

Reply to Maguire and Hassabis: Autobiographical memory and future imagining

The role of the hippocampus in recollecting past events and imagining future events is of some theoretical interest, but experimental work on this issue is difficult because it depends on analysis of spoken narrative and the availability of appropriate patients. Because lateral temporal and frontal damage can markedly impair the ability to produce well-formed autobiographical memories about specific events (1), it is especially useful to obtain quantitative MRI data about these regions (and medial temporal lobe structures). This information was not available for the four patients with limbic encephalitis who had difficulty imagining future events (2), but descriptions of three of them in other reports, as cited (3), suggested to us that they have abnormalities outside the hippocampus. Patient P02 has “some generalized atrophy” and 4 mo after treatment was described as having “blank spells thought to represent seizures” (see ref. 5 in *Supporting Information* of ref. 2). P03 was described at the 27-mo follow-up as having persisting personality change and was taking antiepileptic medication. The IQ of P04 fell from 112 to 99 (4) and was at this level when he participated in tests of imagining (2).

Our own hippocampal patients exhibit none of these features. The letter (5) finds significance in their “lack of impairment” for recent events (because impairment would be expected after hippocampal lesions). However, the marked anterograde and retrograde impairment of these same patients has been documented repeatedly, including impaired autobiographical memory for recent events (1, 6). While our study (3) found recent remembering in these patients to be only marginally impaired ($P = 0.08$), patient G.P. (with severe amnesia and large medial temporal lobe lesions) was profoundly deficient at remembering recent events but fully intact at future imagining.

It is striking that one patient (P01) had marked amnesia from a different etiology than the other four patients (2) and had measured reductions in hippocampal volume similar to

our patients and others (3). He was wholly successful at future imagining, like our patients, raising the possibility that hippocampal damage itself does not impair this ability. We suggest that, whenever remote memory is intact after medial temporal lobe lesions, patients can use remote memory as a foundation for constructing new scenarios. Procedural differences between our studies, as noted (5), might also account for the different results. Perhaps deficient narratives can sometimes follow from the anterograde amnesia itself (e.g., difficulty remembering a developing narrative).

It exaggerates to write that our findings contradict “a number of previous reports” (5). Beyond their own study (2) and two unpublished abstracts, two case reports are cited: head-injury patient K.C., whose damage includes frontal, temporal, and occipital lobes and whose impairments cannot, therefore, be isolated to hippocampus; and M.C., who successfully imagined future events for the next day. With the informal questionnaire that was used, there was no evidence of a failure to construct well-formed autobiographical narratives in the rigorous sense that we discuss here. For resolution of these issues, we welcome a visit to our laboratory so that our patients can be tested with the same methods that yielded an impairment after limbic encephalitis.

Larry R. Squire^{a,b,c,d,1}, Susan G. McDuff^b, and Jennifer C. Frascino^b
^aVeterans Affairs Medical Center, San Diego Healthcare System, San Diego, CA 92161; and Departments of ^bPsychiatry, ^cNeurosciences, and ^dPsychology, University of California at San Diego, La Jolla, CA 92093

1. Bayley PJ, Gold JJ, Hopkins RO, Squire LR (2005) The neuroanatomy of remote memory. *Neuron* 46:799–810.
2. Hassabis D, Kumaran D, Vann SD, Maguire EA (2007) Patients with hippocampal amnesia cannot imagine new experiences. *Proc Natl Acad Sci USA* 104:1726–1731.
3. Squire LR, et al. (2010) Role of the hippocampus in remembering the past and imagining the future. *Proc Natl Acad Sci USA* 107:19044–19048.
4. Chan D, Henley SM, Rossor MN, Warrington EK (2007) Extensive and temporally ungraded retrograde amnesia in encephalitis associated with antibodies to voltage-gated potassium channels. *Arch Neurol* 64:404–410.
5. Maguire EA, Hassabis D (2011) Role of the hippocampus in imagination and future thinking. *Proc Natl Acad Sci USA* 108:E39.
6. Kirwan CB, Bayley PJ, Galván VV, Squire LR (2008) Detailed recollection of remote autobiographical memory after damage to the medial temporal lobe. *Proc Natl Acad Sci USA* 105:2676–2680.

Author contributions: L.R.S., S.G.M., and J.C.F. wrote the paper.

The authors declare no conflict of interest.

¹To whom correspondence should be addressed. E-mail: lsquire@ucsd.edu.

Role of the hippocampus in imagination and future thinking

Squire et al. (1) recently asserted that patients with bilateral hippocampal damage can imagine future experiences. This contradicts a number of previous reports where amnesia and bilateral hippocampal lesions have been found to cause significant impairment in imagining fictitious and future scenarios (2–4). Based on their findings, Squire et al. (1) concluded that the capacity for imagining the future is independent of the hippocampus. However, there are several aspects of their study that make this conclusion uncertain.

A striking feature of the patients of Squire et al. (1) was their apparent lack of impairment—they could recall events from the remote past, were able to recall recent events, and could imagine future scenarios. Despite the absence of statistically significant findings, the paper by Squire et al. (1) repeatedly stated that the patients were impaired at recalling recent autobiographical events, but their own statistics showed that this was not the case [$t(11) = 1.9, P = 0.08$; p. 19044 in ref. 1]. Given that patients with impaired imagination and future thinking typically have co-occurring anterograde amnesia for autobiographical events (2–4), which was not true here, makes the patients of Squire et al. (1) distinct from the other reported cases.

Although Squire et al. (1) used some aspects of a previous scoring system to examine event descriptions (3), the most crucial measure, the spatial coherence index, was omitted. This index assesses the contiguousness and spatial integrity of an imagined experience. A lack of spatial coherence was found to underpin the performance deficit of patients in a previous study of imagination and future thinking (3). Interestingly, the number of spatial references made by both controls and patients in the study by Squire et al. (1) was far less than controls in other studies using this scoring protocol (3, 5). This strongly suggests that participants did not have vivid and coherent scenarios in mind but may, instead, have supplied descriptions that were more semantic in nature, and recall from semantic memory is spared in patients with damage to the hippocampus. This semantic bias is likely caused by the single word cues used by

Squire et al. (1) compared with the full sentence descriptors used in other studies (3, 5), which specifically encourage rich visualization.

Squire et al. (1) concluded that deficits in imagining the future reported by Hassabis et al. (3) were caused by the specific etiology of their patients (limbic encephalitis) causing more extensive damage and impairments than just to the hippocampus and memory. However, the patients of Hassabis et al. (3) were tested long after their acute illness, had normal neuropsychological profiles at the time of testing (excepting memory), and were specifically selected for their circumscribed hippocampal lesions. Moreover, the fact that other independent studies^{*,†} with a range of etiologies have since replicated the results of Hassabis et al. (3) renders the limbic encephalitis notion untenable.

In conclusion, a number of independent studies have shown that bilateral hippocampal damage and amnesia impair the ability to imagine fictitious and future events. Specific features of the participants and methods in the study by Squire et al. (1) likely contributed to their anomalous result.

Eleanor A. Maguire^{a,1} and Demis Hassabis^b

^aWellcome Trust Centre for Neuroimaging and ^bGatsby Computational Neuroscience Unit, University College London, London WC1N 3BG, United Kingdom

1. Squire LR, et al. (2010) Role of the hippocampus in remembering the past and imagining the future. *Proc Natl Acad Sci USA* 107:19044–19048.
2. Rosenbaum RS, Gilboa A, Levine B, Winocur G, Moscovitch M (2009) Amnesia as an impairment of detail generation and binding: Evidence from personal, fictional, and semantic narratives in K.C. *Neuropsychologia* 47:2181–2187.
3. Hassabis D, Kumaran D, Vann SD, Maguire EA (2007) Patients with hippocampal amnesia cannot imagine new experiences. *Proc Natl Acad Sci USA* 104:1726–1731.
4. Andelman F, Hoofien D, Goldberg I, Aizenstein O, Neufeld MY (2010) Bilateral hippocampal lesion and a selective impairment of the ability for mental time travel. *Neurocase* 16:426–435.
5. Berryhill ME, Picasso L, Arnold R, Drowos D, Olson IR (2010) Similarities and differences between parietal and frontal patients in autobiographical and constructed experience tasks. *Neuropsychologia* 48:1385–1393.

Author contributions: E.A.M. and D.H. wrote the paper.

The authors declare no conflict of interest.

¹To whom correspondence should be addressed. E-mail: e.maguire@fil.ion.ucl.ac.uk.

*Kurzcek JC, et al., Hippocampal amnesia impairs the generation of mental representations across all time periods. Society for Neuroscience Annual Meeting, November 13–17, 2010, San Diego, CA, abstr 600.8.

[†]Race E, Keane M, Verfaellie M, Remembering the past and envisioning the future in amnesia: A comparison of personal events and public facts. Society for Neuroscience Annual Meeting, November 13–17, 2010, San Diego, CA, abstr 600.10.