Journal Club

Editor's Note: These short, critical reviews of recent papers in the *Journal*, written exclusively by graduate students or postdoctoral fellows, are intended to summarize the important findings of the paper and provide additional insight and commentary. For more information on the format and purpose of the Journal Club, please see http://www.jneurosci.org/misc/ifa_features.shtml.

Could Frequency-Specific Coupling between Single-Cell Activity and the Local Field Potential Underlie Memory Encoding in the Hippocampus?

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Review of Jutras et al.

Since the remarkable case of H.M., researchers interested in identifying the neural substrates of memory have been drawn to the hippocampus, an evolutionarily old part of the cortex known as the archicortex. Despite a truly multidisciplinary effort from fields as wide ranging as molecular biology and cognitive psychology, surprisingly little is known about the precise neurophysiological mechanisms mediating declarative memory (memory for facts and events) in the primate brain. Part of the problem is that in the primate brain, the hippocampus is tucked away deep in the medial temporal lobe, making electrophysiological recordings, which are fairly routine in the rodent, significantly more challenging. The inability to reliably and consistently reach and record from a target area is not a predicament to be taken lightly; notwithstanding, a recent study in *The Journal of Neuroscience* by Jutras et al. (2009) reexamines and sheds new light on possible hippocampal mechanisms underlying memory formation in the monkey.

Jutras et al. (2009) concentrated specifically on recognition memory, which in an experimental setting is the ability to realize that a particular stimulus has been shown repeatedly. To assess visual recognition memory, the researchers presented 200 novel images to subjects in each experimental session, repeating each image exactly once, resulting in 400 total image presentations per day. Although in most human recognition experiments of this kind the encoding and recall phases are separated, to ease the memory demands on the monkey subjects, the two phases were interleaved in the present study, such that the first and second presentation of any given stimulus were separated by no more than 8 intervening stimuli. The subjects' task was to simply view these images. The authors then took advantage of the monkeys' preference for novel stimuli, which is present in many animal species, and quantified memory strength as the proportional decrease in looking time for the repeat presentation of a stimulus, with larger decreases indicating better memory [Jutras et al. (2009), their Fig. 1C]. Simultaneously, both single unit activity and the local field potential (LFP) were recorded from the hippocampus, including the CA3 region, the dentate gyrus, and the subiculum. Focusing their analyses only on electrodes that had well isolated single units to ensure that their LFP signal came from cell-rich layers, the authors report several intriguing findings.

First, although the majority of neurons (66%) exhibited visual responses, the response magnitude during the encoding phase was not correlated with the decrease in looking time for repeat viewings of stimuli [Jutras et al. (2009), their Fig. 3A]. Specifically, the average firing rate across stimuli that were subsequently well recognized did not differ from the average firing rate across stimuli that were subsequently forgotten. Despite this lack of correlation, a significant proportion of the visually responsive neurons (36%) exhibited a response difference (the authors do not report whether it was suppression or enhancement) to repeat presentations of the stimuli, a phenomenon referred to as novelty effects (data not shown). Therefore, the neurons must have retained some stimulus information from the first encounter to respond differentially to the repeat presentation.

The absence of a specific link between firing rate changes and decreases in looking time contrasts with a recent study from Wirth et al. (2003). In that study, subjects learned on a daily basis two to four novel image-location associations. Specifically, in a single session, monkeys learned that one image required an eye movement to the top, another image an eye movement to the right, and so on. Because of the trial-and-error nature of the task, each novel image was presented tens of times throughout the day. Analyses revealed that individual hippocampal neu-

rons underwent stimulus-specific firing rate changes that correlated with the monkey's ability to execute the correct eye movement. So, for example, as the monkey learned that a particular image required an eye movement to the top, the neuron's response to that image would increase, and this increase was tightly linked to the increase in behavioral performance. Critically, a given cell did not necessarily signal all of the day's learned image-location associations but only an arbitrary subset (most often just one image); presumably, other hippocampal cells carried information about the other associations. Because Jutras et al. (2009) were studying single-exposure recognition memory, to obtain reliable estimates of the firing rate for well recognized stimuli, they had to average rates across different stimuli identities; the same process was repeated for the forgotten stimuli. This averaging method may have obscured any subtle and stimulus-specific firing rate differences that correlated with decreases in looking time. Similarly, as the subjects in the present study simply observed the stimuli and did not have to learn them explicitly, as in the Wirth et al. (2003) study, firing rate changes may have not emerged. Future work will be needed to examine this issue in more depth.

The second main finding the authors report is that the coherence between single units and the LFP during the encoding portion of the task covaried with the strength of memory expression [Jutras et al. (2009), their Fig. 4, left column]. In particular, the magnitude of the spike-field coherence, which measures the amount of linear correlation between two time series as a function of frequency, was selectively increased by ~10% from a baseline value of ~0.10 in the high gamma range (60–100 Hz) for items that resulted in subsequent large decreases in looking time [Jutras et al. (2009), their Fig. 3B–F]. The authors hypothesize that by phase-locking their discharge to the underlying gamma oscillations, select groups of hippocampal neurons may undergo the spike-timing-dependent modifications that many believe underlie long-term memory encoding and consolidation. Likewise, such phase coherence could also lead to temporary neuronal assemblies that establish the temporal and spatial pattern of activations necessary for accurate memory reinstatement (Womelsdorf et al., 2007). Importantly, however, these observations are limited to the encoding phase of the task, leaving unaddressed the question of what neural mechanisms are at play during the recognition phase.

Could the described novelty effects address this question? Although the authors do not directly report this, it is implied that there was a lack of a specific correlation between the magnitude of response modulation across the two stimuli presentations and decrease in looking time. At first glance, then, novelty effects seem like a poor neural candidate for recognition. Nonetheless, we know from previous work that the cortical regions surrounding the hippocampus, including the entorhinal, perirhinal and inferior temporal cortices, contain a large proportion of neurons that exhibit a response decrement to repeat presentations of stimuli, an effect known as repetition suppression (Baylis and Rolls, 1987; Miller et al., 1993). It is intuitive to speculate that this repetition suppression somehow underlies the overall decrease in looking time for repeat viewings. Interestingly, it was recently shown that long-term depression in the perirhinal cortex of the rat is crucial for visual recognition memory (Griffiths et al., 2008). Could this long-term depression be the driving force behind repetition suppression? If so, an interesting question is whether spike-field coherence in the hippocampus is related to repetition suppression in the perirhinal cortex. Providing an answer could provide us with a neural link between the encoding and recall phases of recognition memory.

I offer one speculative hypothesis. It is widely believed that gamma oscillations are generated in large part by populations of inhibitory interneurons (Wang and Buzsáki, 1996; Cardin et al., 2009). This rapid oscillation of inhibition gives excitatory neurons relatively narrow temporal windows during which they can be driven to fire action potentials. Because the gamma oscillations have spatial extent, this implies that multiple excitatory neurons within a circumscribed region synchronize their membrane potential excursions. The increased synchronization of small groups of hippocampal output neurons likely leads to more precise temporal summation of EPSPs in downstream neurons, thus allowing the downstream neurons to undergo long-term changes in their excitability (Jutras et al., 2009). Applying this line of reasoning to the present topic, it may be that neurons in the surrounding parahippocampal region have their response properties rapidly modified by hippocampal output. Increased spike-field coherence in the hippocampal output would in turn give rise to more robust plasticity in the parahippocampal expression

neurons, and as a consequence, to better memory recall.

Could this same coupling between spike-field coherence and firing rate changes be present within the hippocampus itself? The Wirth et al. (2003) study mentioned above did not examine coherence, leaving open the possibility that spike-field synchronization precedes, or is concomitant with, hippocampal firing rate changes that happen during the learning of arbitrary associations. Hypotheses of this sort posit a very strong interdependence between these two seemingly different neurophysiological mechanisms.

On the other hand, very different memory tasks could recruit distinct hippocampal mechanisms, and the spike-field coherence and the firing rate changes could be much more independent than postulated here. Indeed, recognition memory is typically divided into two categories, familiarity and recollection, wherein recollection, in addition to evoking a sense of familiarity also allows the subject to remember specific details about previous encounters with that stimulus (e.g., it was presented in the top left quadrant of the screen) (Yonelinas, 2002). Although it is widely accepted that the hippocampus is crucial for recollection-like tasks, exemplified by Wirth et al. (2003), a point of contention has been the extent to which the hippocampus contributes to familiarity, with some ascribing the lion's share of responsibility to the surrounding parahippocampal regions (Brown and Aggleton, 2001) and others positing an equally important role for the hippocampus itself (Manns et al., 2003). In the present study, the task design was much more similar to familiarity paradigms than to recollection paradigms, thus providing new support for a contribution of the hippocampus to familiarity-based recognition memory. At the same time, the qualitative nature of the most convincing findings, namely the increase in spike-field coherence and gamma-band LFP (see below), could help explain why neural evidence for a hippocampal involvement in familiarity judgments is not always observed.

A third contribution of the Jutras et al. (2009) paper is the finding that the power of the encoding related gamma-band LFP (30–100 Hz) was, like the spike-field coherence, also a reasonable predictor of whether the animal subsequently recognized a particular stimulus [Jutras et al. (2009), their Fig. 5]. The increased power of the gamma band implies an overall increase in the temporal precision with

which all the neurons in a given area fire. Such increased accuracy could confer additional computational properties upon these neurons, such as phase of firing coding. The increased gamma-band power in the hippocampus could also entrain the oscillations in other cortical areas, leading to a temporary strengthening of the functional connection between them. In fact, previous intracranial EEG work with humans has shown that the hippocampal and rhinal cortices increase their phase coupling in the gamma range for subsequently remembered words (Fell et al., 2001). Simultaneous recordings from multiple areas will need to be performed to test for this possibility in the nonhuman primate.

In summary, the paper by Jutras et al. (2009) has uncovered several additional candidate neural mechanisms subserving memory in the hippocampus. As stressed here, these results concern mostly the encoding phase. Future work will be needed to determine to what extent the hippocampus itself is involved in the recall phase of the task, to describe in detail the functional relevance of the spike-field coherence and the gamma-band LFP, and to elucidate how these mechanisms interact with and modify other parts of the recognition memory circuit.

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