News and Views

Neurobiology: Caught in the act

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Researchers may have seen the signature of a memory in the making. In monkeys that learnt to associate two stimuli, single neurons changed their responses before, during or after learning became evident.

When Captain Lemuel Gulliver visited Balnibarbi, he was fortunate enough to be allowed into the hall of Speculative Learning at the Academy of Lagado, where, with great admiration, he watched how the nuts and bolts of a knowledge machine generated new sentences of great wisdom in real time[1]. Neurobiologists can only envy him to this day. How nice it would be to watch biological learning machines in action, and see how experience is converted into a memory trace. In the real world, this is more easily wished for than done. Writing in *Science*, however, Wirth and colleagues[2] have moved a step closer to this goal. Their report is of particular interest because it gives fresh insight into the activity of the hippocampus — part of the brain machinery that forms and stores declarative (consciously accessible) memories, and a focus of attention for experimenters, clinicians and theoreticians alike[3].

Wirth *et al.*[2] trained their monkeys in an instrumental conditioning task, in which the subject learns, by trial-and-error, the impact of its actions on the world[4]. Briefly, the monkey was placed in front of a computer screen, and each trial started with the animal fixating on a central spot for 0.3 seconds. The monkey, continuing to fixate, was then presented with four identical visual targets simultaneously, superimposed for half a second on a complex, coloured visual scene. The background scene, but not the four targets, then disappeared, and after a delay of 0.7 seconds the fixation spot also disappeared, cueing the animal to move its eyes towards one of the targets. Only one of these targets was associated with a reward — a squirt of fruit juice. An experienced monkey required about a dozen trials to learn the correct position of the rewarded target in each new scene. On their road to fame, the two monkeys involved in this study saw a total of 378 new scenes over the course of 18 months, of which they learned 290 as required.

And as the monkeys' eye muscles worked for the juice, so too did the neurons in their hippocampus. Wirth *et al.* recorded the electrical activity of these neurons in order to get a handle on their role in learning. This was made feasible by the fact that the associative task is, on the one hand, not too easy, so

that it takes a monkey some time to master it — enough time for the experimenter to follow neuronal dynamics. On the other hand, however, the task is not too difficult, meaning that the monkey can still succeed while the experimenter 'holds' a given nerve cell (in practice, not more than 30 to 50 minutes). So this is an example of cross-level analysis, tapping into behavioural and cellular processes concurrently — virtually essential for studies that aim to analyse the biology of memory.

Wirth *et al.*[2] recorded from 145 neurons in total, and found that 89 responded in a scene-specific manner at one or another phase of the session; of these, 25 changed their activity in close association with the animal's behavioural learning curve. It is this latter subset, dubbed 'changing cells', that attracted the authors' attention. Each of the 25 neurons showed robust changes in firing rate at some point following the presentation of a new scene, but little or no response to a highly familiar scene.

Furthermore, these changing cells fell into two categories. One category consisted of neurons that showed little or no response when a new background scene was presented or during the delay period of the task. But they then signalled that the animal had learned the location of the reward-associated target in that scene by significantly increasing or decreasing their firing rate. This altered activity was maintained throughout the recording session, suggesting that the cells were engaged in storing memories, or in monitoring their storage. The second category comprised neurons that responded to new scenes by either increasing or decreasing their activity relative to the baseline, and then signalled learning by returning to baseline firing rates. Using analytical tools developed in modelling the response of cortical neurons[5], Wirth *et al.* determined that both types of change reflected a modification of the selectivity of the neuronal response to learned stimuli compared with new stimuli.

The authors also compared the number of the trial in the recording session (trial 1, trial 2, and so on) in which behaviourally detected learning occurred, with the number of the trial in which neural activity changed. The results showed that the change took place in individual cells before, at the same time as, or after behavioural learning became evident. Wirth *et al.* took this to mean that hippocampal nerve cells that subserve the new associative memory were recruited into action progressively.

The hippocampus is part of the mediotemporal lobe of the brain, and Wirth and colleagues' study is not the first to report experience-dependent alterations in this overall region as a consequence of associative learning. For example, such phenomena have been seen in the perirhinal cortex[6, 7]. What distinguishes the new study[2] is the focus on the hippocampus, combined with the improved ability to monitor, in real time, the changes in activity of individual hippocampal neurons in correlation with the development of the learned behavioural response.

Aficionados of the hippocampus, learning, or both, might be tempted by the new data to pose additional questions. For example, predominant theories of learning consider the hippocampus and neocortex to be complementary memory systems that together subserve the acquisition and consolidation of long-term memories[8]. So, what is the relationship between the changes seen in the hippocampus and the learning-correlated changes that have previously been observed in neocortical neurons[9, 10]?

And how do we interpret the observation that the neuronal changes occurred at different time points relative to the emergence of behavioural learning? Does this, as Wirth *et al.* suggest, reflect an incremental learning process — a continuous time- and experiencé-dependent recruitment of pieces of the memory puzzle — which must cross a certain quantitative threshold to become behaviourally noticeable? Or are we on the trail of qualitatively different phases in learning, such as the encoding of 'online' information versus its registration as a new memory[4]? Do the cells indeed store the new memory, or instead only take notice of, or index, memories stored elsewhere? And what are the types of nerve cells involved and the modulatory inputs they receive from other brain areas?

These and other questions notwithstanding, this study[2] reflects the fact that we are at an interesting stage in memory research. The paper epitomizes our ability to eavesdrop on neuronal conversations in the brain. Alas, no matter how skilfully the antennas are operated, without deciphering the semantics of the language we are unlikely to come up with definitive answers to some of the key questions. Yet the approach itself is also an attempt to produce a dictionary of neuronal language, and may in due course generate the tools it needs to succeed.

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