

REPLY

Memory, Language, and Neuroanatomy: A Reply

Larry R. Squire,*†‡ Heike Schmolck,†§ and Lisa Stefanacci‡

**Veterans Affairs Medical Center, San Diego; †Department of Psychiatry, and ‡Department of Neurosciences and Psychology, University of California, San Diego; and §University of Iowa Hospital and Clinics, Iowa City*

Published online June 8, 2001

The work of ours that MacKay (2001) discusses followed on the interesting report that the noted amnesic patient H.M., who has large medial temporal lobe lesions along with some more lateral damage to the rostralmost aspects of the superior and middle temporal gyri (Corkin, Amaral, Gonzalez, Johnson, & Hyman, 1997), was impaired at understanding ambiguity in sentences (MacKay, Stewart, & Burke, 1998). Our findings were based on 7 patients and 11 controls and made two simple points (Schmolck, Stefanacci, & Squire, 2000a). First, when bilateral damage is limited to the medial diencephalon or to the hippocampal formation (the hippocampal cell fields, dentate gyrus, subicular complex, and entorhinal cortex), memory impairment occurs in the absence of an impairment in detecting or explaining ambiguity in sentences. Second, memory impairment together with an impairment in understanding sentence ambiguity occurs in patients who have extensive bilateral damage to the medial temporal lobe as well as some damage to more lateral temporal cortex.

We sought to extend the original observation by MacKay et al. (1998) by asking what damage (or what other factors) might be responsible for the deficit reported in patient H.M. The finding that damage limited to the hippocampal formation did not impair the appreciation of sentence ambiguity seems a constructive step in this direction. Our interpretation is that the hippocampal formation is not essential for understanding ambiguity and that memory impairment can occur in isolation from an impairment in understanding ambiguity. MacKay objects that we did not show that our study patients were amnesic, although their memory deficits and their neuropathology have been documented in numerous earlier articles (cf. Reed & Squire, 1997). And he objects that our three “hippocampal” patients and their five controls were not well matched, apparently because the controls exhibited “variability” and underperformed the three patients by a nonsignificant 3.8 points in the Vocabulary subtest of the WAIS-R (in fact, the controls slightly overperformed the patients on the Information subtest and were within 1.5 years of age of the patients). He fairly reminds us of the difficulty of rejecting the null hypothesis (the three patients averaged within

This work was supported by the Medical Research Service of the Department of Veterans Affairs, NIMH Grant 24600, the Metropolitan Life Foundation, and the National Alliance for Research on Schizophrenia and Depression.

Address correspondence and reprint requests to Larry Squire at VA Medical Center, V116A 3350 La Jolla Village Dr., San Diego, CA 92161. E-mail: lsquire@ucsd.edu.

8.9, 7.9, and 4.8% of the mean control score on the three measures of ambiguity detection and explanation (our Figs. 4–6). There was extensive overlap between the scores of the two groups on all three measures (all $ps > .25$). Moreover, on all measures the patients with restricted damage performed significantly better than, and did not overlap with, the patients with more extensive damage.

As for H.M.'s performance on these and other tests, we did not write, as MacKay asserts, that H.M.'s severe memory deficits arise solely from his damaged hippocampus and have stated otherwise in earlier writings (Squire & Zola-Morgan, 1991; Zola & Squire, 2000). We also did not write, as MacKay asserts, that H.M.'s impairments on the sentence tasks arise solely from his extrahippocampal damage. We did write that the deficits in our three patients with extensive damage were likely due to damage lateral to the medial temporal lobe. MacKay also misdescribes patient E.P. as having extensive neocortical lesions, which include frontal cortex. However, E.P.'s lesion is strikingly similar to H.M.'s lesion and does not involve frontal cortex so far as we can determine (see Stefanacci, Buffalo, Schmolck, & Squire, 2000).

The difficulty in interpreting H.M.'s impairments on the sentence tasks is that he differed in several ways from the three patients with large lesions whom we tested. First, H.M. has a premorbid history of seizures beginning at the age of 10, whereas all our patients acquired their lesions well into adulthood. Second, H.M., but not our three patients, had difficulty deciding whether nonambiguous sentences were ambiguous. Third, H.M. had difficulty explaining even one meaning of the ambiguous sentences he was given (21.9% of the time), whereas none of our patients had this difficulty (range, 0 to 1.5%). Finally, in tests of semantic knowledge, H.M. made many linguistic and grammatical errors in his speech, whereas our three patients did not (Schmolck, Stefanacci, Kensinger, Corkin, & Squire, 2000b).

Yet, despite these differences, H.M.'s lesion is less extensive both medially and laterally than the damage in the other three patients. These considerations raise the possibility that some or all of H.M.'s language deficiencies are related, not to his medial temporal lobe resection, but to his early-developing epilepsy and his limited education and that his language skills may not have developed fully prior to his surgery at the age of 27. Such are the difficulties of developing theories of memory and language around the performance of a single patient.

In light of the original finding that patient H.M. has difficulty in comprehending sentence ambiguity (MacKay et al., 1998), additional studies of patients with well-characterized lesions will be useful in understanding the nature of this deficit, its relation to other aspects of semantic processing, and the anatomy of the impairment. Our study of seven amnesic patients provides some new information along these lines. In view of the fact that H.M. has language impairments not exhibited by other patients with even larger lesions, it is unlikely that further argument founded on H.M. will illuminate the issues under discussion here.

REFERENCES

- Corkin, S., Amaral, D. G., Gonzalez, R. G., Johnson, K. A., & Hyman, B. T. (1997). H.M.'s medial temporal lobe lesion: Findings from magnetic resonance imaging. *Journal of Neuroscience*, *17*, 3964–3980.
- MacKay, D. G. (2001). A tale of two paradigms or metatheoretical approaches to cognitive neuropsychology: Did Schmolck, Stefanacci, and Squire (2000) show above that hippocampal lesions only impair memory, whereas adjacent (extrahippocampal) lesions impair detection and explanation of sentence ambiguity? *Brain and Language*, *78*, 265–272, doi:10.1006/brln.2001.2470.
- MacKay, D. G., Stewart, R., & Burke, D. M. (1998). H. M. revisited: Relations between language

- comprehension, memory, and the hippocampal system. *Journal of Cognitive Neuroscience*, **10**, 377–394.
- Reed, J. M., & Squire, L. R. (1997). Impaired recognition memory in patients with lesions limited to the hippocampal formation. *Behavioral Neuroscience*, **111**, 667–675.
- Scholck, H., Stefanacci, L., & Squire, L. R. (2000a). Detection and explanation of sentence ambiguity are unaffected by hippocampal lesions but are impaired by larger temporal lobe lesions. *Hippocampus*, **10**, 759–770.
- Scholck, H., Stefanacci, L., Kensinger, E., Corkin, S., & Squire, L. R. (2000b). Semantic memory in patient H.M. and other patients with bilateral medial and lateral temporal lobe lesions. *Society for Neuroscience Abstracts*, **26**, 1241.
- Squire, L. R., & Zola-Morgan, S. (1991). The medial temporal lobe memory system. *Science*, **253**, 1380–1386.
- Stefanacci, L., Buffalo, E. A., Scholck, H., & Squire, L. R. (2000). Profound amnesia following damage to the medial temporal lobe: A neuroanatomical and neuropsychological profile of patient E.P. *Journal of Neuroscience*, **20**, 7024–7036.
- Zola, S. M., & Squire, L. R. (2000). The medial temporal lobe and the hippocampus. In E. Tulving & F. I. M. Craik, *The Oxford handbook of memory*. New York: Oxford Press. Pp. 501–520.