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Review authors' response

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Brown objects to a statement in our Review[1] that, in his study with monkeys[2], 34% of hippocampal cells responded differently depending on whether the stimulus was familiar or novel. If familiarity and novelty were defined as Brown defines them, then our statement would be in need of correction. In Brown's view, a novel stimulus is one that is being presented for the first time, whereas a familiar stimulus is one that has been regularly encountered in the past. Yet, familiarity is also relative. Thus, an animal trained in a discrimination task can learn to make one response when the test item is relatively familiar and a different response when the test item is relatively unfamiliar, even if in common parlance both stimuli would be described as being familiar to the animal. Hippocampal neurons are sensitive to relative familiarity.

Some neurons in the perirhinal cortex are especially sensitive to differences in the absolute level of familiarity, regardless of their task relevance (and the signal is often stimulus-specific). By contrast, some neurons in the hippocampus are sensitive to differences in the relative familiarity of task-relevant stimuli (and the signal is often abstract — that is, these neurons signal prior occurrence, not specific information about the familiar event)[3,4]. Our article also cited two reviews[5,6] that describe familiarity–novelty (or match–nonmatch) signals in the hippocampus and that contrast these signals with what is observed in the perirhinal cortex. Thus, as explicitly noted in our article, we did not propose that familiarity is treated the same way in both the perirhinal cortex and the hippocampus. Brown apparently takes a different view — that the same familiarity signal that is evident in the perirhinal cortex is not also evident in the hippocampus — and he concludes on that basis that a familiarity signal is not evident in the hippocampus.

It is fair of Professor Brown to question whether his particular result convincingly reflects a familiarity signal. The publication that we cited[2] describes a delayed matching-to-sample task in which "Fruit juice was delivered following a right-panel press when both stimuli were the same and following a left-panel press when they differed." Thus, left and right responses were confounded with matching and non-matching trials. The fact that 34% of hippocampal cells responded differently depending on whether the trial was a match or a non-match was interpreted by the authors to reflect coding of left and right responses in the hippocampus. We interpreted these responses to reflect coding of the relative familiarity and novelty of task-relevant stimuli, but the design of their study does not allow one to choose between these two views.

Other studies are better suited to address this issue and, contrary to what Brown suggests in his correspondence, they show compelling evidence of a long-term familiarity signal in the hippocampus. In one study[7] involving a yes/no recognition task, 21% of cells recorded in the human hippocampus responded according to whether a stimulus was new or old (usually by increasing their activity in response to the familiar stimulus). The retention delay in this case was 1 to 10 hours. A particularly clear example of a long-term recognition signal can be found in two studies by Rutishauser *et al.*[8,9]. On trials in which source memory (recollection) failed but yes/no recognition succeeded (presumably on the basis of familiarity), hippocampal neurons were more responsive to familiar items than to novel items. These responses were not stimulus-specific (that is, the familiarity signal was abstract), and they were evident at delays of 30 minutes and 24 hours. Evidence that these signals are important for recognition comes from the finding that circumscribed hippocampal lesions in memory-impaired patients impair recognition (which is based partially on familiarity) to the same extent that they impair recall (which is based on recollection)[10,11,12].

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