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Emotional enhancement of memory via amygdala-driven facilitation of rhinal interactions

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Emotions generally facilitate memory, an effect mediated by the basolateral amygdala (BLA). To study the underlying mechanisms, we recorded BLA, perirhinal and entorhinal neurons during an appetitive trace-conditioning task. We focused on the rhinal cortices because they constitute the interface between the hippocampus, a mediator of memory consolidation, and the neocortex, the storage site of declarative memories. We found that, after unexpected rewards, BLA activity increased impulse transmission from perirhinal to entorhinal neurons and that this effect decayed as the association between conditioned stimuli and rewards was learned. At this late phase of learning, the BLA effect occurred when the animals were anticipating the reward. By enhancing the processing of sensory cues, the BLA-mediated facilitation of rhinal interactions may explain how the amygdala promotes memory formation in emotional conditions.

Humans generally form more vivid memories of emotionally charged events than of mundane experiences[1]. How do emotions facilitate memory? It is known that the facilitation of memory by emotions requires an intact BLA in humans[2–4] and animals[5,6]. Moreover, there is evidence that the amygdala facilitates memory by enhancing attention during encoding and by modulating consolidation and storage after learning[5,7].

In humans, attention is enhanced by emotional stimuli and this effect is absent in a subject with amygdala lesions[8]. Consistent with these results, functional imaging studies indicate that the amygdala is activated by emotional stimuli[9]. In addition, there is a strong positive correlation between amygdala activity at encoding and the long-term recall of emotional material[10,11].

In animals, evidence shows that the amygdala is a critical site of plasticity when using classical fear-conditioning protocols[12]. However, for many other types of emotional memories, including striatal- and hippocampal-dependent ones, the amygdala does not seem to be a storage site but rather modulates memory consolidation in its targets. Indeed, post-training injections of drugs that presumably enhance or reduce BLA activity respectively facilitate or impair retention, even when memory was tested long after the effects of these drugs has dissipated[13]. In contrast, injections of lidocaine into the BLA days after training, just before testing retention, do not affect performance on striatal- and hippocampal-dependent memory tasks[14].

Although emotional arousal recruits the BLA by means of stress hormones[15–17], causing a long-lasting increase in BLA firing rates[18], the impact of this increased activity on target structures has received little attention so far. Here, we investigated how the presentation of biologically significant and arousing stimuli affects neuronal interactions between the BLA and rhinal cortices, by simultaneously recording neurons of the BLA, perirhinal areas 35 and 36, and entorhinal cortex in cats performing a trace-conditioning task known to be dependent on the amygdala, rhinal cortices and hippocampus[19–23]. Indeed, the rhinal cortices receive massive BLA inputs[24,25] and form the interface[26,27] between the hippocampus, a critical mediator of memory consolidation, and the neocortex, thought to be long-term repository of declarative memories[28–30]. We found that BLA activity enhances the processing of sensory cues during behaviorally salient events by facilitating impulse transmission from the perirhinal to the entorhinal cortex. Furthermore, this effect was tightly linked to learning.

RESULTS

To test the possibility that amygdala projections to the rhinal cortices facilitate memory by promoting impulse transfer between the neocortex and hippocampus, we simultaneously recorded from BLA ($n = 390$), perirhinal ($n = 282$) and entorhinal ($n = 232$) neurons in cats, by means of 24 microelectrodes (**Fig. 1a**,**b**). We analyzed BLA-related changes in rhinal activity in four conditions: under anesthesia, during waking periods where no rewards were administered, after unexpected rewards and during a trace-conditioning task. The following analyses include only neurons whose location was confirmed by *post-hoc* histological reconstructions of microelectrode tracks (**Fig. 1c–f**).

Impact of BLA activity on spontaneous rhinal interactions

To study how BLA activity affects impulse traffic in the rhinal cortices, we first computed cross-correlations of spontaneous firing generated by perirhinal and entorhinal neurons located in the same coronal plane (**Fig. 1g–i** and **Supplementary Fig. 1** online). Despite the strong reciprocal connections between the perirhinal and entorhinal cortices,

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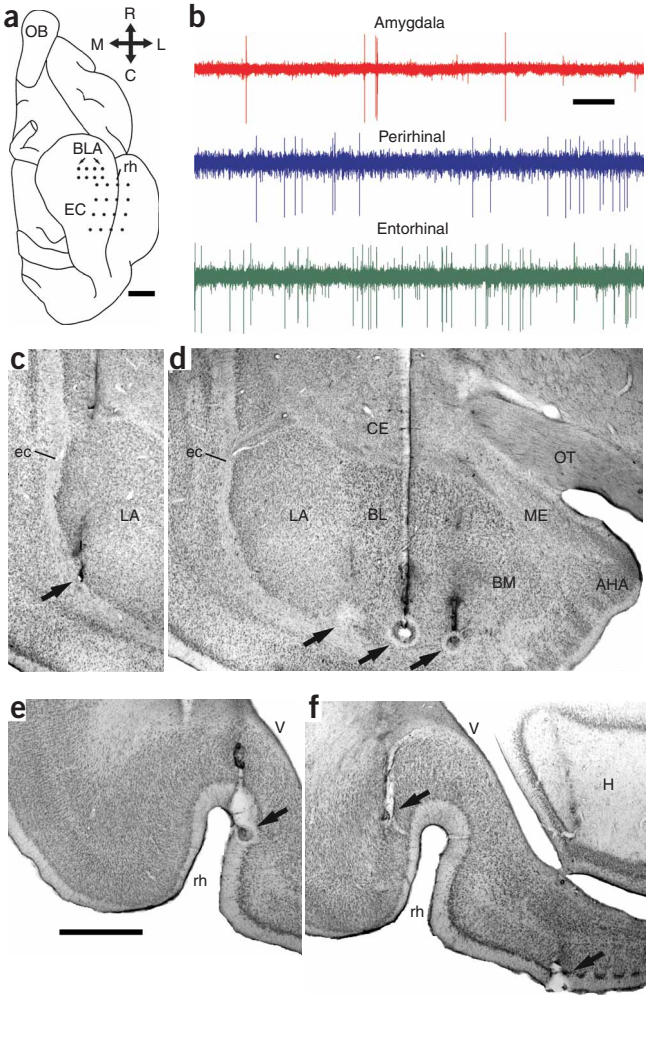

Figure 1 Simultaneous recordings of amygdala, perirhinal, and entorhinal neurons. (**a**) Ventral view of cat brain showing position of microelectrodes (dots). Cross indicates orientation. EC, entorhinal cortex; OB, olfactory bulb; rh, rhinal sulcus. (**b**) Spontaneous activity. (**c**–**f**) Histological verification of recording sites. Coronal brain sections. Arrows, electrolytic lesions performed at the end of the experiments to mark the tip of electrodes that coursed through the lateral amygdala (LA; **c**), basal amygdaloid nuclei (BL, BM; **d**), area 35 (**e**), and area 36 and the entorhinal cortex (**f**). AHA, amygdalohippocampal area; CE, central nucleus; ec, external capsule; H, hippocampus; ME, medial nucleus; OT, optic tract; V, ventricle. (**g**–**i**) Activity of an entorhinal neuron around perirhinal (**g**), BLA (**h**) or perirhinal and BLA (± 30ms, **i**) firing as illustrated in cross-correlations (top) or raster plots (bottom). PRH, perirhinal. Scale bars: 3 mm in **a**, 1 s in **b**, 2 mm in **c**.

impulse propagation occurs with a low probability in the transverse axis of the rhinal cortices[31]. In keeping with this, we observed a low proportion of significant perirhinal-entorhinal cross-correlations (**Fig. 1g**; 20% of 445 cell couples, $P < 0.05$, Methods) under anesthesia and during quiet waking. Similarly, entorhinal cells were generally not coactive with BLA cells (**Fig. 1h**; 26% of 245). However, when this analysis was restricted to perirhinal spikes that occurred within 30 ms of a BLA spike, an interval corresponding to the average latency of synaptically evoked discharges in the BLA-rhinal network[32], the proportion of significant perirhinal-entorhinal cross-correlations nearly doubled (**Fig. 1i**; 38% of 445; χ^2 test, $P < 0.001$).

However, cross-correlations have severe limitations because they relate the activity of only two cells, forcing one to choose arbitrary intervals when studying how a third neuron affects the relation between them. To overcome this difficulty, we studied triplets of perirhinal, entorhinal and BLA cells ($n = 445$) using spike-triggered joint histograms (STJH), an adaptation of the joint peristimulus time histogram (JPSTH) method[33], in which BLA spikes were used as a temporal reference[34] to study correlated perirhinal and entorhinal firing.

STJHs (**Fig. 2a**) are computed by taking segments (± 150 ms) of rhinal activity around BLA spikes (time 0 in x and y). The spikes (red ticks) generated by the perirhinal and entorhinal cells are plotted on the x- and y-axes, respectively. STJH bins containing a coincidence of spikes (squares) are incremented. Thus, if around a given BLA spike, there was a spike from the perirhinal cell at time x and one from the entorhinal cell at time y, one count is added to the matrix bin (x,y). Repeating this process for each BLA spike gradually produces the raw STJH (**Fig. 2b**).

Because we were interested in BLA-related rhinal correlation, we tested the raw STJHs against two null hypotheses (Methods): (i) that the observed correlation is similar to that expected independently of BLA activity, and (ii) that the correlation merely reflects independent responses of rhinal neurons to BLA activity. To test the first possibility, we compared the raw STJH to the average of 50 STJHs computed after shuffling the BLA spike train (**Fig. 2c**). This is equivalent to computing the STJH around random times. To test the possibility that the correlations evidenced in the STJHs reflect independent responses of rhinal neurons to BLA activity, we computed STJHs by shuffling the BLA spike train of one of the two rhinal cells with respect to the other 50 times and averaging the result (**Fig. 2d**). This technique corresponds to the shift predictor[33]. We then performed bin-to-bin comparisons of significance between the raw and the two randomized sets of STJHs, using a Poisson distribution with a threshold P-value corrected for multiple comparisons (0.05 divided by the number of bins: 900; **Fig. 2e**). Finally, we verified that most significant bins clustered around one dominant peak (Methods and **Supplementary Fig. 2** online).

Another important property disclosed by the STJH is the relative timing of perirhinal and entorhinal firing in relation to BLA spikes. Bins above or below the main diagonal of the STJH represent correlated activity where entorhinal firing respectively follows or precedes perirhinal spikes (**Fig. 2f**). We used this information to compute a directionality index (Methods). We will return to the directionality index in the section describing the impact of rewards on BLA-rhinal interactions.

We computed cross-correlations of perirhinal-entorhinal cell couples (**Fig. 3a–d**), along with the corresponding STJH conditioned on BLA spikes (**Fig. 3e–h**) and a control STJH (**Fig. 3i–l**) produced by random shuffling of the BLA spike train. These STJHs (**Fig. 3**, middle) showed that, in relation to BLA spikes, there was a high degree of

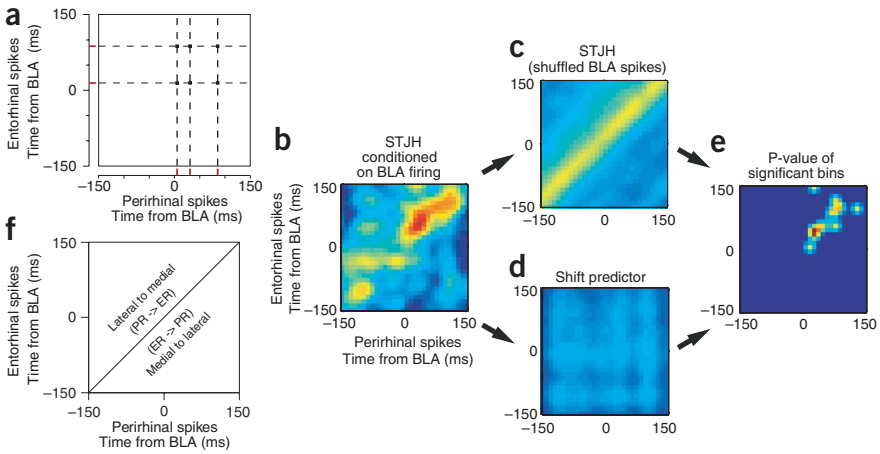

Figure 2 Method used to compute STJHs and determine whether they are statistically significant. (**a**) Segments of entorhinal (*y*-axis) and perirhinal (*x*-axis) activity centered on BLA spikes were isolated to identify bins that contained a coincidence (squares) of entorhinal and perirhinal spikes (red ticks). The matrix bins containing coincident rhinal spikes were incremented and this process was repeated for all BLA spikes, gradually producing the STJH. (**b**–**e**) Method used to assess whether STJHs were statistically significant. To determine whether the observed rhinal correlation (**b**) was dependent on the timing of BLA activity, the BLA spike trains were shuffled 50 times and the result averaged (**c**). To test whether the correlation in the STJH reflects independent responses of rhinal neurons to BLA activity, the BLA spike train of one of the two rhinal cells was shuffled 50 times and the result averaged (**d**). STJH bins were considered significant when they differed from both of the randomly generated sets of values, at a significance level of $P < 0.05/900$ (the number of bins, **e**). (**f**) The location of significant bins in the STJHs indicates the prevalent direction of impulse traffic in the rhinal cortices. A concentration of significant bins above the main diagonal of the STJH indicates that perirhinal cells tended to fire before entorhinal neurons in relation of BLA spikes. A concentration of significant bins below the main diagonal indicates that the opposite firing sequence prevailed.

correlated perirhinal-entorhinal activity, even when the corresponding cross-correlograms showed little (**Fig. 3a**) or no (**Fig. 3b**,**c**) evidence of correlated firing. Moreover, even a high cross-correlation (**Fig. 3d**) could actually be centered on and related to BLA spikes (**Fig. 3h**–**i**). Thus, the STJHs reveal that buried in the cross-correlations are periods of enhanced rhinal interactions that prevalently occur when BLA cells are active.

Using the criteria mentioned above, we found that 34% and 18%, respectively, of STJHs were deemed significant in the anesthetized and quiet waking conditions (higher than expected by chance, $P < 0.0001$, Fisher exact test). These results suggest that in relation to BLA activity, impulse transfer is facilitated in the rhinal cortices.

Impact of BLA activity during behaviorally salient events

To examine whether the BLA-related facilitation of rhinal interactions is influenced by behaviorally salient events, we studied the impact of unexpected liquid rewards on the incidence of significant STJHs. These rewards were salient because they were delivered at random intervals (30–90 s) and the cats ($n = 3$) were fed only during the recordings. The proportion of significant STJHs (computed in 250-ms windows) increased markedly after reward (from 23% to 44% of 151; $P < 0.001$, χ^2; **Fig. 4a** and **Supplementary Fig. 3** online). The grand average of significant post-reward STJHs (**Fig. 4b**) revealed that correlated rhinal activity (red patch) tended to occur after BLA firing (at time 0).

These findings indicate that, after behaviorally salient events, rhinal interactions are facilitated in relation to BLA activity. But does this effect participate in memory formation?

BLA-related rhinal interactions in a learning context

To address this question, cats ($n = 3$) were trained on a trace-conditioning task in which a visual conditioned stimulus (CS) predicted reward delivery 3 s later. The CS was a global change in the illumination of an LCD screen placed 1 ft in front of the cats. Learning in this task is dependent on the amygdala, rhinal cortices and hippocampus[19–23]. The predictive value of the CS was learned

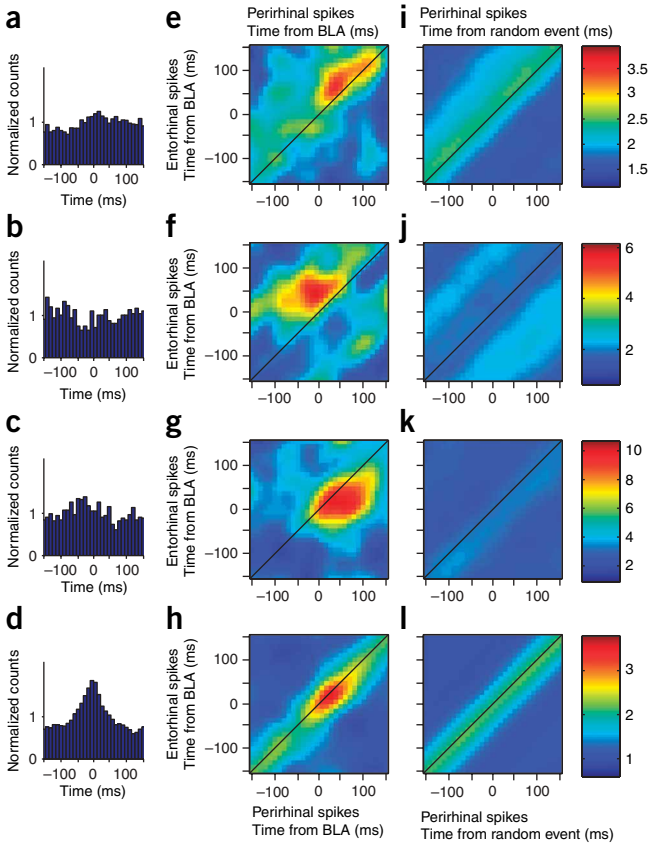

Figure 3 Enhanced neuronal interactions within rhinal cortices around BLA activity. Four pairs (rows) of simultaneously recorded perirhinal and entorhinal neurons. (**a**–**d**) Cross-correlations of spontaneous activity. (**e**–**h**) STJHs for same cell couples (perirhinal, *x*-axis; entorhinal, *y*-axis) conditioned on BLA firing (at time 0). STJHs were normalized to the mean of the BLA-shuffled matrix and the counts were color-coded. (**i**–**l**) Control STJHs computed around random times (average of 50 shuffles). In panels **e** and **h**, STJHs reveal that BLA spikes tend to be followed by correlated rhinal firing, which is smeared across the diagonal in the shuffled STJHs (**i**,**l**). This suggests that BLA activity is a major contributing factor to the peaks of the cross-correlations.

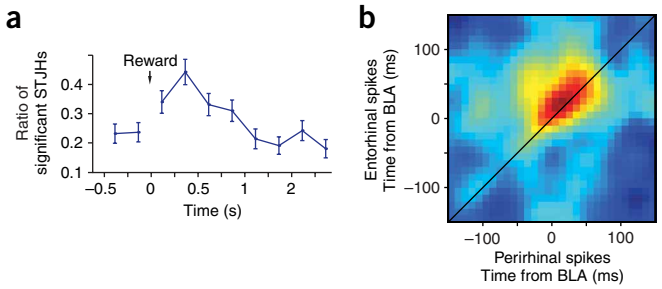

Figure 4 BLA-related modifications of rhinal interactions during the presentation of unexpected liquid rewards. (**a**) Proportion of significant STJHs (*y*-axis; ± s.e.m.) as a function of time (*x*-axis) around unexpected rewards. (**b**) Average of all significant STJHs after reward delivery. Note that correlated rhinal activity (red patch) tended to occur after BLA firing (time 0) and that this activity was higher above the main diagonal, indicating that perirhinal cells generally fired before entorhinal neurons. Similar results were obtained whether we considered reward-related activity within or outside the training context.

gradually, as evidenced by a gradual increase in CS-evoked anticipatory (pre-reward) licking over training sessions (**Fig. 5a**, dashed line; $r = 0.61$; $P < 0.01$).

To determine if there were learning-associated changes in the relation between BLA activity and rhinal interactions, the results obtained in early (days 1–3) and late (days 8–10) phases of learning were considered separately. In the early phase (**Fig. 5b**), the proportion of significant STJHs increased markedly after reward delivery (by 60%, $n = 81$; $P < 0.01$, χ^2) but not in relation to the CS or the delay. In contrast, in the late learning phase (**Fig. 5c**), the proportion of significant STJHs increased during the late part of the CS and delay (by 67%, $n = 81$; $P < 0.01$, χ^2) but not after reward.

Consistent with the idea that the enhancement of rhinal interactions seen in relation to BLA activity facilitates memory formation, analysis of day-to-day fluctuations in the proportion of significant post-reward STJHs revealed that as learning progressed (**Fig. 5a**, dashed line), the BLA-related facilitation of rhinal interactions gradually decreased (**Fig. 5a**, continuous line). Moreover, the ratio of significant post-reward STJHs was tightly and inversely correlated ($r = –0.79$, $P < 0.0001$) with memory strength as inferred from behavior (anticipatory licking) in all tested cats, considered individually or as a group (**Fig. 5d**). In contrast, as learning progressed, the ratio of significant STJHs during the delay increased (**Fig. 5e**, continuous line) and was positively correlated with behavior ($r = 0.48$, $P < 0.02$; **Fig. 5f**). Notably, these effects were probably related to learning, as in the previous experiments, where rewards remained unexpected, there was no time-dependent decrease in the proportion of significant STJHs after reward ($r = 0.02$, $P = 0.4$). Overall, these findings indicate that in relation to BLA discharges, rhinal interactions are facilitated in a learning context and this phenomenon is tightly related to the learning phase.

Directionality of facilitated rhinal interactions

An important question for the mechanisms of memory encoding and retrieval is whether, in relation to BLA activity, there is a facilitation of impulse transmission from perirhinal to entorhinal neurons (lateral to medial)[35] or in the reverse direction. In the STJHs, a predominance of counts above the main diagonal indicate that BLA firing is preferentially associated with lateromedial rhinal interactions, whereas counts below the main diagonal indicate the opposite (**Fig. 2f**). Thus, we calculated a directionality index (DI) for all cell triplets (Methods). The DI ranges from –1 to 1, with positive values indicating a preference for lateral (perirhinal) to medial (entorhinal) communication.

In periods associated with a low proportion of significant STJHs (quiet waking, pre-CS and pre-reward, outside and within the learning context), the DI had an average near 0 (**Fig. 6a**, blue curve, 0.02 ± 0.07, $P > 0.1$). In contrast, after rewards, the DI distribution was skewed to the right (**Fig. 6a**, red curve) with a mean significantly higher than 0 (0.11 ± 0.04, $P < 0.01$, *t*-test), consistent with the average of significant post-reward STJHs (**Fig. 4b**) where significant bins were concentrated above the main diagonal. Analyzing the time course of fluctuations in

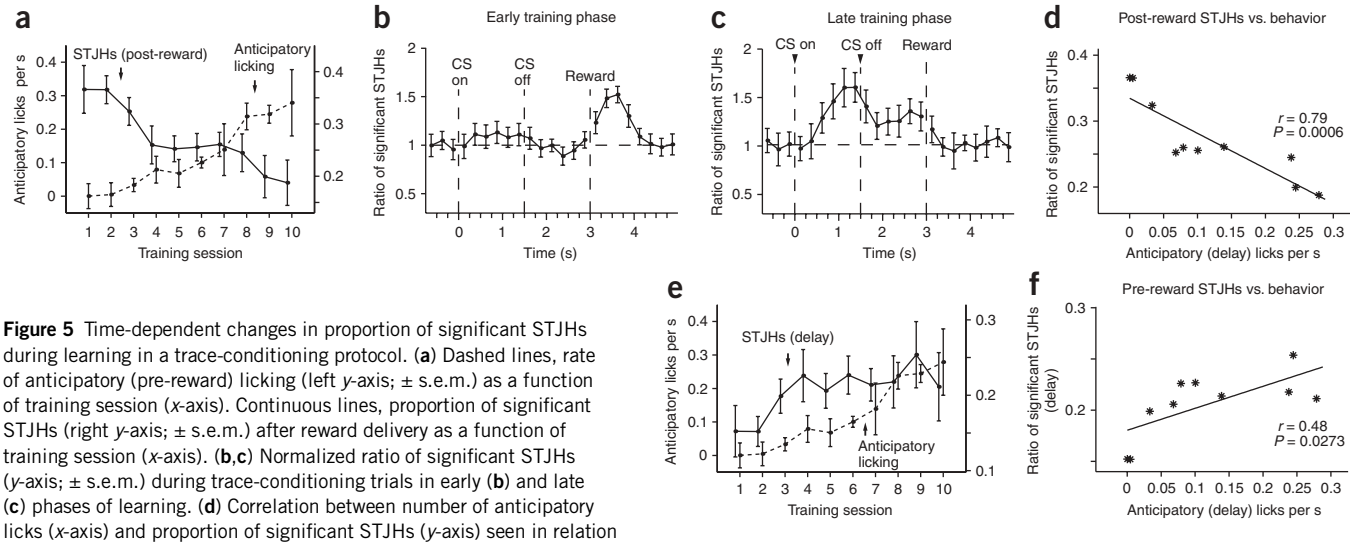

Figure 5 Time-dependent changes in proportion of significant STJHs during learning in a trace-conditioning protocol. (**a**) Dashed lines, rate of anticipatory (pre-reward) licking (left *y*-axis; ± s.e.m.) as a function of training session (*x*-axis). Continuous lines, proportion of significant STJHs (right *y*-axis; ± s.e.m.) after reward delivery as a function of training session (*x*-axis). (**b**,**c**) Normalized ratio of significant STJHs (*y*-axis; ± s.e.m.) during trace-conditioning trials in early (**b**) and late (**c**) phases of learning. (**d**) Correlation between number of anticipatory licks (*x*-axis) and proportion of significant STJHs (*y*-axis) seen in relation to reward delivery. Each data point represents one training session (average across cats). (**e**) Dashed lines, rate of anticipatory (pre-reward) licking (left *y*-axis; ± s.e.m.) as a function of training session (*x*-axis). Continuous lines, proportion of significant STJHs (right *y*-axis; ± s.e.m.) during delay period as a function of training sessions (*x*-axis). (**f**) Correlation between number of anticipatory licks (*x*-axis) and proportion of significant STJHs (*y*-axis) seen during the delay period. Each data point represents one training session (average across cats).

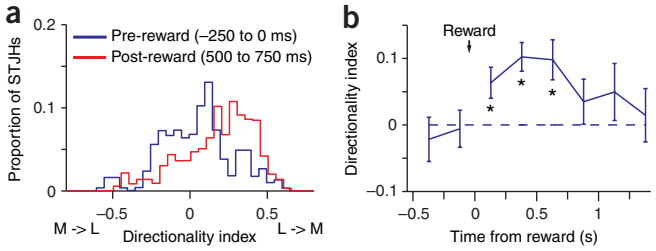

Figure 6 Directionality of rhinal interactions facilitated by BLA activity. (**a**) Frequency distribution of directionality index (DI) for statistically significant STJHs. (**b**) DI (*y*-axis; mean ± s.e.m.) as a function of time (*x*-axis) around reward delivery (arrow) in the early learning phase.

the average DI around reward delivery (**Fig. 6b**) revealed a shift in directionality that peaked around 500 ms after reward delivery (similar results were obtained when separately considering the unexpected rewards and those administered during the early learning phase). Thus, these results suggest that, in relation to BLA activity, there is an enhanced impulse propagation from the perirhinal to entorhinal cortex.

Mechanisms of BLA facilitation of rhinal interactions

We further analyzed the temporal dynamics of the impact of each BLA spike on rhinal correlations by calculating normalized probabilities of entorhinal firing as a function of the timing of perirhinal and BLA spikes. These analyses revealed that the probability of an entorhinal spike was greatest when both a BLA spike and a perirhinal spike occurred within $\leq$50 ms (**Fig. 7a**, blue curve). This effect was significantly higher than predicted (**Fig. 7a**, black curve, $P < 0.01$, *t*-tests) from the probability of entorhinal firing associated with isolated perirhinal or BLA spikes (**Fig. 7a**, green and red curves, respectively; **Supplementary Fig. 4** online). Thus, each BLA spike has a facilitating effect (lasting $\sim$50 ms) on impulse transfer in the rhinal cortices. This timescale is consistent with the monosynaptic glutamatergic projections from the BLA to the rhinal cortices[24].

Fluctuations in the proportion of significant STJHs were not simply tied to variations in firing rates. In BLA neurons for instance (**Fig. 7b**), a reward-related increase in firing rate occurred at early and late stages of learning. Yet, the proportion of significant STJHs only increased in the initial learning phase. We observed similar dissociations in rhinal neurons (**Supplementary Fig. 5** online). To further assess the impact of BLA firing rates, we compared the proportion of significant STJHs based on BLA cells with versus without post-reward increases in firing rate; it was 41% for neurons with and 28% for neurons without increases in firing rate (both proportions were significantly higher than chance, $P < 0.001$, Fisher exact test). Thus, changes in firing rates, although they contribute, do not account for all cases of significant STJHs.

Next, we considered the possibility that a more synchronized BLA output underlies the facilitation of rhinal interactions, as such synchrony would enhance the summation of inputs. Hence we calculated cross-correlations for all pairs of simultaneously recorded BLA neurons and found that the overall cross-correlation was higher after than before unexpected rewards (**Fig. 7c**, $n = 543$, $P < 0.001$, *t*-test). To correct for firing-rate effects, we randomly shuffled the trials of one neuron in relation to those of the other and compared the averaged shuffled cross-correlations to the original one. The ratio of significant post-reward cross-correlations significantly decreased from the early ($n = 189$) to the late ($n = 235$) phase of learning (**Fig. 7d**, $P < 0.01$, χ^2). The opposite was seen in relation to the delay (**Fig. 7d**, $P < 0.05$, χ^2). Overall, these analyses suggest that the BLA-related facilitation of rhinal interactions involves a higher and more synchronized BLA output.

DISCUSSION

The present study was undertaken to examine how the presentation of biologically significant and arousing stimuli affects neuronal interactions between the BLA and rhinal cortices. The interest of this question stems from previous work showing that the BLA facilitates memory for emotionally arousing events. Here we focused on the impact of BLA activity on perirhinal and entorhinal neurons because the rhinal cortices constitute the main route for impulse traffic into and out of the hippocampus. Our findings suggest that BLA activity is associated with facilitated neuronal interactions in the rhinal cortices, a phenomenon that was most pronounced in relation to behaviorally salient events. Moreover, in a trace-conditioning task, we observed that the BLA-mediated facilitation of rhinal interactions was tightly linked to memory formation. In the following account, we consider the significance of these findings for the facilitation of memory by emotions and for the role of amygdala activity in enhancing the associability of unexpected cues.

The rhinal cortices occupy a pivotal position

Multiple lines of evidence suggest that the rhinal cortices have a critical role in various aspects of learning and memory, including the formation of spatial representations[36,37], the encoding of the configuration of visual stimuli[38,39], the representation of stimulus familiarity[40,41] as well

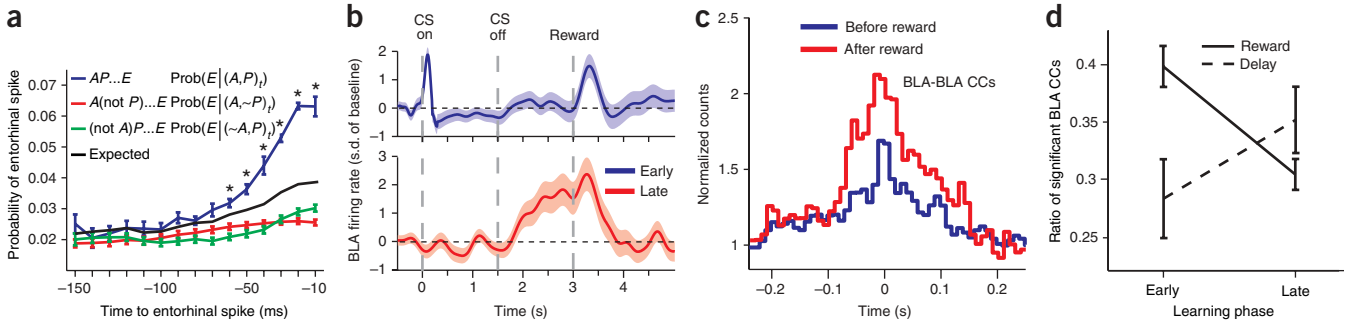

Figure 7 Mechanisms underlying BLA modulation of rhinal interactions. (**a**) Plot of probability of entorhinal firing (*y*-axis) as a function of the timing of perirhinal and BLA spikes. See **Supplementary Figure 5**. (**b**) BLA firing rates (± s.e.m.) in the trace-conditioning protocol, at early (top, blue) and late (bottom, red) phases of learning. (**c**) Average cross-correlation between couples of BLA neurons. (**d**) Proportion of significant cross-correlations as a function of the learning phase (early versus late) in relation to reward (solid line) and during the delay (dashed line). CC, cross-correlation.

as the acquisition, consolidation and retrieval of declarative memories[28]. Furthermore, tract-tracing data indicate that the rhinal cortices receive multimodal sensory inputs from the neocortex and that they constitute the interface between the neocortex and the hippocampus[42].

Despite the fact that the perirhinal cortex forms strong reciprocal connections with the temporal neocortex and the entorhinal cortex, perirhinal transmission of neocortical and entorhinal inputs occurs with a low probability[43]. For instance, electrical stimulation of the lateral olfactory tract in the whole brain *in vitro* evokes large field potentials in the entorhinal cortex but no responses in area 36 (ref. 44). Similarly, stimulation of the temporal neocortex or area 36 evokes no local field responses in the entorhinal cortex[44], and recent *in vivo* studies reached the same conclusions[31,32].

However, the discrepancy between anatomical and physiological data about this network is only apparent because recent ultrastructural observations suggest that an important proportion of the connectivity between the perirhinal and entorhinal cortices involves excitatory inputs to GABAergic neurons as well as long-range GABAergic projections to principal neurons[45]. As a result, perirhinal transfer of neocortical and entorhinal impulses is subjected to strong inhibitory pressures[43].

BLA-related facilitation of rhinal interactions

Consistent with the above, cross-correlating the activity of perirhinal and entorhinal neurons generally yielded little evidence of correlated activity in the present study. However, restricting the analyses to rhinal spikes that occurred in close temporal proximity to BLA activity revealed that buried in the cross-correlations are periods of enhanced rhinal interactions that prevalently occur when BLA cells are active. Thus it seems that the strong inhibitory pressures regulating perirhinal-entorhinal interactions[43] can be counteracted by BLA inputs. This contention is supported by pharmaco-behavioral studies indicating that BLA activity is required for the facilitation of memory consolidation produced by immediate post-training manipulations of entorhinal excitability[46,47].

Notably, the BLA-related facilitation of rhinal interactions was most pronounced in response to unexpected rewards, both outside and within a learning context. Analyzing the behavior of BLA neurons revealed that although increased rhinal interactions were more likely to occur when BLA neurons increased their firing rate, firing rates alone could not account for all cases of increased rhinal interactions. In fact, sensory events that caused an increase in the firing rate of BLA neurons were not necessarily associated with facilitated rhinal interactions. Instead, it seemed that this effect depended critically on a more synchronized BLA output. This contention is based on the fact that in all BLA-related periods of facilitated rhinal interactions, cross-correlating the activity of simultaneously recorded BLA neurons revealed that they fired in a more synchronized manner, even after controlling for changes in firing rate.

Overall, these observations suggest that in relation to behaviorally salient events, afferents to the medial temporal lobe produce conditions that favor the emergence of a higher and more synchronized BLA output. In turn, via the massive glutamatergic BLA projections to the rhinal cortices[24], BLA activity produces a depolarization of target neurons, facilitating communication in the rhinal cortices and thus enhancing the processing of sensory cues. Although it is likely that other rhinal and BLA afferents participate in this effect, the precise locking of correlated rhinal activity to BLA spikes observed in the STJHs suggest that BLA inputs to the rhinal cortices are key contributors. In fact, the higher and more synchronized BLA outputs to the rhinal cortices probably enhance the likelihood that these other afferents will trigger orthodromic spikes in rhinal neurons.

The presentation of unexpected rewards caused a short (1 s long) BLA-mediated facilitation of rhinal interactions, and our conditional probability analyses revealed that each BLA spike had a brief effect on rhinal interactions (50 ms). However, this is only the effect of one spike. When BLA firing rates increase for long periods of time, as after highly arousing events, the BLA-driven facilitation of rhinal interactions should also have a long duration, as each BLA spike will produce a facilitation of rhinal interactions. Consistent with this, stimuli causing a more intense emotional response (unexpected electric shock to the paws) produces a long-lasting increase (around 2 h) in the firing rate of BLA cells coupled to a more synchronized BLA output[18]. In this context, it is important to realize that because BLA neurons are glutamatergic, once stress hormones have recruited them (either directly in the case of glucocorticoids or indirectly via noradrenaline in the case of adrenaline), they depend on short-lived glutamatergic effects for the facilitation of memory. Although each spike has a brief impact, the influence of long-lasting increases in firing rates, as seen after intense emotional arousal, will also have a prolonged time course.

By enhancing the processing of sensory cues, the BLA-related enhancement of rhinal interactions probably participates in the facilitation of memory formation by emotions. This contention is supported by the close temporal parallel between the BLA effect and learning in the trace-conditioning task. At early stages of learning, when the reward was still unexpected, the BLA-related facilitation of rhinal transmission increased in connection with the reward. However, this effect gradually decreased as learning progressed and the reward came to be predicted by the CS. At these late stages, the BLA-related facilitation occurred earlier, when the cats were anticipating the reward.

Notably, BLA activity did not facilitate rhinal interactions randomly but in a specific direction, from perirhinal to entorhinal neurons. In light of studies indicating that the rhinal cortices form the interface between the neocortex and hippocampus[26,27], this suggests that BLA activity preferentially enhances impulse transfer from neocortical association areas toward the hippocampus, as would be expected for a facilitation of memory encoding.

Finally, our data is also consistent with the extensive literature linking the amygdala and reward to multiple associative processes. In particular, it was shown that amygdala activity enhances the associability of unexpected cues and is required for the acquisition and representation of reinforcement value[23,48,49]. Our findings support and extend these findings by revealing that BLA activity might facilitate the associability of arousing and unexpected cues at the level of the rhinal cortices. Although this effect might depend on enhanced interactions between the neocortex and the hippocampus, the evidence showing that the rhinal cortices can store associative representations in the absence of the hippocampus[50] raises the possibility that the enhanced reward-related BLA activity might facilitate storage in the rhinal cortices themselves. A challenge for future experiments will be to test these two possibilities.

METHODS

BLA, perirhinal and entorhinal neurons were recorded simultaneously by means of a microelectrode array in anesthetized ($n = 4$) or unanesthetized ($n = 6$) cats (2.5–3.5 kg body weight). Procedures were approved by the Institutional Animal Care and Use Committee of Rutgers State University, in compliance with the Guide for the Care and Use of Laboratory Animals (Department of Health and Human Services).

Acute surgeries. In acute experiments, cats were preanesthetized with a mixture of ketamine (15 mg per kg body weight) and xylazine (2 mg per kg body weight) intramuscularly (i.m.), and artificially ventilated with a mixture of ambient air, oxygen and isoflurane. Atropine (0.05 mg per kg body weight, i.m.)

was administered to prevent secretions. The end-tidal CO_2 concentration was maintained at 3.7 ± 0.2% and the body temperature at 37–38 °C (using a heating pad). The bone overlying the amygdala and rhinal cortices was removed and the dura mater opened. Then an array of tungsten electrodes (FHC) was stereotaxically lowered into the brain until the electrodes reached the deep layers of the rhinal cortices. This array was constructed by drilling small holes in a Teflon block and inserting the electrodes into the block. The Teflon block was then inserted into a tightly fitting Delrin sleeve, which was cemented to the skull. During the recording sessions, the electrodes could be lowered as a group by means of a micrometric screw. The lengths of the electrodes were adjusted so that unit recordings could be obtained simultaneously from the BLA and the perirhinal and entorhinal cortices.

Survival surgeries. Survival surgeries were performed as above with the following exceptions. First, the cats were administered penicillin (20,000 UI per kg body weight, i.m.) and an analgesic (Ketophen, 2 mg per kg, subcutaneously, daily for 3 d). In addition, electrodes were implanted in the supraorbital cavity to monitor eye movements. The electro-oculographic measurements were performed to distinguish waking from paradoxical sleep, as both states are characterized by a desynchronized electroencephalogram (EEG) but rapid eye movements only occur in paradoxical sleep. Finally, four screws were cemented to the skull so that the the cat's head could be fixed later without pain or pressure. Recording sessions began 8 d after the surgery.

Recordings. During the acute and survival experiments, neuronal activity was sampled at ≥100 μm intervals. Each time the electrodes were moved to a new recording site, we allowed 30 min to elapse before data were acquired, to ensure mechanical stability. The signals picked up by the electrodes (0.1 Hz to 20 kHz) were observed on an oscilloscope, digitized and stored on a hard disk. Spike sorting was performed offline using a clustering algorithm based on principal component analysis and K-means.

Behavior. In survival experiments, the cats were fed only during recording sessions. They were given liquid rewards (Gerber's pureed baby food, 'Sweet potatoes and turkey') either outside ($n = 3$) or within ($n = 3$) a behavioral training context. In the former case, rewards (2 ml per trial) were delivered at unexpected times (intervals of 30–90 s). In the latter case, the cats were trained on an appetitive trace-conditioning protocol: a 1.5-s-long visual CS was followed by a 1.5-s-long delay period, after which the same liquid reward was administered. These trials occurred at random intervals (30–90 s). We monitored behavior by means of a switch that detected when the cat's tongue contacted the receptacle where the food reward was administered. The visual CS was a global change in the illumination (from black to white) of a 12" LCD screen placed 1 ft in front of the cats. Detection of the visual CS did not necessitate that a cat maintain a fixed gaze at the center of the LCD screen for the following reasons: (i) because the monitor was placed 1 ft from the cat's head, the screen encompassed most of its visual field; and (ii) the difference in illumination was so pronounced that even with eyes closed, the CS could be easily detected. However, it should be mentioned that because the cats were hungry, they were highly aroused and remained awake at all times (as assessed by EEG recordings) with their eyes opened.

Previous experiments have shown that the hippocampus, rhinal cortices and BLA are involved in the acquisition of trace-conditioning tasks using lesions or drug injections[19–22]. However, the exact parameters of these studies varied. One study, implicating the hippocampus in the acquisition of an appetitive trace-conditioning task[19], used water rather than liquid food as the unconditioned stimulus. A second study also implicating the hippocampus in this form of learning[21] used a trace eye-blink conditioning task with an aversive unconditioned stimulus (air puff to the eye). Both these studies used a shorter duration delay period (around 0.5 s) than the present study (1.5 s) and an auditory rather than a visual CS. The study implicating the rhinal cortices in this form of learning[22] also involved a trace eye-blink conditioning, an auditory CS and a shorter delay period (750 ms). Last, the study implicating the BLA in this form of learning[20] involved an olfactory trace-conditioning task with an olfactory CS, a longer delay period and an aversive unconditioned stimulus (sickness).

Histology. At the end of the experiments, recording sites were marked with electrolytic lesions (0.5 mA, 5 s). The cats were then given an intravenous (i.v.) overdose of sodium pentobarbital (50 mg per kg body weight) and perfused-fixed. The brains were later sectioned on a vibrating microtome (at 100 μm) and stained with cresyl violet to verify the position of recording electrodes. Microelectrode tracks were reconstructed by combining micrometer readings with the histology.

Computation of STJHs. The STJH is an adaptation of the joint peristimulus time histogram (JPSTH) method[33]: instead of external stimuli, BLA spikes are used as a temporal reference (time 0 in **Fig. 2b**; see also ref. 34) to study correlated perirhinal and entorhinal firing. Thus, like JPSTHs, STJHs are 'trial-based'. Only instead of stimuli, as in the standard JPSTHs, our STJHs were BLA spike–based. The method used to construct the STJHs is described in the results (**Fig. 2**). STJH counts are color-coded as in **Figure 2b**. The raw STJHs were then normalized to the mean of the BLA-shuffled matrix. For presentation purposes only, the STJHs were smoothed using a two-dimensional gaussian with variance equal to 25 ms (when the bins are 10 ms).

Statistical significance of the STJHs. Statistical significance was assessed using unsmoothed data by performing bin-by-bin comparisons with two control STJH matrices. The first control tests that peaks in the STJH are indeed locked to BLA firing, and the second tests that they are not merely due to independent rhinal responses to the BLA. To obtain the first control STJH, we randomized the BLA spike train and recomputed the STJH; repeating this process 50 times and averaging the result produced the BLA-shuffled control STJH. The second control STJH was obtained by computing STJHs after shuffling the BLA spike–based train of one of the two rhinal cells with respect to the other, repeating this 50 times and then averaging to produce the second control STJH. Note that this technique corresponds to the shift predictor[33]. We then performed bin-to-bin comparisons of significance between the raw and the two randomized STJHs, using a Poisson distribution with a threshold *P*-value corrected for multiple comparisons (0.05 divided by the number of bins: 900). For a bin to be considered significant, it had to meet this criterion when compared to both randomly generated sets of values.

Interpretation of the STJHs. The reason why the STJHs reveal correlations that are invisible in raw cross-correlations is that cross-correlations between perirhinal and entorhinal neurons include all the spikes these cells generate, whereas the STJHs consider only rhinal spikes that occur in close temporal proximity to BLA spikes. Because BLA neurons fire at very low rates compared to rhinal neurons, raw cross-correlations are dominated by BLA-independent interactions between perirhinal and entorhinal neurons. As the raw cross-correlations show, BLA-independent rhinal interactions are typically uncorrelated (the cross-correlations are usually flat). However, when one considers only the few rhinal spikes that occurred just after BLA firing, evidence of correlated activity is observed.

Test for unimodality of STJHs. Visual inspection of the STJHs indicated that most of them had a single dominant peak. This was further quantified by calculating Hartigan's dip statistical test for unimodality. Using this approach, we found that as many as 83% of the STJHs were indeed unimodal. For the remaining, we fitted a mixture of 2 gaussians to the data (using a standard expectation maximization (EM) algorithm) and found that in most of them (73%), one weight was more than twice the other, indicating that this gaussian was much more dominant.

Calculation of the ratio of significant STJHs. For each cat, we computed the ratio of significant STJHs in nonoverlapping 250-ms-long time windows and normalized the data to the pre-CS period. We then averaged the results obtained in all cats.

Directionality index. The DI was obtained by separately adding all bins above the main diagonal (a) versus those below the main diagonal (b) in the STJHs and then computing $((a - b/a + b))$ for each STJH. The DI ranges from –1 to 1; positive values indicate that the perirhinal neuron tended to fire before the entorhinal cell, negative values indicate the opposite.

Assessing the significance of cross-correlograms. For cross-correlograms of spontaneous activity, we compared the central bins (–50 to 50 ms) to the values of peripheral bins (–250 to –200 ms, and 200 to 250 ms). This computation was

based on a Poisson distribution of peripheral bin values ($P < 0.05$) and we used a Bonferroni correction for multiple comparisons. This approach amounts to calculating the probability of observing the central bin values given a Poisson process with a mean determined from the periphery of the histograms. For event-based cross-correlations, such as around the time of reward and CS, the trials of one neuron were shuffled with respect to the other and cross-correlations were recomputed. This process was repeated 100 times. The center bins (–50 ms to 50 ms) of the original cross-correlation (calculated from the unshuffled trials) were then compared to the derived distribution ($P < 0.05$, corrected for multiple comparisons).

Calculation of conditional probabilities. To investigate the time course of BLA effects on rhinal interactions, we calculated direct probabilities using the following equations for all available spikes:

$$p_1 = p(E|(A,P)_t) = \frac{p(E,(A,P)_t)}{p((A,P)_t)},$$

where E, A and P represent the occurrence of an entorhinal spike, a BLA spike and a perirhinal spike, respectively. The two control conditional probabilities were calculated as

$$p_2 = p(E|(\neg A,P)_t) = \frac{p(E,(\neg A,P)_t)}{p((\neg A,P)_t)}$$

and

$$p_3 = p(E|(A,\neg P)_t) = \frac{p(E,(A,\neg P)_t)}{p((A,\neg P)_t)}.$$

For comparison and statistical significance, we normalized each to $p(E)$, because for long time delays (for example, those >100 ms), the event E is independent of the event (A,P) and therefore $p_1 = p_2 = p_3 = p(E)$.

The expected probability was then calculated by the addition rule $p_{\text{control}} = p_2 + p_3 - p_2 \cdot p_3$, and compared to p_1 at each time point using a t-test.

Note that when computing conditional probabilities, we had to choose from many possible conditions (perirhinal before entorhinal, entorhinal before perirhinal, and so on). The specific example depicted in **Figure 7a** is based on a previous analysis (of directionality index), where it was found that perirhinal cells tended to fire before entorhinal neurons. **Supplementary Figure 4** analyzes other conditions but shows the same time course. We also investigated the condition where entorhinal firing precedes perirhinal activity (data not shown); in accordance with the directionality index, the effect was of much lower magnitude and shorter duration (~20 ms).

Note: Supplementary information is available on the Nature Neuroscience website.

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COMPETING INTERESTS STATEMENT

The authors declare that they have no competing financial interests.

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1. Christianson, S.A. *Handbook of Emotion and Memory: Current Research and Theory* (Erlbaum, Hillsdale, New Jersey, 1992).
2. Cahill, L., Babinsky, R., Markowitsch, H.J. & McGaugh, J.L. The amygdala and emotional memory. *Nature* **377**, 295–296 (1995).
3. Adolphs, R., Cahill, L., Schul, R. & Babinsky, R. Impaired declarative memory for emotional material following bilateral amygdala damage in humans. *Learn. Mem.* **4**, 291–300 (1997).
4. Adolphs, R., Tranel, D. & Buchanan, T.W. Amygdala damage impairs emotional memory for gist but not details of complex stimuli. *Nat. Neurosci.* **8**, 512–518 (2005).
5. McGaugh, J.L. *et al.* Involvement of the amygdaloid complex in neuromodulatory influences on memory storage. *Neurosci. Biobehav. Rev.* **14**, 425–431 (1990).
6. Roozendaal, B. & McGaugh, J.L. Amygdaloid nuclei lesions differentially affect glucocorticoid-induced memory enhancement in an inhibitory avoidance task. *Neurobiol. Learn. Mem.* **65**, 1–8 (1996).
7. Phelps, E.A. Human emotion and memory: interactions of the amygdala and hippocampal complex. *Curr. Opin. Neurobiol.* **14**, 198–202 (2004).
8. Anderson, A.K. & Phelps, E.A. Lesions of the human amygdala impair enhanced perception of emotionally salient events. *Nature* **411**, 305–309 (2001).
9. Phelps, E.A. & LeDoux, J.E. Contributions of the amygdala to emotion processing: from animal models to human behavior. *Neuron* **48**, 175–187 (2005).
10. Cahill, L. *et al.* Amygdala activity at encoding correlated with long-term, free recall of emotional information. *Proc. Natl. Acad. Sci. USA* **93**, 8016–8021 (1996).
11. Hamann, S.B., Ely, T.D., Grafton, S.T. & Kilts, C.D. Amygdala activity related to enhanced memory for pleasant and aversive stimuli. *Nat. Neurosci.* **2**, 289–293 (1999).
12. LeDoux, J.E. Emotion circuits in the brain. *Annu. Rev. Neurosci.* **23**, 155–184 (2000).
13. Cahill, L. & McGaugh, J.L. Mechanisms of emotional arousal and lasting declarative memory. *Trends Neurosci.* **21**, 294–299 (1998).
14. Packard, M.G., Cahill, L. & McGaugh, J.L. Amygdala modulation of hippocampal-dependent and caudate nucleus-dependent memory processes. *Proc. Natl. Acad. Sci. USA* **91**, 8477–8481 (1994).
15. Quirarte, G.L., Roozendaal, B. & McGaugh, J.L. Glucocorticoid enhancement of memory storage involves noradrenergic activation in the basolateral amygdala. *Proc. Natl. Acad. Sci. USA* **94**, 14048–14053 (1997).
16. Ferry, B., Roozendaal, B. & McGaugh, J.L. Role of norepinephrine in mediating stress hormone regulation of long-term memory storage: a critical involvement of the amygdala. *Biol. Psychiatry* **46**, 1140–1152 (1999).
17. Roozendaal, B., Okuda, S., Van der Zee, E.A. & McGaugh, J.L. Glucocorticoid enhancement of memory requires arousal-induced noradrenergic activation in the basolateral amygdala. *Proc. Natl. Acad. Sci. USA* **103**, 6741–6746 (2006).
18. Pelletier, J.G., Likhtik, E., Filali, M. & Pare, D. Lasting increases in basolateral amygdala activity after emotional arousal: implications for facilitated consolidation of emotional memories. *Learn. Mem.* **12**, 96–102 (2005).
19. Seager, M.A., Asaka, Y. & Berry, S.D. Scopolamine disruption of behavioral and hippocampal responses in appetitive trace classical conditioning. *Behav. Brain Res.* **100**, 143–151 (1999).
20. Ferry, B., Wirth, S. & Di Scala, G. Functional interaction between entorhinal cortex and basolateral amygdala during trace conditioning of odor aversion in the rat. *Behav. Neurosci.* **113**, 118–125 (1999).
21. Munera, A., Gruart, A., Munoz, M.D. & Delgado-Garcia, J.M. Scopolamine impairs information processing in the hippocampus and performance of a learned eyeblink response in alert cats. *Neurosci. Lett.* **292**, 33–36 (2000).
22. Ryou, J.W., Cho, S.Y. & Kim, H.T. Lesions of the entorhinal cortex impair acquisition of hippocampal-dependent trace conditioning. *Neurobiol. Learn. Mem.* **75**, 121–127 (2001).
23. Baxter, M.G. & Murray, E.A. The amygdala and reward. *Nat. Rev. Neurosci.* **3**, 563–573 (2002).
24. Smith, Y. & Pare, D. Intra-amygdaloid projections of the lateral nucleus in the cat: PHA-L anterograde labeling combined with postembedding GABA and glutamate immunocytochemistry. *J. Comp. Neurol.* **342**, 232–248 (1994).
25. Pitkanen, A., Pikkarainen, M., Nurminen, N. & Ylinen, A. Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. A review. *Ann. NY Acad. Sci.* **911**, 369–391 (2000).
26. Witter, M.P. & Groenewegen, H.J. Connections of the parahippocampal cortex in the cat. III. Cortical and thalamic efferents. *J. Comp. Neurol.* **252**, 1–31 (1986).
27. Burwell, R.D. & Witter, M.P. Basic anatomy of the parahippocampal region in monkeys and rats. in *The Parahippocampal Region.* (eds. Witter, M.P. & Wouterlood, F.) Ch. 3, 53–59 (Oxford University Press, New York, 2002).
28. Suzuki, W.A. & Eichenbaum, H. The neurophysiology of memory. *Ann. NY Acad. Sci.* **911**, 175–191 (2000).
29. Sutherland, G.R. & McNaughton, B. Memory trace reactivation in hippocampal and neocortical neuronal ensembles. *Curr. Opin. Neurobiol.* **10**, 180–186 (2000).
30. Squire, L.R., Stark, C.E. & Clark, R.E. The medial temporal lobe. *Annu. Rev. Neurosci.* **27**, 279–306 (2004).
31. Pelletier, J.G., Apergis, J. & Pare, D. Low-probability transmission of neocortical and entorhinal impulses through the perirhinal cortex. *J. Neurophysiol.* **91**, 2079–2089 (2004).
32. Pelletier, J.G., Apergis-Schoute, J. & Pare, D. Interaction between amygdala and neocortical inputs in the perirhinal cortex. *J. Neurophysiol.* **94**, 1837–1848 (2005).
33. Palm, G., Aertsen, A.M. & Gerstein, G.L. On the significance of correlations among neuronal spike trains. *Biol. Cybern.* **59**, 1–11 (1988).
34. Prut, Y. *et al.* Spatiotemporal structure of cortical activity: properties and behavioral relevance. *J. Neurophysiol.* **79**, 2857–2874 (1998).
35. Kajiwara, R., Takashima, I., Mimura, Y., Witter, M.P. & Iijima, T. Amygdala input promotes spread of excitatory neural activity from perirhinal cortex to the entorhinal-hippocampal circuit. *J. Neurophysiol.* **89**, 2176–2184 (2003).
36. Muir, G.M. & Bilkey, D.K. Theta- and movement velocity-related firing of hippocampal neurons is disrupted by lesions centered on the perirhinal cortex. *Hippocampus* **13**, 93–108 (2003).
37. Leutgeb, S., Leutgeb, J.K., Moser, M.B. & Moser, E.I. Place cells, spatial maps and the population code for memory. *Curr. Opin. Neurobiol.* **15**, 738–746 (2005).
38. Buckley, M.J. & Gaffan, D. Perirhinal cortex ablation impairs configural learning and paired-associate learning equally. *Neuropsychologia* **36**, 535–546 (1998).

39. Bussey, T.J., Saksida, L.M. & Murray, E.A. Perirhinal cortex resolves feature ambiguity in complex visual discriminations. *Eur. J. Neurosci.* **15**, 365–374 (2002).
40. Murray, E.A. & Mishkin, M. Visual recognition in monkeys following rhinal cortical ablations combined with either amygdalectomy or hippocampectomy. *J. Neurosci.* **6**, 1991–2003 (1986).
41. Brown, M.W. & Bashir, Z.I. Evidence concerning how neurons of the perirhinal cortex may effect familiarity discrimination. *Phil. Trans. R. Soc. Lond. B* **357**, 1083–1095 (2002).
42. Witter, M.P., Wouterlood, F.G., Naber, P.A. & Van Haeften, T. Anatomical organization of the parahippocampal-hippocampal network. *Ann. NY Acad. Sci.* **911**, 1–24 (2000).
43. de Curtis, M. & Pare, D. The rhinal cortices: a wall of inhibition between the neocortex and the hippocampus. *Prog. Neurobiol.* **74**, 101–110 (2004).
44. Biella, G., Uva, L. & de Curtis, M. Propagation of neuronal activity along the neocortical-perirhinal-entorhinal pathway in the guinea pig. *J. Neurosci.* **22**, 9972–9979 (2002).
45. Pinto, A., Fuentes, C. & Pare, D. Feedforward inhibition regulates perirhinal transmission of neocortical inputs to the entorhinal cortex: ultrastructural study in guinea pigs. *J. Comp. Neurol.* **495**, 722–734 (2006).
46. Roesler, R., Roozendaal, B. & McGaugh, J.L. Basolateral amygdala lesions block the memory-enhancing effect of 8-Br-cAMP infused into the entorhinal cortex of rats after training. *Eur. J. Neurosci.* **15**, 905–910 (2002).
47. Luft, T., Pereira, G.S., Cammarota, M. & Izquierdo, I. Different time course for the memory facilitating effect of bicuculline in hippocampus, entorhinal cortex, and posterior parietal cortex of rats. *Neurobiol. Learn. Mem.* **82**, 52–56 (2004).
48. Holland, P.C. & Gallagher, M. Amygdala circuitry in attentional and representational processes. *Trends Cogn. Sci.* **3**, 65–73 (1999).
49. Everitt, B.J., Cardinal, R.N., Parkinson, J.A. & Robbins, T.W. Appetitive behavior: impact of amygdala-dependent mechanisms of emotional learning. *Ann. NY Acad. Sci.* **985**, 233–250 (2003).
50. Murray, E.A., Graham, K.S. & Gaffan, D. Perirhinal cortex and its neighbours in the medial temporal lobe: contributions to memory and perception. *Q. J. Exp. Psychol. B* **58**, 378–396 (2005).