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Autobiographical memory in semantic dementia: Implications for theories of limbic-neocortical interaction in remote memory

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Abstract

We examined autobiographical memory performance in two patients with semantic dementia using a novel measure, the Autobiographical Interview [Levine, Svoboda, Hay, Winocur, & Moscovitch (2002). Aging and autobiographical memory: Dissociating episodic from semantic retrieval. *Psychology and Aging, 17*, 677–689], that is capable of dissociating episodic and personal semantic recall under varying levels of retrieval support. Earlier reports indicated that patients with semantic dementia demonstrate autobiographical episodic memory loss following a "reverse gradient" by which recent memories are preserved relative to remote memories. We found limited evidence for this pattern at conditions of low retrieval support. When structured probing was provided, patients' autobiographical memory performance was similar to that of controls. Retesting of one patient after 1 year indicated that retrieval support was insufficient to bolster performance following progressive prefrontal volume loss, as documented with quantified structural neuroimaging. These findings are discussed in relation to theories of limbic-neocortical interaction in autobiographical memory.

Keywords: Episodic; Semantic; Temporal neocortex; Frontal lobes

The roles of limbic (hippocampal) and neocortical interactions in remote memory have been hotly debated in recent years. According to the "standard" model of memory consolidation, episodic memories become consolidated in temporal neocortex following a temporary period of storage in the hippocampus, after which the hippocampus is no longer required for storage or for retrieval of these memories (Lechner, Squire, & Byrne, 1999; Squire, Cohen, & Nadel, 1984). Support for this conclusion is drawn from experimental work confirming Ribot's (1882) observation that some amnesic patients show temporally-graded memory loss whereby consolidated memory for early life events is preserved relative to impaired memory for recent (unconsolidated) events (Bayley, Hopkins, & Squire, 2003; Scoville & Milner, 1957). In contrast to the standard model, Multiple Trace Theory (MTT; Moscovitch et al., 2005; Nadel & Moscovitch, 1997) holds that the hippocampus is involved in episodic memory recall in perpetuity. According to MTT, the hippocampus stores indices or pointers to neocortical memory representations. New traces are created each time a memory is reactivated. Older memories are less vulnerable to disruption than are recent memories because of their frequent re-instatement and multiply distributed traces.

Semantic dementia (SD) is a form of pre-senile dementia classified under the broader category of frontotemporal lobar degeneration (FTLD; Hodges & Miller, 2001; Neary et al., 1998). The behavioral presentation of SD includes marked semantic memory impairment (e.g., impaired confrontation naming), with evidence for relative preservation of episodic memory (Snowden, Griffiths, & Neary, 1994). This behavioral pattern has been linked to lateral temporal neocortical pathology, with the hippocampus and medial temporal regions relatively pre-

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served, although it is now accepted that significant hippocampal atrophy occurs in SD (Galton et al., 2001).

Research addressing temporal gradients in SD has yielded mixed results. Some studies have revealed disproportionate sparing of recall of episodic memories from the most recent 18-month to 2-year period (Graham & Hodges, 1997; Graham, Kropelnicki, Goldman, & Hodges, 2003; Nestor, Graham, Bozeat, Simons, & Hodges, 2002; Piolino, Belliard, Desgranges, Perron, & Eustace, 2003) with relative impairments emerging across the remaining time periods tested in these studies (some of which were as recent as 5 years past) in patients with SD. Notably, this reversal of the memory loss function reported in amnesic people (Graham & Hodges, 1997), namely relative sparing of recent memories, resembles the typical pattern observed in controls when performance is not at ceiling (Moscovitch & Nadel, 1999; Rubin and Wenzel, 1996), though the controls' loss may be more gradual than the step function often observed in SD. Other studies, however, have found sparing of episodic memory across the lifetime in SD, a pattern most obvious when structured or non-verbal cues (e.g., family photographs) are available to assist in retrieval, compensating for prefrontal cortical (PFC) dysfunction or for linguistic deficits, and revealing preserved episodic memory across the lifetime relative to controls (Moss, Kopelman, Cappelletti, De Mornay Davies, & Jaldow, 2003; Westmacott, Leach, Freedman, & Moscovitch, 2001, but see Graham et al., 2003).

One possible explanation for the conflicting findings is variance in methods used to assess autobiographical memory. Autobiographical memory consists of episodic elements that are recollections of experiences specific in time and place as well as semantic elements that are facts about the world and oneself. The most common method for dissociating episodic and semantic autobiographical memory, the Autobiographical Memory Interview (AMI; Kopelman, Wilson, & Baddeley, 1990), relies on separate interviews that are not matched for difficulty or content. Yet episodic and semantic autobiographical information are not separated in natural discourse; they occur in varying degrees within a single narrative (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002). Furthermore, the AMI and other instruments (Graham & Hodges, 1997; Piolino et al., 2003b) derive scores for episodic autobiographical memory using an ordinal scale that encompasses both generic and specific autobiographical events and is therefore subject to contamination by semantic autobiographical memory.

As stated above, the standard model predicts relative sparing of recent compared to remote episodic memory in SD (a reverse gradient in comparison to amnesic people), whereas MTT predicts equivalent sparing of episodic memory across time periods relative to controls, if the hippocampus is preserved. In the case of semantic memory, a reverse gradient, namely relative sparing of more recent semantic memories, is consistent with both theories, as both predict that temporal neocortical damage can affect remote semantic memories (albeit by different mechanisms; Nadel, Samsonovich, Ryan, & Moscovitch, 2000; Westmacott et al., 2001). To the extent that a putative measure of recent episodic autobiographical memory in SD is contaminated by semantic processes, a reverse gradient may occur due to the semantic contribution.

Yet another source of variance relates to patterns of parenchymal volume loss in SD. Patients with SD often have prefrontal cortical damage (Rosen et al., 2002a, 2002b) leading to speculation that autobiographical memory impairment in this disorder may be related to strategic retrieval deficits (Moscovitch & Nadel, 1999). Previous studies of autobiographical memory in SD have relied upon free (unstructured) recall, providing little or no compensation for PFC-mediated deficits in this population (Graham & Hodges, 1997; Graham et al., 2003; Nestor et al., 2002; Piolino et al., 2003a, 2003b). This may disproportionately affect remote memories, which may require more strategic effort to retrieve than recent memories (see Moss et al., 2003).

Methods that allow for separation of the episodic and semantic components of recall, and that include compensation for PFC-mediated retrieval deficits, should allow for more precise specification of medial temporal lobe (MTL) and temporal neocortical contributions to episodic recall in SD. The purpose of the present study was to examine patterns of autobiographical memory loss in SD using the Autobiographical Interview (AI; Levine et al., 2002; Rosenbaum, McKinnon, Levine, & Moscovitch, 2004; Steinvorth, Levine, & Corkin, 2005). This measure has several advantages over tests of autobiographical memory used previously with SD. The AI dissociates episodic from semantic elements of autobiographical memory within a single, transcribed autobiographical protocol at the time of scoring (rather than at the time of test administration, as in the AMI (Kopelman et al., 1990) using a reliable, text-based scoring system. The AI also examines autobiographical memory across the lifespan at different levels of retrieval support, allowing for the testing of hypotheses concerning strategic contributions to autobiographical memory.

We hypothesized that separation of episodic and semantic components of autobiographical recall and compensation for frontally-mediated retrieval deficits would eliminate the reverse gradient seen under free recall in other studies (Graham & Hodges, 1997; Graham et al., 2003; Nestor et al., 2002; Piolino et al., 2003a), and show unimpaired episodic autobiographical memory performance in our patients.

We administered the AI to two patients with SD, A.A. and B.B. The AI data are interpreted in the context of quantified regional neocortical and limbic volume loss derived from high resolution three-dimensional MRI. One of the patients, A.A., was tested at two intervals, allowing us to examine the effects of disease progression on AI performance.

1. Methods

1.1. Participants

We tested two semantic dementia patients: patient A.A., assessed in two testing sessions held 1 year apart, and patient B.B., assessed on one occasion.

Patient A.A., a right-handed female with 14 years of education, was 62 years old at the time of testing in 2001. Patient B.B., a right-handed female with 13 years education, was 67 years old at the time of testing. Both A.A.'s and B.B.'s most prominent impairments were in the domain of linguistic and semantic functioning, although they also showed evidence of executive dys-

Table 1
Neuropsychological test scores

Test	* Control (n=15 or 16)	A.A. Test 1	A.A. Test 2	B.B.
MMSE [a]	29(1)	18	10	25
WCST [b]				
Categories	7 (3.11)	2	0	2
Perseverative errors	21 (9.81)	53	124	52
Trail Making Test, Part A	27 (8.31)	55	74	36
Trail Making Test, Part B	88 (56.15)	200	249	62
Phonemic Fluency (F, A, S)	46 (16.11)	12	0	16
Semantic Fluency (animals) [c]	18.2(4.2)	3	2	4
Hopkins Verbal Learning Test - Revised [d]				
Recall - Learning	10 (1.41)	2		0
Recall - Total	25 (4.10)	4		9
Recall: 20-minute delay	9 (2.16)	0		0
Recognition	12 (0.63)	6		12
Rey-Osterrieth copy [e]	31.1(4.0)	29	34	36
Symbol-Digit Modality Test (Written) [f]	49 (11.03)	38	17	
Pyramids and Palm Trees				
Pictures (52) [g]	46.8	35	33	*37
Words (52) [g]	46.8	30	24	
Boston Naming Task [h]	N/A	4 (out of 30)	1 (out of 30)	3 (out of 15)
Neuropsychiatric Inventory [i]	0.43	23	34	

[a]Lezak (1995); [b]Stuss et al. (2000); [c]Tombaugh, Kozak, and Rees (1999); [d]Benedict, Schretlen, Groninger, and Brandt (1998); [e]Chiulli et al. (1989); [f]Smith (1978); [g]Howard and Patterson (1992); cut off for impairment (90th percentile); [h]Kaplan, Goodglass, and Weintraub (1983); [i]Cummings et al. (1994). *Local norms were used except where noted. Framed cells fall more than 2 SDs below control means; **administered approximately 1 year prior to test session.

function (see Table 1). Although there was evidence of impairment on word list learning, this likely reflects impaired semantic processes rather than a global anterograde amnesia as visual anterograde memory for a complex figure was not impaired.

1.1.1. Patterns of regional brain atrophy

Regional atrophy was quantified from patients' high-resolution, three-dimensional T1-weighted images (taken concurrent to testing) using a processing pipeline developed in our laboratories that includes extraction of brain from non-brain tissue, segmentation of tissue compartments, and reporting of regional volumes derived from a mask fit to each subject's brain (Dade et al., 2004; Kovacevic et al., 2002). Regional volumes of parenchyma in A.A. and B.B. were compared to those obtained for 10 neurologically-intact and age-matched control participants (mean age = 66.80 years, S.D. = 8.70 years; these were not the same participants that were used for the behavioral study).

Consistent with these patients' diagnosis of semantic dementia, volume loss was greatest over the temporal lobe region which includes the hippocampus, amygdala, parahippocampal, and entorhinal cortices. Loss was particularly evident in the anterior regions (see Table 2). Both patients had markedly reduced medial temporal lobe volume bilaterally, with the exception of A.A. at initial scanning, where only the left MTL showed significant volume loss (see Fig. 1). At initial scanning, A.A. had prefrontal atrophy in the left ventral region; analysis of her scan taken 1 year later indicated significant atrophy over the right ventral and left dorsal prefrontal regions, as well as increased temporal atrophy. Parietal and occipital volumes were not significantly different from controls, with the exception that atrophy encroached bilaterally on the inferior parietal regions of A.A. at re-scanning.

1.1.2. Control participants

Performance of the semantic dementia patients was compared to that of 16 neurologically-intact control participants matched in terms of age (M = 57.56, S.D. = 9.22) and education (M = 16.38, S.D. = 3.03). Patients and controls gave informed consent to be involved in the study, which was approved by our ethics committees.

Table 2
Regional brain volumes

		Controls *	AA				BB	
			Time 1		*Time 2*			
Region[a]	Side	Parenchyma	Parenchyma	Z-score	Parenchyma	Z-score	Parenchyma	Z-score
Dorsal frontal	R	141097 (9452)	136811	-0.45	122671	-1.95	129024	-1.28
	L	139546 (8289)	124140	-1.86	108835	-3.71	134111	-0.66
Ventral frontal	R	21294 (1759)	17933	-1.91	15220	-3.45	18748	-1.45
	L	19814 (1329)	15961	-2.90	13758	-4.56	18685	-0.85
Anterior temporal	R	19261 (1557)	12251	-4.50	8503	-6.91	9314	-6.39
	L	18345 (1268)	7761	-8.35	5696	-9.98	10634	-6.08
Medial temporal	R	20584 (1742)	17625	-1.70	14326	-3.59	12466	-4.66
	L	19499 (1735)	13594	-3.40	10318	-5.29	13005	-3.74
Posterior temporal	R	80728 (5963)	76358	-0.73	67291	-2.25	56978	-3.98
	L	81063 (5796)	65063	-2.76	55212	-4.46	66390	-2.53
Inferior parietal	R	71574 (3711)	64528	-1.90	59548	-3.24	69440	-0.58
	L	72885 (4254)	66554	-1.49	60841	-2.83	66121	-1.59
Superior parietal	R	48061 (3813)	42721	-1.40	45061	-0.79	45734	-0.61
	L	46194 (3757)	42717	-0.93	41151	-1.34	45550	-0.17
Occipital	R	54264 (4947)	56626	0.48	53912	-0.07	47231	-1.42
	L	54148 (4657)	48840	-1.14	45850	-1.78	52965	-0.25

[a]Regions are defined as specified in Dade et al. (2004), with the exception of dorsal and ventral frontal regions, which were defined as lying above and below an extension of a line drawn through the anterior and posterior commisures. Regional volumes were adjusted for intracranial capacity using a regression-based procedure (Raz, Lindenberger, Rodrigue, Kennedy, Head, Williamson, Dahle, Gerstorf, & Acker, 2005); *Framed cells fall more than two SDs below control means.

1.2. Procedure

1.2.1. Event selection and instructions

The procedure was administered as described by Levine et al. (2002), with slight modifications. Briefly, participants were asked to provide a detailed description of a personal event from each of five life periods: early childhood (to age 11), teenage years (ages 11–17), early adulthood (ages 18–35), middle age (35–55), and the past year. In cases where participants were unable to generate an event independently, a list of typical life events (e.g., a memorable concert) was presented. Participants were instructed that each event selected must be personally experienced and have occurred at a specific time and place.

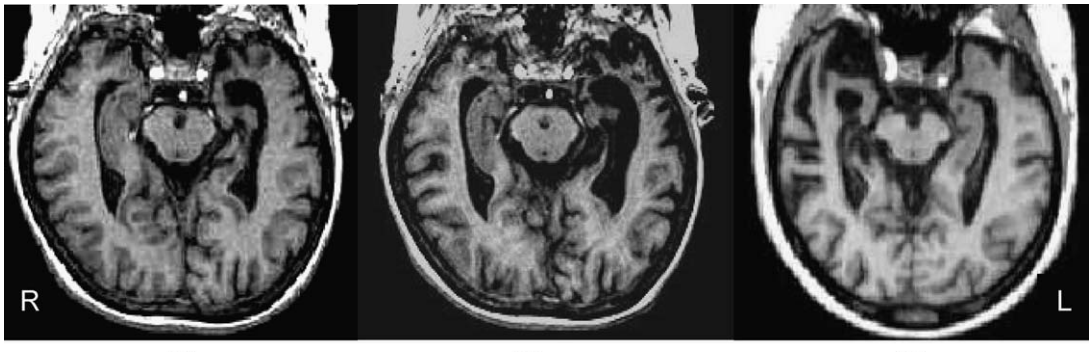

Fig. 1. Axial view of the MTL at the level of the ICS in (A) patient A.A. (scan 1); (B) patient A.A. (scan 2); and (C) patient B.B.

1.2.2. Conditions of retrieval support

In order to examine facilitative effects of retrieval support on memory, we manipulated the level of structure available to participants across three conditions: recall, general probe, and specific probe. For recall, participants 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 participant was given the option of selecting a different event that was more likely to result in successful recall. General probes were limited strictly to non-specific statements or repetitions of the instructions.

At the specific probe phase, a structured interview was administered that was designed to compensate for impairments in search and monitoring functions. Cues were organized into five categories: event details, time, time integration, place, other sensory information, and emotion/thought. Each was addressed with a standardized question, with modifications made according to the event described. In order to prevent the specific probe process from contaminating recall of subsequent memories, this condition was administered after all five events were recounted under the recall and general probe conditions.

1.2.3. Protocol scoring

Following transcription, each memory was segmented into informational bits or details. A detail was defined as a unique occurrence, observation, or thought, generally expressed as a grammatical clause. Each detail was then classified according to the procedure outlined in Levine et al. (2002); the scoring manual is available on request from B.L. Briefly, details were defined as "internal" or episodic and assigned to one of five categories (event, place, time, perceptual, and emotion/thought; analysis of these categories is not reported in present manuscript) if they 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 or editorializing (see Fig. 2 for scoring example). Both internal and external details provide important information concerning autobiographical memory. Internal details reflect recovery of remote episodic autobiographical information relatively uncontaminated by semantic processes. External details are also of theoretical interest, reflecting non-episodic speech output, particularly semantic autobiographical information. A pattern of reduced internal details and elevated external details therefore suggests an autobiographical episodic amnesia, with intact access to non-episodic autobiographical information.

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.

Scorers in our laboratory are personally trained by the main developer of the instrument (B.L.). For each scorer, inter-rater reliability is statistically evaluated using a set of 20 memories selected randomly from our files. The memories in this study were scored by four scorers with reliability coefficients of 0.85 or higher for all composite indices (as assessed by the intra-class correlation coefficient, two-way, random effects model; Shrout & Fleiss, 1979). To avoid bias in scoring, scorers were blind to group identity.

1.2.4. Statistical analyses

We combined details from the five life periods to form a single score for each of the internal and external categories. As preliminary analyses indicated that the effect of general probe was minimal in comparison to specific probe, data from recall and general probe were combined, providing two levels of retrieval support: *low retrieval support* (recall plus general probe, hereafter referred to as recall) and *high retrieval support* (specific probe). Temporal gradients in autobiographical memory recall were assessed by comparing internal and external details across the five lifetime periods.

Data were analyzed using a modified *t*-test procedure that treats an individual patient as a sample, allowing for comparison of the patients' test score against norms derived from control samples of small to moderate size (Crawford & Garthwaite, 2002; Crawford, Howell, & Garthwaite, 1998).

2. Results

2.1. Low retrieval support

2.1.1. Internal details

Analysis of internal details collapsed across all five life periods revealed little evidence of episodic autobiographical memory impairment in A.A. and B.B. under conditions of low retrieval support, $ts(15) = -1.73$ and -1.06, for A.A. and B.B., respectively, n.s. (see Fig. 3, upper left panel). However, A.A. failed to recall any internal details from the early childhood lifetime period, suggesting a slight recency effect. Due to

sem-ext **sem-ext** **ed-int**
We grew up on a farm and we had, my sister and I, had two horses and we were riding, each
ed-int **pl-int** **ed-int**
of us were riding one of the horses in the field beside the house and I remember I was riding
pl-int **pl-int**
my little pony up towards a little jump in the field and my sister was down around the bottom,
pl-int **ed-int**
which is down a little hill on the other side of the field and my horse came up to the jump and
perc-int **ed-int** **perc-int**
skidded to a stop right in front of the jump and I, because it was so fast, I flew off over his
perc-int **ed-int**
head and went flying through the air and as I was flying through the air, I looked over at the
perc-int
other side of the field where my sister was and she was flying through the air at the same time
ed-int
off of her horse because her horse had just kicked her off.

Fig. 2. Scoring example. This example includes 15 internal details (7 event details, 4 place details, and 4 perceptual details) and 2 external details (both semantic). Note that the category analysis is not reported in this manuscript.

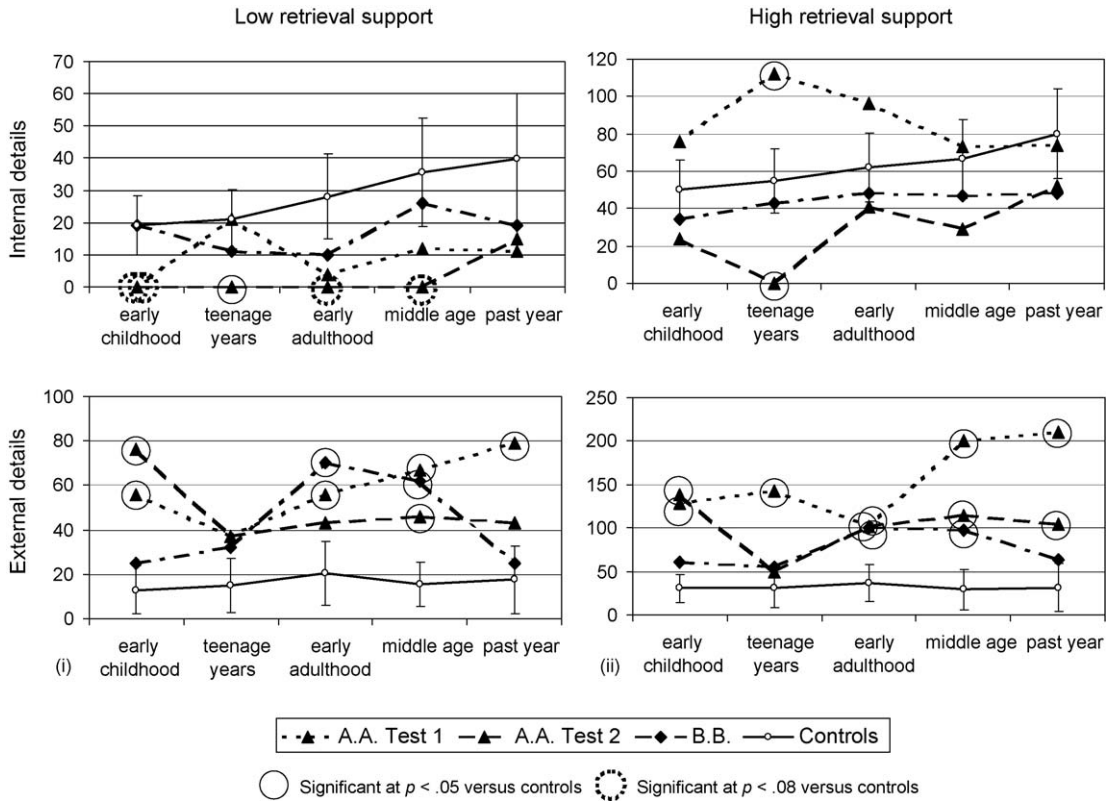

Fig. 3. Number of internal and external details produced across life periods under low and under high retrieval support. Error bars represent standard error of the mean for controls. Note that *X*-axis maxima were adjusted to allow for better visualization of effects. The range of control scores on the internal detail composite was (i) low retrieval support, 0–99; (ii) high retrieval support, 24–141. Control scores on the external detail composite ranged from (i) low retrieval support, controls: 2–52; (ii) high retrieval support, controls: 4–113.

the floor effect, this difference was only marginally significant [$t(15) = -2.03$, $p = .06$]. Patient B.B. was not impaired at any time point relative to controls.

On repeat testing in 2002, the minor differences between A.A. and controls widened such that A.A.'s internal detail composite was significantly lower than that of controls [$t(15) = -2.32$, $p < .05$]. Indeed, A.A. generated no internal details for the lifetime periods spanning early childhood to middle age [$ts(15) = -2.03$, -2.24, -2.07, and -2.04, $ps < .07$, .05, .06, and .06, for periods one to four, respectively]. The event for lifetime period five was later determined to be an amalgamation of similar events.

2.1.2. External details

Both A.A. and B.B. produced more external details than did control participants [ts (15) = 4.73 and 2.94, $ps < .00$ and .01, for A.A. and B.B., respectively; see Fig. 3, lower left panel]. A.A. continued to produce more external details than controls upon re-testing [$t(15) = 3.63$, $p < .01$].

2.2. High retrieval support

2.2.1. Internal details

Both controls and patients generated substantially more details under high retrieval support conditions (see also Levine et al., 2002). In general, recall of internal details was elevated to a similar degree across patients and controls, with the patients still unimpaired relative to controls [$ts(15) = 1.59$ and -1.27 for A.A. and B.B., respectively, n.s.; see Fig. 3, upper right panel].

Analysis of lifetime periods indicated that any gradients present during low retrieval support were eliminated in the high retrieval support condition. A.A.'s gradient was in the direction of a standard Ribot (amnesic) pattern, with no instance of reduced internal details and significantly increased internal details at the teenage period [$t(15) = 3.25$, $p < .01$]. B.B. had a flat gradient, with the exception of a lower ratings composite score for the early adult period [$t(15) = -2.53$, $p < .05$].

On re-testing, A.A.'s generation of internal details was significantly impaired [$t(15) = -2.27$, $p < .05$]. The teenage period remained significantly lower than that of controls [$t(15) = -3.10$, $p < .01$].

2.2.2. External details

A.A.'s and B.B.'s external composite scores remained higher than those of control participants [$ts(15) = 6.19$ and 2.14, respectively, $ps < .001$ and .05, respectively; see Fig. 3, lower right panel]. At re-testing in 2002, A.A.'s production of external details continued to exceed that of control participants [external detail composite: $t(15) = 3.43$, $p < .01$].

3. Discussion

Autobiographical memory was assessed in two patients with SD using a novel method for separating episodic from semantic components of autobiographical memory and manipulating retrieval support. With these modifications in autobiographical memory assessment, there was little evidence for a reverse gradient in autobiographical episodic memory as previously reported for patients with SD (Graham & Hodges, 1997; Graham et al., 2003; Nestor et al., 2002; Piolino et al., 2003a, 2003b). Although one patient showed weak evidence of a reverse gradient with disease progression, this was eliminated when retrieval support was provided via structured probing. Both patients produced more non-episodic (mostly semantic) information than controls. These findings suggest that patients with SD are capable of achieving episodic memory performance equivalent to that of control participants, at least during early stages of their disease, when prompted properly. These findings are consistent with Multiple Trace Theory, which predicts that recent and remote episodic autobiographical memory would be similarly affected by SD if compensation is made for retrieval failure due to linguistic deficits or executive dysfunction. The inconsistent results reported in the literature on autobiographical memory and SD may be due, in part, to methodological differences across studies.

3.1. Separation of episodic from semantic memory

Our data suggest conclusions regarding episodic and semantic autobiographical recall in patients with SD (as well as other patients and controls) can be affected by method variance with respect to the separation of episodic from semantic autobiographical recall. The AI uses a reliable coding scheme to classify personal semantic details as "external", whereas in other measures these same details, which are related to the event but do not require recreation of temporal, spatial, and other contextual information, may contribute to indices of episodic memory (for a related example using the AI in patient H.M., see Steinvorth et al., 2005). Indeed, one of our patients (A.A.) recalled the greatest number of semantic details for the most recent time periods, suggesting that previous findings of a reverse gradient may be explained in part by contamination from personal semantic memory. Elevation of personal semantic details likely reflects preservation of conceptual knowledge relevant to semantic dementia patients' personal experience, as suggested by Snowden, Griffiths, and Neary (1994, 1996, 1999).

To the extent that internal details reflect a relatively "pure" estimate of episodic memory, our findings suggest that autobiographical episodic memory loss in SD parallels that observed in controls, as predicted by MTT. One exception to this was noted for patient A.A. in her second test session, where her only memory was for the most recent time period. Although this may appear to replicate earlier findings of a reverse gradient (Graham & Hodges, 1997; Graham et al., 2003; Nestor et al., 2002), this memory was subsequently determined to be an amalgamation of similar events and thus can be regarded as an instance of semantic contamination that evaded detection by our test (Neisser, 1981; for a similar example, see Rosenbaum et al., 2004). Moreover, even this weak evidence for a reverse gradient was eliminated with retrieval support (see below).

3.2. Effect of retrieval support

Retrieval of remote episodic memories requires more strategic search operations than is required for retrieval of recent memories. Retrieval support augments remote episodic memory recall in both controls and patients, especially when the patients have PFC damage (Levine et al., 2002; Rosenbaum et al., 2004). Accordingly, retrieval support substantially improved remote episodic autobiographical memory recall in our patients, particularly patient A.A at initial testing, where we observed weak evidence of a reverse gradient under low retrieval support. Although she remained unable to recall episodic details for one early memory (teenage years), her episodic recall for the childhood period was not significantly different from that of controls. In test session 2, however, when prefrontal atrophy increased (particularly in the dorsal frontal regions, among other regions), the benefit of cuing was attenuated significantly and her overall episodic recall remained below that of controls, including recall of teenage events that had been enhanced 1 year earlier under supportive cuing. This finding lends support to earlier observations that the extent of episodic memory deficit in patients with PFC damage varies with volume loss in this region (Simons et al., 2002). Indeed, our structural neuroimaging data suggest that a combination of temporal and PFC damage likely contributed to our patients' memory performance; when damage to both regions is extensive, episodic memory loss across all time periods (ungraded loss relative to controls) would be predicted (as in A.A. at test session 2; Wiltgen, Brown, Talton, & Silva, 2004). This is contrasted to studies of patients with frontal-variant FTLD showing autobiographical retrieval deficits irrespective of time period (Nestor et al., 2002; Piolino et al., 2003b), likely reflecting the combined effects of PFC damage and lack of retrieval support.

Moss et al. (2003) also showed intact memory performance following a standard Ribot gradient in a SD patient tested under high retrieval support. Although Moss et al. counted details from transcribed autobiographical recollections, there was no attempt to separate episodic from non-episodic details. The present findings extend those of Moss et al. by demonstrating that temporal gradients in SD patients' autobiographical memory are modulated not only by retrieval support, but also by the type of autobiographical memory examined.

3.3. Limitations and future directions

One limitation of our study is the restriction to a single memory per time period. Sampling of more memories per time period may have increased power to detect temporal gradient effects. Our memory selection method was similar to that of others (Graham et al., 2003, Experiment 3; Steinvorth et al., 2005). By probing each memory in depth, we were able to maximize patients' mnemonic production. Sampling a greater number of memories but with less depth may reduce power to detect these

effects by restricting the number of details per memory (e.g., Bayley et al., 2003).

As with any case study, statistical power was low, especially in the context of the high variance that is inherent to autobiographical memory. For example, a score of 0 in the low retrieval support condition does not fall below the threshold of statistical significance relative to controls. Conclusions regarding lack of group differences in this condition must therefore be interpreted with caution. Nonetheless, the conclusions of this study do not rest upon interpretation of this statistical comparison in isolation, but rather on the pattern of results across conditions of retrieval support, internal and external detail composites, and test sessions.

A.A.'s and B.B.'s temporal lobe atrophy was not restricted to the neocortex; there was evidence of volume loss in the medial temporal region (including the hippocampus, amygdala, parahippocampal, and entorhinal cortices) in both patients. The amount of medial temporal lobe damage observed here is typical for SD (Rosen et al., 2002a, 2002b). Indeed, in some samples, hippocampal atrophy in SD is equivalent to or greater than that observed in patients with Alzheimer's dementia, especially in anterior regions (Chan et al., 2001; Galton et al., 2001). Medial temporal lobe atrophy in SD is asymmetrical, as was the case in our patients. It appears that residual hippocampal tissue (likely posterior; Rosen et al., 2002a, 2002b) in A.A. and B.B. was sufficient to mediate memory recall when retrieval support was available to compensate for concomitant frontal lobe damage (see Gilboa, Winocur, Grady, Hevenor, & Moscovitch, 2004; Gilboa, 2004, for discussion of the differential role of the anterior and posterior, left and right MTL in remote memory).

4. Conclusions

Our results reveal that patients with early stage semantic dementia exhibit autobiographical memory performance similar to that of controls when performance is assessed using a measure which is capable of dissociating episodic and personal semantic recall and that provides retrieval support to compensate for frontally mediated retrieval processes. Earlier reports indicating that patients with semantic dementia demonstrate autobiographical episodic memory loss following a "reverse gradient" are likely due to contamination of episodic recall by enhanced semantic recall, as observed in our patients, and to uncompensated retrieval deficits mediated by damaged frontal lobe regions. With disease progression, extensive damage to both PFC and MTL regions leads to ungraded episodic memory loss relative to controls. Our findings are best explained by MTT theory, where the perpetual involvement of the hippocampus/MTL in episodic recall predicts that recent and remote episodic autobiographical memory would be similarly affected by SD.

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