

Neuroimaging H.M.: A 10-Year Follow-Up Examination

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ABSTRACT: In 1997, Corkin et al. described the anatomical boundaries of the amnesic patient H.M.'s surgical resection, based on a comprehensive analysis of magnetic resonance imaging (MRI) scans collected in 1992 and 1993 (Corkin et al. (1997) *J Neurosci* 17:3964–3979). We subsequently scanned H.M. on several occasions, employing more advanced data acquisition and analysis methods, and now describe additional details about his brain anatomy and pathology. This account combines results from high-resolution T1-weighted scans, which provide measures of cortical and subcortical morphometry, diffusion tensor images, which provide quantitative information about white matter microstructure and the anatomy of major fasciculi, and T2-weighted images, which highlight damage to deep white matter. We applied new MRI analysis techniques to these scans to assess the integrity of areas throughout H.M.'s brain. We documented a number of new changes, including cortical thinning, atrophy of deep gray matter structures, and a large volume of abnormal white matter and deep gray matter signal. Most of these alterations were not apparent in his prior scans, suggesting that they are of recent origin. Advanced age and hypertension likely contributed to these new findings. © 2006 Wiley-Liss, Inc.

KEY WORDS: amnesia; medial temporal lobe; human; explicit/declarative memory; diffusion tensor imaging; cortical thickness

INTRODUCTION

The patient H.M. is now 80 years old. In 1953, he received a bilateral medial temporal lobe (MTL) resection, an experimental operation intended to relieve his severe, intractable epilepsy. This procedure reduced the frequency of his seizures, but also deprived him of almost all new memory for facts and events, as well as information from at least 11 years preceding his surgery (Scoville and Milner, 1957; Corkin, 1984; Sagar et al., 1985). The specific attributes of the cognitive deficits induced by this lesion have been of great importance in the years since his operation. Through this novel surgical procedure, neuroscientists were first able to understand the significance of the hippocampus and other MTL structures for specific aspects of memory processing (Milner et al., 1968; Corkin, 1984, 2002).

For decades, knowledge of the anatomical borders of H.M.'s resection was based solely on drawings in a 1957 research article by William Beecher Scoville,

the neurosurgeon who performed H.M.'s operation, and Brenda Milner, the neuropsychologist who first tested him postoperatively (Scoville and Milner, 1957). Scoville described his "medial temporal lobotomy" procedure in 1953; that report contained the first hint that MTL damage could affect memory profoundly. One woman was reported to have a "... retrograde amnesia for her entire psychosis (of 3 years' duration)" (Scoville et al., 1953, p 363). Scoville however, made no mention of an anterograde amnesia, which we now recognize as the hallmark of bilateral MTL lesions. The final line of his report states that "Further work will be done to determine the effects of MTL surgery on epilepsy" (p 368), a foreshadowing of the radical version of this procedure performed in H.M. (Scoville and Milner, 1957).

Although an extraordinary amount of insight about memory systems was gained from subsequent cognitive studies with H.M., the precise borders of his lesion were unknown. In 1984, Corkin presented the first modern images of H.M.'s brain, computed tomography (CT) scans (Corkin, 1984). She followed this report with a comprehensive magnetic resonance imaging (MRI) study of H.M.'s lesion boundaries, including scans collected in 1992 and 1993 (Corkin et al., 1997). This manuscript provided the first insights into the actual tissue damage that produced H.M.'s profound anterograde amnesia, demonstrating that his lesion was bilaterally symmetrical, yet significantly less radical than the 8 cm lesion Scoville estimated.

Neuroimaging procedures have improved considerably in recent years. A variety of commonly available MRI techniques are differentially valuable in providing sensitive contrast to specific tissue or pathology types. Images can now be collected at higher signal and resolution for the same amount of scan time compared to prior methods. Analysis techniques have advanced to include quantitative measures of tissue morphometry and tissue integrity. Taking advantage of these continuous improvements in MRI technologies, we scanned H.M. on several occasions from 2002–2004, and now report new insights about his brain, discovered from these data.

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Grant sponsor: National Institutes of Health; Grant number: NIH AG24898; Grant sponsor: The National Center for Research Resources; Grant number: P41RR14075; Grant sponsors: Dana Foundation, Mental Illness and Neuroscience Discovery (MIND) Institute.

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Accepted for publication 27 July 2006

DOI 10.1002/hipo.20222

Published online 2 October 2006 in Wiley InterScience (www.interscience.wiley.com).

MATERIALS AND METHODS

H.M.'s Case History

At the time of the imaging studies (2002–2004), H.M. was 74–77 years old. Corkin et al. described his relevant

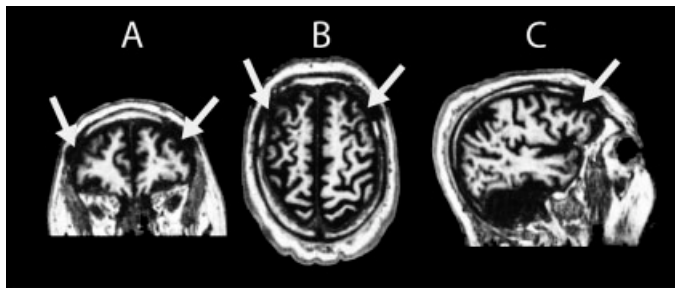


FIGURE 1. The supraorbital trephine holes made by Scoville to access the temporal lobes for H.M.'s resection [previously diagrammed by Scoville, (1949) and exhibited by Corkin et al. (1997)]. Images are presented in the coronal (A), axial (B), and sagittal (C) planes. Arrows indicate the location of the openings.

history in their 1997 manuscript. Notably, H.M. sustained a head injury at Age 7 (Corkin, 1984). (This injury was incorrectly noted to have occurred at Age 9 in other manuscripts.) He experienced his first minor seizure at Age 10, and his first generalized convulsion at Age 16. Scoville offered to perform the bilateral temporal resections that he had performed previously in psychotic individuals (Scoville et al., 1953) as an experimental therapy for H.M. The operation was carried out in 1953, when H.M. was 27 years old (Scoville and Milner, 1957). This procedure reduced the frequency of H.M.'s seizures, but also produced a severe anterograde amnesia (Scoville and Milner, 1957; Milner et al., 1968; Corkin, 1984).

A description of H.M.'s neurological history is presented in Corkin et al. (1997). Since this account, H.M. has had, at most, two seizures a year, with some years having no seizures at all. We have seen occasional evidence of confabulation. For example, he believes that he does not wear glasses because someone stole them from him in his nursing home. In fact, he had laser surgery in 2003 to remove cataracts bilaterally, and he no longer needs to wear corrective lenses. H.M.'s health has declined in recent years. He is now wheelchair bound because of osteoporosis, and has a bloated abdomen, possibly due to an enlarged, distended spleen. He has had sleep apnea for years. He is motivated to help with research that would benefit other people (an example of his metaknowledge about his deficit). At the time of scanning, he was aware of his surroundings and talkative, but generally slow in his responses. He showed a sense of humor. For example, when asked if he was hungry, he readily smiled and responded, "I'm always hungry."

H.M.'s amnesia is still profound. For example, he was unable to remember that he was eating a ham sandwich after the flavor was removed by taking a sip of juice. Anecdotal evidence shows sparing of portions of his remote memory, with continued interest in the *I Love Lucy* television show and the "western" television genre. Since the time of the 1997 magnetic resonance imaging (MRI) investigation, a variety of new facts have come to light about H.M.'s preserved and impaired memory capacities (summarized in Postle and Corkin, 1998; Hood et al., 1999; Kensinger et al., 2001; Xu and Corkin, 2001; Corkin, 2002; O'Kane et al., 2004; Skotko et al., 2004; Steinworth et al., 2005).

Activities of daily living were recorded for H.M. on May 25, 2005. He is able to assist staff with oral care with cues and supervi-

sion, with no change in this behavior in the last few years. He can shave himself with direct supervision using an electric razor, yet on occasion attempts to shave other hair on his face, such as his eyebrows. He is able to feed himself with occasional assistance required when lethargic. He no longer works on crossword puzzles or plays BINGO and checkers, and his attention span for television is reduced.

H.M. underwent a neurological examination on June 28, 2005. His medications at this time included Tegretol, Paxil, Tegretol-XL, Tetracycline, Tylenol-XS, Primidone, Seroquel, Alprazolam, Prednisone, Plavix, Ducolax, Glycolax, Amoxicillin, milk of magnesia, and Fleet Enema p.r.n. Importantly, Primidone, Seroquel, and Alprazolam likely contributed to his dysarthria, lethargy, and somnolence. His blood pressure was 150/65 and his pulse was 60 beats per minute. He was awake and cooperative with slightly dysarthric speech. He named four of five common objects to confrontation, and performed five of five gestures to command. Pertinent neurological signs included decreased vertical gaze but full visual fields and no nystagmus. He showed good proximal arm strength but

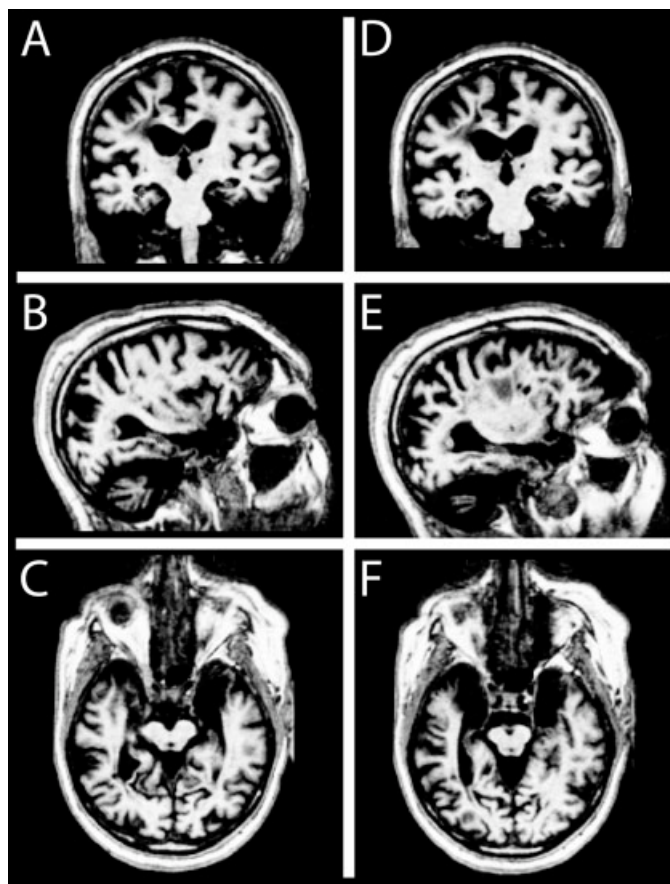


FIGURE 2. H.M.'s medial temporal lobe resection presented coronally (A, D), sagittally (B, E), and axially (C, F) in the left (A–C) and right (D–F) hemispheres on his T1-weighted MPRAGE scan. These images demonstrate the bilateral, symmetrical nature of Scoville's resection, sparing the posterior $\sim 0.65 \text{ cm}^3$ of hippocampus in the left hemisphere and $\sim 0.88 \text{ cm}^3$ of hippocampus in the right hemisphere. Generalized brain atrophy is also apparent in these images.

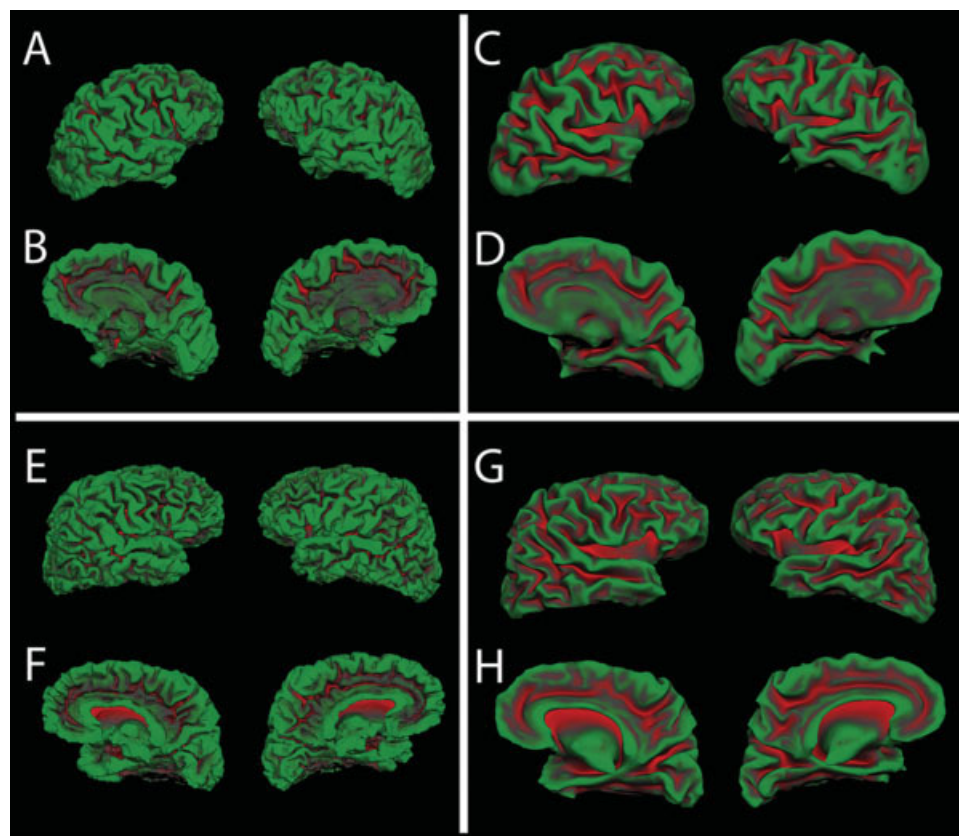


FIGURE 3. Computerized reconstruction of H.M.'s cortical mantle in folded (A, B) and semi-inflated (C, D) representations for the lateral (A, C) and medial (B, D) views. Gyral regions are

shown in green and sulcal regions in red. The approximate extent of H.M.'s temporal polar excision can be appreciated in these models compared to an individual age-matched participant (E–H).

weak hand grips bilaterally, with atrophy of the intrinsic hand muscles. Deep tendon reflexes were hypoactive throughout, and plantar reflexes were neutral. Leg strength was greatly reduced, and he was unable to stand or walk. Limb coordination was normal and sensation was preserved. Recent tests indicated that H.M.'s blood pressure was in the normal range in July of 2000 (136/78), but his systolic blood pressure was high in April 2005 (155/72). It is unclear exactly when he transitioned from normal to high blood pressure. His blood cholesterol levels are normal (157 in January of 2005) and have been normal, since at least 1996.

MRI Acquisition

Consent to image H.M. was obtained through his conservator, who is a distant relative. The new data described here were collected during four scan sessions (September 5, 2002, June 14, 2003, May 2, 2004, and October 10, 2004). The first three scans were performed on a Siemens 1.5 Tesla Sonata scanner. The last session was performed on a 1.5 Tesla Siemens Avanto scanner, using a Siemens 12 channel head coil. The Sonata sessions included three 3D MPRAGE scans (TR = 2,730 ms, TE = 3.31 ms, TI = 1 s, 128 slices, 1.33 mm thick, matrix 256×256 [for in plane resolution of 1 mm], bandwidth = 195 Hz/pixel, flip angle = 7° , sagittal acquisition), a T2 turbo spin echo scan (TR = 4,000 ms, TE = 95 ms, 19 slices, slice thickness 5 mm, 1.5 mm

gap, matrix = 256×224 , FOV = 230×201 mm² [for 1.1 mm in plane resolution], flip angle = 150°). The Avanto session included 30 diffusion tensor scans (six direction diffusion-weighted scans with an additional $b = 0$ volume; 60 slices, 2 mm slice thickness, no gap, 128×128 matrix, FOV = 256 mm [for 2 mm isotropic in plane resolution], flip angle = 90° , TR = 6,700 ms, TE = 68 ms, b value = 700 s/mm²). We introduced several procedures to reduce the influence of motion during these scans, such as collecting multiple averages of short sequences, discarding images with excessive motion, and reminding H.M. between scans about the need to keep still. Nevertheless, we do see motion artifacts in some of these scans. Thus, the data presented here, with comparisons to control participants, should be considered approximate effects, and should not be considered absolutely quantitative.

MRI Analysis

The MR data were first evaluated qualitatively through visual inspection of the scans; the majority of our findings came from these informative evaluations. Secondary analyses included comparisons of cortical thickness and regional fractional anisotropy (FA) between H.M. and 4 age- and sex-matched control participants. MRI images were analyzed using a variety of procedures described in previous manuscripts. Briefly, these procedures included reconstruction of the cortical surface using multistep seg-

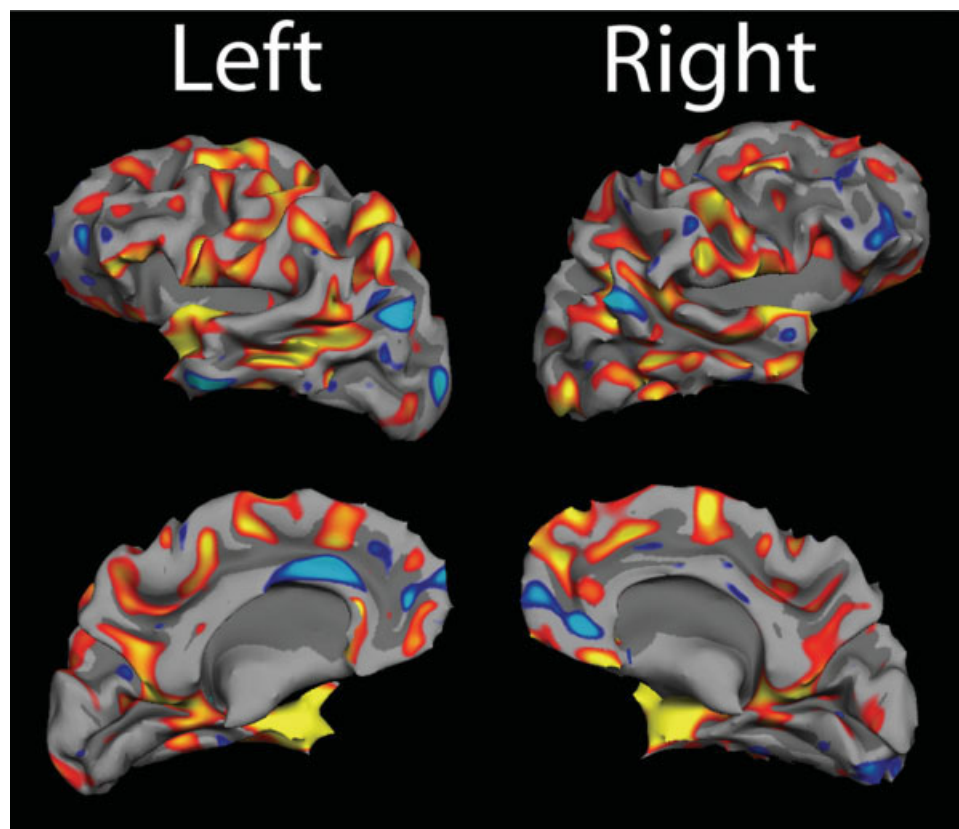


FIGURE 4. Cortical thinning in H.M. Widespread thinning was apparent in both hemispheres across H.M.'s cortical ribbon compared to four matched control participants. Thinning was regionally variable. Qualitative examination suggested most promi-

nent thinning in precentral and posterior frontal regions (red to yellow indicates regions of increasing thinning, with red = ~ 0.3 mm thinning and yellow = ~ 0.7 mm thinning).

mentation and surface tessellation procedures to develop computerized models of the cortex (Dale et al., 1999; Fischl et al., 1999; Fischl et al., 2001; Segonne et al., 2004) and to measure morphometric properties, such as cortical thickness (Fischl and Dale, 2000; Salat et al., 2004). DTI data were processed using a multi-step procedure as described previously (Salat et al., 2005b) to achieve motion and eddy current distortion correction, and for calculation of FA maps of white matter tissue integrity. The diffusion tensor was calculated for each voxel in the volume using a least-squares fit to the diffusion signal (Basser et al., 1994). The FA metric was derived from the diffusion tensor as previously described (Pierpaoli and Basser, 1996). Analyses combined tools developed at the Martinos Center as well as tools available as part of the Freesurfer (<http://surfer.nmr.mgh.harvard.edu>) and FSL (<http://www.fmrib.ox.ac.uk/fsl>) processing streams.

RESULTS

Scoville approached the temporal lobes through bilateral 3.8 cm supraorbital trephine holes (Fig. 1; also diagrammed in Scoville, 1949 and noted by MRI in Corkin et al., 1997).

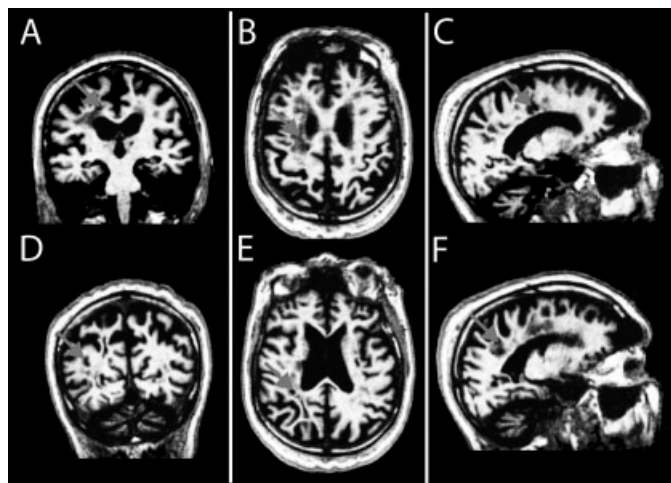


FIGURE 5. White matter lesions in H.M.'s T1-weighted images. A number of regions exhibiting white matter damage, potentially due to infarct, are apparent in these images presented in the coronal (A, D), axial (B, E), and sagittal (C, F) planes. The hypointensity of the lesions (e.g., C, D) and the volume of damage are severe compared to those seen in healthy aging, and suggest some amount of small vessel disease.

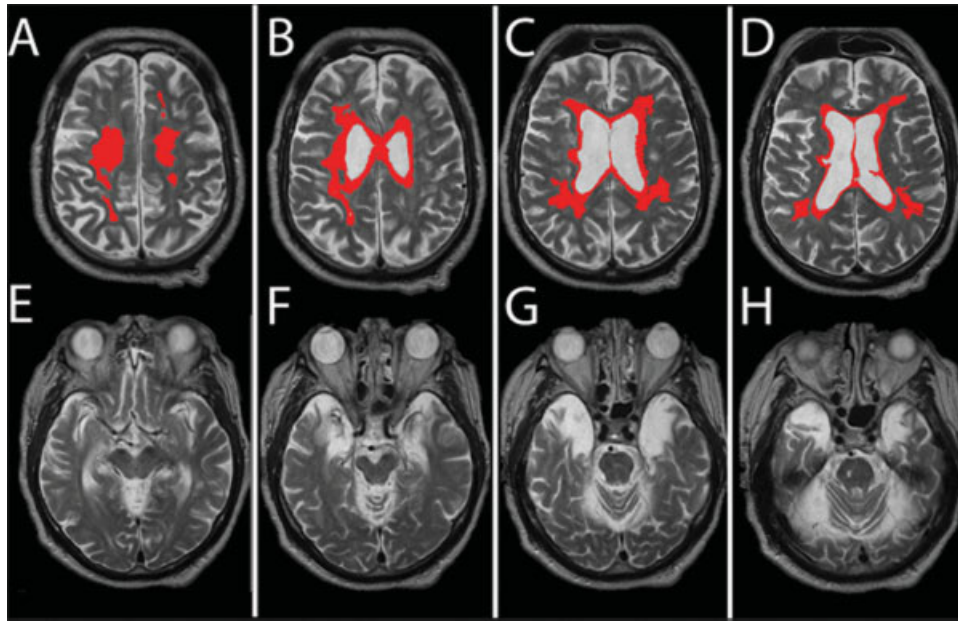


FIGURE 6. White matter lesions apparent on H.M.'s T2-weighted images. A number of regions of non-specific white matter damage are apparent in these T2-weighted images (a portion of this damage is highlighted in red). These alterations are severe compared to those seen in healthy aging, extending outward almost all the way to the cortical ribbon (e.g., D).

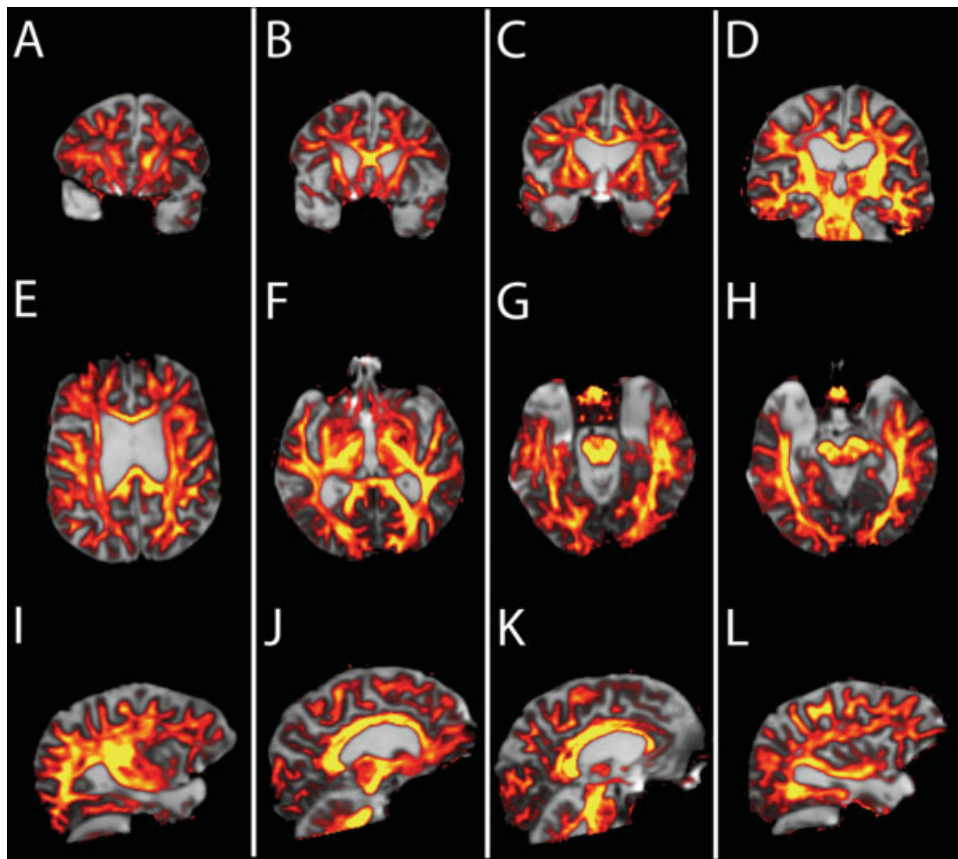


FIGURE 7. White matter lesions apparent in H.M.'s DTI FA maps. FA images presented in the coronal (A–D), axial (E–H), and sagittal (I–L) views. Regions of white matter damage had particularly low

FA, with values reduced to those approximating gray matter and cerebrospinal fluid (e.g., 0.1–0.2; red to yellow indicates regions of increasing FA, with red = ~ 0.1 and yellow = ~ 0.6 and higher).

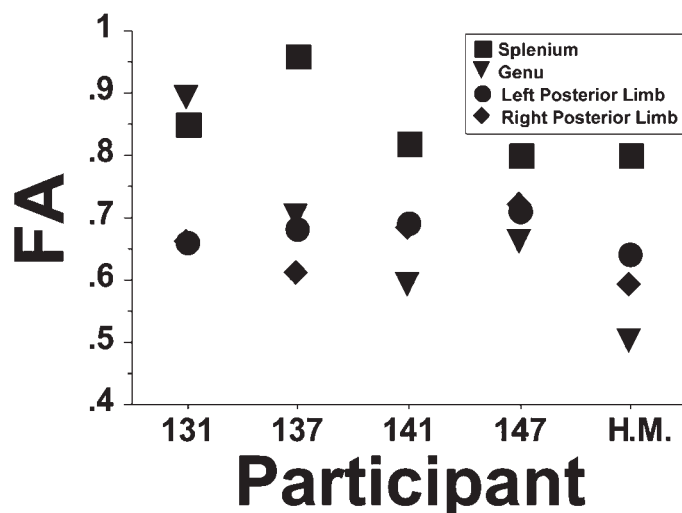


FIGURE 8. FA in selected ROI's. FA was sampled from normal appearing white matter in the genu and splenium of the corpus callosum, and the left and right posterior limb of the internal capsule. One-sample analysis demonstrated that FA was reduced in H.M. compared to the control participants in all regions ($P < 0.05$), except for sparing of the splenium of the corpus callosum (squares).

The drawings in Scoville and Milner's (1957) manuscript were made by another neurosurgeon, Lamar Roberts, based on Scoville's drawings and notes at the time of operation (Scoville and Milner, 1957, Fig. 2). Prior to performing the MTL resection, he had described his method of "orbital undercutting" to disrupt function in Brodmann areas 9 and 10 and cingulate cortex, a procedure he believed was worth optimizing due to the "... favorable alteration of human behavior ..." with disruption of the function and connectivity of these cortical areas (Scoville, 1949, p 65). Scoville subsequently extended his undercutting procedure to access uncus and MTL regions for electroencephalogram and electrical stimulation studies (Liberson et al., 1951), and ultimately, for lobotomy in psychotic individuals (Scoville et al., 1953). The 1949 manuscript also described findings from a series of other surgical patients who received similar but less radical resections than H.M.'s (i.e., anterior to the head of the hippocampus). The most extreme removal, other than H.M.'s, was performed in a psychotic man in whom approximately the anterior two thirds of the hippocampus was removed (patient D. C.). About these two cases, the authors stated, "There has been one striking and totally unexpected behavioral result; a grave loss of recent memory in those cases in which the MTL resection was so extensive as to involve the major portion of the hippocampal complex bilaterally" (Scoville and Milner, 1957, p 14). Thus, the 1957 Scoville and Milner manuscript opened the eyes of neuroscientists to the potential role of the hippocampus in memory processing, and also provided "... a warning to others of the risk to memory involved in bilateral surgical lesions of the hippocampal region" (p 11).

Corkin et al.'s (1997) findings updated Scoville's description of H.M.'s surgery with precise anatomical localization of the lesion, demonstrating that although Scoville had indicated that the resection extended ~8 cm rostrocaudally, the rostrocaudal extent of the

ablation was actually ~5.4 cm in the left hemisphere and ~5.1 cm in the right hemisphere. Figure 2 shows the results of this surgical procedure in recently collected T1-weighted images in the coronal (A,D), sagittal (B,E), and axial (C,F) planes of the left (A–C) and right (D–F) hemispheres. Our quantitative analyses suggest that 0.65 cm³ of hippocampal tissue was spared in the left hemisphere, and 0.88 cm³ was spared in the right hemisphere (best viewed in Figs. 2B and E). Hippocampal volumes vary across studies, but in our laboratory sample of control participants his age we find a mean volume of 3.3 ± 0.4 cm³.

A detailed description of the extent of H.M.'s MTL damage can be found in the original MRI study (Corkin et al., 1997). Briefly, the ablation damaged extensively the anterior medial temporal polar cortex bilaterally and most of the amygdaloid complex. Our recent quantitative analyses suggest that approximately 0.2 cm³ of the amygdala remains in the left hemisphere and 0.3 cm³ in the right hemisphere. The amygdala could be expected to be ~1.7 cm³ at his age. This remaining tissue may include small portions of the most dorsal aspects of basomedial and dorsal basolateral nuclei, the periamygdaloid and piriform cortices, the anterior cortical nucleus, and the central nuclei. Posterior portions of the intraventricular hippocampal formation were also spared. This tissue was atrophic bilaterally in his 1993 scans, and has continued to atrophy to the present day. White matter associated with these regions, including the temporal stem, was damaged anteriorly, likely affecting fibers of the uncinate fasciculus. The lateral temporal neocortex was spared from damage, yet substantial atrophy is now apparent there.

We created a computerized model of H.M.'s brain with his recent MPRAGE data (Fig. 3) in folded (A,B) and semi-inflated (C,D) representations. These images allowed us to visualize the amount of temporal pole resected and the approximate extent of preserved temporal lobe tissue, compared to a matched control participant (E–H). Additionally, these models provided a qualitative view of the gyral atrophy and sulcal widening in H.M.'s brain. For example, the temporal polar region apparent in control participant (panels E–H) is absent in H.M.'s brain (panels A–D).

We examined differences in cortical thickness between H.M. and 4 age- and sex-matched control participants (Fig. 4). These maps suggest that nonspecific thinning of H.M.'s cortex has occurred to a greater degree than would be expected for his age. In fact, his cortical thinning is widespread and does not precisely follow patterns that we find for age-related thinning (Salat et al., 2004), such as thinning in the precentral gyrus and superior and inferior frontal gyri, with relative sparing of the postcentral gyrus and middle frontal gyrus. Thus, this atrophy may be related to comorbid medical factors and not aging.

In Corkin et al.'s initial MRI study, the most noticeable nontemporal lobe region of pathology was marked and diffuse atrophy of the vermis and hemispheres of the cerebellum, and atrophy of the mammillary nuclei (Corkin et al., 1997). Our new data provide evidence of a number of additional alterations in H.M.'s brain that likely developed in recent years. Most notably, we found clear evidence of widespread white matter damage as seen in his T1 (Fig. 5), T2 (Fig. 6), and diffusion tensor scans (Fig. 7). Older adults often exhibit some degree of white matter damage, but H.M.'s alterations were more extensive than would be expected, particularly in frontal

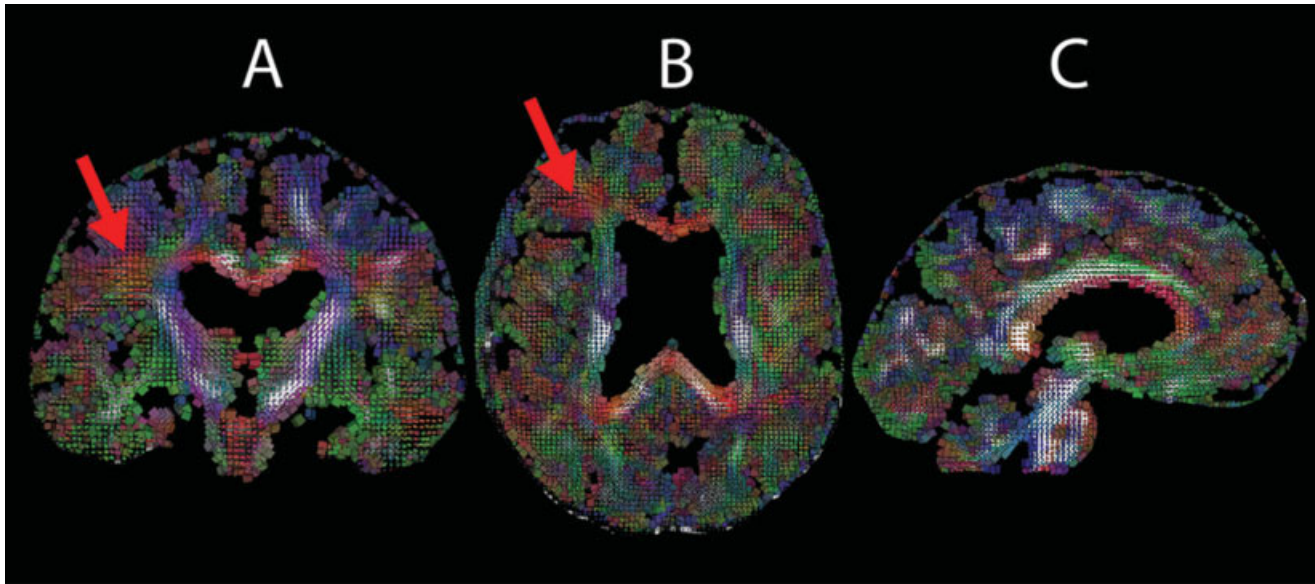


FIGURE 9. Tensor map of H.M.'s white matter fiber anatomy. The tensor map is created from DTI scans and describes the direction of mean diffusion of water molecules at each voxel. Water tends to diffuse along the longitudinal axis of fiber bundles, and thus, tensor maps provide a general description of white matter anatomy. Blue shades represent approximately superior–inferior

oriented fibers, red shades represent approximately medial–lateral oriented fibers, and green shades represent approximately anterior–posterior oriented fibers. Red arrows indicate regions of likely abnormal fiber structure. This area is infarcted on H.M.'s T1 and T2 images (e.g. see Figures 5 and 6).

and parietal lobe white matter, where patches extended from the periventricular regions almost completely out to sulcal cortical gray matter (e.g., 5A and F, 6D, 7A). Additionally, these patches showed more prominent signal abnormality than is seen in typical aging, with very dark regions apparent on T1 images (e.g., Figs. 5A, B, F).

White matter damage was highlighted in the FA maps created from H.M.'s diffusion tensor scans (Fig. 7). These images showed a wide range of FA values, with measures approaching those of cerebrospinal fluid in regions of white matter damage and in the region of his resection (e.g., Figs. 7A, D, and J). Other areas, such as the posterior limb of the internal capsule and the corpus callosum, showed relatively higher FA values. We used region of interest (ROI) analyses to determine whether white matter areas with higher FA values were preserved in H.M. relative to matched controls. Specifically, we examined FA in the anterior and posterior corpus callosum, and the posterior limb of the internal capsule in each hemisphere (Fig. 8). These analyses showed that FA was reduced in H.M.'s white matter in regions where damage to the white matter was not obvious, suggesting a more general decline in integrity throughout his brain. A one-sample statistical analysis showed that FA was reduced in all regions relative to control participants (all t values > 3.2 , P -values < 0.05), except the splenium of the corpus callosum. Qualitative examination of H.M.'s tensor maps (Fig. 9) suggested that prominent white matter disruption was anatomically localized to frontopontine and frontothalamic fibers, as well as long association fibers (superior and inferior longitudinal fasciculi). The image in Figure 9B demonstrates an asymmetric tensor pattern in H.M.'s inferior frontal gyrus, with the right hemisphere showing a prominent region of heterogeneous medial-lateral projecting fibers, and the left hemisphere showing

the more standard pattern of anterior–posterior dominant fibers with some infiltration of medial–lateral projecting fibers. It is currently difficult to interpret such data, but it is possible that the white matter architecture is significantly altered in this right hemisphere region.

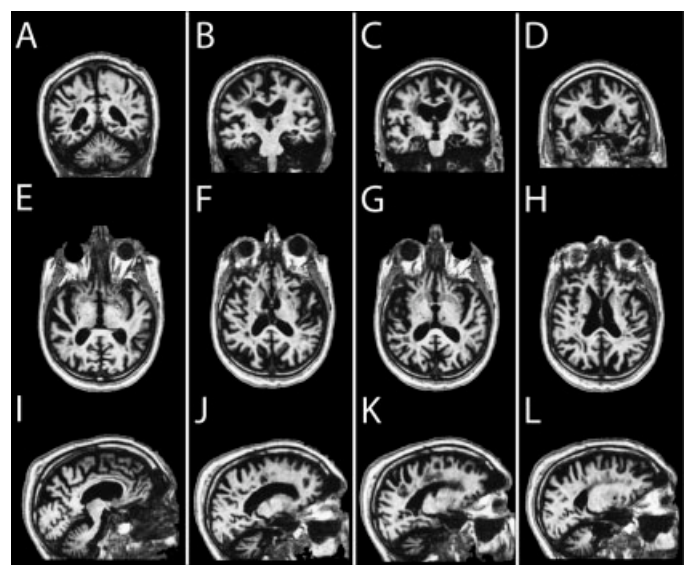


FIGURE 10. T1-weighted images showing gray matter regions of atrophy and infarct outside of the neocortex and medial temporal lobes. A number of subcortical gray matter structures showed infarcts indicative of small vessel disease, including the thalamus (B, F, K), and putamen (B, D, H, I, J, L). His cerebellum was severely atrophic (A, I, J, K, L) as previously noted (Corkin et al., 1997).

We observed a number of infarcts in H.M.'s subcortical gray matter (Fig. 10). Most notably, abnormalities were found bilaterally in the putamen (Figs. 10C, D, H, I, J) and thalamus (possibly in the left mediodorsal nucleus; and the right laterodorsal/ventro-posteriolateral nucleus; Figs. 10B, F, G, K). His remaining posterior hippocampal regions were seemingly free from any large infarcts. The finding of infarcts in the putamen and thalamus with concomitant white matter damage is consistent with small vessel disease, in which there is a reduction in the blood supply to the small vessels of the brain, often due to hypertension (e.g., Tanaka et al., 1999; Wahlund et al., 2001; Schmidt et al., 2004). Nevertheless, smaller infarcts were seen on his 1998 scans, suggesting that other medical comorbidities could have contributed to the observed damage.

When we examined images collected in 1998 (i.e., prior to the 2002 imaging session), we found the beginnings of tissue damage. Figure 11 demonstrates the locus of abnormalities apparent in 1998 and the progression of this damage up to 2003. Thus, neural alterations likely occurred gradually over the period from around 1998 to 2002, yet the overall damage from 1998 to 2003 is qualitatively much worse than the damage from 1992 to 1998.

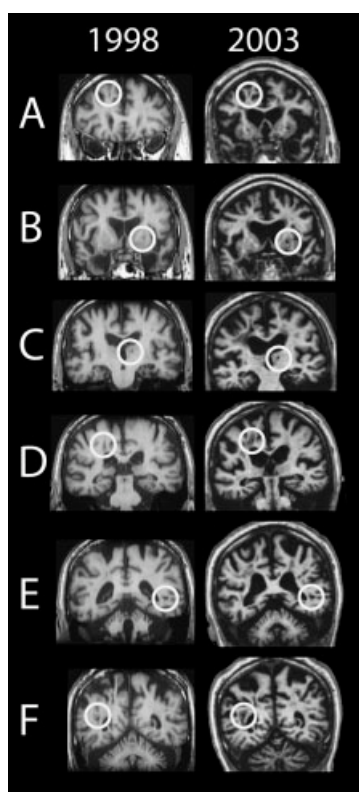


FIGURE 11. Evidence of H.M.'s neural damage in his 1998 images (A, C, E, G) compared to his 2003 images (B, D, F, H) (the slices are slightly different due to the differences in head placement in the scanner). The circles highlight similar brain regions in the two images (A, right superior frontal white matter; B, left putamen; C, left thalamus; D, right parietal/periventricular white matter; E, posterior lateral temporal white matter; F, parietal/occipital/periventricular white matter).

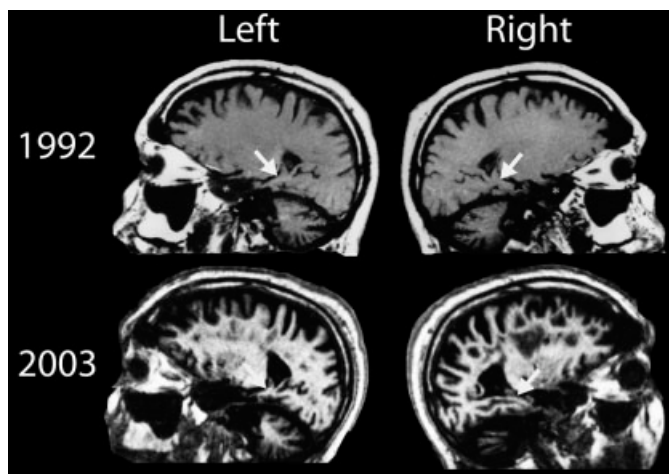


FIGURE 12. H.M. then and now. Images from H.M.'s scans obtained in 1992 (modified from Corkin et al., 1997), and similar slices from his scans collected in 2003 (the slices are slightly different due to differences in head placement in the scanner). The arrows point to the remaining hippocampus in each hemisphere.

DISCUSSION

We have further evaluated the brain of the amnesic patient H.M., originally described by Scoville and Milner (1957), and first described using MRI by Corkin et al. (1997). The amnesic syndrome resulting from H.M.'s bilateral MTL tissue resection opened the door to the field of cognitive neuroscience of memory, and the vast amount of research on his deficit has had a major impact on this field. We were interested in understanding the full spectrum of brain destruction in H.M. that could contribute to his cognitive profile, and in examining new patterns of brain changes compared to a matched cohort of participants. Over a decade has passed since his first MRI scans. Around the area of the resection, little has changed in H.M.'s brain, and his recent images match the description provided by Corkin et al. (1997). Figure 12 presents images from that prior investigation in tandem with images from the current investigation for direct assessment of some of the neural lesions that occurred across the decade between these studies. In contrast to MTL regions, we found a number of abnormalities outside of this area, including cortical and subcortical atrophy, large amounts of abnormal white matter, reduced integrity of normal appearing white matter, and infarcts in subcortical gray matter. Notably, the changes from 1998 to 2002/2003 are qualitatively far more significant than those from 1992/1993 to 1998. The most recent brain changes must be considered in the current context: H.M. was in his mid-to-late 70s when the current scans were acquired, and he has taken numerous medications. He has experienced sleep apnea for decades, and such irregular breathing is noted to be a cause or consequence of white matter infarcts (Bassetti et al., 1997; Harbison et al., 2003). More recently, his systolic blood pressure has been elevated. Thus, the origin of these tissue irregularities is unclear. Most of the findings outside of his resec-

tion reported in the current study were not seen in his 1992 and 1993 scans, suggesting that the pathologic mechanisms resulting in those abnormalities occurred over the last decade. The composite of these abnormalities, particularly white matter damage and infarcts in the thalamus and putamen, fit the description of small vessel disease, potentially due to hypertension (e.g., Wahlund et al., (2001); Schmidt et al., (2004) for a description and examples of this type of white matter damage). Earlier changes apparent in his 1998 images could be due to his long standing apnea, but the actual cause of this damage is presently unknown. This issue will be addressed at autopsy.

White matter damage was visible in T1, T2, and FA images. We quantified white matter integrity through FA measures in a number of regions of interest where obvious white matter lesions were not apparent. These analyses showed that even normal appearing white matter regions had reduced FA, suggesting a more global process of white matter degeneration in H.M.'s brain. One exception to this finding was in the splenium of the corpus callosum, where white matter was somewhat spared relative to the control participants. This finding is interesting in light of our unpublished data showing that alterations in the posterior corpus callosum may be a component of Alzheimer-related degeneration (Salat et al., 2005a). Thus, these findings suggest indirectly that H.M. does not have Alzheimer's disease, although the diagnostic value of FA measures for Alzheimer's disease has not been demonstrated.

Although it is unclear exactly when the newly reported changes occurred in H.M.'s brain, it is important that this information be integrated with his past and current behavioral data. Some abnormalities were apparent in his 1998 scans but were exacerbated in his 2002 and 2003 images. H.M. continued to participate in cognitive experiments through 2002. Thus, changes were present at the time of his most recent cognitive test sessions. At each of these sessions, however, he was attentive and able to follow task instructions. He was able to retrieve remote memories in conversation, although he substituted gist for detail (Steinvorth et al., 2005). In fact, he has been unable to recount autobiographical episodes (i.e., those linked to a specific time and place) for at least a decade. In contrast, despite the additional neural changes, he could still demonstrate impressive retrieval of old and even new semantic knowledge. For example, O'Kane et al. (2004) showed that he could distinguish famous names from names drawn from the Boston telephone directory, and that he knew a few facts about a small number of celebrities who became famous after his operation (i.e., the 1960s and beyond). Thus, H.M. was able to acquire a small amount of public semantic knowledge in some circumstances. In addition, he also demonstrated evidence of some personal semantic knowledge. During testing sessions, he knew that he has a memory impairment, that he had had brain surgery, and that his doctor was Scoville. These insights are likely due to slow (nondeclarative) learning over many years. H.M.'s ability to perform nondeclarative learning tasks was demonstrated over 4 decades ago (Milner, 1962; Corkin, 1968). Various types of nondeclarative learning have been linked to striatal function. In this respect, H.M.'s putamen was recently infarcted, but his caudate nucleus appeared relatively intact. Thus, it is likely that nondeclarative learning and memory were resistant to recent neural insults and to the radical bilateral MTL resection.

Equally striking in view of the current imaging results is Steinvorth et al.'s (2005) demonstration of a dissociation between H.M.'s semantic knowledge of events that occurred preoperatively, which was preserved, and his memory for remote autobiographical (episodic) information, which was virtually absent. The finding of an inability to retrieve specific personal episodes from the distant past was replicated in another amnesic patient with MTL lesions (patient W.R.). This evidence, combined with the selectivity of the impairment for remote autobiographical (but not remote semantic) knowledge suggests that this deficit was a consequence of H.M.'s MTL resection and not the changes noted in the more recent imaging findings.

H.M.'s surgical resection provided the earliest indication that damage to MTL structures results in a profound global amnesic syndrome. Subsequent cognitive studies have been critical in defining precisely the cognitive processes impaired by this lesion, and similarly, in providing clear support for a distinction between declarative and nondeclarative memory systems (Corkin, 1968). Because of the plethora of brain changes exhibited in his recent images and comorbid medical factors, the goal of recent and future examinations of H.M.'s cognitive capacities is simply to document his clinical course.

Advances in neuroimaging technologies currently allow for the visualization of the human brain and neural insult in ways that Scoville could only have imagined when developing his neurosurgical procedures. Structural and functional imaging have already led to major breakthroughs in knowledge about the cognitive and neural processes that support different kinds of memory (reviewed in Pigué and Corkin, in press). Cutting edge methods, such as those used here and others still under development, promise to take the cognitive neuroscience of memory to an even deeper level in coming years.

Acknowledgments

We are grateful to Mary Foley, Richard Clarke, Anne Krendel, Emily Connally, Charlene Peterson, Keyma Prince, and David Kennedy for assistance with these studies. We additionally thank Steven Stufflebeam for consultation about H.M.'s lesions, Sarah Steinvorth for review of the manuscript, and John H. Growdon for evaluating H.M. neurologically and commenting on this manuscript.

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