Ca^{2+} influx, causing insertion of new GluR1-containing AMPARs into the postsynapse after which unidentified subsequent events adapt the presynaptic elements. However, such a model is in contrast to recent findings in other systems in which pre- or postsynaptic modifications had been described (for review see Burrone and Murthy, 2003). The discrepancy may be due to differences in developmental stages, the type of neurons investigated (e.g., cortex versus hippocampus), and the specific interventions used.

To further complicate this issue, here, acute application of philantotoxin not only changed mini-EPSC amplitude and kinetics but also the frequency of minis to control levels. In classical terms, a change in mEPSC frequency is interpreted as a sole alteration at the presynaptic element, but we now know that pure postsynaptic modifications can also change the frequency of detected mini events. Well aware of the caveat of such an interpretation, the authors argue that postsynaptic modifications (e.g., AMPAR insertion) can only explain a small part of the NBQX-induced increase in mini frequency. Therefore, one might speculate that philantotoxin has direct effects at the presynaptic terminal (unlikely, because controls are not changed), that acute application of philantotoxin antagonizes the release of a retrograde messenger, or that the toxin preferentially mutes XL synapses, the most GluR1-rich and presynaptically active synapses. Further experiments will hopefully help to differentiate between these different models.

Another important issue is whether the observed effects are developmentally regulated. Interestingly, a recent paper showed that the silencing of individual neurons within a neuronal network caused bidirectional effects dependent on the developmental stage of the network (Burrone et al., 2002). When activity was reduced before synapse formation, a competitive loss of synaptic inputs to the silenced neuron occurred, whereas a homeostatic increase in synaptic input could be seen when activity was lowered after most synapses had already formed.

Last but not least, the finding that synaptic inactivity provokes the insertion of GluR1 homomers has direct implications for metaplasticity. Metaplasticity generally describes modulatory changes that modify the ability of synapses to undergo subsequent episodes of plasticity. Evidently, insertion of GluR1-containing AMPARs introduces a new source for Ca^{2+} entry and may thereby alter the threshold for any after plasticity events (Abraham and Tate, 1997; Jia et al., 1996). An experimental proof for this hypothesis should be on the agenda of inquisitive neuroscientists in the near future.

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Less Is More: How Reduced Activity Reflects Stronger Recognition

The mechanisms of recognition involve reductions of activity in the medial temporal lobe. This preview discusses recent fMRI and MEG data from Gonsalves et al. (this issue of *Neuron*) that provide some of the strongest evidence to date demonstrating that reduced medial temporal activity is correlated with stronger recognition of items in humans. This result provides an important test of theories of recognition memory function based on previous neuroimaging and unit recording data.

In thinking about memory, we tend to believe that "more" is a good thing. We "have" a memory, and when we cannot recognize something, we have "lost" our memory. Despite this intuitive impression, studies of neurophysiological activity suggest that in some cases recognition memory for an item involves less, not more, as shown by recordings of single neuron spiking activity during performance of a serial recognition task by monkeys (Riches et al., 1991). In this task, monkeys see a series of novel stimuli, with occasional repeat presentations of familiar stimuli. The familiar stimuli cause a reduced level of spiking activity in single neurons recorded from parahippocampal cortices (Riches et al., 1991). A similar reduction of neuronal spiking activity to familiar stimuli was observed in the inferotemporal cortex of monkeys with repeated presentation of stimuli in a delayed non-match-to-sample task (Miller et al., 1991). However, these previous studies were not able to answer the question of whether the reduction in spiking activity correlated with the parametric graded strength of recognition memory performance.

The article by Gonsalves et al. (2005) in this issue of *Neuron* provides crucial data to answer this question. This study presents the first explicit demonstration of a

correlation between reduced activity (as measured using fMRI and MEG) and higher confidence recognition of stimuli. This study builds on extensive cognitive research using the Remember versus Know recognition memory paradigm. In this paradigm, subjects are presented with previously viewed stimuli and novel stimuli and are instructed to respond based on the nature of their memory for the stimulus. They must respond with a "remember" response if they can recollect the exact episode in which they saw the stimulus. They must respond with a "know" response if they have a "feeling of knowing" the stimulus. They must respond with "new" if they think the stimulus has not been seen before. In the Gonsalves study, activity levels show graded differences in these conditions. Stimuli given the highest confidence recognition rating ("recollected," or R-hit) showed the least activity in the perirhinal and parahippocampal cortices, while stimuli showed somewhat more activity when the subject was less confident and merely had a "feeling of knowing" the stimulus (K-hit). Even greater activity was seen for the incorrect responses ("miss") and correct rejections ("CR"). These compelling data clearly demonstrate that the reduction of activity for familiar stimuli is correlated with stronger recognition of the stimuli as measured behaviorally.

This paper provides a crucial extension of previous neuroimaging studies showing a reduction in activation associated with novel stimuli becoming familiar. The first demonstration of robust changes in medial temporal lobe fMRI activity during a memory task showed less activity during repeated presentation of a single stimulus versus substantial activity during sequential presentation of different novel stimuli being encoded for subsequent recognition (Stern et al., 1996). Studies have demonstrated that the repetition reduction occurs for both visual and verbal stimuli and that greater activity for novel stimuli in hippocampal and parahippocampal regions is associated with the encoding of information into long-term memory (Brewer et al., 1998; Kirchhoff et al., 2000). Though these and other studies have shown correlations between increased medial temporal lobe activity during encoding and subsequent performance on recognition tasks, and others have shown reduced activity associated with recognition of old stimuli (Weis et al., 2004), no studies before the study by Gonsalves et al. evaluated correlations between reduced activity during recognition testing and the concurrent graded levels of performance on recognition tasks.

These rich experimental data have motivated extensive theoretical modeling work. Biological mechanisms for reduced neural activity have been analyzed in neural simulations. The fact that reductions in activity occur even after long intervals between the first and second presentation of a stimulus suggests that the reduction results from changes in synaptic strength. The changes in synaptic strength could occur at feedforward connections from sensory cortices into parahippocampal cortices, or they could involve feedback from other regions, such as hippocampus or prefrontal cortex, which would take a longer time to influence activity after a new stimulus is presented. Because the reduced level of single neuron spiking activity appears early in the response to the presentation of a familiar stimulus, most models focus on reductions in feedforward strength. In some models, Hebbian strengthening of a small subset of synapses causes competitive reductions of the strength of other synapses (Sohal and Hasselmo, 2000; Norman and O'Reilly, 2003), whereas other models reduce synaptic strength using Hebbian long-term depression of synapses (Bogacz and Brown, 2003). Though the focus on changes in feedforward connections is consistent with the monkey unit recording data, no previous data have answered the question of whether the reduction in activity at short delays correlates with graded levels of recognition performance.

The Gonsalves article also answers this important question, by providing evidence on the time course of the effect, as demonstrated using anatomically constrained MEG. MEG provides temporal resolution unavailable in fMRI studies, and the MEG data allow a detailed analysis of the time course of the changes in activation associated with recognition. The Gonsalves et al. MEG data indicate that better recognition is associated with a reduction in the MEG signal which appears between 150 and 450 milliseconds after stimulus onset. This time course appears to be too rapid to allow for cycles of top-down processing to activate feedback synapses, suggesting that this effect involves a reduction of the strength of the feedforward input to these regions. These data support models that focus on reducing the strength of feedforward synapses. The use of methods with a high temporal resolution in humans enhances the capacity for direct comparison with the high temporal resolution data in nonhuman primate unit recording studies (Miller et al., 1991; Riches et al., 1991).

Integrating the results of the Gonsalves study with current theoretical models suggests several options for further study. Biological models (Sohal and Hasselmo, 2000; Bogacz and Brown, 2003) have generated a number of predictions for further experiments. For example, modeling has addressed the presence of two time courses for reduction in single neuron spiking activity (Miller et al., 1991; Riches et al., 1991; Sohal and Hasselmo, 2000). Short-term reductions in spiking can be modeled with spike frequency accommodation (Sohal and Hasselmo, 2000) or sustained activity causing enhanced feedback inhibition, in contrast to the longer-term reductions involving synaptic changes. The MEG techniques presented here could test for a similar presence of two time courses in the human data and could compare the time constants to single neuron data and to computational modeling. The authors are cautious in interpreting their data with regard to whether recognition involves a single process (Wixted and Stretch, 2004) or dual processes of recollection and familiarity (Yonelinas et al., 2005). Their data indicate that the Remember and Know responses could reflect separate thresholds imposed on a single dimension of activation (Wixted and Stretch, 2004), but they further suggest that a recollection response could have been observed with stronger hippocampal activation in their study. More biologically detailed modeling may provide more explicit tests of this distinction, as might additional studies to examine whether a truly linear relationship exists between activation level and recognition confidence. This could be tested with a finer resolution of recognition confidence (for instance, using the six point scale used in the behavioral component of the study or

other recognition tests). This would require a substantial increase in the number of behavioral trials, but the Gonsalves study provides a strong motivation for further analysis of these mechanisms.

Overall, the innovative use of multimodal techniques in this study reflects an important move toward a tighter integration of neuroimaging data with the vast wealth of data at the cellular and circuit level.

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