calculate the probability of each LV having occurred by chance. The stability of each brain region's salience contribution to the LV was determined through bootstrap resampling (subjects were resampled 500 times; McIntosh et al., 1996; Wasserman & Bockenholt, 1989). Brain regions in the singular images were considered reliable if they had a ratio of salience to standard error (hereafter referred to as the boostrap ratio), interpreted similar to a *Z*-score (McIntosh et al., 2004; Efron & Tibshirani, 1986) greater than 3, corresponding to 99.9% confidence limits. The bootstrap procedure yields 99% confidence intervals around the correlations between test scores and the pattern of regional brain volume changes. Because image-wide statistical assessment is done in a single analytic step, no correction for multiple comparisons across brain regions is required.

For the purposes of characterizing the degree of brain atrophy in our patient sample, the 19 SABRE regions per hemisphere were reduced to eight (ventral frontal, dorsal frontal, anterior, medial, and posterior temporal, inferior parietal, superior parietal, and occipital). Reduction in parenchymal volumes (gray + white matter) were assessed via planned comparisons between the FTD, FTD/SD, and PNFA subgroups and the 10 matched scanning comparison subjects. Interval change between the first and second scans for the seven rescanned FTLD patients was also assessed via planned comparisons.

RESULTS

Patterns of Brain Atrophy in FTLD Patients

FTLD patients showed a characteristic pattern of significantly reduced parenchymal volumes maximal over the frontal and temporal lobes. For illustration, the left dorsolateral frontal and posterior temporal volumes are displayed in Figure 2. The FTD group had volume loss over the dorsolateral frontal regions bilaterally, left ($p < .009$) greater than right ($p < .05$), as well as significant volume loss in the right posterior temporal region ($p < .005$). The FTD/SD group had marked volume loss over anterior, posterior, and medial temporal lobe sectors (ps ranging from .0001 to .02) as well as all frontal sectors (ps ranging from .001 to .007). Volume loss in PNFA patients was more restricted, maximal in the left dorsolateral region ($p < .001$), but also in the right posterior temporal and right inferior parietal regions (ps < .05). It should be noted that only four PNFA patients

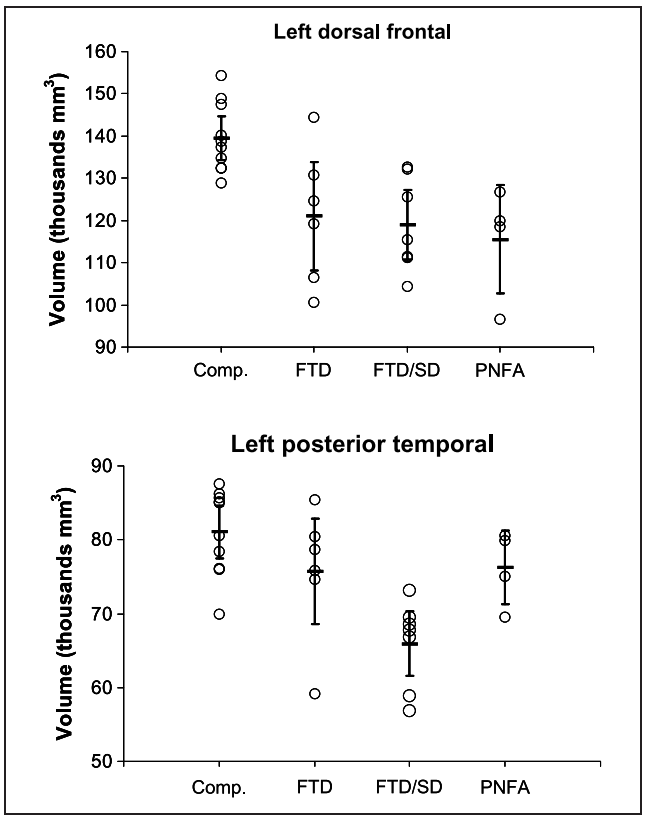

Figure 2. Regional parenchymal volumes in FTLD patients and comparison subjects in left dorsolateral prefrontal and in left posterior temporal regions. Comp. = comparison subjects. Vertical lines indicate 95% confidence intervals. Group means are indicated by bold horizontal lines. Relative to comparison subjects, patients in all groups showed significant decline in left dorsolateral prefrontal volume, whereas only the FTD/SD subgroup had significant volume loss in the left posterior temporal region.

were scanned, one of whom was left-handed with primarily right-sided degeneration, suggesting crossed lateralization of language. Interval change for the seven rescanned FTLD patients was statistically significant over all regions of interest (*p*s ranged from .0005 to .03).

Autobiographical Memory

Recall

A significant interaction between detail type and group [$F(3, 132) = 14.18, p < .01$], during the free recall phase of the Autobiographical Interview, was due to reduced production of internal details in the FTD, FTD/SD and PNFA groups relative to comparison subjects (*p*s < .001, .001, and .05 for the FTD, FTD/SD, and PNFA groups, respectively); there were no group differences for external details. The main effect of group was not significant ($p > .05$), indicating that the patients' reduction in internal details was not attributable to an overall reduction in protocol length among the patient groups.

Analysis of individual detail categories provided more information concerning group differences in the elements of autobiographical memory. A significant Detail category × Group interaction [$F(24, 272) = 7.03, p < .001$] was due to lower production of internal details in the FTD and the FTD/SD groups than in comparison subjects for all internal detail categories (*p*s < .001–.05) except for time, which was uniquely impaired in the FTD/SD group ($p < .05$), and for place, which was uniquely impaired in the FTD group ($p < .05$). The FTD/SD group produced more semantic details than did the comparison group ($p < .05$). Significant differences between the PNFA patients and comparison subjects were limited to the internal perceptual and thought/emotion categories (*p*s < .05).

Specific Probe

Following specific probing, the significant Detail type × Group interaction remained [$F(3, 128) = 8.38, p < .001$], with greater production of internal details by the comparison group as compared to the FTD and FTD/SD groups ($p < .01$; see Figure 3). Whereas the PNFA group produced significantly fewer internal details in the recall condition than did comparison subjects, after specific probing, the PNFA group's production of internal details differed neither from the comparison subjects nor from the FTD group. There were again no group differences for external details. The main effect of group was not significant, indicating that all groups generated protocols of similar length.

The Detail category × Group interaction [$F(24, 272) = 4.49, p < .001$] remained significant at specific probe. Whereas the FTD/SD group produced fewer internal details than did the comparison group for all internal detail categories (*p*s < .001–.01) except for time, where this group was unimpaired, the FTD group was impaired relative to the comparison group for the perceptual and thought/emotion internal categories only (*p*s < .01).

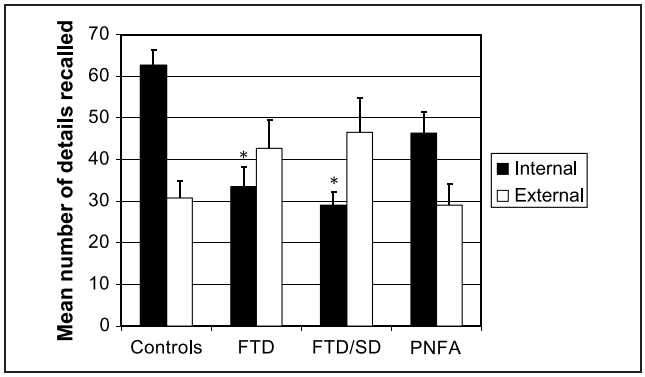

Figure 3. Mean number of internal (episodic) and external (nonepisodic) details generated by comparison subjects, FTD, FTD/SD, PNFA, on the Autobiographical Interview (specific probe phase). FTD ($n = 8$) and FTD/SD ($n = 9$) patients generated fewer internal details and, in the case of FTD/SD, more external (semantic) details, whereas PNFA patients ($n = 5$) were not significantly different from comparison subjects. *Significantly different from comparison subjects, $p < .01$.

The FTD/SD group continued to produce more semantic details than did the comparison group ($p < .05$). Significant differences between the PNFA patients and comparison subjects were limited to the thought/emotion category ($p < .01$).

One-year Follow-up Testing

Among the eight patients retested 1 year later, there was a significant Test session × Detail type interaction at specific probe [$F(1, 7) = 8.77, p < .05$] that was due to a reduction of internal ($p < .005$) details across the test sessions (see Figure 4). External details increased across test sessions, although this difference fell short of statistical significance due to high variability. There were no significant main effects involving test session or detail type at recall or specific probe. The Test session × Detail type interaction at recall was not significant.

Relation of Autobiographical Memory to Neuropsychological Test Scores

Both FTLD patients and comparison subjects showed a positive relation between performance on the phonemic word list generation and scores on the internal detail composite at recall [$\rho(21, 16) = 0.54$ and 0.64, for patients and comparison subjects, respectively, ps $< .02$ and .01]. There was a correlation between Trail Making, Part A and internal details at recall in FTLD patients [$\rho(21) = 0.45, p < .05$]. There were no significant correlations between neuropsychological test performance and internal details at specific probe. External details at specific probe were negatively correlated with Trail Making, Part B in patients [$\rho(20) = -0.47, p < .05$]; there were no other significant correlations between neuropsychological tests and the external detail composites.

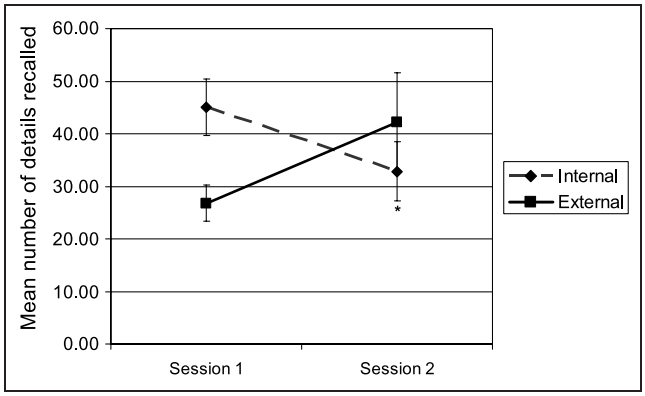

Figure 4. Effects of FTLD ($n = 8$) progression on internal (episodic) and external (nonepisodic) autobiographical details from the Autobiographical Interview (specific probe phase). *Significantly different from Session 1, $p < .005$. Error bars represent standard error of the mean.

Relation to Regional Brain Atrophy

The PLS analysis allowed us to examine the pattern of regional volume loss associated with patients' impaired performance on the Autobiographical Interview. One LV was identified ($p = .05$) by permutation test. This LV accounted for 41% of the covariance between test scores and regional volumes. The pattern of Autobiographical Interview scores associated with this LV indicated a separation of episodic from nonepisodic details concentrated at specific probe (see Figure 5A). Specifically, increased event, time, place, and perceptual details at specific probe and event details at recall were related to increased parenchymal volumes across the identified brain regions, whereas increased semantic details and repetitions at specific probe were related to decreased volumes.

Figure 5B depicts significant negative bootstrap ratios for CSF (i.e., indicating increased parenchymal volume positively associated with internal details and negatively associated with external details) with foci in the left posterior and anterior temporal lobes and the medial temporal lobes bilaterally. The left inferior parietal lobe, the left posterior cingulate/retrosplenial region, and the bilateral posterior basal ganglia regions also emerged as significant in this analysis. There were additional significant positive bootstrap ratios for gray and white matter (not displayed in the figure) that mirrored those depicted in Figure 5: left posterior temporal and left occipital gray and white matter, bilateral posterior basal ganglia white matter, and left anterior basal ganglia white matter. Significant negative bootstrap ratios were observed for the left anterior cingulate gyrus and bilateral internal capsule/corona radiata gray matter regions.

In Figure 5C, the brain scores (reflecting each patient's contribution to the pattern of volume loss identified by the LV) and the behavior scores (reflecting each patient's contribution to the pattern of test scores identified by the LV) are plotted against each other. Although the sample is small and there is overlap across the diagnostic groups, it can be seen that the lower ends of the behavioral and brain score distributions are mainly occupied by patients in the FTD/SD group, whereas FTD and PNFA patients occupy the upper end.

DISCUSSION

Lifespan autobiographical episodic recall was impaired in patients with FTLD relative to comparison subjects, whereas semantic autobiographical memory was spared or elevated in patients with FTLD. Narrative episodic specificity was associated with the integrity of a left-lateralized posterior network centered on the temporal lobe. The specificity of the episodic relative to semantic impairment was further supported by longitudinal data. When the medial temporal lobes are spared, as in PNFA, retrieval support is effective in increasing autobiographical recall to normal levels. Contrary to expectation, we

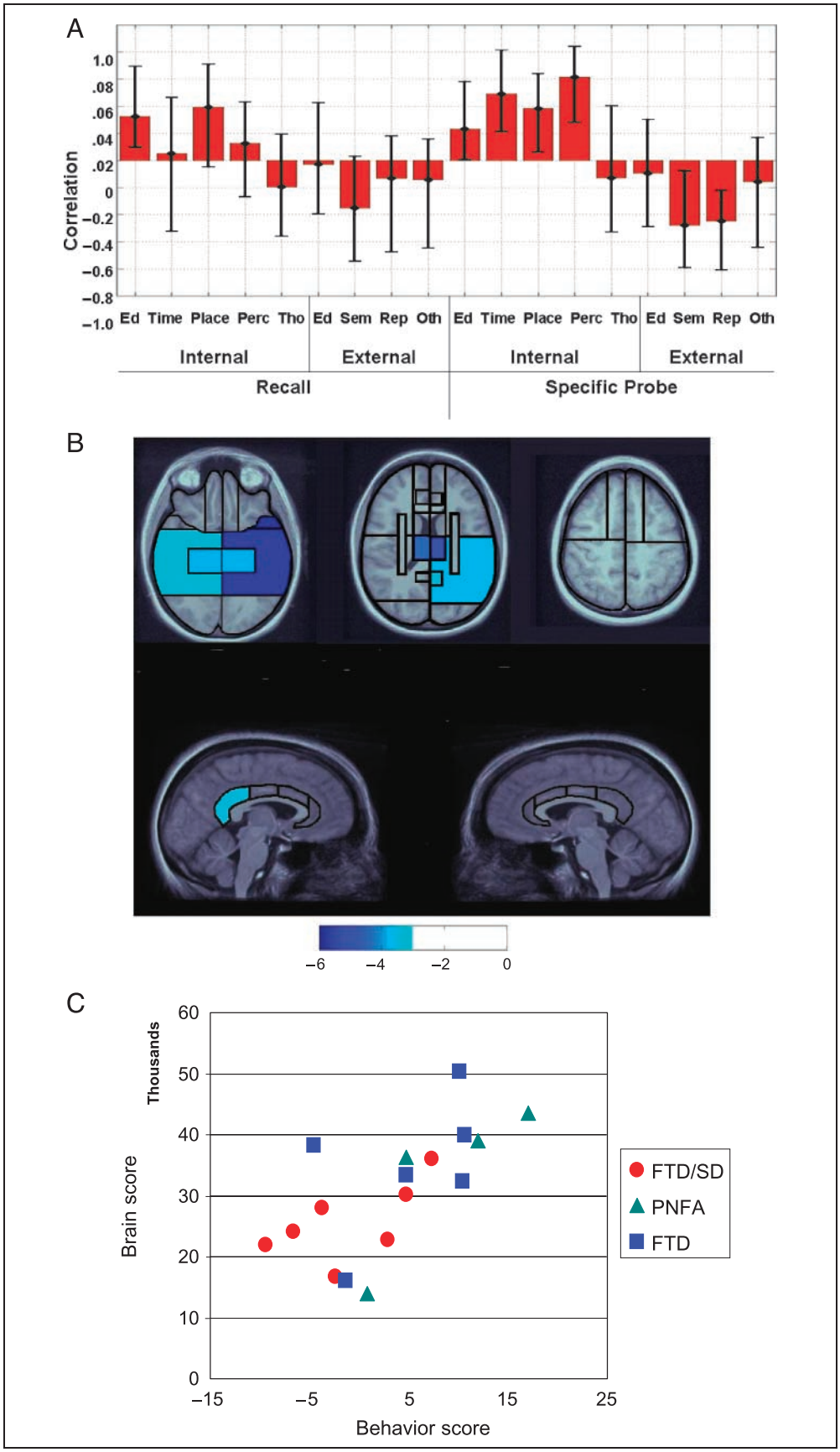

Figure 5. LV from PLS analysis indicating the association of performance on the Autobiographical Interview with patterns of regional brain volume changes. (A) The pattern of Autobiographical Interview measures associated with the LV, expressed as correlations between test scores and the pattern of brain volume changes depicted in B. Error bars represent 99% confidence intervals. Measures with error bars crossing the horizontal axis did not significantly contribute to the LV. This panel shows that internal event details at recall and internal event, place, time, and perceptual details at specific probe were positively correlated with the pattern of brain volume changes depicted in B, whereas external semantic and repetition details at the specific probe phase were negatively correlated with the pattern of brain volume changes. Ed = event details (note that event details can be either internal or external, depending on whether they concern the main event); Perc = perceptual details; Tho = thought details; Sem = semantic details; Rep = repetitions; Oth = other details (e.g., metacognitive or editorializing). (B) The pattern of regional CSF volume (expressed as color-coded bootstrap ratios) associated with the pattern of test scores depicted in the top panel. The color bar indicates the coding scheme according to the level of the bootstrap ratio, interpreted similar to a *Z*-score. Lower values (darker blue) correspond to brain volume decreases (i.e., less CSF, greater parenchyma) associated with higher internal details and lower external details. Images were thresholded at a bootstrap ratio of 3.0, corresponding approximately to $p < .001$. Axial images are displayed in radiological convention (right hemisphere displayed on left side of image). The right and left cingulate volumes are displayed on the right and left side of the images, respectively. Not pictured: Bootstrap ratios for gray and white matter (see text). (C) A scatterplot of individual patients' brain scores (indicating the degree to which the pattern of atrophy identified by the LV is expressed in each patient) and behavior scores (indicating the degree to which the pattern of test scores identified by the LV is expressed in each patient), with each patient color-coded according to diagnosis, allowing for the appreciation of the how FTLD diagnosis contributes to the brain–behavior relationships.

found no significant relation of frontal lobe volumes to autobiographical memory retrieval. Overall, these findings support a behavioral and neuroanatomical distinction between episodic and semantic autobiographical memory. They further suggest that, contrary to standard diagnostic criteria, memory function can be significantly affected in FTLD.

Dissociating Episodic and Semantic Autobiographical Memory across FTLD Diagnoses

Prior results indicating impaired episodic autobiographical memory and spared semantic autobiographical memory in FTLD (Piolino et al., 2003; Nestor et al., 2002) are based on the use of ordinal ratings that can be elevated by inclusion of nonepisodic details that are related to the event, but do not require recreation of temporal, spatial, and other contextual details. One approach to this issue is to apply a binary transformation to the ordinal data that divides those receiving the highest ratings (considered ''strictly episodic'') from those receiving lower ratings (Matuszewski et al., 2006; Piolino et al., 2003). Our approach is to extract estimates of episodic and semantic elements from within each memory, under the assumption that such elements occur simultaneously to varying degrees within all naturalistic autobiographical narratives and that these can be independently affected by normal or pathological intersubject variables (e.g., aging, brain disease; Rosenbaum et al., 2008; Addis et al., 2007; Steinvorth et al., 2005; Levine, 2004; Levine et al., 2002) or by intrasubject manipulations (e.g., retrieval support, emotional state; St.-Jacques & Levine, 2007; Levine et al., 2002).

The PNFA group was less impaired than the FTD and FTD/SD groups. Indeed, retrieval support selectively bolstered recall of episodic autobiographical details in patients with PNFA such that they were not statistically differentiated from comparison subjects. Mild episodic autobiographical deficits in patients with PNFA are therefore likely attributable to strategic retrieval or speech initiation deficits that are ameliorated by retrieval support. Patients with FTD and FTD/SD remained impaired relative to comparison subjects after retrieval support, although effects across individual categories of episodic details were more reliable among those with FTD/SD. As described in more detail below, this may be attributable to the constraining effects of medial temporal lobe damage on episodic autobiographical recall. These results cannot be attributed to reduced speech output, as there were no effects of overall detail production across groups.

Patterns of spared and impaired autobiographical memory across these groups are further clarified by consideration of nonepisodic (external) autobiographical details. Although there was no overall effect on external details, detail category analyses revealed that semantic autobiographical details were uniquely elevated in the FTD/SD group, indicating that these patients produce an excess of generic autobiographical information in addition to reduced richness of happenings, spatial references, perceptual information, and mental states.

Patients with PNFA are distinguished from patients with FTD by a relative preservation of insight and social and personal conduct (Neary et al., 1998), an observation confirmed by these patients' normal scores on inventories of behavioral and social cognitive changes. Although deficits in these areas are not core to the diagnosis of SD in its original formulation, there is evidence that behavioral features in SD and FTD significantly overlap (Rosen et al., 2006; Bozeat, Gregory, Ralph, & Hodges, 2000). Our findings are consistent with the notion that self-referential processing is fundamental to the capacity for episodic autobiographical memory (Tulving, 2002; Conway & Pleydell-Pearce, 2000), with both processes spared in PNFA relative to FTD and SD.

It is acknowledged that interpretation of results may be limited by low power as there were only five patients in the PNFA groups. Yet these patients were differentiated from the FTD and FTD/SD groups not just by degree, but by their pattern of distribution of details across internal and external categories, which paralleled that of the comparison group. Although there were no significant group differences for disease duration, PNFA patients may have tested at an earlier stage of disease progression as those with significant aphasia were excluded. We directly assessed the effects of disease progression by retesting patients after 1 to 2 years, where the pattern of reduced episodic but not semantic autobiographical memory was enhanced, reinforcing the specificity of episodic autobiographical memory loss in FTLD. We did not have sufficient data to differentiate disease progression effects according to diagnosis. Given evidence that differences across FTLD diagnostic entities blur with disease progression (Kertesz, McMonagle, Blair, Davidson, & Munoz, 2005), it is likely that the autobiographical profile in late PNFA is similar to that of FTD and SD.

Relation of Autobiographical Memory Performance to Patterns of Regional Volume Loss

For the purposes of analyzing the effects of diagnosis, we sought to define groups with distinct clinical syndromes. In our brain–behavior analysis, we directly assessed the effects of individual differences in patterns of brain atrophy across clinical diagnoses, rather than inferring lesion location from diagnosis. The dissociation between episodic and semantic autobiographical memory was further reinforced by the brain–behavior analyses. Critically, the patterns of regional atrophy that emerged in relation to this dissociation were not specified in a priori planned contrasts (as is typically done in brain–behavior analyses, for example, by contrasting groups with presumed focal patterns of damage), but

rather from unrestricted multivariate analyses of brain–behavior correlations.

Regional volumes in a distributed network over the temporal lobes, posterior subcortical regions, and left inferior parietal and occipital regions were positively related to four out of five indices of episodic autobiographical memory at specific probe, as well as one (event details) at recall. Volumes in these same regions were negatively related to semantic details and repetitions at specific probe. Thus, in FTLD, specificity and richness of narrative production of lifespan autobiographical memory are related to the integrity of a left-lateralized posterior network centered on the temporal lobes.

Our findings are consistent with other patient and functional neuroimaging studies emphasizing the diverse mnemonic, attentional, and multimodal sensory processes that enable autobiographical re-experiencing (Svoboda et al., 2006; Kopelman et al., 2003). In interpreting the brain behavior analysis, we emphasize CSF volumes (i.e., the inverse of parenchymal volume). Gray and white matter volume paralleled the CSF effects, although not all regions identified in the CSF emerged as significant in the gray and white matter analyses, and some regions (left occipital lobe, left anterior basal ganglia) emerged in gray and white matter analyses, but not CSF analyses. Although these were consistent with the overall CSF pattern, the left anterior cingulate and internal capsule/corona radiata gray matter showed a relationship opposite to the direction of the other regions (i.e., negatively correlated with internal details, positively correlated with external details). As these regions have relatively small volumes (e.g., mean gray matter volume for the left anterior cingulate gyrus: 1777 mm^3 vs. 41,166 mm^3 for the left posterior temporal lobe), they may be relatively unstable and will not be interpreted further.

Right and left medial temporal lobe volumes were related to autobiographical memory specificity. Our medial temporal lobe region included the hippocampus and surrounding structures, regarded as critical for the binding of features required for recall of contextual details (Eichenbaum, 2000), a distinction that holds within autobiographical memory (Spiers, Maguire, & Burgess, 2001; Kapur, 1999; Cermak, 1985). The dependence of episodic autobiographical memory on the medial temporal lobes is reinforced by recent studies of patients with focal damage in these regions and selective impairment on episodic details as assessed by the Autobiographical Interview (Rosenbaum et al., 2008; Addis et al., 2007; Steinvorth et al., 2005; but see Bright et al., 2006; Kirwan, Bayley, Galvan, & Squire, 2008; and Squire & Bayley, 2007, for different results), as well as functional neuroimaging data (see also Svoboda et al., 2006; Moscovitch et al., 2005).

The left posterior cingulate/retrosplenial region was also significantly related to autobiographical memory specificity. This region is connected to the hippocampus and the prefrontal cortex (Morris, Pandya, & Petrides, 1999; Rosene & Van Hoesen, 1977), facilitating integration of mnemonic and higher level cognitive processing. It is also directly connected to multiple thalamic nuclei (Morris, Petrides, & Pandya, 1999) including the anterior thalamus (Vogt, Pandya, & Rosene, 1987) that is part of a midline diencephalic system involved in episodic memory (Aggleton & Brown, 1999). Damage to this region, which is frequently activated in functional neuroimaging studies of autobiographical memory (Svoboda et al., 2006), can cause retrograde amnesia (Valenstein et al., 1987).

The left anterior and posterior temporal regions were strongly associated with episodic autobiographical memory retrieval, along with the left inferior parietal region. These regions are also strongly associated with autobiographical memory in functional neuroimaging studies (Svoboda et al., 2006) due to retrieval of specific factual information (anterior temporal cortex), semantic processing (posterior temporal cortex), and visuospatial processing (temporo-parietal junction). Occipital involvement (derived from analyses of gray and white matter) is consistent with the importance of visual processes in recollection (Rubin & Greenberg, 1998). The left-lateralization of neocortical activation associated with autobiographical memory and the present findings are inconsistent with evidence of asymmetric right lateral temporal lobe involvement in episodic autobiographical memory (Gilboa et al., 2005; Eustache et al., 2004; Kopelman et al., 2003; Eslinger, 1998; for exception, see Piolino et al., 2007). Our findings cannot be explained by asymmetric damage in our patients, as the left and right temporal regions were similarly affected. As an alternative account, it is noted that our findings were concentrated at the specific probe phase as contrasted to prior studies that used the autobiographical memory interview (AMI) (or variants thereof) that is more comparable to procedures in our recall phase. Conversely, AMI probing of semantic autobiographical memory, which is highly structured, has been related to left temporal volumes (Gilboa et al., 2005; Eslinger, 1998). Thus, the left-lateralized findings may indicate lack of access to queried specific autobiographical details. Our patients with compromised ability to retrieve such details produced an excess of nonspecific semantic autobiographical details, reflecting compensation, disinhibition, and impaired monitoring of mnemonic output. The semantic autobiographical details elevated in association with left posterior pathology are not equivalent to the central semantic concepts affected by temporal lobe damage in SD. Rather, they reflect autobiographical information not specific in time and place that can be preserved in association with left lateral temporal damage (Westmacott & Moscovitch, 2003; Snowden, Griffiths, & Neary, 1994).

The regions related to autobiographical memory performance composed only part of the overall pattern of volume loss in our patients, which included the significant frontal lobe changes. Given the established role

of the prefrontal cortex in autobiographical memory (McKinnon et al., 2007; Svoboda et al., 2006; Kopelman et al., 2003), it is surprising these regions did not emerge as related to behavior in our analysis. SABRE-defined frontal volumes also were not related to autobiographical memory performance in patients with Alzheimer's disease (Gilboa et al., 2005). On the other hand, left orbito-frontal FDG uptake was related to autobiographical memory performance in patients with frontal-variant FTD (Piolino et al., 2007; for a related study in Alzheimer patients, see Eustache et al., 2004), a discrepancy attributable to interstudy differences in patient selection, assessment methods, and imaging platform. Although performance on neuropsychological tests of executive functioning has been related to autobiographical memory performance in FTLD (Matuszewski et al., 2006), we found that speeded neuropsychological tests (phonemic word list generation and Trail Making, Part A) were related to episodic autobiographical memory, but not a widely used untimed test of executive functioning, the Wisconsin Card Sorting Test. These correlations were limited to the free recall phase of the Autobiographical Interview. These findings suggest a relation between lexical semantic retrieval and generalized cognitive functioning and strategic autobiographical memory retrieval, perhaps due to the cognitive demands involved in cue specification at recall, whereas the structured cueing at the specific probe phase lessens the demands on these processes. At specific probe, the negative relationship between Trail Making, Part B and external details suggests that an excess of nonepisodic autobiographical information may be related to higher-level attentional deficits, especially among FTD/SD patients, who performed poorly on Trail Making, Part B and had significantly elevated semantic details.

In another study using an overlapping sample of FTLD patients (Söderlund et al., 2008), performance on laboratory tasks of episodic memory, including source memory and remember/know judgments, was associated with the integrity of the left temporal lobe and not the frontal lobes. These findings suggest that although retrieval can be reliably associated with temporal lobe damage in FTLD, the functional localization of advanced states of mnemonic consciousness may be more distributed, without a specific mapping to prefrontal regions, at least in FTLD, although functional changes in frontal regions, possibly reflecting alternations in frontal–posterior networks, cannot be ruled out as contributing to patients' altered autobiographical memory function.

As noted above, the brain–behavior relationships were most strongly evident at the specific probe phase, where prefrontally mediated executive-retrieval mechanisms might be less in demand (Matuszewski et al., 2006). This may reflect the fact that, in the context of significant temporal lobe damage limiting access to episodic autobiographical information, prefrontal function does not contribute to autobiographical retrieval, even with retrieval support (Rosenbaum, McKinnon, Levine, & Moscovitch, 2004; Kopelman et al., 2003). This also may explain why patients with PNFA, with less medial temporal lobe damage, benefited from retrieval support, whereas those with FTD/SD did not.

Conclusion

Autobiographical memory has recently received increasing attention by cognitive neuroscientists interested in human remote memory processes. Although it is clear that autobiographical memory is multifactorial, with an accordingly distributed functional neuroanatomy, the delineation of specific brain–behavior relationships has been elusive, likely owing to significant heterogeneity in behavioral measures, imaging methods, and neuropsychological populations.

In this study, FTLD, a form of presenile dementia affecting key regions in the autobiographical memory network, was used as a model for autobiographical memory impairment. With the Autobiographical Interview, we localized this impairment to episodic autobiographical memory in both cross-sectional and longitudinal analyses. Contrasting FTLD subtypes further specified patterns of altered autobiographical memory. Despite their mild speech abnormalities, PNFA patients were the least impaired and were unique among subgroups in their capacity to benefit from retrieval support. FTD/SD patients were the most impaired, failed to benefit from retrieval support, and generated an excess of semantic autobiographical details. FTD patients occupied a middle position, impaired episodic, but not semantic autobiographical memory, and a failure to benefit from retrieval support. The identified pattern of impaired episodic but not semantic autobiographical memory was related to volume loss in a distributed network over the temporal lobes, posterior subcortical regions, and left inferior parietal and occipital regions. The capacity of patients with PNFA to benefit from specific cueing may relate to these patients' relative sparing of the medial temporal regions. The lack of relation between frontal lobe volumes and autobiographical memory performance suggests that this brain–behavior correlation may be more complex than previously recognized.

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