

## Keeping the memories flowing

Gregory J Quirk & Ivan Vidal-Gonzalez

**Transmission of sensory information through the rhinal cortices is essential for hippocampus-dependent learning. In this issue Paz *et al.* show that amygdala activity elicited by an unexpected reward facilitates communication from perirhinal to entorhinal cortex, providing a physiological mechanism for emotional modulation of memory.**

“So short is love, and so long is forgetting,” wrote Pablo Neruda in a testimony to the tenacity of emotional memories. How is it that emotions, positive and negative, strengthen memories for particular events in our lives? At the heart of emotional modulation of memory lies the amygdala, a structure activated by emotional stimuli. It is widely accepted that the basolateral complex of the amygdala (BLA) strengthens consolidation of emotional memories through its projections to widespread cortical areas<sup>1,2</sup>. Despite a wealth of neuropharmacological data, however, there is still no neurophysiological model to account for this important function. In a *tour de force* of behavioral neurophysiology, Paz and colleagues<sup>3</sup> demonstrate that amygdala activity strengthens memories by facilitating transmission of sensory information from the neocortex to the hippocampus.

Amygdala neurons increase their sensory responses to cues associated with positive or negative outcomes<sup>4–6</sup>. Such responses could provide a means for emotional responses to influence memory, but the mechanism by which amygdala activity might strengthen learning in other systems has remained unclear. To address this important issue, Paz *et al.* used an appetitive ‘trace’ conditioning task in cats, in which a light and food are separated by a brief interval. Over time, the cat learns to lick a food spout when the light is presented. The hippocampus is needed for the animal to learn the association between the light and food.

Sensory information reaches the hippocampus primarily through a cascade

of sequential projections—from sensory cortices to the perirhinal cortex, from there to entorhinal cortex, and finally to the hippocampus. Paradoxically, there is little communication between perirhinal and entorhinal cortex owing to strong feed-forward inhibition, thereby diminishing the flow of information into and out of the hippocampus<sup>7</sup> under normal circumstances.

Both perirhinal and entorhinal cortex receive a robust projection from the BLA, raising the possibility that the BLA might facilitate perirhinal-entorhinal transmission in the presence of an arousing stimulus, thereby enhancing memory. To test for such interactions, Paz *et al.* recorded simultaneously from neurons in all three structures. As previously observed, perirhinal cortex neurons on average only weakly excited entorhinal cortex neurons, as evidenced by few significant cross-correlations between their spike trains. Paz *et al.* then modified the cross-correlation technique to examine all three structures at once, using a spike-triggered joint histogram (STJH). This approach reveals how the perirhinal-entorhinal correlation is modulated by a reference event, in this case the occurrence of BLA spikes (Fig. 1), by computing the cross-correlation conditioned on the presence of the reference event. Surprisingly, this analysis revealed that highly significant correlations between perirhinal and entorhinal cortex neurons emerged within 150 ms of a spike in the BLA. In other words, BLA action potentials briefly enabled coordinated activity between perirhinal and entorhinal cortex. Previous studies of rhinal areas missed these interactions because they did not record simultaneously from the BLA.

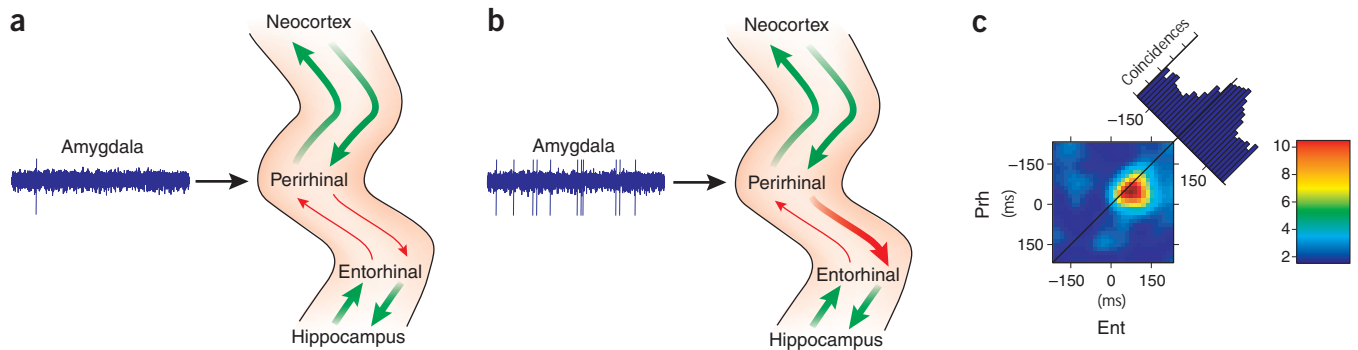
The finding that BLA activity induces interactions between cortical structures is

interesting, but the crucial test of the role of these interactions in emotional modulation is whether the incidence of BLA-triggered interactions (the STJH signal) increases with arousal. Impressively, Paz *et al.* report that the STJH signal increased following each unexpected food reward. Furthermore, as the cat learned that the light predicted the food, the STJH signal shifted from being elicited by the food to being elicited by the light. Thus, as the presentation of the food became reliably predicted by the light, the food no longer triggered the STJH signal. This is an important observation because it implies that it is not the reward *per se* that triggers the rhinal interactions, but the unexpectedness of the reward.

These results agree with classical learning theory, which says that learning rates are maximal following unexpected outcomes<sup>8</sup>. Accordingly, emotional events would be expected to modulate learning most strongly when they are surprising, so that future encounters with associated sensory stimuli will not catch the animal off-guard. Not mentioned by Paz *et al.* is that a similar shift of neuronal responses from the unconditioned stimulus to the conditioned stimulus occurs in brainstem dopaminergic neurons<sup>9</sup>. This suggests that dopaminergic signaling could be involved in the synchronization of BLA activity and the development of the STJH signal, an idea supported by the observation that dopamine suppresses local inhibitory circuits in the BLA (ref. 10).

Perirhinal and entorhinal cortex are reciprocally connected, and transmission through this bottleneck is necessary for information both entering and exiting from the hippocampus. Calculating a directionality index from the STJHs, Paz *et al.* observed that reward shifted rhinal interactions in the perirhinal-to-entorhinal

Gregory J. Quirk and Ivan Vidal-Gonzalez are in the Department of Physiology, Ponce School of Medicine, P.O. Box 7004, Ponce, Puerto Rico. e-mail: giquirk@yahoo.com



**Figure 1** The amygdala enhances transfer of sensory information. Sensory input flows from the neocortex to the hippocampus via the rhinal cortices (descending arrows). The hippocampus in turn assists in consolidating and storing this information through projections back to neocortex (ascending arrows). **(a)** During spontaneous activity, with low amygdala firing rates (blue traces on left), transfer of information from perirhinal cortex (Prh) to entorhinal cortex (Ent) is minimal (thin red arrows). **(b)** Following reward, the amygdala increases its firing rate and synchrony. This enables the transfer of sensory information through the rhinal cortices into the hippocampus (large red arrow). **(c)** The dependence of transfer through the rhinal cortices on amygdala activity is evidenced by peaks in the spike-triggered joint histogram (STJH, colored square). The STJH calculates the cross-correlation between perirhinal and entorhinal spike trains with reference to a third event, in this case a BLA spike. In the color plots, the *x*- and *y*-axes represent the latencies of entorhinal and perirhinal spikes relative to the occurrence of a BLA spike, respectively. Each cell of the grid represents the number of spike pairs that occurred with the corresponding latencies relative to a BLA spike. The red peak in the STJH indicates that shortly after a BLA spike, entorhinal cortex fires after perirhinal cortex, consistent with facilitated transmission in the perirhinal→entorhinal direction. The plot on the upper right corner of the STJH is a crosscorrelogram resulting from summing the leftward diagonal rows of the STJH along the rightward diagonal (indicated in black). This represents the number of pairs of entorhinal and perirhinal spikes that occur in the vicinity of a BLA spike. The effect of amygdala activity on rhinal throughput is a plausible mechanism for facilitation of emotional memory by the amygdala.

cortex direction, favoring the transfer of information from the neocortex to the hippocampal formation. This intriguing finding suggests that the BLA facilitates memory encoding, rather than memory readout, which makes sense for the acquisition phase of learning. Later consolidation phases were not examined, but a testable prediction from their findings is that such phases of learning should produce a reversal of information flow, in the entorhinal-to-perirhinal cortex direction, consistent with storage of hippocampal memories in the neocortex.

Although one might think that BLA facilitation of rhinal interactions could be explained solely by increased firing rate in the BLA, this was not the case. STJH changes did not follow changes in firing rate but were correlated with the degree of BLA synchrony. Thus, as previously observed<sup>11</sup>, task-relevant information can be signaled by the timing of action potentials, rather than their average firing rate. Paz *et al.* extend this idea by demonstrating that these interactions occur across structures. The combination of multisite recording with the STJH is a powerful new tool for investigations of neuronal networks

of learning, which have traditionally used techniques with lower temporal resolution, such as *c-Fos* immunocytochemistry or deoxyglucose mapping. One wonders if STJH signals would be observed for other structures implicated in memory consolidation, such as the hippocampus<sup>12</sup> and medial prefrontal cortex<sup>13</sup>.

How prolonged is the effect of the amygdala on cortical circuits? Although the increase in the rhinal STJH signal following each reward was relatively short (approximately 1 second), a previous study by this group showed that footshocks increased firing rate and synchrony in the BLA for as much as 2 hours<sup>14</sup>. Rhinal activity was not recorded in that study, but an important prediction following from the results of Paz *et al.* is that STJH signals should show prolonged increases following aversive stimuli. Persistence of STJH signals long after shock would agree with infusion studies showing that activity after training in the BLA is required for its memory-enhancing effects<sup>1</sup>. An intriguing possibility is that STJH signals may reflect rehearsal of earlier events as part of the consolidation process<sup>12,15</sup>. Future studies combining pharmacological approaches with an STJH analysis of the

BLA's influences on target structures hold great promise for explaining emotion's strong influence on our memories.

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