Hippocampal and perirhinal functions in recognition memory

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I would like to correct a statement that was made by *Squire et al.* in a recent Review of recognition memory¹. On page 879, the Review¹ states that 'In one study in monkeys⁷², 34% of hippocampal cells responded differently depending on whether the stimulus was familiar or novel.' Reference 72 is a paper by Wilson *et al.*²: their figure for the number of neurons that respond differently to novel stimuli (that is, stimuli that have never previously been presented or stimuli that have not been seen for many days) presented for the first time than to familiar stimuli (stimuli being shown for the second time in a brief period) is zero out of >650 neurons recorded in the hippocampus and subicular cortex — that is, 0% (see REF. 2, page 315).

The figure of 34% actually refers to repeated presentations of *familiar* stimuli in a delayed matching-to-sample task (DMS task; see REF. 2, page 319). It is important to understand that these familiar stimuli are repeated frequently within short time periods and that the response difference being referred to is that between stimuli being presented for the second time on match trials and stimuli being presented for the second time on non-match trials. Before such response differences between match and non-match trials can be accepted as providing a substrate for general, long-term familiarity discrimination, evidence must be given that they satisfy the appropriate criteria. The delay interval between the first and second stimulus presentations in the experiments referred to was 0.5 seconds — well within the time range of short-term memory or attentive mechanisms. Such match–mismatch differences have not been demonstrated across time delays appropriate to long-term memory, when so many items must be retained that they are outside the capacity of short-term memory, and when the delay intervals are filled with distraction. Other references^{3,4,5} cited in the Review¹ also do not provide such evidence.

Indeed, Wilson *et al.*² provided evidence that the match–mismatch differences do not

provide a possible general substrate for long-term familiarity discrimination and are not related to novelty detection: referring to 395 hippocampal neurons recorded in a serial-recognition task, they state (on page 318) that, "For none of these units were consistent differences found between trials on which novel stimuli were presented and those on which the stimuli reappeared as familiar. An additional >250 units tested with objects and in the DMS task for stimuli varying in their novelty/familiarity did not show consistent responses dependent on the novelty/familiarity of the stimuli." Crucially, agreeing with these findings, Riches *et al.*⁶ further confirmed that when novel stimuli were introduced into such a delayed matching-to-sample task, the responses of hippocampal neurons did not differentiate between stimuli that were novel and stimuli that were highly familiar. Hence, it is possible to dissociate responses to novelty from those to repeated familiar stimuli on match or mismatch trials in a delayed matching-to-sample task.

This situation contrasts with findings for the perirhinal and adjacent cortex. Here, the responses of up to 25% of the neurons are reduced when initially novel stimuli are seen for a second time, regardless of whether the stimuli are presented in a delayed matching-to-sample task or in other situations^{2,6–12}. Such response reductions have been shown to occur when the time delay between presentations is long (~24 hours in many cases), when the delay interval is filled with distractions, and when the number of items needing to be held in the memory is well over the capacity of short-term memory^{6,8,12–14}. Accordingly, such response reductions do satisfy the criteria of general long-term familiarity discrimination.

By contrast, when more complex discriminations of prior occurrence are required, particularly when subjects are taught to encode spatial information, hippocampal neurons are often involved (for example, in monkeys¹⁵, rats^{5,16} and humans¹⁷). It is unsurprising that

the perirhinal cortex and the hippocampus work cooperatively when it is appropriate — this does not prevent their different functions from being dissociated under other circumstances^{2,6,12–14,16}.

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