

had sufficient time to decay. Another study found a mixture of improvements and impairments, depending on the exact timing of the drug administration<sup>14</sup>. In that study, animals were also tested in the water maze, and the differences in the drug administration schedule make comparison with Villarreal *et al.* difficult. Perhaps most crucially, the animals were treated with the drug LY326325, whose primary effect is the blockade of AMPA receptors, and only indirectly prevents Ca<sup>2+</sup> influx through NMDA receptors. Such disparities in results and methods, though difficult to interpret at present, may eventually reveal new subtleties in the mechanisms of learning and memory.

A final note concerns the ongoing attempts to prove that LTP is the experimental analog of memory formation in the brain<sup>4</sup>. McNaughton and Morris proposed three critical experiments that would be necessary to support the hypothesis that LTP underlies some forms

of memory<sup>15</sup>. The first was that saturation of LTP should disrupt existing memories and prevent further acquisition. The second was that blockade of LTP should impair acquisition without disrupting retention. The third was that selective erasure of LTP should disrupt retention without preventing further acquisition. While there is support for the first two conjectures, to our knowledge, no method for selective erasure has yet been achieved that would enable testing the third. The study by Villarreal *et al.*<sup>3</sup>, however, represents the complement to the third postulate: prevention of the naturally occurring erasure of LTP prevents the loss of a memory. These results have thus added another critical piece of information to the puzzle of the relationship between synaptic plasticity mechanisms and memory dynamics.

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## Neural correlates of human memory

Paul Fletcher and Lorraine Tyler

**By making recordings from the human temporal lobe while subjects performed memory tasks, Ojemann and colleagues identify new functional subdivisions of the cortex.**

The neural basis of memory in the human brain is most often studied indirectly. For example, researchers may explore the effects of brain damage on cognitive abilities, or measure neuronal activity in terms of its hemodynamic consequences or the electrical or magnetic field changes that it engenders on the surface of the scalp. Although undoubtedly valuable, such measurements often lack a combination of high spatial and temporal resolution. Now, in a paper in this issue, Ojemann and colleagues record from over 100 temporal lobe neurons in superi-

or, middle and inferior temporal regions of awake patients performing a series of tasks engaging different aspects of memory<sup>1</sup>. (The patients were undergoing temporal lobe surgery.) These direct measurements of neuronal responses offer unique and potentially valuable insights into the organization of memory processes within lateral and inferior temporal cortex.

Memory may be broadly divided into explicit (conscious) and implicit (unconscious) components<sup>2</sup>. In the explicit memory task, subjects memorized (encoded) and recalled (retrieved) words and pictures. Retrieval was further subdivided according to the nature of the cue used to provoke it: in one task, subjects simply saw a symbol indicating that they should recall the item that they had learned. In the other (recognition), they were presented with an item they had seen several days earlier. They were required to indicate whether or not they

recognized it from the pre-operative study phase.

Implicit memory was tested using a simple task in which subjects were required simply to repeat or read words or to name pictures. Stimuli were presented twice, and neuronal activity provoked by the first and second presentation of any given item was compared. Crucially, subjects' attention was not focused on this manipulation, so there was no overt memory component.

Although the findings are complex, they point to some broad patterns of functional specialization in lateral temporal cortex for different types of memory processes. During the encoding stage, neurons were responsive across each of the temporal regions, with no evidence of regional specialization. However, neurons in the dominant hemisphere were less specialized, responding to more than one modality of presentation (written word, spoken word or picture). In contrast to the lack of regional specialization in encoding, when memory states changed—moving from encoding to storage to recall—neurons in inferior aspects of the temporal cortex were especially sensitive.

When recognition memory for items presented several days earlier was tested, neurons in superior temporal regions showed firing-rate changes. Intriguingly, in the other recall task, a different pattern was observed. There was no evidence of regional specialization, and only four neurons were commonly sensitive to both types of

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memory retrieval. The distribution of neuronal sensitivity to the implicit memory task was similar to that for recognition memory, albeit more posteriorly located. Very few neurons, however, showed both recognition and implicit memory changes.

Thus, the current results provide unequivocal evidence for the sensitivity of lateral and inferior temporal neurons to the chosen memory tasks. The authors suggest that these results are incompatible with the majority of functional neuroimaging studies. Although it is certainly true that such studies have emphasized frontal and medial temporal contributions to memory, imaging techniques are not insensitive to more lateral temporal regions. In fact, most PET and fMRI memory studies have shown activation in these regions, but have ignored them. Previously, we considered prefrontal activation in 50 studies of verbal memory<sup>3</sup> and, in light of the current results, have revisited these papers in search of evidence for lateral temporal sensitivity. About 70% of studies that included lateral temporal cortex in the scanning field found task-related activity here. The findings of Ojemann and colleagues perhaps caution us that this area should receive more attention in functional imaging studies of memory. Their findings, for example, of regional specialization for different types of memory retrieval are compatible with at least one imaging study that showed that different areas of lateral temporal cortex are sensitive to different types of memory cues<sup>4</sup>. Moreover, Ojemann and colleagues observe that whereas different memory processes may overlap at the regional level, there is little overlap at the neuronal level. This observation would be beyond the spatial precision of other human brain mapping techniques.

One potentially important way in which the Ojemann *et al.* data differ from those reported in functional neuroimaging studies is in the change associated with implicit memory. Ojemann *et al.* observed an increase in firing rate as a result of repetition, suggesting more activity in response to a repeated stimulus. In contrast, neuroimaging studies show decreased activation<sup>5,6</sup>, suggesting a reduced response. The fMRI measurements of a reduction in activation could reflect simply a smaller spread of activation (even though certain neurons within the area are actually increasing their response). The results from electrophysiology and functional imaging are not necessarily at odds: individual neurons could increase their firing rate, whereas the size of the population responding to the item could diminish. However, it is not so easy to equate these results with the repetition

suppression observed in monkeys<sup>7</sup>. Another possibility is that subjects were aware of the item repetition. Thus, this task could involve incidental recognition of stimuli, producing an effect more akin to an explicit memory task. A study exploring recognition memory using PET<sup>8</sup> is relevant to this issue: left superior temporal gyrus showed increased activity both when subjects attempted to recognize material and when they happened to recognize previously seen material in the setting of a different type of task.

Because all materials used in the Ojemann *et al.* study were language-based, it is important to consider how the current findings relate to functional imaging studies of language. Both neuroimaging and lesion data suggest that the lateral temporal cortex is involved in the representation and processing of semantic knowledge, with consistent activation of lateral and inferior temporal cortex<sup>9,10</sup>. Furthermore, patients with semantic deficits invariably have extensive damage to inferior and middle temporal cortex<sup>11</sup>. The organization of semantic knowledge is contentious. Some researchers argue for a non-fractionated distributed semantic system in which input modality produces a regionally specific effect but the particular category of semantic knowledge does not<sup>12,13</sup>. Others argue for regional specialization according to knowledge category; for example, tools and animals are represented in different areas of temporal cortex<sup>14</sup>. Some have suggested that artifacts such as tools, and the actions associated with them (for example, hitting) are stored in posterior middle temporal gyrus, whereas biological motion (such as perceived hand or whole body movements) preferentially activates superior temporal sulcus<sup>15</sup>. Although the Ojemann *et al.* study was not designed to address the issue of category-specificity in temporal cortex, it is nevertheless informative. First, it presents evidence of process-based specialization of temporal function. Second, it provides some evidence for modality specificity. A substantial proportion of neurons showed firing-rate changes in response to a single presentation mode. Thus, modality specificity could exist within small regions of temporal cortex, making it difficult to address this question using group imaging studies alone.

The strength of this study lies in the spatial and temporal resolution that it brings to mapping of human brain function. Like all attempts at brain mapping, the precise interpretation of regional effects ultimately depends on the confidence with which the

task design may be supposed to have engaged and manipulated the cognitive processes of interest. Residual ambiguity must, of course, exist until we have confidence in our cognitive models of memory. Insights provided by studies using this technique should be involved in developing these cognitive models. This development would benefit from parallel studies in which identical tasks are performed using intracranial recording and the non-invasive techniques such as PET, fMRI, EEG and MEG. Whereas the approach used here boasts great sensitivity and precision, for ethical reasons, the number and distribution of microelectrodes must be limited. We do not, therefore, have information about what is happening elsewhere in the brain. We cannot determine how the brain as a whole is engaged in these tasks, and a systems-level analysis is not possible. It is crucial, therefore, that these results are ultimately integrated with those of techniques that do provide whole-brain information (and *vice versa*). This integration is especially important in view of the fact that, by necessity, the subjects for such experiments have some degree of cerebral abnormality, which may influence the results. An exciting approach would be for these subjects to undergo pre-operative functional neuroimaging and then to carry out identical tasks during operative mapping. This, ultimately, would allow a more direct comparison with the normative neuroimaging literature.

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