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Supplementary information

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Stimulus-specific recruitment of human amygdala neurons predicts episodic memory encoding success

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Supplementary Table

	VTC	Amygdala	Hippocampus	vmPFC
people	22(27%)	65(28%)	45(41%)	15(31%)
animal	18(22%)	44(19%)	20(18%)	6(12%)
cars	19(23%)	26(11%)	19(17%)	7(15%)
food	18(22%)	58(25%)	14(13%)	16(33%)
landscapes	5(6%)	37(16%)	12(11%)	4(8%)

Supplementary Table 1: Distribution of preferred categories across regions. Number (and percentage) of category neurons for each preferred semantic category in VTC, amygdala, hippocampus, and vmPFC. Percentages are calculated relative to the total number of category neurons recorded in each region.

Supplementary Results

Robust subsequent memory effect across time windows

To evaluate the robustness of the subsequent memory effect across different time windows, we tested the subsequent memory effect using two different windows and found that firing rates were significantly higher for subsequently remembered items in both cases (Extended Data Fig. 2a-b, Window = 200-1000 ms, n = 196 neurons, t = 4.29, $p = 2.8 \times 10^{-5}$; Window = 350-1850 ms, n = 196 neurons, t = 5.19, $p = 5.17 \times 10^{-7}$). To more systematically characterize the temporal profile of the effect, we applied a sliding-window analysis with 500 ms windows moving in 100 ms steps. This analysis revealed that the subsequent memory effect emerges early, around 100-600 ms after stimulus onset and remains significant until approximately 1600-2100 ms following stimulus onset (Extended Data Fig. 2c). The activity beyond 2000 ms did not reach statistical significance. These results demonstrate that the subsequent memory effect is robust across a wide range of time windows during the encoding period.

Amygdala category cells enhance memory selectively for preferred stimuli

To test whether this effect differed between selective and non-selective trials, we fit a GLM model with firing rate as the dependent variable, later memory accuracy (remembered vs. forgotten), trial type (preferred vs. non-preferred), and their interaction as predictors. This revealed a significant Memory × trial type interaction ($\beta = 20.23$, $t = 5.19$, $p = 2.1 \times 10^{-7}$), confirming that the subsequent memory effect is stronger for trials in which the images shown belong to the preferred category of the cell. Together, this data shows that category cells in the amygdala show a robust subsequent memory effect for the subset of stimuli belonging to their preferred category.

Could this effect also be seen when considering all trials across all recorded amygdala cells? This was the case: there was a significant positive relationship between mean firing rate and later retrieval success or failure across all trials ($\beta = 4.70$, $t = 3.30$, $p = 9.5 \times 10^{-4}$, $n = 496$ cells included), indicating that on average, higher firing rates of amygdala cells are associated with a higher likelihood of successfully forming a long-term memory. However, this effect was driven by the preferred-category trials of category cells: when repeating above analysis after removing, for all cells, the trials of the category to which the response was maximal of that cell, no significant effect remained ($\beta = 2.30$, $t = 1.57$, $p = 0.12$, $n = 496$ cells). This indicates that the overall memory-related modulation was driven primarily by responses to preferred stimuli of category cells, indicating that these cells specifically are part of the mechanism for modulating memory encoding strength.

Firing rates during encoding, but not recognition, predict memory strength

To further assess whether firing rates during encoding predict memory strength, we used 6-level confidence ratings from the recognition part (see Fig. 1b). Ratings of 1–3 indicate decreasing certainty that the picture is new, while ratings of 4–6 reflect increasing certainty that it is old. Thus, the higher the confidence rating, the stronger the underlying memory trace. Firing rates of category-selective amygdala neurons (preferred trials only) were modeled using a generalized linear model, with memory strength (confidence ratings 1–6) as the predictor and neurons nested within recording sessions as random effects (all trials of the preferred category were included, regardless of whether they were remembered or forgotten). This analysis revealed

a significant positive relationship between memory strength as indicated by confidence and firing rate during encoding ($\beta = 6.38$, $t = 5.26$, $p = 1.4 \times 10^{-7}$).

To determine whether the relationship between memory strength and firing rate in the amygdala was specific to encoding, we repeated the analysis using neural activity from the recognition part (only considering familiar stimuli, comparing those remembered and forgotten). Unlike during encoding, the firing rates of category cells (preferred trials) did not differ significantly between remembered and forgotten trials during recognition ($\beta = 1.35$, $t = 0.21$, $p = 0.84$), nor was there a significant relationship between firing rate and confidence ratings (during preferred trials, $\beta = 0.95$, $t = 0.60$, $p = 0.55$). These results suggest that the observed change in firing rate of category cells associated with memory strength is driven by processes occurring during encoding rather than during retrieval.

Our findings show that a higher firing rate of category neurons is not only associated with successful memory encoding but also with greater confidence during retrieval. This pattern suggests that increased amygdala activity supports the formation of detailed episodic memories, as opposed to familiarity-based recognition alone.

Subsequent memory effects are independent of emotional valence and arousal

We also confirmed our findings related to emotional modulation by adding valence and arousal ratings as fixed effects to the mixed-effects GLM, along with memory encoding outcome (remembered vs. forgotten). Memory encoding outcome continued to have a significant relationship to the firing rate of amygdala category neurons after controlling for both emotional factors ($\beta_memory = 27.31$, $t = 3.64$, $p = 2.7 \times 10^{-4}$). Among the emotional factors, arousal but not valence significantly predicted firing rate in category cells ($\beta_arousal = 77.65$, $t = 3.25$, $p = 1.2 \times 10^{-3}$; $\beta_valence = -2.27$, $t = -0.14$, $p = 0.89$). Lastly, the association between firing rate and memory outcome was also present when analyzing positively and negatively valenced images separately (Positive: $\beta = 22.14$, $t = 2.40$, $p = 0.016$, Negative: $\beta = 45.40$, $t = 3.66$, $p = 2.5 \times 10^{-4}$). Thus, although arousal predicted variability in firing rates, the relationship to memory encoding outcome remained significant.

Hemispherical asymmetry is robust across control analyses

To assess the robustness of the hemispherical asymmetry in amygdala category neurons, we performed additional control analyses (Extended Data Fig. 5d-g). First, there was no significant difference in the strength of category tuning between the left and right amygdala (mean DOS = 0.34 and 0.36, respectively, t = −1.20, $p = 0.23$). Second, to address the potential confound of seizure-onset zone lateralization, we repeated the analysis after excluding neurons recorded from electrodes located within the seizure-onset zone. We observed a significant stronger effect in the right than the left amygdala (Extended Data Fig. 5d, observed t-value difference = 3.69, $p < 0.001$, permutation test), indicating that our findings are unlikely to be driven by the asymmetry related to seizures. Third, we tested the effect separately in each dataset. In both Task 1 and Task 2, the difference in t values between right and left amygdala neurons showed a stronger right-hemisphere effect (Extended Data Fig. 5e-f, Task 1: observed t-value difference = 2.33, $p = 0.026$; Task 2: observed t-value difference = 2.32, $p = 0.027$, permutation test; neurons located within the SOZ were excluded in this analysis). Third, to ensure that the combined analysis was not influenced by repeated measures from overlapping patients, we excluded Task 2 sessions contributed by patients who also participated in Task 1 (14 sessions were excluded). The hemispherical asymmetry remained significant after removing these sessions (Extended Data Fig. 5g, observed t-value difference = 3.59, $p = 0.001$, permutation test), indicating that the effect is not driven by overlapping patient samples. Together, we conclude that the difference between the right and left amygdala we observed was robust.

The amygdala effect is stronger than the hippocampal effect independent of sample size

As a control, to assure that differences in sample size did not give rise to the stronger and earlier subsequent memory effect in the amygdala we observed, we performed a random-subsampling analysis. Across 1000 iterations, 91 amygdala neurons were randomly selected to match the number of hippocampal category neurons, and t values comparing firing rates for subsequently remembered versus forgotten images were computed. The hippocampal t value was significantly smaller than the subsampled amygdala distribution (Extended Data Fig. 6a, mean difference in t value = 1.2, $p = 0.026$), indicating that the weaker hippocampal effect is not due to differences in neuron count. Using a cluster-based permutation approach, onset latencies of the subsequent memory effect were estimated for each subsampled amygdala iteration. The

amygdala onset was consistently earlier than the hippocampal onset (Extended Data Fig. 6b, mean difference = 884 ms, $p = 0.019$). Similarly, for within-region spike-field coherence, subsampled amygdala neuron-LFP pairs produced t values higher than those in the hippocampus (Extended Data Fig. 6c-d, mean difference in t value = 2.3, $p < 0.001$ at 10.5 Hz). These results suggest that the larger and earlier subsequent memory effect observed in amygdala category neurons was not due to differences in statistical power.

Amygdala-hippocampal coordination is specific to preferred stimuli

Lastly, we repeated the SFC analysis using trials from the non-preferred category. While a weaker memory effect within the amygdala remained, no significant coordination (SFC) between the amygdala and hippocampus was seen during the encoding of non-preferred items (Extended Data Fig. 7). Similarly, when analyzing all trials regardless of category preference, no significant coordination was observed. These findings suggest that the effect is specific to trials in which the neuron is actively engaged in processing the stimulus, underscoring the functional specificity of these interactions.

Supplementary Discussion

Our study shows evidence for a role of the amygdala in modulating the strength of rapid single-trial learning of episodic memories from single exposures to novel visual stimuli, a type of learning that humans excel at[34]. While humans excel in such learning, the coding principles and neural mechanisms that enable such fast plasticity without causing any apparent catastrophic interference remain largely unknown[67–69]. Our results build upon those by Mackay et al., who showed in 13 patients that concept cells in the amygdala exhibit higher firing rates for highly familiar items for which the location on the screen was later successfully recalled following a 15-second distraction task that separated encoding from cued retrieval[35]. Consistent with this work, we also observe that the subsequent memory effect is strongest in the amygdala and not the hippocampus. Our results go beyond these prior findings by demonstrating that amygdala activity specifically predicts the success of episodic memory formation, a result that relied on the confidence ratings our subjects provided to declare the strength of their memory for a given item. We did so using novel stimuli that were shown only once and using a relatively long delay of 10-

30 min between encoding and retrieval, both of which are constituent features of episodic memory not examined in[35]. A further critical difference is that we revealed this effect for category neurons, which respond to novel stimuli of a broad class of items such as animals, people, or cars. Category cells constituted 40% of the recorded amygdala cells in our study, thereby revealing a much broader effect compared to the 7% of amygdala cells that were concept cells in[35]. Jointly with[35], this body of work robustly establishes that across 3 different tasks, in the amygdala, the activity of both concept[35] and category (this study) cells is predictive of the success of memory formation, with the former predicting spatial associations and the latter predicting behaviorally measured episodic memory strength.

This conclusion is further supported by our behavioral ROC analysis to estimate the extent to which a given subject utilizes recollection and familiarity-based memory in making their new/old decision. This analysis showed that the more a subject relies on recollection, the larger the firing rate difference (during encoding) is between images that are later retrieved with high compared to low confidence. Together, our work therefore shows a parametric relationship between firing rate for stimuli of the preferred category of category cells during encoding and memory strength as declared by the subjects using confidence ratings.

In the present study, memory performance in patients was assessed on the same day of encoding. An important next step will be to extend this approach using a design that includes an additional recall session on a subsequent day. Such a design would make it possible to examine whether activity during encoding differentiates items that are initially remembered but not maintained across longer retention intervals, which would improve our understanding of the neural mechanisms that support memory consolidation across extended time periods.

We observed that phase locking of spikes fired by category cells with LFP in the amygdala and hippocampus was significantly stronger during the encoding of subsequently remembered items. This effect was again specific to only the images that belonged to the preferred category of a cell, further highlighting the specificity of the circuit engaged by specific images. This enhanced phase locking implies that these regions communicate more effectively when information is successfully being encoded. Previous studies reported that stronger within-region spike field coupling in the amygdala and hippocampus predicts memory encoding success for images and words[27,70]. In contrast, a spatial memory study found robust theta phase locking

of neurons but no difference in SFC between later remembered and forgotten locations, which may have been because the task tested spatial memory and/or the short interval between encoding and retrieval[71]. Here we found a subsequent memory effect in within-region SFC in the amygdala, but not in the hippocampus, suggesting that distinct medial temporal regions may differentially contribute to encoding. Prior studies either pooled neurons between the two areas[27,71] or excluded the amygdala entirely[70], so did not identify that amygdala (but not hippocampal) activity is strongly predictive of encoding success. Although within-region SFC measures can be influenced by factors such as electrode distance, our analyses focus on differences between remembered and forgotten trials. Any such effects would likely be similar across conditions and are therefore less likely to account for the observed subsequent memory effect. Beyond local SFC, we also observed that interregional SFC between the amygdala and hippocampus predicts memory encoding success, which involves spatially separated electrodes and is less likely to be affected by local signal spread, thereby extending prior evidence of within-region phase locking in the medial temporal lobe. Temporal coordination between amygdala rhythms and hippocampal spiking may help optimize synaptic plasticity through mechanisms such as spike-timing-dependent plasticity[72–75]. Overall, these results underscore the critical role of low-frequency neural activity in temporally organizing distributed neuronal processes to support effective memory encoding. Because spike-field coherence could be assessed only in Task 1 due to insufficient trial numbers in Task 2, future studies with larger trial numbers will be important to determine whether this coordination mechanism generalizes across paradigms.

Our findings indicate that the amygdala might be a suitable therapeutic target for treating memory disorders, for example through deep brain stimulation[6,7,76,77] or functional ultrasound stimulation[78,79]. Such an approach is of particular interest given that direct stimulation of the hippocampus has frequently been reported to impair, rather than enhance, memory performance[11,12,80]. Our findings also highlight a major obstacle that has to be overcome for this approach to become effective: stimulation has to be selective to the cells which are excited by a given stimulus (and not all cells in general). Recent work on electrical stimulation highlights that this might be feasible: depending on the stimulation protocol, electrical stimulation can be remarkably selective to certain cell types[81], and our recent work shows that low-amplitude

stimulation can selectively engage only excited cells[82], which in the present case would be category cells when exposed to a stimulus belonging to their preferred category.

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