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The nature of anterograde and retrograde memory impairment after damage to the medial temporal lobe

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ABSTRACT

The study of anterograde and retrograde amnesia (AA and RA) in the laboratory and the clinic has provided important information about the structure and organization of memory. The severity of AA is usually correlated with the severity of RA. Nevertheless, variations in the expression of AA and RA have been reported, which presumably reflect variation in the locus and extent of brain damage. The relationship between AA and RA has rarely been described quantitatively in groups of patients where detailed anatomical information is available. We have quantified the severity of AA and RA for factual information in 11 memory-impaired patients with bilateral medial temporal lobe lesions, including 5 for whom detailed post-mortem neurohistological information was available. The findings describe an orderly relationship between AA and RA, such that patients with more severe AA also had more extensive RA. In addition, RA was measurable only after AA reached a substantial level of severity. This relationship between AA and RA in patients with identified medial temporal lobe lesions appears to describe a general principle, which applies to a range of etiologies, including traumatic amnesia, where the locus and extent of brain damage is less well understood. Whenever patients deviate substantially from the relationship described here, one should be alert to the likelihood that significant damage has occurred outside or in addition to the structures in the medial temporal lobe.

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1. Introduction

The phenomena of anterograde and retrograde amnesia have been described in the laboratory and clinic for more than 100 years (Ribot, 1881) and have been an important source of information about the structure and organization of memory. Anterograde amnesia (AA) refers to an impaired capacity for new learning. Retrograde amnesia (RA) refers to the loss of information that was acquired before the onset of amnesia. It has long been recognized that AA and RA tend to occur together in the same patients (Barbizet, 1970; Rose & Symonds, 1960; Russell, 1971; Victor, 1969). In addition, the severity of AA is usually correlated with the severity of RA (Kopelman, 1989; Squire & Alvarez, 1995; Wickelgren, 1979). Yet it is also true that RA can sometimes appear disproportionately severe in comparison to AA (Barr, Goldberg, Wasserstein, & Novelly, 1990; Bright et al., 2006; Hornberger et al., 2010; Kapur, Ellison, Smith, McLellan, & Burrows, 1992; Milton et al., 2010; O'Connor, Butters, Miliotis, Eslinger, & Cermak, 1992; Reed & Squire, 1998; Sehm et al., 2011). Moreover, AA can sometimes occur in the absence of RA (Corkin, Hurt, Twitchell, Franklin, & Yin, 1987; Russell & Nathan, 1946). These examples illustrate variations in the expression of AA and RA, which presumably depend on the locus and extent of brain injury or disease. Detailed neuroanatomical information should clarify the relationship between AA and RA.

The most comprehensive study of the relationship between AA and RA was carried out in more than 1000 patients who had sustained closed head injury (Russell & Nathan, 1946). Fig. 1 shows the relationship between the duration of post-traumatic amnesia and the extent of RA for 972 cases. RA was assessed informally, usually by querying about autobiographical information. We take the duration of AA to be indicated by the time after injury when post-traumatic amnesia resolves. As the duration of AA increased, the number of cases exhibiting pronounced RA also increased. Interestingly, when AA covered one day or less, only a small number of cases ($N=19$) exhibited substantial RA (Russell & Nathan, 1946; Table 4a). In fact, out of the 503 cases exhibiting AA of one day or less, 32 had no RA at all. These data describe an

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orderly relationship between AA and RA and also suggest that AA may need to reach some threshold of severity before RA is observed. Put differently, it appears to be easier to disrupt new learning ability and harder to disrupt already acquired information, presumably because some fixation or consolidation of memory has occurred (McGaugh, 2000; Squire & Alvarez, 1995). Unfortunately, in cases of (non-penetrating) traumatic brain injury, the locus and extent of damage is often difficult to determine. In patient groups with identified neuroanatomical change, little information is available about how the severity of AA relates to the severity of RA.

To obtain quantitative information about AA and RA in patients with identified neuropathological change, we have determined the severity of AA and RA in 11 memory-impaired patients with identified bilateral lesions within the medial temporal lobe. For five of the patients, detailed post-mortem neurohistological information was available. Patients were assessed with five measures of AA and one measure of RA. The AA measures assessed both verbal and nonverbal learning ability. For measures of RA, we considered using either tests of autobiographical information or tests of factual information.

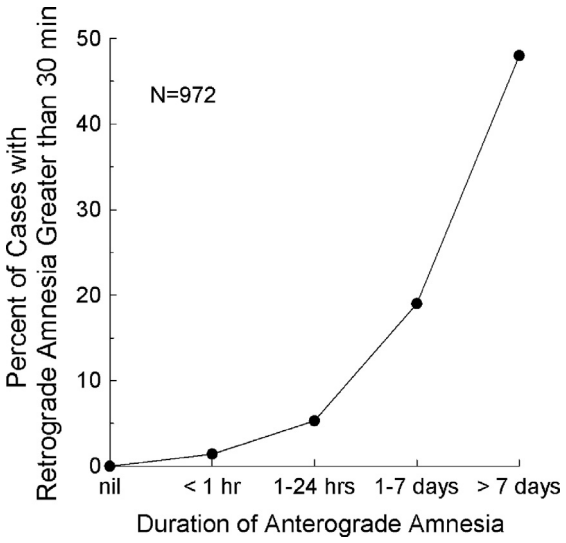

Fig. 1. The relationship between the duration of anterograde amnesia (AA) and the severity of retrograde amnesia (RA) in 972 cases of traumatic brain injury. Note the orderly relationship between AA and RA. Data from Russell and Nathan (1946); Table 4. We have considered the duration of AA to be the time after injury when post-traumatic amnesia resolves.

Whereas early studies of RA depended on informal interviews that focused on autobiographical information, beginning in the 1970s methods were developed to assess RA quantitatively by asking factual questions about news events or famous persons from different past time periods (Albert, Butters, & Levin, 1979; Marslen-Wilson & Teuber, 1975; Sanders & Warrington, 1971). Quantitative assessments of autobiographical memory were also subsequently developed (Crovitz & Schiffman, 1974; Kopelman, Wilson, & Baddeley, 1989), but these do not easily achieve the kind of temporal resolution that is afforded, for example, by news events tests. Accordingly, to explore the quantitative relationship between AA and RA, we assessed RA with a test of approximately 100 news events that covered most of the life span prior to the onset of amnesia.

2. Materials and methods

2.1. Participants

Data are presented for eleven memory-impaired patients with damage limited to the MTL (Table 1). For the first five patients described below, the description of damage was based on post-mortem neurohistological analysis. Patient RB became amnesic in 1978 at age 52 as the result of an ischemic event that occurred as a complication of open heart surgery. After his death in 1983, he was found to have bilateral damage limited to the CA1 field of the hippocampus (Zola-Morgan, Squire, & Amaral, 1986). Patient GD became amnesic in 1983 at age 43 following a period of hypotension that occurred during major surgery. After his death in 1992, he was also found to have bilateral damage limited to the CA1 field of the hippocampus (Rempel-Clower, Zola, Squire, & Amaral, 1996). Patient WH became amnesic in 1986 at age 57 possibly due to cerebral ischemia. After his death in 1993, he was found to have bilateral damage involving all fields of the hippocampus as well as damage to the dentate gyrus, subiculum, and some of entorhinal cortex (Rempel-Clower et al., 1996). Patient LM became amnesic in 1984 at age 54 as the result of respiratory distress that occurred during an epileptic seizure. After his death in 1990 he was found to have bilateral damage involving all fields of the hippocampus as well as damage to the dentate gyrus (Rempel-Clower et al., 1996). Patient EP became amnesic in 1992 at age 70 after contracting viral encephalitis. After his death in 2008, he was found to have large, bilaterally symmetric lesions of the MTL that eliminated the temporal pole, the amygdala, the entorhinal cortex, the hippocampus, the perirhinal cortex, and rostral parahippocampal cortex. His lesion also extended laterally to substantially involve the fusiform gyrus. Perhaps because of loss of connectivity between medial and lateral structures, there were secondary changes in the superior, middle, and temporal gyri, which were atrophic, and the underlying white matter was gliotic (Insausti, Annese, Amaral, & Squire, 2013).

Of the remaining six patients, five have damage thought to be limited to the hippocampus (CA fields, dentate gyrus, and subicular complex), and one has large bilateral lesions of the MTL. Patient KE became amnesic in 2004 at age 63 after an episode of ischemia associated with kidney failure and toxic shock syndrome. LJ (the only female) became amnesic at age 51 during a 6-month period in 1988 with no known precipitating event. Her memory impairment has been stable since that time. Patient GP became amnesic in 1987 at age 41 after contracting viral

Table 1
Characteristics of memory-impaired patients.

Patient	Sex	Age (yr)	Education (yr)	Anatomical findings	IQ (WAIS-R)	WMS-R				
						Attention	Verbal	Visual	General	Delay
RB	M	53	10	H*	103	–	–	–	–	–
GD	M	45	12	H*	92	109	86	88	85	60
WH	M	64	17	H	113	88	72	82	67	< 50
LM	M	55	15	H	109	124	94	82	89	62
EP	M	79	12	MTL	98	94	59	92	68	56
KE	M	64	13.5	H	108	114	64	84	72	55
LJ	F	68	12	H	101	104	85	87	81	54
GP	M	57	16	MTL	98	102	79	62	66	< 50
RS	M	49	12	H	99	99	85	81	82	< 50
GW	M	46	12	H	108	105	67	86	70	< 50
JRW	M	42	12	H	90	87	65	95	70	< 50

Note: The Wechsler adult intelligence scale-revised (WAIS-R) and the Wechsler memory-scale revised (WMS-R) yield mean scores of 100 in the normal population, with a SD of 15. The WMS-R does not provide numerical scores for individuals who score < 50. KE, LJ, EP, GP, and GW were given the WAIS-III rather than the WAIS-R. RB was not given the WMS-R. Age indicates the age of the patient when given the news events test. Neurohistological information is available for the first five patients listed. Asterisk indicates a lesion limited to the CA1 field of the hippocampus. H, bilateral damage to the hippocampus with minimal damage to adjacent cortex; MTL, bilateral damage to the hippocampus and parahippocampal gyrus; IQ, intelligence quotient.

encephalitis. Patients RS and GW became amnesic in 1998 and 2001, respectively (ages 41 and 42), after drug overdoses and associated respiratory failure. Patient JRW became amnesic in 1990 at age 27 following an anoxic episode associated with cardiac arrest.

Estimates of MTL damage for these six patients were based on magnetic resonance images from 19 age-matched, healthy males for KE, GP, RS, GW, and JRW, and 11 age-matched, healthy females for patient LJ (Gold & Squire, 2005). Patients KE, LJ, RS, GW, and JRW have an average bilateral reduction in hippocampal volume of 49, 46, 33, 48 and 44% respectively (all values > 2.9 SDs from the control mean). On the basis of patients LM and WH, who had similar bilateral volume loss in the hippocampus (estimated from magnetic resonance images) and for whom detailed postmortem neurohistological information was obtained (Rempel-Clower et al., 1996), the degree of volume loss in these five patients likely reflects nearly complete loss of hippocampal neurons. For these same five patients, the volume of the parahippocampal gyrus (temporopolar, perirhinal, entorhinal, and parahippocampal cortices) is reduced by 11, −5, 10, 12 and −17%, respectively (all values within 2 SDs of the control mean). The post-encephalitic patient GP has a 96% reduction in hippocampal volume bilaterally and a 94% reduction in parahippocampal gyrus volume. Eight coronal magnetic resonance images from each of these patients, together with detailed descriptions of the lesions, can be found in Supplementary material. The volumes for parahippocampal gyrus differ a little from volumes reported previously for these patients and are based on recently published, more detailed guidelines for identifying the caudal border of the gyrus (Franko, Insausti, Artacho-Perula, Insausti, & Chavoix, 2012).

Additional measurements, based on four controls for each patient, were carried out for the frontal lobes, lateral temporal lobes, parietal lobes, occipital lobes, insular cortex, and fusiform gyrus (see Bayley, Gold, Hopkins, & Squire, 2005). For patients KE, LJ, RS, GW, and JRW, volumes of these regions are within 16% of control values. The only volume reduction greater than 1.3 SDs of the control mean was the parietal lobe for RS (Bayley et al., 2005). For patient GP, the volumes of the insular cortex and the fusiform gyrus were reduced bilaterally by 65% and 49%, respectively.

Forty-two healthy volunteers served as controls for the news events test (12 female, 60.4 ± 1.8 years of age, 13.6 ± 0.5 years of education; means ± SEMs). Eleven of these also served as controls for four of the anterograde memory tests (2 female, 61.3 ± 3.3 years of age, 15.7 ± 1.1 years of education; means ± SEMs). A separate group of eight volunteers (Squire & Shimamura, 1986) served as controls for one anterograde memory test: Rey Auditory Verbal Learning Test (5 female, 50.9 ± 1.2 years of age, 14.8 ± 0.7 years of education; means ± SEMs). All procedures were approved by the Institutional Review Board at the University of California San Diego. Participants gave written informed consent prior to participation in accordance with the Declaration of Helsinki.

2.2. Measuring anterograde amnesia

2.2.1. Delayed recall of a complex figure

Participants copied a complex diagram (Rey-Osterrieth figure; Osterrieth, 1944) and then reproduced it from memory after a 10–15 min delay. The copy and the reproduction of the figure were each scored on a 36-point scale (Taylor, 1998).

2.2.2. Paired-associate learning

Participants completed three study-test trials with a list of 10 unrelated word pairs (Squire & Shimamura, 1986). To begin, the word pairs were displayed one at a time while the experimenter read each pair aloud. Immediately after all 10 pairs were presented, participants were shown the first word from each pair and asked to recall the second word. This procedure was repeated two more times with the same pairs in different orders, and the score was the total number of pairs recalled (maximum = 30).

2.2.3. Rey auditory verbal learning test (RAVLT)

For the recall portion of the RAVLT, 15 words were presented orally, and then recall was tested. The study-test sequence was then repeated four times. The recognition portion of the test used 15 different words. Five successive study-test trials were given, and testing on each trial followed a yes-no format with 30 words (15 old 15 new). The score was the average percent correct score across all 10 trials. RB was not given this test.

2.2.4. Dementia rating scale

Participants were administered the memory subscale from the dementia rating scale (Mattis, 1976). The maximum score is 25 points. RB was not given this test.

2.2.5. Wechsler memory scale-revised (WMS-R) logical memory subtest

Recall was tested for two short prose passages, each consisting of 25 segments. The first passage was read aloud to the participant, followed by an immediate recall test. The second passage was then read aloud, also followed by an immediate recall test. Recall of both passages was then tested 30 min later. The score was the sum of segments recalled from both passages at the 30-min test. Patient RB received the WMS rather than the WMS-R.

Based on the performance of controls, *z*-scores were calculated for each patient for each of the five anterograde memory tests. The five *z*-scores were then averaged to create a measure of AA for each patient.

2.3. Measuring retrograde amnesia

News events test. The test was constructed from a pool of 289 questions covering notable news events that occurred in a specific year between 1938 and 2004. For each patient, the questions spanned from the onset of amnesia to the time when the patient was 15 years old (mean = 105.0 ± 17.5 questions per patient). We did not query earlier time periods, because even for healthy individuals performance is poor for news events that occurred during childhood or early adolescence (Squire, 1974). The news events test was administered in a free recall format (e.g., What caused a suspension bridge to collapse over the Narrows at Tacoma, Washington? [1940]; Who killed John Lennon? [1980], Who is Elizabeth Smart? [2003], the year for each event was not included as part of the question). The score was the percentage of questions answered correctly from each 5-year time interval covered by the test-from the five years immediately preceding the onset of amnesia to the time when the patient was 15 years old. An average of 13.1 questions (range 7.5 to 31.1 questions) was available for each 5-year time interval.

Eight to sixteen controls for each patient were identified from a pool of 42 controls, based on age, education, and when they took the test relative to the patient (within about 1 year). Some controls were matched to more than one patient. For each control, the questions were assigned to 5-year time intervals according to the time of onset of amnesia for the patient to whom the control was matched. The extent of RA for each patient was defined as the number of 5-year time intervals where the patient's score was significantly below the score of the controls for the same time interval (one-sample *t*-test). The AA and RA measures were obtained at roughly similar times (mean = 2.8 ± 0.9 years apart). This interval was calculated by averaging the dates when the five AA tests were given and subtracting this value from the date when the RA test was given.

Data for patients and the news events test have been published previously in a different format (Bayley, Hopkins, & Squire, 2006; Squire, Haist, & Shimamura, 1989; Zola-Morgan et al., 1986).

3. Results

Fig. 2 shows the severity of AA and RA for each patient. Across all 11 patients, there was a significant relationship between AA and RA ($r = 0.81$, $p < 0.005$), such that patients with more severe AA had more severe RA. Thus, when damage extended outside the hippocampus to substantially involve the parahippocampal gyrus (EP and GP), substantial RA was consistently observed, and AA was

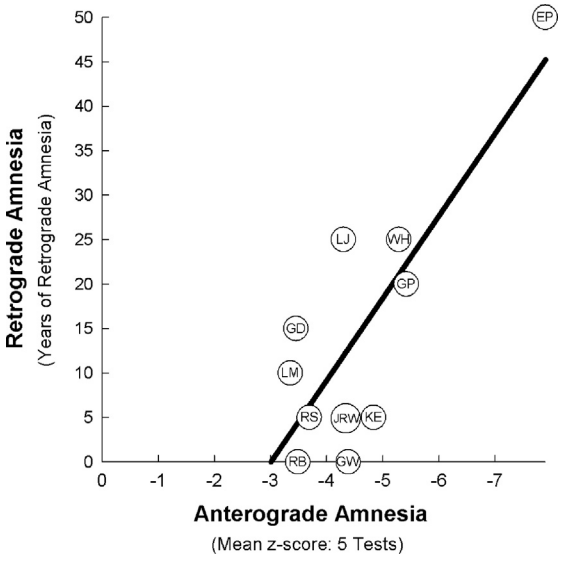

Fig. 2. The relationship between the severity of anterograde amnesia (AA) and the severity of retrograde amnesia (RA) in 11 patients with bilateral damage to the medial temporal lobe ($r = 0.81$, $p < 0.005$). Patients are represented by their initials (see Table 1). AA is the mean *z*-score from five tests of new learning ability (see Section 2.2). RA was measured by a test of approximately 100 questions about notable news events that covered most of the lifespan prior to the onset of amnesia. The extent of RA was measured in 5-year intervals (see Section 2.3).

very severe ($z=-6.7$). Patient EP had the most severe AA and also had more RA than any other patient. Finally, when the lesion was limited largely to the hippocampus, RA and AA were less severe (for AA, $z=-4.1$).

We also estimated the severity of RA by calculating each patient's mean percent correct score across the entire test (instead of calculating the number of 5-year time periods in which patients obtained impaired scores). A significant relationship between AA and RA was found with this method ($r=0.73$, $p<0.05$; Fig. S2A). The relationship was also strong when the mean percent correct scores were converted to z-scores based on how many standard deviations each patient's score fell below the control group's score ($r=0.79$, $p<0.01$; Fig. S2B).

It has been suggested that comparisons of AA and RA would be advantaged by using the same kind of test to assess both AA and RA (Kopelman, 2000; Mayes, 2002; Mayes, Daum, Markowisch, & Sauter, 1997). Ten of the 11 patients in our study were tested not only about news events that occurred before they became amnesic but also about news events that occurred after they became amnesic. For these patients a mean of 71.6 questions covered the period after they became amnesic. AA was estimated by calculating a mean percent correct score for each patient. By this method, AA and RA were related ($r=0.73$, $p<.05$; Fig. S3A). A marginal relationship between AA and RA was found when the percent correct scores were converted to z-scores ($r=0.59$, $p<.08$; Fig. S3B). The results of two additional analyses are illustrated in Fig. S4A, B.

It is apparent in Fig. 1 that measurable RA was observed only after AA reached a substantial level of severity. While RA covering less than 5 years would not have been detected by our method, which depended on 5-year time intervals, the results indicated that RA does not typically reach back 5 years or more unless AA is quite severe. In addition, one should not conclude that patients without detectable RA (RB and GW) had no RA at all. Rather, RA may not have covered a sufficient number of years in the most recent 5-year interval for impairment to be detected. In fact, GW did exhibit two years of RA on the news events test when the 5-year interval immediately prior to the onset of amnesia was rescored year by year.

4. Discussion

We measured AA and RA in 11 patients with damage to the MTL. As the severity of AA increased, so did the severity of RA. Patients with damage to both the hippocampus and parahippocampal gyrus exhibited the most severe AA and the most severe RA. Patients with damage limited largely to the hippocampus exhibited less severe AA and less severe RA. Although there was variability in the severity of RA, the average severity of RA in the two patient subgroups (mean=10 years, median=5 years for the hippocampal group and mean=35 years, median=35 years for the MTL group) are in line with previous reports (Bayley et al., 2006; Manns, Hopkins, & Squire, 2003).

Our findings for memory-impaired patients with bilateral MTL lesions parallel the findings from a large study of closed-head injury (Russell & Nathan, 1946) as well as the findings from a smaller study of 25 patients (Blomert & Sisler, 1974). For all these patient groups the relationship between AA and RA was similar. RA was substantial only after a threshold of AA was reached (compare Figs. 1 and 2). In the case of our patients (Fig. 2), one could wonder if RA might have been detected in association with less severe AA if the test of RA had been more sensitive (i.e., if our test could have detected an RA of less than five years). Yet, Russell and Nathan observed a threshold even when AA and RA were measured in minutes and days instead of years. For example, when AA was 1 day or less, 6–10% of patients exhibited no RA at all (Russell & Nathan, 1946, Tables 4 and 5). Moreover, even when AA covered more than 1 day, 27% of patients had RA of less than 1 min (Russell & Nathan, 1946, Table 5). Lastly, in the case of gunshot wounds to the head, 65 of 185 cases had a definite period of AA but no RA at all (Russell & Nathan). Thus, anterograde memory is easier to disrupt than retrograde memory, and this conclusion does not depend on the sensitivity of the measures.

All these studies found variable severity of RA in patients with a similar severity of AA. For example, in our study RA ranged from no RA to 15 years in patients with similar AA (GD, LM, RB, and RS). In the study of traumatic amnesia, RA ranged from 0 to 12 h when AA was 1 day or less (Russell & Nathan, 1946, Tables 4 and 5). In addition, RA was consistently observed when AA was sufficiently severe. [Note one report of traumatic amnesia ($N=109$) that found no relationship between AA and RA (Corkin et al., 1987), though in this study patients with the mildest and most severe symptoms were excluded.]

Although patients with MTL lesions, as presented here, and patients with traumatic amnesia provide the most complete information about the relationship between AA and RA, the fact that AA and RA are often associated has been noted in patients with a range of etiologies. Thus, AA and RA have been described as appearing and then diminishing together (though not necessarily at the same rate) in cases of transient global amnesia (Evans, 1966; Fisher & Adams, 1964; Kritchevsky & Squire, 1989; Shuttleworth & Morris, 1966), Wernicke's encephalopathy/Korsakoff's psychosis (Victor, Adams, & Collins, 1989), tumors or cysts near the third ventricle (Ignelzi & Squire, 1976; Victor, 1969), electroconvulsive therapy (Squire & Chace, 1975; Squire, Slater, & Miller, 1981), and transient epileptic amnesia (Zeman, Boniface, & Hodges, 1998). Note that interpretation of remote memory performance in transient epileptic amnesia can be complicated by the fact that poor memory performance (particularly for recent time periods) may result from impaired new learning (secondary to seizures) as well as from retrograde memory loss itself (Butler & Zeman, 2008; Hornberger et al., 2010). Note too that this association between AA and RA need not hold in all circumstances, for example, in Korsakoff's syndrome (Fama, Marsh, & Sullivan, 2004; Mayes et al., 1997), when remote memory impairment can be extensive and its severity related in part to abnormalities in neocortex (Fama et al., 2004), rather than the MTL.

It is worth mentioning that in some of these studies, and in the work by Russell and Nathan (1946) RA was assessed with measures of autobiographical memory. Our study assessed RA by testing semantic memory for public events, so that our conclusions about the relationship between AA, RA, and MTL damage are limited to non-autobiographical material. It would be useful to study the relationship between AA and RA in patients with medial temporal lobe damage using tests of autobiographical memory. Unfortunately, the tools available to measure autobiographical memory do not easily lend themselves to such an analysis. Specifically, most of the tests (Kopelman et al., 1989; Levine, Svoboda, Hay, Winocur, & Moscovitch, 2002) sample only a few time periods. Better tests could be constructed [see Bayley, Hopkins, and Squire (2003) for use of the method introduced by Crovitz and Schiffman (1974)], but even then it would be difficult to achieve good temporal resolution across the life span.

Patient EP had the most severe AA and the most severe RA, which covered as much as 50 years prior to the onset of his amnesia (Fig. 2). Nonetheless, his performance improved somewhat when questions concerned events that had occurred >30 years before his amnesia and reached normal levels for the period 46–50 years before amnesia when he was 20–24 years old. Although EP's score for RA did fall within the 95% confidence interval of the regression line (even when his data were not used

to construct the regression line), he differed from the other patients in that his neuropathology extended into lateral temporal cortex. These changes appeared to be secondary to the primary focus of his encephalitic lesion (Insausti et al., 2013). Accordingly it is possible that these changes in lateral temporal cortex made some contribution to the extent and severity of his retrograde memory loss.

Lateral temporal cortex is essential for long-established semantic knowledge about objects and word meanings (Hodges & Graham, 2001; Hodges, Patterson, Oxbury, & Funnell, 1992; Levy, Bayley, & Squire, 2004). Damage to this region has also been associated with cases where RA is disproportionately severe in comparison to AA (Barr et al., 1990; Bright et al., 2006; O'Connor et al., 1992; Reed & Squire, 1998). Particularly notable are cases of what has been termed focal retrograde amnesia (Hornberger et al., 2010; Kapur, 1993; Kapur et al., 1992; Kopelman, 2000; Sehm et al., 2011). [Note that it can be difficult to distinguish focal retrograde amnesia from psychogenic amnesia (Kopelman, 2000; Markowitsch, 2002)].

In summary, we examined the relationship between AA and RA for factual information in patients with MTL lesions where detailed anatomical information was available. There was an orderly relationship between the severity of AA and the extent of RA. A similar relationship between AA and RA appears to hold in the case of patients with a range of etiologies where the locus and extent of brain injury is less well understood. In these cases [for example, in patients with traumatic amnesia from closed head injury (Russell & Nathan, 1946)], we suggest that significant dysfunction has occurred within the MTL. Similarly, for new cases, one might propose that, when AA and RA scores are in a similar relationship to what we report here, significant damage has occurred within the MTL. Furthermore, when patients have AA and RA scores that deviate substantially from the relationship described here, one should be alert to the likelihood that significant damage has occurred outside of or in addition to structures in the MTL.

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Appendix A. Supplementary Material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.neuropsychologia.2013.09.015.

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Supplemental Material

Figure S1

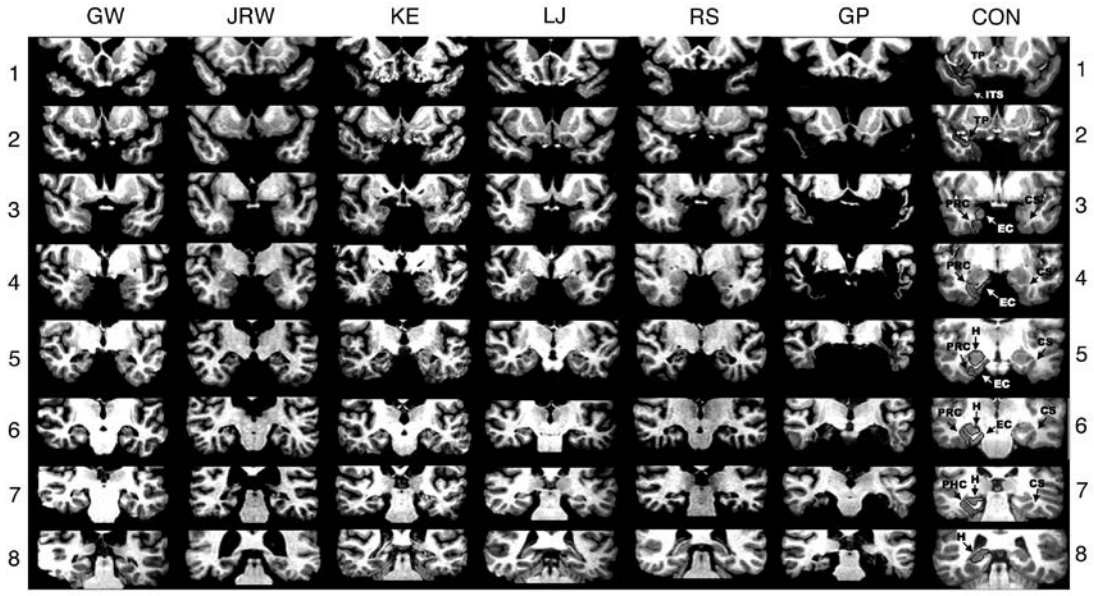

Figure S2

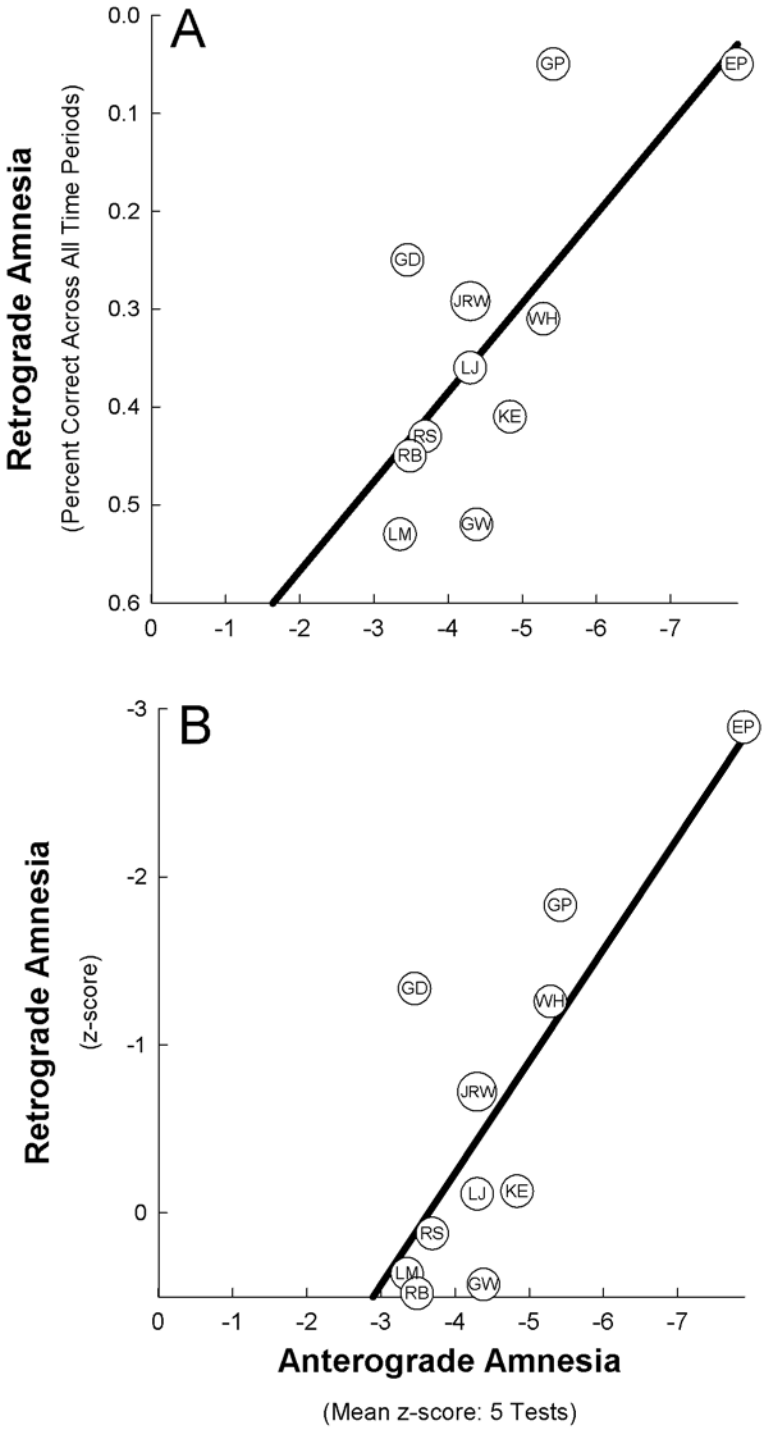
A
Retrograde Amnesia
(Percent Correct Across All Time Periods)
0.0
0.1
0.2
0.3
0.4
0.5
0.6
0
-1
-2
-3
-4
-5
-6
-7
GP
EP
GD
JRW
WH
LJ
KE
RS
RB
LM
GW
B
Retrograde Amnesia
(z-score)
-3
-2
-1
0
Anterograde Amnesia
(Mean z-score: 5 Tests)

Figure S3

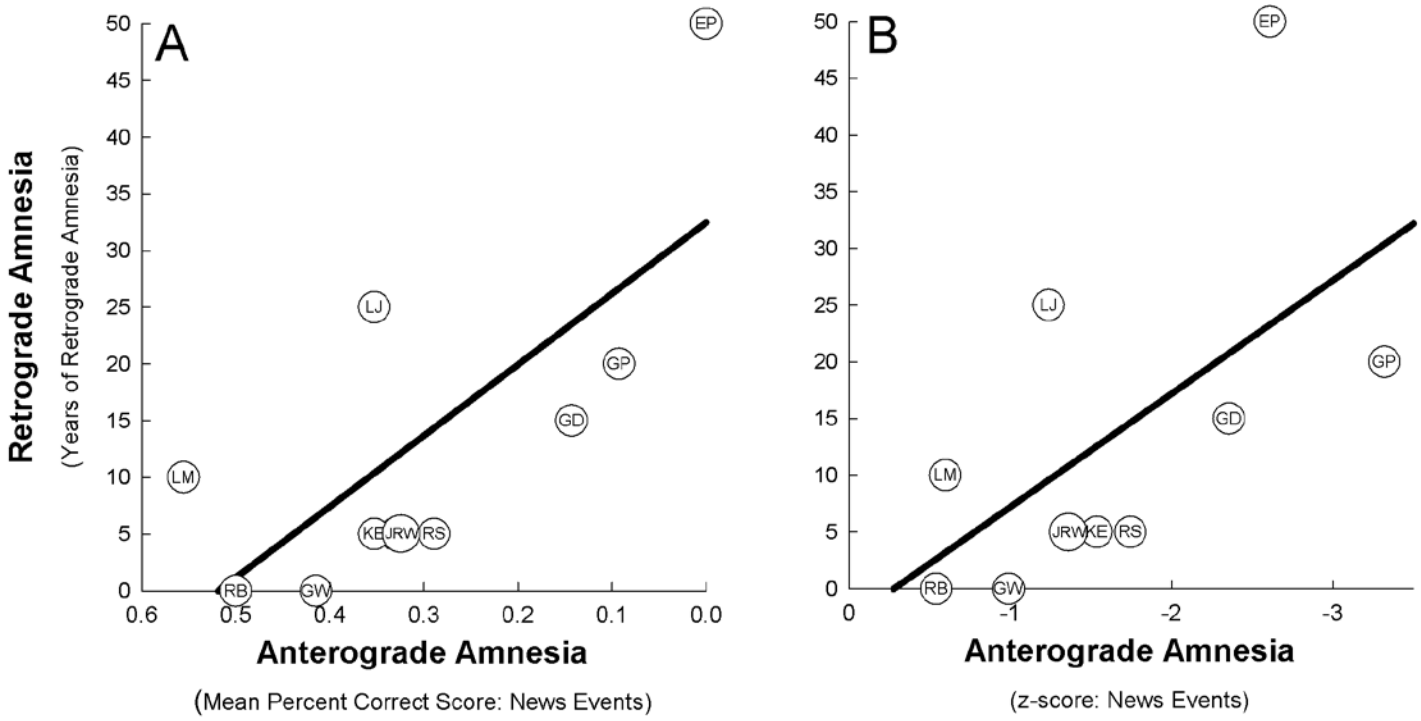
A
B
Retrograde Amnesia
(Years of Retrograde Amnesia)
Anterograde Amnesia
(Mean Percent Correct Score: News Events)
Anterograde Amnesia
(z-score: News Events)
EP
LJ
GP
GD
LM
KE
JRW
RS
RB
GW

Figure S4

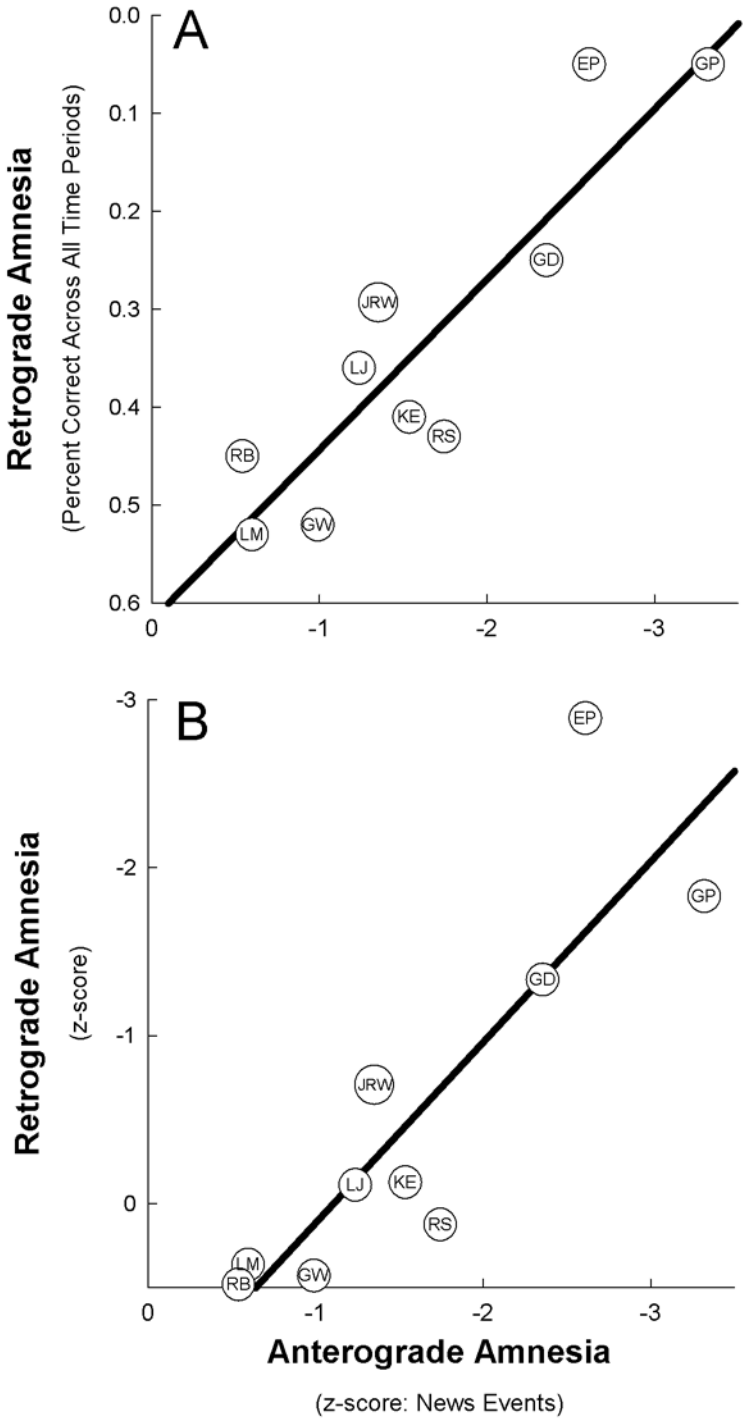
A
B
Retrograde Amnesia
(Percent Correct Across All Time Periods)
Retrograde Amnesia
(z-score)
Anterograde Amnesia
(z-score: News Events)
EP
GP
GD
JRW
LJ
KE
RS
RB
LM
GW
0.0
0.1
0.2
0.3
0.4
0.5
0.6
-3
-2
-1
0

Figure Captions

Figure S1. Series of eight T1-weighted coronal images of six patients are illustrated with limited hippocampal lesions (GW, JRW, KE, LJ, and RS), one patient with extensive medial temporal lobe damage (GP), and one control (CON). The sections proceed posteriorly in 7mm intervals from the temporopolar (TP) cortex in the top section. The left side of the brain is on the right side of each image.

As described by Insausti et al. (1998), TP cortex extends medially from the inferotemporal sulcus (ITS) to the fundus of the TP sulcus. TP cortex extends rostrally from the tip of the temporal pole caudally to the limen insula (LI), which approximates the border between the TP cortex and perirhinal cortex (PRC). Caudal to TP cortex, the collateral sulcus (CS) is the most important structure for the identification of medial temporal lobe cortices. At its most rostral extent, the CS is surrounded entirely by PRC. Caudally, entorhinal cortex (EC) extends from the midpoint of the medial bank of the CS to the subiculum, while PRC extends laterally from the midpoint of the medial bank of the CS to the inferotemporal cortex. Two millimeters caudal to the disappearance of the gyrus intralimbicus of the hippocampus (H), the CS is surrounded by parahippocampal cortex (PHC). The caudal border of the posterior PHC is defined as lying 1.5mm posterior to the crus of the fornix at the point where the fimbria turns upwards to continue as the posterior pillars of the fornix and posterior to the pulvinar nucleus of the thalamus (Franko et al., 2012).

The top section (1) shows the TP cortex and the ITS in the control brain. None of the patients with limited hippocampal lesions have damage evident at this level. For GP, the TP cortex is missing. The ITS is visible bilaterally at this level for patients GW, JRW, KE, and RS. For LJ, only the right ITS is visible. The second section (2) shows TP cortex and the ITS in the control brain. The ITS and TP cortex is evident in all patients with limited hippocampal lesions at this level. None of the patients with limited hippocampal lesions has damage evident at this level. For GP, note that the portion of the temporal lobe missing corresponds to TP cortex and involves the lateral temporal lobe to a minimal extent (~10%). The CS is visible, indicating the beginning of PRC, in patients KE and RS (right side only). The third section (3) shows the CS and surrounding PRC and EC in the control brain. None of the patients with limited hippocampal lesions have damage evident at this level with the exception of KE, who has damage in the basal ganglia secondary to toxic shock syndrome (and to a lesser extent in section 4). For patients GW, KE, and LJ, the PRC is evident on the left side, bounded by the LI and CS. On the right side, both EC and PRC are evident. For patients JRW and RS, both EC and PRC are evident bilaterally. For GP, no CS or surrounding tissue is evident. The fourth section (4) shows the anterior hippocampus and the adjacent PRC and EC in the control brain. The hippocampus is not yet visible at this level in any of the other patients with limited hippocampal lesions. No damage to the PRC or EC is evident for any of the patients at this level, except for GP who has no medial temporal lobe tissue at this level. The fifth section (5) shows the hippocampus and the adjacent PRC and EC in the control brain. The CS and the surrounding PRC and EC appear normal in all patients at this level with the exception of GP, who has no medial temporal lobe tissue at this level. Damage is evident in the hippocampal region of all patients. The sixth section (6) shows the hippocampus and the adjacent PRC and EC in the control brain. Damage is evident in the hippocampal region for all patients at this level. The surrounding PRC and EC appear normal in all patients except GP, who has little normal medial temporal lobe tissue in either hemisphere. Both the PRC and EC are visible in all hippocampal patients bilaterally, with the exception of JRW for whom only PRC is visible on the left side, indicated by the disappearance of the gyrus intralimbicus 2 mm rostral to the sixth section (not shown). The seventh section (7) shows the hippocampus and the CS, surrounded by PHC in the control brain. Damage to the hippocampus is evident in all patients at this level. In all patients with damage limited to the hippocampus, the PHC is evident. Patient GP has little normal medial temporal lobe tissue in either hemisphere. The eighth section (8) shows the hippocampus in the control brain. Bilateral hippocampal damage is evident in patients GW, KE, and GP at this level. Patient

LJ shows hippocampal damage only on the left side, and no damage is evident in patient RS. At this level, the hippocampus is no longer evident in patient JRW. PHC is no longer evident at this level in patients JRW, KE, LJ, or RS and PHC appears normal in patient GW. Patient GP has some spared PHC on the right at this level. The warping artifact in the right lateral temporal lobe of GW on this section did not interfere with the assessment of his damage. Posterior to this level, GP exhibits hippocampal damage and damage to the PHC. No damage is evident posterior to this level for any of the other patients.

Figure S2. The relationship between the severity of anterograde amnesia (AA) and the severity of retrograde amnesia (RA) in 11 patients with bilateral damage to the medial temporal lobe. Patients are represented by their initials (see Table 1). AA is the mean z-score from five tests of new learning ability (see section 2.2). RA was measured by a test of approximately 100 questions about notable news events that covered most of the lifespan prior to the onset of amnesia. A. The severity of RA was estimated by calculating each patient's mean percent correct score across the entire test($r = 0.73$, $p < 0.05$). B. The severity of RA was estimated by calculating each patient's mean percent correct score across the entire test and then converting the percent correct score to a z-score ($r = 0.79$, $p < 0.01$).

Figure S3. The relationship between the severity of anterograde amnesia (AA) and the severity of retrograde amnesia (RA) in 10 patients with bilateral damage to the medial temporal lobe. Patients are represented by their initials (see Table 1). RA was measured by a test of approximately 100 questions about notable news events that covered most of the lifespan prior to the onset of amnesia. The extent of RA was measured in 5-year intervals (see section 2.3). A. AA is the mean percent correct score for questions about news events that occurred after the onset of amnesia ($r = 0.73$, $p < 0.05$). B. AA was estimated by calculating each patient's mean percent correct score for questions about news events that occurred after the onset of amnesia. This score was then converted to a z-score ($r = 0.59$, $p < 0.08$).

Figure S4. The relationship between the severity of anterograde amnesia (AA) and the severity of retrograde amnesia (RA) in 10 patients with bilateral damage to the medial temporal lobe. Patients are represented by their initials (see Table 1). AA was estimated by calculating each patient's mean percent correct score for questions about news events that occurred after the onset of amnesia. This score was then converted to a z-score. RA was measured by a test of approximately 100 questions about notable news events that covered most of the lifespan prior to the onset of amnesia. A. The severity of RA was estimated by calculating each patient's mean percent correct score across the entire test ($r = 0.89$, $p < 0.001$). B. The severity of RA was estimated by calculating each patient's mean percent correct score across the entire test and then converting the percent correct score to a z-score ($r = 0.86$, $p < 0.01$).

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