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Neuroscience: Out of Sight but Not Out of Mind

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How does the brain hold information about multiple stimuli online after they have disappeared? A new study shows that neurons in the human medial temporal remain active while images are memorized, demonstrating that spiking activity keeps multiple memories online.

Imagine you are at a dinner party. The host introduces you to four people who tell you their names. Your partner walks over and you decide to introduce them to your new acquaintances. What was the name of the first person again? Keeping information in memory in the face of distracting or competing information is a critical process, not only to avoid social embarrassment, but for almost all cognitive tasks. We refer to the process that holds information online for later recall as working memory. Previous studies have revealed that the identity of a single item in working memory is coded as a pattern of persistently firing neurons across multiple brain regions. It is not yet clear, however, how multiple items are stored in working memory. Suppose that the host introduces you to the third dinner guest: is the memory of the first guest still actively maintained as a pattern of persistent activity? There are alternative possibilities: coding schemes have been proposed in which memorized information outside the focus of attention is rapidly encoded as changes in the strength of connections between neurons, without the need for persistent firing. A new study reported in this issue of *Current Biology* [1] investigated the activity of neurons in the medial temporal lobe of subjects who had to remember three or four pictures that were presented sequentially. The spiking activity of many neurons coded for the identity of the most recently presented picture: but a small percentage of the neurons also coded for the memory of pictures that had been presented earlier in the sequence, supporting the idea of persistent firing for multiple items in memory.

Recordings of neural activity during working memory tasks have repeatedly demonstrated that neurons in many brain areas maintain an elevated firing-rate during delay-periods, even in the face of competing or distracting stimuli [2]. Initially, working memory was assigned to the prefrontal cortex on the basis of lesion studies and electrophysiological recordings in monkeys [3–6]. But many different brain areas have been found to contain neurons that exhibit sustained firing during delay-periods (reviewed in [7]). The wide distribution of cells with delay-period activity supports the view that working memories are held online in the enhanced activity of neurons in a distributed network of brain areas, although the mechanisms by which activity is sustained remains unknown [8].

Working memory has a limited capacity of around four items [9], and not all items in working memory are equal. Items that are actively being used for the current task have much stronger representations than items which are currently not relevant, but still held in memory [10]. At first sight, the representations of these unattended

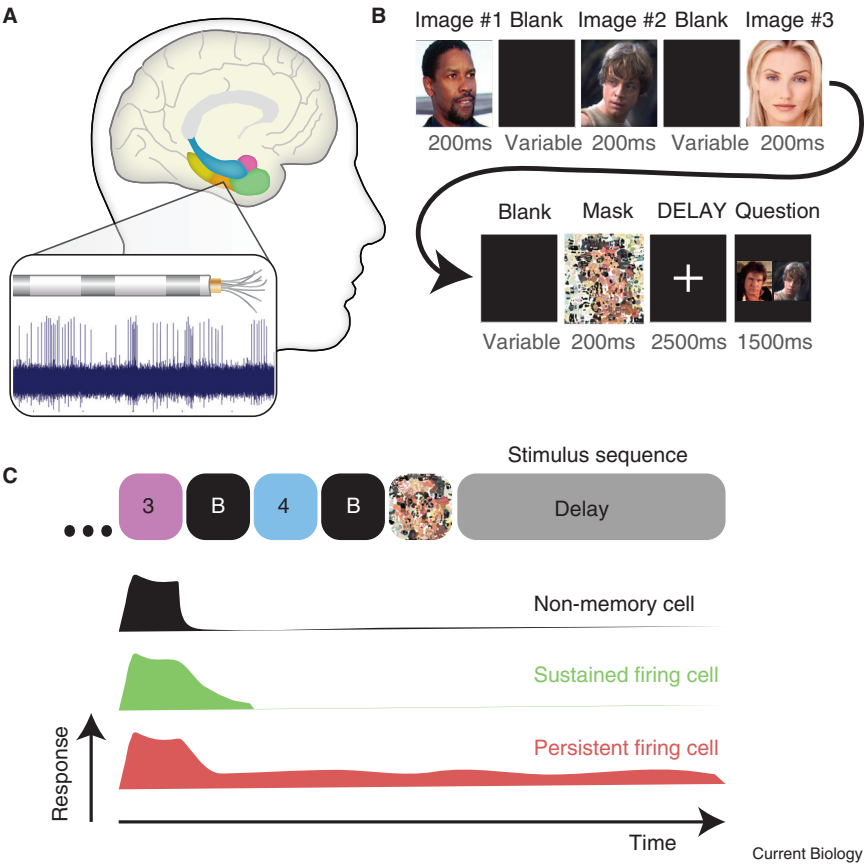

Figure 1. Working memory signals in the medial temporal lobe.
(A) Neural activity was recorded from the medial temporal lobe of epileptic patients implanted with depth electrodes. The medial temporal lobe includes structures such as the hippocampus (blue), amygdala (pink), entorhinal cortex (green), perirhinal cortex (orange), and parahippocampal cortex (yellow). The electrodes contain a bundle of micro-wires that extend from tip of the macro-electrode and allow sampling of single-neuron activity (inset). (B) The working memory task. Patients viewed a sequence of three or four images of famous people, places and animals on a screen. Each image was followed by a blank period of variable duration. The final mask was followed by a memory maintenance period of 2.5 seconds. After the delay, the patient was asked to indicate which image had been present in the previous sequence. (C) Responses from different classes of neurons. A partial stimulus sequence is depicted with the third and fourth images plus the blanks, mask and delay period. Non-memory cells give a strong response to their preferred image (#3) but their activity returns to baseline after the image is removed from the screen. Sustained firing cells maintain their activity after the image is removed, but their activity is curtailed by the subsequent image. Persistent firing cells are able to maintain an elevated firing-rate during the presentation of intervening images and the delay period and may be important for performance on working memory tasks.

memory items seemed to be indistinguishable from items that are not in memory [11]. This has led some [12] to propose that working memories are encoded into the weights of synaptic connections between neurons, forming 'silent' memory traces, rather than in patterns of sustained activity. In support of this view, a study in monkeys [13] performing a dual task paradigm found that the delay activity of pre-frontal neurons is attenuated by cognitive interference from other tasks, but that it was reactivated later. Furthermore, a recent study in humans [14] suggested that silent memories can be reawakened by stimulating the brain using a transcranial magnetic stimulation.

Kornblith *et al.* [1] investigated whether the activity of single neurons in the human medial temporal lobe remains elevated during delays in a working memory task. The authors collected data from a large number of human epilepsy patients who were temporarily implanted with intracranial electrodes to help localize the source of their epilepsy. The electrodes contain several large contacts to allow monitoring of intracranial EEG, which is used to localize the epileptic focus. In addition, these electrodes can contain a bundle of micro-wires (a few tens of microns in diameter) which are pushed out of the tip of the electrode during surgery and can be used to monitor the activity of single neurons (Figure 1A). These electrodes are used to answer purely research-related questions, but the small size of these electrodes mean that they cause negligible damage to brain tissue in comparison to the much larger clinical electrode.

Kornblith *et al.* [1] recorded activity from the medial temporal lobe, a collection of regions including the parahippocampal cortex, entorhinal cortex, hippocampus and amygdala (Figure 1A). The choice for these brain regions was determined by the fact that these areas are likely candidates as the epileptic focus, and they are therefore almost always implanted with electrodes during these surgeries. In addition, medial temporal lobe structures are known to be critical for the formation of long-term declarative memories — such as what you did on your 18th birthday — and may be important for the transfer of working memories into long-term memory.

The patients performed a working memory task in which they had to remember the identities of three or four images of famous faces, places and animals separated by blank intervals (Figure 1B). The images were followed by a memory maintenance period during which the patients had to keep in mind the identities of the images. The patient was then shown two images and had to select which image had been presented in the previous sequence. The patients were able to perform this task with 80% accuracy, on average, indicating that they were successfully able to encode multiple stimuli into memory. Many neurons in medial temporal lobe structures give tuned responses to particular concepts, for example a cell might respond strongly to a picture of Harrison Ford, or his name spelt out on the screen, but not to other famous faces or names [15].

Kornblith *et al.* [1] found that around 17% of recorded MTL neurons were significantly tuned for one of the presented images. The responses of many of these tuned neurons were only high while the image was present on the

screen (Figure 1C, non-memory cells), but in approximately half of the tuned neurons the activity evoked by the preferred image persisted during the blank period between the images (Figure 1C, sustained firing cells). Most interestingly of all, they found a small number of cells whose responses to their preferred stimulus persisted during the presentation of other stimuli and throughout the maintenance period at the end of the sequence (Figure 1C, persistent firing cells). These cells were able to keep online the fact that their preferred image had been presented, even in the face of competing images that also had to be encoded into memory.

The number of neurons that showed such persistent activity was small. Only 8% of the stimulus-selective neurons had significantly higher firing-rates during the maintenance delay period, and rigorous control of statistical error-rates was required to ensure that this finding was reliable. Interestingly, the response of these persistent firing cells predicted memory accuracy: their delay activity during the maintenance period was higher on trials in which the patient correctly recalled the preferred image compared to trials on which they failed to do so.

The study of Kornblith *et al.* [1] demonstrates that multiple pictures can be temporarily stored as the persistent firing of tuned neurons in the human brain. The small percentage of neurons that maintained elevated firing-rates may explain why non-invasive brain-imaging studies have sometimes failed to find sustained activity in working memory tasks and that care should be taken when interpreting 'silent' periods during memory delays. This new study therefore opens up the exciting possibility of studying the neural circuits that help us to keep multiple memories online.

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Peroxisome Biogenesis: A Union between Two Organelles

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Peroxisomes are considered to form either by growth and division of existing peroxisomes or *de novo* from the endoplasmic reticulum. A recent study now demonstrates that mitochondria-derived vesicles are also required for *de novo* peroxisome biogenesis.

James Arthur Baldwin, an American writer, once wrote, "If you know whence you came, there are absolutely no limitations to where you can go." If this aphorism applies to peroxisomes, the recent findings reported by Sugiura *et al.* in *Nature* [1] bring us closer to understanding whence peroxisomes have come. The origin of these organelles,