Journal Club

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What Can Immediate-Early Gene Expression Tell Us about Spatial Memory Retrieval?

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Review of Gusev et al. (http://www.jneurosci.org/cgi/content/full/25/41/9384)

Introduction

Memory researchers have long been fascinated with what happens to memories with time. Historically, two theories have made different predictions about the involvement of the hippocampus (HC) in the retrieval of remote memories. Systems consolidation theory predicts a diminishing role of the HC, whereas multiple memory trace theory (MTT) suggests a continued involvement, regardless of the age of the memory. Recently, activation patterns of immediate-early genes have been used to shed light on this issue (Frankland and Bontempi, 2005). In a recent article in *The Journal of Neuroscience*, Gusev et al. (2005) characterized the pattern of HC activation during the retrieval of recent or remote place memories acquired in the Morris water maze task using mRNA expression of the immediate-early gene *Arc*. The authors suggest that their results favor systems consolidation theory over MTT because they found a decrease in the magnitude and complexity of *Arc* expression in the HC as the memory aged.

The authors report a reduction in *Arc* mRNA in the HC during the retrieval of a remote memory for the platform compared with a recent memory [Gusev et al. (2005), their Fig. 9 (http://www.jneurosci.org/cgi/content/full/25/41/9384/FIG90]. The expression pattern differed across HC subregions. *Arc* mRNA decreased the most across the retention span in CA1 and in the ventral HC. Activity in CA3, the dorsal HC, and the entorhinal cortex was more consistent across both recent and remote time points, although it still decreased somewhat. The authors conclude that this difference between subregions indicates a more persistent role for CA3 and dorsal HC neurons in the retrieval of water maze memory. By analyzing sections of the HC along the rostrocaudal axis, Gusev et al. detected clusters of activation within subregions in dorsal and ventral HC [Gusev et al. (2005), their Figs. 6 (http://www.jneurosci.org/cgi/content/full/25/41/9384/FIG6), 7 (http://www.jneurosci.org/cgi/content/full/25/41/9384/FIG7)]. These results suggest that subdivisions at a finer grain may play specific roles in spatial memory.

We appreciate the fine level of analysis this paper presents and the detailed description of the differential involvement of HC subregions in spatial memory retrieval across time. However, empirical, methodological, and conceptual issues constrain some of the interpretation. First, there is evidence suggesting that systems consolidation does not occur in the Morris water maze task (Sutherland et al., 2001; Clark et al., 2004; Martin et al., 2005). That is, hippocampus lesions always result in spatial memory impairment, regardless of the age of the memory. In addition, retention of the platform location reported by the authors was quite poor during both the recent and remote probe trials. Search time in the target quadrant is just above that predicted by chance, even at the recent time point, leaving one to wonder whether the rats really preferred this quadrant [Gusev et al. (2005), their Table 1 (http://www.jneurosci.org/cgi/content/full/25/41/9384/TBL1)]. The authors attribute this to the fact that the rats were not trained to dwell near the platform, but rats with strong spatial memory can show selective search without this sort of training (Micheau et al., 2004). It is clear from the latency data during the first probe trial in the remote memory group that forgetting of some sort occurred, and the search time in the target quadrant appears to actually increase across probe trials. This argues against extinction but seems to indicate an active memory process. Given these behavioral issues, it is more difficult to interpret the meaning of the *Arc* activation during probe tests.

Immediate-early genes are used to map the brain regions involved in the retrieval of memories because it is assumed that retrieval produces activity at the synapses supporting the memory. This activity leads to a signal to the nucleus that drives the transcription of immediate-early genes. The authors measure the density of staining for *Arc* mRNA in regions of the hippocampus and conclude that because this activity marker decreases between recent and remote retrieval tests, the involvement of those regions in supporting the memory must also be decreas-

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ing over time. They suggest that this decrease provides evidence for systems consolidation but not MTT. However, we argue that standard densitometry cannot differentiate between these two competing theories. We believe this because (1) most plasticity researchers agree that the synapse is the basic unit of memory storage; (2) memory traces may be stored in multiple cells or on single cells via the involvement of multiple synapses; (3) densitometric analysis quantifies mRNA content throughout the cell rather than measuring a synapse-specific signal, so it cannot differentiate between the possibilities in (2).

For example, a decrease in the number of *Arc*-expressing cells could occur at the same time as an increase in the number of synapses (multiple memory traces) on the remaining "active" cells that support retrieval of the memory. In this case, although the absolute number of active cells may decrease, the brain region under examination is no less involved in the retrieval of the memory. A higher-resolution method focusing on mRNAs or proteins localized to active synapses is required to detect this type of reorganization.

In conclusion, Gusev et al. provide a detailed description of the pattern of *Arc* mRNA in the HC after recent and remote memory retrieval in the Morris water maze task. Although the issues discussed here limit the conclusions, the data stimulate conceptual questions about what the activation patterns in the brain can tell us about the involvement of those structures in memory retrieval.

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