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Behavioral and functional neuroanatomical correlates of anterograde autobiographical memory in isolated retrograde amnesic patient M.L.

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ABSTRACT

Patient M.L. [Levine, B., Black, S. E., Cabeza, R., Sinden, M., Mcintosh, A. R., Toth, J. P., et al. (1998). Episodic memory and the self in a case of isolated retrograde amnesia. *Brain*, *121*, 1951–1973], lost memory for events occurring before his severe traumatic brain injury, yet his anterograde (post-injury) learning and memory appeared intact, a syndrome known as isolated or focal retrograde amnesia. Studies with M.L. demonstrated a dissociation between episodic and semantic memory. His retrograde amnesia was specific to episodic autobiographical memory. Convergent behavioral and functional imaging data suggested that his anterograde memory, while appearing normal, was accomplished with reduced autonoetic awareness (awareness of the self as a continuous entity across time that is a crucial element of episodic memory). While previous research on M.L. focused on anterograde memory of laboratory stimuli, in this study, M.L.'s autobiographical memory for post-injury events or *anterograde autobiographical memory* was examined using prospective collection of autobiographical events via audio diary with detailed behavioral and functional neuroanatomical analysis. Consistent with his reports of subjective disconnection from post-injury autobiographical events, M.L. assigned fewer "remember" ratings to his autobiographical events than comparison subjects. His generation of event-specific details using the Autobiographical Interview [Levine, B., Svoboda, E., Hay, J., Winocur, G., & Moscovitch, M. (2002). Aging and autobiographical memory: dissociating episodic from semantic retrieval. *Psychology and Aging*, *17*, 677–689] was low, but not significantly so, suggesting that it is possible to generate episodic-like details even when re-experiencing of those details is compromised. While listening to the autobiographical audio diary segments, M.L. showed reduced activation relative to comparison subjects in midline frontal and posterior nodes previously identified as part of the autobiographical memory network. Reductions were also evident in M.L. in association with personal semantic stimuli (e.g., recordings describing personal habits and routines). These data suggest an association between M.L.'s impoverished recollection of autobiographical material and reduced activation in midline sectors of the autobiographical memory network that support the autonoetic, first-person element of episodic memory.

1. Introduction

In focal or isolated retrograde amnesia, retrieval of pre-morbid memories is impaired relative to acquisition and retrieval of anterograde or post-morbid memories (Kapur, 1999). This pattern contrasts to the usual amnesic presentation of greater impairment for which anterograde memory is impaired while remote, pre-morbid memories are spared. Following recovery from a severe traumatic brain injury, M.L. reported a dense retrograde amnesia for his entire lifespan pre-dating his injury, with normal performance on tests of anterograde learning (Levine et al., 1998). This anterograde learning capacity also supported relearning of or memory for facts about him pre-dating the accident, as well as memory for events occurring since the accident. The subjective quality of M.L.'s anterograde memory, however, was not normal. M.L. reported a feeling of personal detachment not only from the facts of his pre-injury life, but also, to a lesser degree, post-injury (anterograde) facts and events. This raised the possibility that M.L.'s retrograde amnesia was not entirely isolated (Kopelman, 2000). That is, although his performance on anterograde memory tests was indistinguishable from controls, the subjective quality of his memories was altered.

M.L.'s self-reported deficit in re-experiencing the contents of anterograde memory was confirmed with the remember/know

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technique (Levine et al., 1998; Levine, Freedman, Dawson, Black, & Stuss, 1999), whereby recognized items are rated as either recollected with accompanying thoughts, feelings or visual images or merely familiar without accompanying elements of recollection (Gardiner, 1988; Tulving, 1985). Structural imaging revealed a focal lesion appearing to affect the frontal projections of the right uncinate fasciculus, a frontotemporal band of fibers previously hypothesized to mediate retrieval of remote autobiographical memory (Markowitsch, 1995). Functional imaging of paired associate recall with $H_2{}^{15}O$ PET revealed hypoperfusion in the areas undercut by M.L.'s lesion, accompanied by hyperperfusion of the left hippocampal region. The functional imaging findings were reliable relative to both healthy controls and to patients with severe TBI who did not have retrograde amnesia.

Taken together, the neuroimaging findings suggested that M.L.'s anterograde memories were being processed via a reorganized neurocognitive system. Enhanced engagement of the left hippocampus enabled anterograde encoding and retrieval of laboratory stimuli, while right frontotemporal disconnection diminished the subjective sense of re-experiencing that normally accompanies episodic retrieval. Furthermore, M.L. was unable to retrieve pre-morbid memories via this reorganized system, although he was able to relearn and subsequently retrieve facts about pre-injury events, which were experienced in the third person.

In this paper, we report recent imaging and behavioral studies of M.L. that update and extend the findings of the original study. Our earlier conclusions concerning M.L.'s subjective sense of disconnection from post-injury events were derived from standard memory tests using stimuli encoded and retrieved in the laboratory. Yet M.L.'s mnemonic complaints, not to mention those of every patient with memory deficits, concern real-life experiences rather than laboratory materials. In the present study, we assessed the quality and functional neuroanatomy of M.L.'s anterograde autobiographical memory (memory for real-life events occurring after M.L.'s accident). This was accomplished by combining two methods recently developed in our laboratory for the study of autobiographical memory: prospective collection of autobiographical events (Levine et al., 2004) and text-based analysis of the contents of autobiographical memory using the Autobiographical Interview (Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002).

Nearly all studies of autobiographical memory rely on events collected retrospectively through interviews or other stimuli such as family photographs. This is necessitated by the extreme impracticalities associated with prospective collection of autobiographical events. A few "diary" studies, most of them using experimenter as subject, have behaviorally assessed retrieval of prospectively recorded events (e.g., Conway, Collins, Gathercole, & Anderson, 1996; Linton, 1975). We studied the functional neuroanatomy of such events by scanning participants while they listened to audio recordings of personal autobiographical events created within hours of the event's occurrence (Levine et al., 2004). The results indicated that episodic autobiographical memory engaged the autobiographical memory network (Maguire, 2001; Svoboda, McKinnon, & Levine, 2006) to a greater degree than did closely matched comparison recording conditions, including semantic autobiographical memory (i.e., recordings about personal facts and repeated events).

For the present study, M.L. and comparison subjects made recordings for these same conditions. The recorded events provide extremely potent retrieval cues of verified, unrehearsed unique events that evoke strong feelings of recollection in healthy adults (Levine et al., 2004). This was assessed through both subjective ratings of re-experiencing upon listening to the recordings (using the remember/know technique) and through quantitative analysis of transcribed autobiographical protocols using the Autobiographical Interview and scoring technique (Levine et al., 2002). The scoring technique provides independent indices of episodic and semantic autobiographical memory through text-based analysis of subjects' verbal autobiographical recollections in response to hearing the recordings. Subjects were also scanned with fMRI to assess functional neuroanatomy associated with listening to the recordings.

Given M.L.'s complaints of subjective disconnection from autobiographical events, we predicted that the recordings would not have such a potent effect for him, as reflected in both subjective ratings and quantified analysis with the Autobiographical Interview. We also predicted that M.L. would show alteration in the autobiographical network relative to controls. Specifically, we predicted that when listening to personal episodic recordings, M.L. would show reduced activation of the autobiographical memory network, particularly the anterior and posterior midline regions that are mediated by self-related processing and recovery of episodic details.

2. Methods

2.1. Case study subject

M.L. is a married right-handed male who was 43 years of age at the time of this assessment. Details concerning his background and case are provided in Levine et al. (1998) and Levine et al. (1999) and are presented briefly here. M.L. had a high school education plus three years of technical training in electronics. At the time of his injury, he was working in sales of high technology factory automation equipment. M.L. sustained a traumatic brain injury in 1993 when he was struck by a car while riding his bicycle. His 6-h Glasgow Coma Scale score of 7.5 (pro-rated), his loss of consciousness of six days in duration, and his duration of post-traumatic amnesia of at least 34 days, classified his brain injury in the severe range. His initial global amnesia resolved to an isolated retrograde amnesia by which he could not recall episodes from his life prior to the accident, but he was able to learn new information, including pre-morbid facts. Neuropsychological testing, including assessment of anterograde memory, conducted in the chronic phase of recovery was normal, with the exception of minor visuoperceptual and visuomotor weaknesses. M.L.'s scores were low relative to comparison subjects on experimental tests of advanced mnemonic and executive processes (Levine et al., 1998, 1999). In the years following our initial assessment, M.L.'s amnesia profile has remained stable; his retrograde amnesia for pre-morbid events is unchanged, and he continues to report a lack of subjective connection to new events. He has assumed the role of "house husband" caring for his two children and has not worked outside the home since his accident.

2.2. Comparison subjects

Two groups of comparison subjects were used, one for functional imaging and another for behavioral analysis with the Autobiographical Interview. The first set of controls consisted of the five subjects reported in our original paper using the prospective event recording methodology (Levine et al., 2004) (age range 26–37, two males). These subjects were scanned three years prior to the present study and they were not administered the Autobiographical Interview for their events. M.L.'s behavioral data were instead compared to those from a separate sample of 5 subjects (mean age = 30, SD = 3.4; mean education = 20, SD = 1.22; three males) who had recently participated in a follow-up imaging study using the same methods of the earlier study. (We could not use these subjects as comparison subjects for the imaging aspect of this study as they were scanned on a different scanner from M.L., using different baseline conditions.) Although different comparison subjects were used across the two imaging and behavioral studies, there is no reason to suspect that the Autobiographical Interview data from the imaging comparison subjects would be systematically different from that of the behavioral comparison subjects. This conclusion is supported by the fact that the patterns of functional imaging results across the two sets of comparison subjects were similar (Svoboda and Levine, in press).

2.3. Collection of autobiographical stimuli

Subjects dictated the stimuli into a microcassette recorder according to methods described by Levine et al. (2004). There were three recording conditions of interest for this study, Personal Episodic (PE), Personal Semantic (PS), and General Semantic (GS). PE recordings comprised a detailed description of a unique event of no more than a few hours in duration (e.g., helping someone move house), including the story line, sensory information, thoughts, and feelings. Semantic information concerning repeated events was minimized. Following each PE recording, subjects rated novelty, importance, and emotional change, each on a 0–4 point scale. PS recordings described personal factual information, mostly consisting of repeated activities (e.g., making coffee). The GS condition included readings from a book about the history of Toronto, Canada. In making non-PE recordings, participants avoided information that would trigger personal episodic memories (e.g., ethnic groups in the GS readings associated with a unique personal episode). All recordings were matched for

time elapsed from time of recording to scanning. Subjects were instructed not to listen to any recordings after making them.

Recordings were drawn from a large pool created by each group. Imaging and behavioral comparison subjects generated an average of 180 and 215 recordings across all conditions, respectively. M.L. generated 77 total recordings. The mean age of recordings selected for this study across imaging comparison subjects was 156 days (range: 151–163; approximately 5 months). The mean age of selected recordings across behavioral comparison subjects was 551 days (range: 438–655; approximately 18 months). The mean age of selected recordings for M.L. was 281 days (range: 112–402; approximately 9 months).

Although these memory ages are different, they are within a compressed range relative to most studies of autobiographical memory, which involve memories spanning years and decades. The accessibility of autobiographical memories is greatest in the days and weeks following the event, followed by an exponential decline (Rubin & Schulkind, 1997) whereby there are relatively fewer differences among memories in the 3–18 month range. To assess this empirically, we computed correlation coefficients between age of memory and internal, external, and ratings scores from the Autobiographical Interview (see below) for 95 memories ranging from 3 to 18 months drawn from a separate study involving 15 healthy adults (mean age = 46, SD = 13, range = 21–73). The mean age of the memories was 279 days, SD = 139, range = 93–628. Neither internal nor external detail composites correlated with age of memory (p's = .29 and .56, respectively). There was a slight positive correlation between age of memory and Autobiographical Interview scorer ratings, $r(114) = 0.23$, $p = .012$.

2.4. fMRI

2.4.1. Imaging

MRI scans were acquired with a 1.5-T scanner (Signa, CV/i hardware, LX8.3 software; General Electric Medical Systems, Waukesha, WI). A three-dimensional fast spoiled gradient echo pulse sequence (TR = 12.4 ms, TE = 5.4 ms, flip angle 35°, 22 cm × 16.5 cm FOV, 256 × 192 acquisition matrix, 124 axial slices 1.4 mm thick) was used to acquire a T1-weighted volumetric anatomical MRI for each participant. Functional scans were obtained using a single shot $T2^*$-weighted pulse sequence with spiral readout, achieving 24 slices 5 mm thick (TR = 2000 ms, TE = 40 ms, flip angle 80°, 90 × 90 effective acquisition matrix, 20 cm FOV).

Recordings were edited to 30 s in length and randomized across four presentation series, each containing two recordings per condition as well as one randomly interspersed rest period of visual fixation, also lasting 30 s. During all conditions, participants listened (or rested) while visually fixating on a cross presented centrally on a back-projection screen and viewed through angled mirrors mounted on the head coil. Whereas comparison subjects had eight memories per condition, M.L. was scanned with 32 personal episodic and 20 personal semantic memories to maximize power. He was scanned with eight general semantic recordings. In the original paradigm, each memory was followed by 45 s of in-scanner ratings for re-experiencing of thoughts, visual images, overall re-experiencing, and ease of retrieval. To allow time for more stimuli, this was reduced to a single 10 s rating of overall re-experiencing ranging from 1 to 10, with 10 representing the highest level of re-experiencing.

2.4.2. Image analysis

Functional neuroimaging data preprocessing and analysis were performed using the Analysis of Functional Neuroimages software package (AFNI version 2005 12 30 0934; (Cox & Hyde, 1997). Only epochs during the 30 s stimulus presentation were analyzed. Timeseries data were motion and slice-timing corrected, co-registered to the high resolution structural scan, and submitted to a deconvolution analysis using the AFNI plugin 3dDeconvolve. The functional data were modeled using a general linear model to derive parameter estimates and corresponding t-statistics for the impulse response functions corresponding to the three experimental conditions (PE, PS, GS). The resulting whole brain, voxel-based maps of the parameter estimates and their statistical (T-statistic) assessments (i.e., the within subject, within condition activation maps) were transformed into stereotaxic space (Cox & Hyde, 1997; Talairach & Tournoux, 1988). Activation maps were spatially smoothed with a Gaussian filter with a full width at half maximum value of 6.0 mm. These steps were performed to facilitate the subsequent group analysis, which consisted of voxelwise, mixed effects (conditions fixed, subjects random), two-factor ANOVA for unbalanced designs. The group image contrast results for PE vs. GS, PE vs. PS, and PS vs. GS closely matched the results reported by Levine et al. (2004) using a different analysis method (Partial Least Squares; PLS).

We used two methods for examining differences between M.L. and comparison subjects: disjunction analysis and region of interest analysis.

2.4.2.1. Disjunction analyses. For each contrast of interest (PE vs. GS, PE vs. PS, PS vs. GS), the average of the comparison subjects' standardized activation maps and M.L.'s standardized activation map were multiplied by a step function to define voxels falling above a threshold of .05. A disjunction was determined by the presence of supra-threshold activation in the comparison group but not in M.L. exceeding a cluster size threshold of 150 ml, or *vice versa*. For a similar application of disjunction analysis in a case study, see Rosenbaum, Winocur, Grady, Ziegler, & Moscovitch (2007).

2.4.2.2. Region of interest analyses. We extracted signal change data in regions of interest as defined by peak activations in the comparison group that corresponded to known elements of the autobiographical memory network as defined by previous studies (Svoboda et al., 2006). For the PE vs. GS contrast, these included left superior medial frontal, left inferior lateral frontal, right inferior lateral frontal, left mid-dorsolateral frontal, left medial temporal, left middle temporal, right superior temporal, left temporoparietal junction, right posterior cingulate, and right cerebellar peaks. The PE vs. PS contrast yielded a very similar pattern, although there were no significant peaks for the left medial temporal, left temporoparietal, and right cerebellar regions. The PS vs. GS contrast yielded peaks for right middle frontal, right superior temporal, left inferior parietal, and left precuneus. Voxels were extracted for all peaks and all subjects, and M.L.'s values were compared to those of the group.

2.5. The Autobiographical Interview

The Autobiographical Interview was administered as described by Levine et al. (2002), with modifications. Instead of using lifetime periods as retrieval cues, the prospectively collected autobiographical events were played back to subjects. Subjects were then asked to provide a detailed description of the event. 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. General probes were limited to non-specific statements or repetitions of the instructions. The Specific Probe phase of the Autobiographical Interview, consisting of a structured interview designed to elicit additional details of the event, was not administered. Following probing, subjects were asked to rate the following on a six-point scale: importance (both at the time of the event and at the time of testing), how clearly they could visualize the event, the degree of emotional change as a result of the event, and frequency of reactivation (how often they thought or spoke about the event). Subjects' descriptions of the selected events were audio-recorded for later transcription and analysis.

M.L. was administered the Autobiographical Interview on the day after his scan. As noted above, the comparison group for the behavioral measures was not the same group as was used for the imaging portion of the study. To equate exposure to the recordings between the comparison subjects and M.L., the comparison subjects listened to the recordings the day before the Autobiographical Interview. Thus all subjects heard the recordings twice: first on the day before the interview, and then during the interview.

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. We also examined the ratio of internal to total details, providing a measure of episodic re-experiencing. Finally, scorers assigned ratings (0–3) to each memory for each of the five categories described above, as well as for overall episodic richness (0–6). The composite sum of these ratings formed an alternative measure of episodic re-experiencing that is less affected by the number of details generated. Scores were analyzed cumulatively across recall and general probe. To avoid bias in scoring, subjects' memories were placed in a common pool and scored at random by four experienced scorers who had achieved high inter-rater reliability (see Levine et al., 2002) and who were blind to group.

Subjects provided remember/know judgments for each memory. Judgments were recorded for three categories per memory: emotions/thoughts, visual re-experiencing, and event details. For each category, "remember" responses were assigned to memories that evoked specific and detailed information conveying a sense of re-experiencing. "Know" responses were assigned to memories for which the information could be retrieved (e.g., "I was sad"), but without a sense of re-experiencing. For simplicity, the memories were referred to as "Type A" and "Type B" memories rather than "remember" and "know" as the latter can be confusing to subjects (Söderlund, Black, Miller, Freedman, & Levine, 2008). When no information concerning a particular category was available, a rating of "None" was assigned.

Crawford's modified t-statistic (Crawford, Howell, & Garthwaite, 1998) for comparing single subject data to a small comparison group was used to assess differences between M.L. and comparison subjects.

3. Results

3.1. Behavioral results

At the time of recording, M.L. rated his memories significantly higher than comparison subjects for novelty (see Table 1). His

Table 1
Subjects' ratings of memories at time of encoding (when recording was made) and retrieval (post-scan).

		Ratings at time of recording				Ratings at time of retrieval				
		Novelty	Importance	Emotion	Sum	Visual	Emotion	Importance-now	Importance-then	Rehearsal
Comparison subjects	Mean	2.21	1.92	1.91	6.04	3.11	2.56	1.85	2.49	1.67
	SD	0.34	0.63	0.35	1.20	0.75	0.84	0.74	0.74	0.63
ML	Mean	3.63	3.16	2.53	9.31	2.88	3.94	4.03	4.56	2.50
	SD	0.61	0.81	0.88	1.71	1.36	0.91	1.00	0.56	1.27
T-statistic		3.81	1.80	1.62	2.49	−0.28	1.50	2.69	2.55	1.20
P-level (2-tailed)		0.02	0.15	0.18	0.07	0.79	0.21	0.05	0.06	0.30

importance and emotional change ratings were higher, although not significantly so. His encoding ratings composite (i.e., the sum of all three ratings) was marginally significantly higher than comparison subjects. Similar trends were observed for M.L.'s ratings of memory characteristics at retrieval, with importance both at the time of the event and at retrieval rated higher than comparison subjects. These data suggest that the experiences recorded by M.L. were as significant or more significant than those of comparison subjects.

In spite of the equivalent or greater rated significance of M.L.'s memories relative to comparison subjects, indices of episodic re-experiencing (i.e., the in-scanner rating of overall re-experiencing, the Autobiographical Interview and remember/know ratings), were reduced relative to comparison subjects (for sample protocols, see Appendix), although to different degrees depending on the measure.

M.L.'s in-scanner rating of overall re-experiencing was 3.94, significantly lower than that of comparison subjects ($M = 8.20$, SD = 1.1, $t(4) = -3.47$, $p < .05$). His ratings for GS and PS, 1.44 and 3.42, respectively, were not different from those of comparison subjects (M's = 1.90 and 2.55, SD's = 0.75 and 0.79, respectively). As seen in Fig. 1, M.L. generated fewer internal details than the comparison subjects, $t(4) = -1.43$, $p = .23$, whereas his generation of external details was equivalent to that of comparison subjects. Accordingly, the ratio of internal to total details, a measure of episodic richness, was reduced relative to comparison subjects, M.L.: $M = 0.41$; comparison subjects: $M = 0.71$; SD = 0.11, $t(4) = 1.83$; $p = 0.14$. M.L.'s memories received lower rating composite scores (as assigned by scorers), M.L.: $M = 5.6$; comparison subjects: $M = 10.2$; SD = 2.3, $t(4) = 1.84$; $p = 0.14$.

There were no significant differences observed for any of the internal or external detail categories. Two ratings categories, however, were marginally significantly lower in M.L. than in comparison subjects: thought/emotion and episodic richness, t's(4) = −2.60 and −2.44, respectively, p's = .06 and .07.

Using the remember/know technique, M.L. assigned significantly fewer "remember" ratings than comparison subjects for visual, emotional, and event characteristics, t's(4) = −3.65, −2.89, and −4.38, respectively; p's = .02, .05, and .01; see Fig. 2.

3.2. Imaging results

3.2.1. Disjunction analysis

Disjunction analysis for the PE vs. GS contrast indicated clusters of activation significantly greater in comparison subjects than in M.L. in left anterior and posterior midline regions, including the anterior cingulate gyrus (BA 32), the superior frontal gyrus (BA 9), and the posterior cingulate gyrus (BA 29; see Fig. 3). There was one area of activation greater in M.L. than in comparison subjects in the left middle temporal gyrus (BA 21; $x, y, z = -37, -56, 21$, volume = 232 ml). No significant disjunctions emerged for the other contrasts (PE vs. PS, PS vs. GS).

3.2.2. Region of interest analyses

In the PE vs. GS analysis, M.L. showed significantly reduced activation in the left inferior frontal gyrus (BA 45), $t(4) = -3.09$, $p = 0.037$), the left superior frontal gyrus (BA 9), $t(4) = -5.02$, $p = 0.007$), and the right posterior cingulate gyrus (BA 29), $t(4) = -3.12$, $p = 0.035$). Reduction in the right superior temporal gyrus (BA 39) and the right inferior frontal gyrus (BA 9) were marginally significant, t's(4) = −2.65 and −2.53, respectively, p's = 0.057 and .065 (Fig. 4).

There were no significant differences among the ROI's selected from the PE vs. PS comparison (see Fig. 5). However, M.L. showed significant reductions in PS vs. GS in the right middle frontal gyrus (BA 6, $t(4) = -3.42$, $p = 0.027$), the left inferior parietal lobule (BA

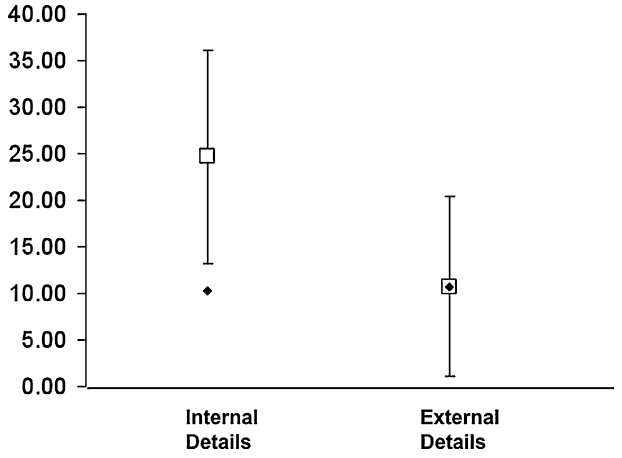

Fig. 1. Internal and external details from the Autobiographical Interview for M.L. and comparison subjects. M.L.'s score is represented by the filled diamond. The open square indicates the comparison subjects' mean. The error bars represent 95% confidence intervals.

Fig. 2. Mean percentage of "remember" responses given for visual, emotional, and event information for M.L. and comparison subjects. M.L.'s score is represented by the filled diamond. The open square indicates the comparison subjects' mean. The error bars represent 95% confidence intervals.

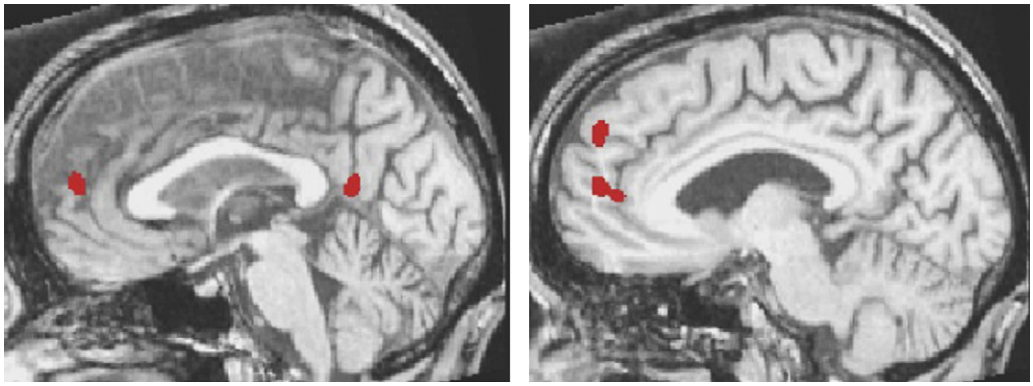

Fig. 3. Disjunction analysis indicated three areas of reduced BOLD response to PE vs. GS in M.L. relative to comparison subjects: the left anterior cingulate gyrus (BA 32; *x*, *y*, *z* = −7, 46, 8; volume = 757 ml), the left superior frontal gyrus (BA 9; *x*, *y*, *z* = −6, 53, 28; volume = 257 ml), and the right posterior cingulate gyrus (BA 29; *x*, *y*, *z* = 1, −51, 9; volume = 195 ml). One area, the left middle temporal gyrus (BA 21; *x*, *y*, *z* = −52, −10, −18; volume = 232 ml) showed increased BOLD response in PE vs. GS in M.L. relative to comparison subjects.

40, $t(4) = -3.28$, $p = 0.031$), and the left precuneus (BA 7, $t(4) = -4.11$, $p = 0.019$; see Fig. 6).

4. Discussion

M.L. has been an important patient in the study of episodic memory theory. In addition to M.L.'s dense episodic autobiographical amnesia for pre-injury material (i.e., retrograde amnesia), he reported a subjective disconnection to the products of anterograde learning and memory, even though he performed normally on standard episodic memory tasks (Levine et al., 1998). Self-reported re-experiencing (via the remember-know technique) was reduced in M.L. relative to comparison subjects for laboratory stimuli, accompanied by reduced right prefrontal brain activation on cued recall, suggesting a reorganization of mnemonic processing that enabled learning and memory to occur without the personal, autonoetic connection. Here, we extended these results to autobiographical stimuli.

The autobiographical stimuli used in this study were recordings created at the time of the event, providing potent retrieval cues that, in comparison subjects, readily evoked a feeling of first-person re-experiencing, as evidenced by "remember" ratings for emotional, visual, and event information for 75–85% of comparison subjects' memories, compared to 25–41% for M.L. (for a similar finding, see Piolino et al., 2005). This is unlikely to be attributed to the nature of M.L.'s events, to which he assigned higher ratings at both encoding and retrieval.

M.L. also generated fewer internal details and received lower ratings for his events as assessed by the Autobiographical Interview. Interestingly, these differences were not as statistically reliable as the self-report ratings generated by the remember/know technique, pointing to some important differences between self-report ratings and quantification of details in the assessment of autobiographical memory. The self-report technique provides a measure of conscious experience within memory that does not entirely overlap with internal details as assessed by the Autobiographical Interview. The Autobiographical Interview scoring instructions dictate that any detail that could reasonably reflect episodic re-experiencing should be classified as internal in order to avoid subjective judgments in scoring. Yet it is self-evident that specific details may be recalled in the absence of episodic re-experiencing (Brewer, 1988). This may be especially the case in patients with impaired autobiographical memory, who recall details that may have been repeated as part of one's personal folklore (Cermak & O'Connor, 1983). Thus even patients with severe amnesia due to medial temporal lobe damage can produce some internal details (Rosenbaum et al., 2008). Conversely, due to individual differences in expository style, some individuals may report highly confident first-person re-experiencing while generating few internal details. Indeed, one of our behavioral comparison subjects produced an average of 14

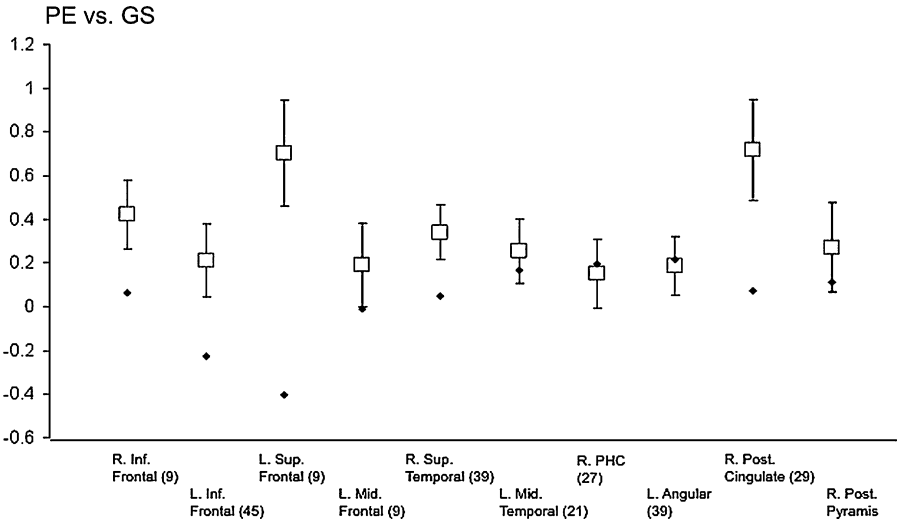

Fig. 4. Region of interest analyses for PE vs. GS in M.L. and comparison subjects. M.L.'s score is represented by the filled diamond. The open square indicates the comparison subjects' mean. The error bars represent 95% confidence intervals.

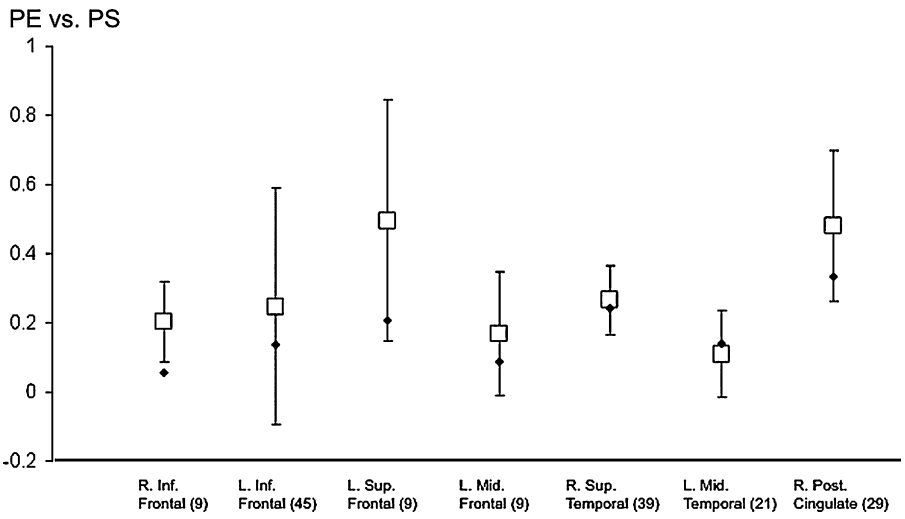

Fig. 5. Region of interest analyses for PE vs. PS in M.L. and comparison subjects. M.L.'s score is represented by the filled diamond. The open square indicates the comparison subjects' mean. The error bars represent 95% confidence intervals.

internal details per memory (external details were similarly low at 6). Due to such individual variability, larger samples are required to more readily detect effects with the Autobiographical Interview. This was unfeasible in the current study owing to the effort involved in the prospective autobiographical recording method.

M.L.'s deficit may be localized to thoughts and feelings rather than visuoperceptual elements of autobiographical recall. Visual "remember" responses were somewhat less impaired than emotional or event information. M.L.'s rated visualization at retrieval was not different from that of controls. Thoughts/feelings and episodic richness were the lowest for M.L. among the scorer-assigned ratings categories in the Autobiographical Interview.

When presented with recordings of personal episodic autobiographical events, M.L. showed reduced activation relative to comparison subjects in core elements of the autobiographical memory network (Maguire, 2001; Svoboda et al., 2006), especially the left medial prefrontal and the posterior cingulate gyrus. These regions, particularly the left medial prefrontal cortex, are strongly implicated in autobiographical retrieval as well as other self-related mentalizing activities (Addis, Wong, & Schacter, 2006; Buckner & Carroll, 2007; Gusnard, Akbudak, Shulman, & Raichle, 2001; Kelley et al., 2002). The caudomedial regions (including the posterior cingulate gyrus) are connected to both the limbic medial temporal region and the anterior cingulate gyrus (Morris, Petrides, & Pandya, 1999; Petrides & Pandya, 2002), another region frequently activated in association with autobiographical recall (Svoboda et al., 2006) that showed reduced activation in M.L. Caudomedial damage can cause amnesia, presumably due to interruption of these connections crucial for mnemonic function (Aggleton & Pearce, 2002; Valenstein et al., 1987).

M.L. showed increased activation relative to comparison subjects in the left middle temporal gyrus during episodic autobiographical retrieval. This effect was observed for the disjunction analysis, but not the ROI analysis. This region, also core to the autobiographical network, is associated with semantic processing. Like M.L., older adults show increased engagement of this region during autobiographical memory (Maguire & Frith, 2003), possibly due to compensatory processes as indicated by their tendency to recall more general semantic information than young adults (Levine et al., 2002). It is also possible, however, that this finding may reflect a by-product of autobiographical memory network reorganization that is not functionally beneficial.

The personal semantic recordings were designed to reflect non-episodic autobiographical information that is not reliant on autonoetic consciousness for retrieval. The validity of this condition was supported by a dissociation between activation patterns associ-

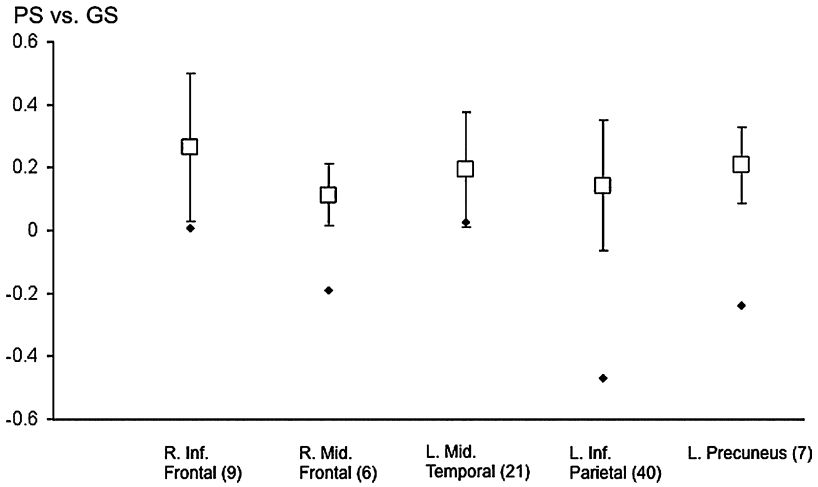

Fig. 6. Region of interest analyses for PS vs. GS in M.L. and comparison subjects. M.L.'s score is represented by the filled diamond. The open square indicates the comparison subjects' mean. The error bars represent 95% confidence intervals.

ated with the PE relative to PS, whereby the former condition more reliably engaged the autobiographical memory network, although these two conditions were not completely dissociated (Levine et al., 2004). We expected M.L.'s autobiographical reductions to be specific to the PE condition. Contrary to expectation, M.L.'s brain activation patterns associated with PE and PS could not be distinguished from each other. His neural response to personal semantic information is not normal, as evidenced by significantly reduced activation in the lateral prefrontal, lateral and medial parietal ROI's in association with PS. This could not be attributed to the nature of M.L.'s PS recordings, the content of which was appropriate to the task instructions.

Thus there is evidence that M.L.'s altered functional neuroanatomy corresponding to autobiographical memory holds when he is processing personal semantic as well as episodic information, although his ability to produce semantic autobiographical information is not impaired. This does not, however, invalidate the dissociation between episodic and semantic autobiographical memory in M.L. The PE and PS conditions are not necessarily process-pure; some degree of contamination across these two conditions is likely in that episodic and semantic autobiographical memory occur simultaneously and interact (Levine et al., 2002). Thus personal episodes contain personal semantic information, and it is likely that recollection of personal episodes occurs during processing personal semantic information. In M.L., dysfunction in the personal episodic system may spread to involve network reductions in other self-related systems.

Certain differences in study design between M.L. and comparison subjects introduced potential confounds that are important to consider in interpreting the results, although we do not believe they can explain the results. Although M.L. was tested on a greater number of recordings, the size of the pool from which recordings were drawn was much larger in the comparison subjects, so that a given event may be considered less unique for comparison participants than M.L., which would work against the findings of this study. A more serious concern relates to the number of *tested* events, which was higher in M.L. than in comparison subjects. This too is unlikely to have affected the scanning results, since the overall scanning time did not differ between M.L. and comparison subjects due to increased in-scanner rating demands for the comparison subjects. Furthermore, M.L. spent a greater percentage of scanning time listening to the more engaging PE recordings than less engaging PS and GS recordings, which may have increased his attention to the task, again working against the main findings reported here. M.L. had to report on more memories than comparison subjects during the Autobiographical Interview, resulting in a lengthier test session, although this difference was attenuated by the fact that M.L. generated shorter protocols per memory than comparison subjects. Furthermore, he showed good effort and attention to the task throughout the test session. The quality of mnemonic retrieval was unrelated to time on task.

4.1. Episodic memory, autonoetic consciousness, and Endel Tulving

Endel Tulving boldly integrated quality of conscious experience into cognitive psychological theory (Tulving, 1985). The modern definition of episodic memory, a conjunction of self, autonoetic awareness, and subjectively sensed time (Tulving, 2001, 2002), evolved to be markedly different from the original definition involving memory for laboratory stimuli specific in time and place (Tulving, 1972), a feat that can be accomplished by non-episodic memory processes. Tulving's ideas were not always welcomed (McKoon, Ratcliff, & Dell, 1986; see also Tulving, 2002). Indeed, the notion of a neuroanatomical system supporting episodic recollection distinct from semantic processing or familiarity continues to be debated (Aggleton & Brown, 2006; Squire, Wixted, & Clark, 2007).

Unlike most cognitive neuropsychologists of his generation, Tulving drew upon neuropsychological patients in the development of his theory (Rosenbaum et al., 2005). Furthermore, he recognized the potential of functional neuroimaging at its advent, and in fact was both experimenter and subject in the first reported activation study of episodic memory (Tulving, 1989), which used autobiographical stimuli. Tulving remains interested in functional neuroimaging to this day because of its potential to reveal dissociations associated with different states of consciousness within memory that cannot be discerned from behavior alone.

When M.L. recovered from his severe traumatic brain injury, he did not appear obviously impaired because he could reproduce information about his autobiographical past. It was not until family members noticed inconsistencies in his reports that it became apparent that he had no recollection of past events. M.L.'s performance on standard laboratory memory tests cannot be distinguished from that of comparison subjects, until he is asked to classify the products of his retrieval as remembered vs. known. He can encode and retain autobiographical information and for at least some events he can produce details that a trained scorer classifies as episodic-like, yet he reports a subjective sense of disconnection from these events.

Functional neuroimaging data provides crucial information required to link such deficits to neurocognitive systems, especially when tasks with established functional neuroanatomy are used. Thus M.L. showed hypoperfusion in right prefrontal regions thought to be crucial to recollection of laboratory test materials. In the present study, he showed reduced activation in crucial nodes within the autobiographical network. Unlike self-report data, these data are not subject to demand characteristics or bias.

M.L. has a focal lesion hypothesized to disconnect the right frontal and temporal lobes in the context of severe diffuse axonal injury. The functional neuriomaging data reported here suggest reductions in the autobiographical network as a result of these injuries. Episodic autobiographical amnesia can be seen in association with temporal lobe epilepsy (Addis, Moscovitch, & McAndrews, 2007), transient epileptic amnesia (Butler & Zeman, 2008), herpes simplex encephalitis (Kopelman et al., 2003), and psychogenic amnesia (Kopelman & Kapur, 2001). Less striking episodic autobiographical memory impairment can also been seen in association with aging (Levine et al., 2002; Piolino, Desgranges, Benali, & Eustache, 2002) and dementia (McKinnon et al., 2008; Piolino et al., 2003). The significance of episodic autobiographical memory impairment therefore goes beyond the theoretical contributions brought about by single cases. The clinical implications follow from Tulving's predictions that autonoetic consciousness that supports episodic memory supports other self-related information processing capacities, notably projection of the self into the future, a topic that has recently received significant attention (Buckner & Carroll, 2007; Schacter, Addis, & Buckner, 2007; Spreng & Levine, 2006) (for further description of M.L.'s future-related behavior, see Levine et al., 1998; Levine et al., 1999). We are indebted to professor Tulving for helping to bring these deficits to light.

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Appendix A

A.1. Sample recordings

A.1.1. Personal episodic

Patient M.L.

First day of the weekend with the kids alone—just with me

Recording

Today was a great day, we were alone just me and the kids. Actually we were alone since yesterday afternoon. However, today was a day we spent whole day together, we did lot of neat things, went to the market, farmers market here in town, bought a box of produce, and vegetable and fruits and stuff. Then we did some shopping, get some household items, then for supper my daughter helped me to prepare supper. And we got some worms just for our fishing trip planned for tomorrow morning. And then we watched the movie tonight with dinner. It was a great night, the kids were enjoying themselves.

Autobiographical Interview transcription

M.L.: A tough one—not whole a lot of recollection I have of this one. Going to the farmers market. . . Going to the Farmer's market. . . .. Worms . . . Honestly this is a though one. I, yeah, I can't place it.

Examiner: Nothing?

M.L.: I mean I'm putting things together, that's only, that's not what we want. Nothing else I bet you if we check the dates we might—what I'm thinking is the worms and the fishing on Father's day, I'm wondering if this was, this the day before I did the fishing, going fishing and my daughter catching the first fish of the day. Yeah, I can't, there is nothing. Nothing there.

Comparison subject

Buying a housewarming gift for Mike and Shannon

Recording

So this is on the road back now from St. Patrick's Day weekend. I stayed at Mike and Shannon in their apartment—second weekend in a row. I wanted to get them a house warming gift. So I went out and decided to get them scotch glasses because I was making scotch drinks on the weekend. So Mike and Shannon took off for work, I got up and drove my car down to the Green Emporium—left the door unlocked so I could get back in. Bought the scotch glasses there. Got them boxed up – got some wrapping paper – went back and I wrapped it on the floor in Mike and Shannon's living room. It was extremely frustrating because I suck at wrapping presents. Anyway, I wrote out the card. It was a sort of paper, environmentally friendly handmade card thing.

Autobiographical Interview transcription

Subject: I remember that I was tired and slept in. It was a day when Mike and Shannon had gone to work. I thought we'd kick around the apartment—try and pack up and get going but I really wanted to get them a house warming gift. I remember pulling up on Banks Street on the west side of the street to one of the meters right outside—Royal Bank was across the street to the left there. Going in, poking around. I can remember that I specifically wanted to get scotch glasses, so I remember looking at the selection of glasses, trying to choose what I thought was a good idea. I remember talking to the sales person who was a woman – middle aged – asking her if what I was looking at was a good scotch glass and she of course encouraged me that they were. She put them in a box—it was a very deep square box with dividers in it. I think I got four glasses maybe. They were kind of rounded square shape glasses—pretty nice. She put them in a box for me and I remember getting the papering. I think that the paper that I got was there hanging in loose sheets over sticks and I picked a piece that I liked and a card. It was sort of fibrous sort of card. And I remember getting back to the apartment. I remember being on the floor trying to get tape and scissors together and stuff to wrap this thing and writing something in the card. I remember specifically leaving the gift, or the card anyway, on the little – Mike's little night table that's light wood – a night stand that we used to have when we kids. It sits in there – top of their stairwell in the lobby – and leaving it there so they would see it when they came in. And that's it.

A.1.2. Personal semantic

Patient M.L.

Location of our laundry room

Our laundry room is located at the end of the hall, downstairs, off the family room. It's the last door off to the right. As you go into the laundry room, on the right hand side is the washer itself, for clothes washing. Next to it is the laundry tub. We have two laundry tubs attached together. In the corner if you're just entering the room, right next to you is a laundry machine. In the far left corner off to your left is the dryer, vents to the outside. It's about a 12 × 15 room—15 being the distance between the washer and the dryer.

Comparison subject

I fill the kettle on the stove with cold water or half way up or however many people are having tea. I put that on the stove and light it. I take the teapot with the broken lid and rinse that out with warm water and then I put enough tea bags in it, which are just above the stove. I take those out and I put enough for the people having tea. Then I finish doing whatever I was doing at the time, wait for the kettle to whistle. When the kettle whistles I take the lid off the kettle pour it into the teapot, put the lid back on the teapot.

A.1.3. General semantic

The Maltese

Every year a carnival with dance and masquerade balls kick off the summer of Toronto's 6000 member Maltese community, the largest in Canada. Thousands of people line the streets for a parade which includes resounding marching bands and festive floats. The parade passes Malta Park, a small park named in recognition of the contributions of Maltese Canadians to Canada. The parkette is encircled by a Maltese neighborhood with shops, clubs, and the community's landmark, St. Paul the Apostle Roman Catholic Church. The entire community dates back to 1840.

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