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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 h 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 h, 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

1. 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.

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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 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 h). 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 h).

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.

2. Methods

2.1. Participants

2.1.1. 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. (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,

Table 1
Demographic (means and S.D.'s) and neuropsychological characteristics (medians, first and third 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 (years)[a]	3.2 (1.2)	n.a.
Cognitive scores		
WCST, p.e.[b]	41 (30; 61)[**]	18 (9; 24)
Trails A, sec[c]	40 (30; 57)[**]	22 (21; 31)
Trails B, sec[c]	111 (70; 165)[*]	62 (57; 90)
FAS, total[b]	22 (14; 34)[**]	44 (33; 63)
PPT, total[d]	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.

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

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

[c] Trails A and B data were unavailable for 1 comparison subject.

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

[*] $p < 0.05$ different from comparison subjects, tested with Mann–Whitney U.

[**] $p < 0.005$ different from comparison subjects, tested with Mann–Whitney U.