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Neuronal activity in the human amygdala and hippocampus enhances emotional memory encoding

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Emotional events comprise our strongest and most valuable memories. Here we examined how the brain prioritizes emotional information for storage using direct brain recording and deep brain stimulation. First, 148 participants undergoing intracranial electroencephalographic (iEEG) recording performed an episodic memory task. Participants were most successful at remembering emotionally arousing stimuli. High-frequency activity (HFA), a correlate of neuronal spiking activity, increased in both the hippocampus and the amygdala when participants successfully encoded emotional stimuli. Next, in a subset of participants ($N = 19$), we show that applying high-frequency electrical stimulation to the hippocampus selectively diminished memory for emotional stimuli and specifically decreased HFA. Finally, we show that individuals with depression ($N = 19$) also exhibit diminished emotion-mediated memory and HFA. By demonstrating how direct stimulation and symptoms of depression unlink HFA, emotion and memory, we show the causal and translational potential of neural activity in the amygdalohippocampal circuit for prioritizing emotionally arousing memories.

We remember emotional events better than neutral ones[1]. This enhanced recollection of emotional information is important practically for protecting our most important memories and may also provide generalizable clues about the fundamental nature of memory[2], by explaining how the brain remembers some events better than others. One of the critical brain regions for processing emotional stimuli[3]—the amygdala—is an early target of Alzheimer's disease[4] and abuts the anterior portion of the hippocampus, the brain region most strongly associated with declarative memory[5]. This aetiological and anatomical proximity converges with behavioural, imaging and lesion evidence that the amygdala may be critical for memory of emotional events[6–10].

One prominent theory of the amygdala's role in memory proposes that the amygdala boosts hippocampal encoding and consolidation of emotional stimuli by facilitating the release of norepinephrine from the locus coeruleus[11,12]. While it is difficult to directly measure human norepinephrine fluctuations, there is indirect evidence for this theory from pharmacological studies showing that enhancing[13,14] or disrupting[15,16] noradrenergic transmission, respectively, enhances and impairs memory for arousing stimuli. Noradrenergic inputs may modulate the amygdalohippocampal circuit by upregulating the mean rate of neuronal activity, as suggested by both direct recordings of neuronal activity[17,18] and recordings of high-frequency activity (HFA) in limbic local field potentials (LFPs)[19,20]. Similarly, data from patients with depression also show links between emotional memory, norepinephrine and amygdala activity. Individuals with depression, who exhibit impaired emotional memory[21], show improvement in symptoms of depression when treated by norepinephrine agonists[22] or when receiving brain stimulation that increases amygdala HFA[23]. Together, these findings

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suggest that HFA in the hippocampus and amygdala is, at least in part, driven by noradrenergic upregulation of neural activity[24].

Building off these ideas, here, we hypothesized that our ability to prioritize emotionally salient information for improved memory would rely on this upregulation of neuronal activity within the amygdala and hippocampus during encoding. We tested this hypothesis in humans using a novel tripartite approach that combined three complementary methods: direct human brain recordings, deep brain stimulation and psychometric assessment of symptoms of depression in patients with epilepsy performing a verbal free recall task. Free recall is an episodic memory task in which participants exhibit enhanced memory for emotional words[25,26] and elicits pupil dilation (thought to reflect norepinephrine release[27]) during successful memory encoding[28]. Thus, we hypothesized that direct brain recordings from participants performing this task would reveal whether HFA, a proxy for local neuronal spiking[29], reflected noradrenergic dynamics during the prioritized encoding of emotional events. Consistent with these predictions, we found that the amplitude of HFA in the amygdala and hippocampus predicted the successful encoding of emotional words[30,31]. We integrated these findings with electrical stimulation and psychometric data to demonstrate how perturbations to the amygdalohippocampal circuit diminished the linkage between HFA, emotion and memory. Specifically, we found that inhibitory brain stimulation weakened HFA and selectively impaired recall of emotional words, suggesting that there is a causal relationship in this circuit between neuronal spiking and the enhanced memory for emotional items. We then demonstrated that participants with depression—whose impaired emotional processing is characterized by disruption of noradrenergic neurotransmission[32]—exhibited a similar reduction in emotion-mediated memory and concurrent HFA in the hippocampus and amygdala. Overall, our findings demonstrate that neuronal activity in the human amygdala and hippocampus, a potential correlate of noradrenergic upregulation, may causally support the prioritization of emotional memories.

Results

Emotional stimuli are better remembered

We analysed data from 148 participants (Supplementary Table 1) who performed a verbal episodic memory task where they viewed and remembered lists of words. After each list, participants performed a math distractor task to prevent rehearsal and were then told to recall as many words as possible, in any order (Fig. 1a). We quantified the emotional properties of each word using valence and arousal typically associated with each word (Fig. 1b). Valence ratings, which capture how positive or negative a word is, and arousal ratings, which capture the emotional intensity of a word, were drawn from a publicly available database. We employed a Bayesian mixed-effects logistic regression approach[33] to assess how the emotional properties of each word impacted participant's memory encoding[34] (Fig. 1c; see Methods for detail) and report the posterior estimate of the mean coefficient (β). We consider an effect to be consistently and meaningfully different from 0 if the 95% high-density interval (HDI) does not include 0 (see Methods for detail). While arousal and valence showed some correlation (Spearman's $\rho = -0.12$, $P = 0.0005$; Fig. 1b), participants best remembered words that were highly arousing ($\beta = 0.34$, 95% HDI = [0.21, 0.48]; Fig. 1d and Supplementary Table 2), while the effects of valence on recall were more variable. To ensure that this distinction between valence and arousal was not driven by the choice of rating scale, we replicated our main behavioural finding using an alternative rating scale (Methods and Supplementary Fig. 1). High arousal also modulated clustering during recall, consistent with earlier work[35] (Extended Data Fig. 1).

The emotional features of each word, particularly arousal, were thus predictive of participants' memory performance, even as the task did not explicitly depend on the emotional features of the words, consistent with earlier work in healthy (non-epileptic) participants[25,26]. These behavioural results suggest that even when emotional context has limited task relevance, it drives memory enhancement and is thus likely predictive of participants' implicit emotional associations. Because the amygdala is broadly involved in the enhancement of memory for emotional events[6–9], and delayed free recall tasks depend on the hippocampus[36], we hypothesized that the joint activation of the amygdala and hippocampus was responsible for this phenomenon.

HFA predicts successful emotional memory encoding

We next tested how neuronal activity in the hippocampus and amygdala corresponded to the effects of emotional context on memory. We analysed brain recordings from intracranial electroencephalographic (iEEG) electrodes ($n = 473$ electrodes in the hippocampus and $n = 273$ electrodes in the amygdala passed exclusion criteria) implanted in these participants while undergoing intracranial monitoring for epilepsy treatment (Fig. 2a). The majority of amygdala electrodes were located in the basolateral nuclei (Extended Data Fig. 2). First, we assessed whether spectral power of the signals at each electrode during encoding was predictive of subsequent recall by comparing the power spectrum of the iEEG signals during encoding between remembered and forgotten items[37,38]. Previous iEEG studies have identified a characteristic decrease in LFP in the hippocampus associated with encoding of successfully recalled words[35,39,40], which we replicated in both hemispheres (Fig. 2b). In addition, we also demonstrated that the amygdala showed similar iEEG power changes during encoding of subsequently remembered items, particularly in the left hemisphere (Fig. 2b). These subsequent memory effects (SMEs) were not a result of differences in spectral tilt[41] or changes to the height or frequency of the spectral peaks (Extended Data Fig. 3).

We next assessed whether memory-related spectral dynamics were mediated by the emotional features of each word, as we hypothesized that such stimuli might upregulate noradrenergic release related to emotional processing, eliciting increased neuronal spiking. Figure 2c shows an example of the signals we observed in the hippocampus and amygdala, depicting z-scored power spectra from individual trials when participants viewed words. For words that were subsequently recalled (left panel), HFA (defined as 30–128 Hz, following previous work[40,42,43]) in both regions was elevated for more arousing words. This arousal-related elevation in HFA was absent for words that participants would subsequently forget (right panel), suggesting that HFA increases correlate with successful memory primarily when participants encoded high-arousal words. We extended our mixed-effects logistic regression model to include trial-wise HFA as a predictor of subsequent recall in addition to arousal and valence, while accounting for electrode region and hemisphere (Methods and Supplementary Table 3). Consistent with the behavioural results, and the examples shown above, increases in amygdalohippocampal HFA during encoding of high-arousal words predicted subsequent recall (HFA:arousal, $\beta = 0.08$, 95% HDI = [0.006, 0.15]; Extended Data Fig. 4a,b). This was particularly true for more negative words (HFA:arousal:valence, $\beta = -0.5$, 95% HDI = [−0.9, −0.1]; Fig. 2d), although not when assessing valence alone (Supplementary Table 3). In contrast to arousal, valence-driven HFA increases during successful memory encoding varied significantly between hemispheres and regions and along the anterior–posterior axis of the hippocampus, suggesting that valence elicits more localized memory-related neural activity than arousal (Extended Data Fig. 5a–c and Supplementary Table 3). Increases in arousal-mediated HFA occurred across multiple timepoints during successful memory encoding in both the hippocampus and the amygdala (Extended Data Fig. 6).

Because low-frequency differences dominated the overall SME effect computed across all words (Fig. 2b), we next assessed whether theta (2–8 Hz) power also correlated with increased memory for emotional words. Theta power did not show a consistent relationship with arousal- or valence-mediated memory (Supplementary Table 4), suggesting that arousal-mediated memory specifically elicited HFA increases in the amygdalohippocampal circuit. Still, we tested the

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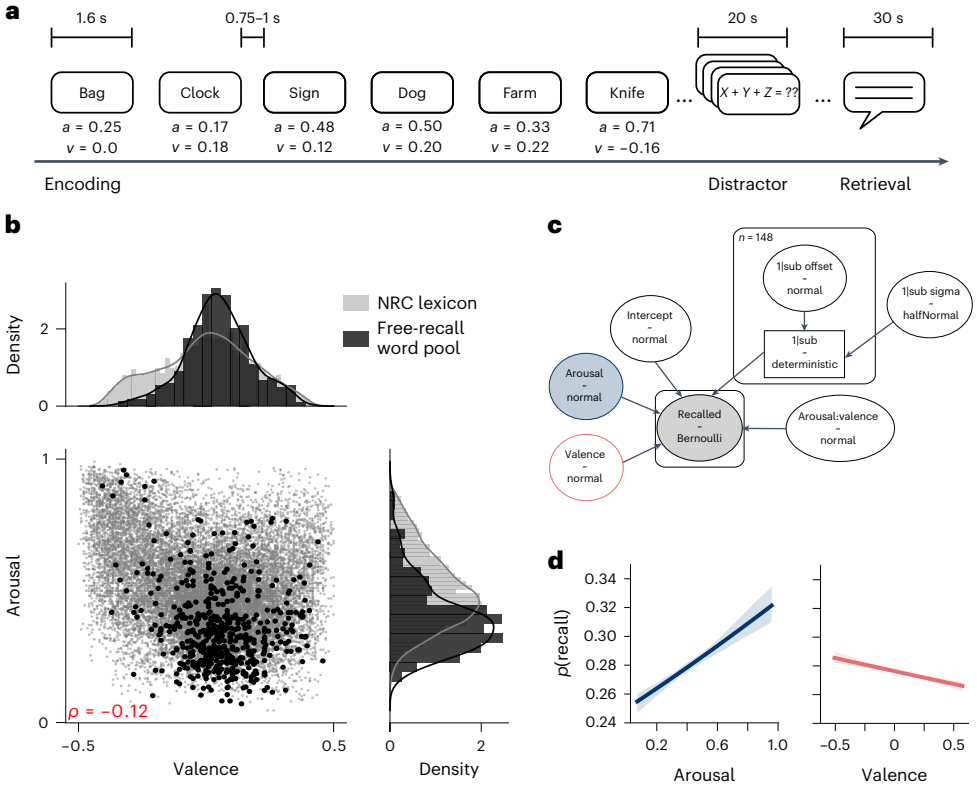

Fig. 1 | Emotional features of stimuli in a verbal free recall task influence recall performance. a, Schematic of task design showing the time intervals during and between task stages. Participants encoded 12 words per list. Arousal (*a*) and valence (*v*) ratings for example words depicted below each word (these were not visible to participants during the task). **b**, Joint scatterplot and marginal distributions of valence and arousal ratings in the National Research Council (NRC) Lexicon (grey) and the word pool for the free recall tasks performed by participants (black). Spearman rank correlation coefficient is indicated in the bottom-left corner. **c**, Graphical model of Bayesian mixed-effects logistic regression used to assess the influence of word features on subsequent recall. Each node depicts a feature of the model and the corresponding distribution (indicated by a tilde). Shading indicates node with estimated 95% HDI excluding 0. **d**, Probability of recall as a function of arousal (left) and valence (right), fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits.

possibility that the increases in HFA were coordinated by the phase of low-frequency activity but discovered no evidence for significant cross-frequency coupling between theta and HFA in the amygdalohippocampal circuit ($P > 0.05$, cluster-based permutation test, Supplementary Fig. 2). These results thus demonstrate that emotional words, particularly those that were highly arousing, specifically upregulated HFA throughout the amygdalohippocampal circuit during encoding of subsequently remembered words.

Hippocampal stimulation disrupts emotional memory and HFA

To better understand whether the HFA we observed reflects neural mechanisms underlying emotional memory encoding, we next tested whether disrupting HFA would impair memory for emotional information. To do so, we analysed the effect of high-frequency (50 Hz) deep brain stimulation on memory performance. This type of stimulation has been shown to modulate HFA[44] and impair memory when applied to medial temporal lobe (MTL)[45]. A group of 19 participants performed 32 sessions of the free recall task, while direct electrical stimulation was applied to their hippocampus ($n = 28$ sessions) and amygdala ($n = 4$ sessions) (Fig. 3a, Supplementary Table 5, Extended Data Fig. 7 and Methods). In addition, 8 participants were stimulated in MTL-neocortical regions, such as the parahippocampal gyrus and perirhinal cortex, which served as nearby control regions that are outside of the amygdalohippocampal circuit but still provide input to the hippocampus ($n = 25$ sessions). We excluded amygdala stimulation data from further analysis due to the small sample size.

We analysed these data to test how stimulation impacted memory for words of varying arousal and valence, accounting for electrode hemisphere and region. Figure 3b shows that high-frequency stimulation, when applied to the hippocampus, specifically impaired encoding for emotional words. Specifically, stimulation had a strong, consistent deleterious effect on recall for more negative words (stimulation:valence, $\beta = 0.7$, 95% HDI = [1.38, 0.003], Fig. 3b). A similar but inconsistent trend was observable for high-arousal words (Supplementary Table 6), although we could not examine whether this trend was driven by negative words due to insufficient sample size to test the interaction between arousal and valence. These results suggest that emotional memory encoding is selectively diminished by hippocampal stimulation.

One alternative possibility was that stimulation simply diminished memory more for any high-memorability word. To rule out this possibility, we tested whether hippocampal stimulation impaired memory for words as a function of serial position, which strongly predicts free recall memorability[46]. Stimulation did not more strongly affect early-position words, despite their increased memorability over late-position words (Supplementary Table 6 and Extended Data Fig. 8), demonstrating that hippocampal stimulation specifically targeted emotional memory-encoding processes. Moreover, stimulation applied to the MTL-neocortical regions did not elicit consistent differences in recall performance related to either valence or arousal, suggesting that hippocampal stimulation was selectively disrupting neural dynamics related to the emotional enhancement of memory (Supplementary Table 6).

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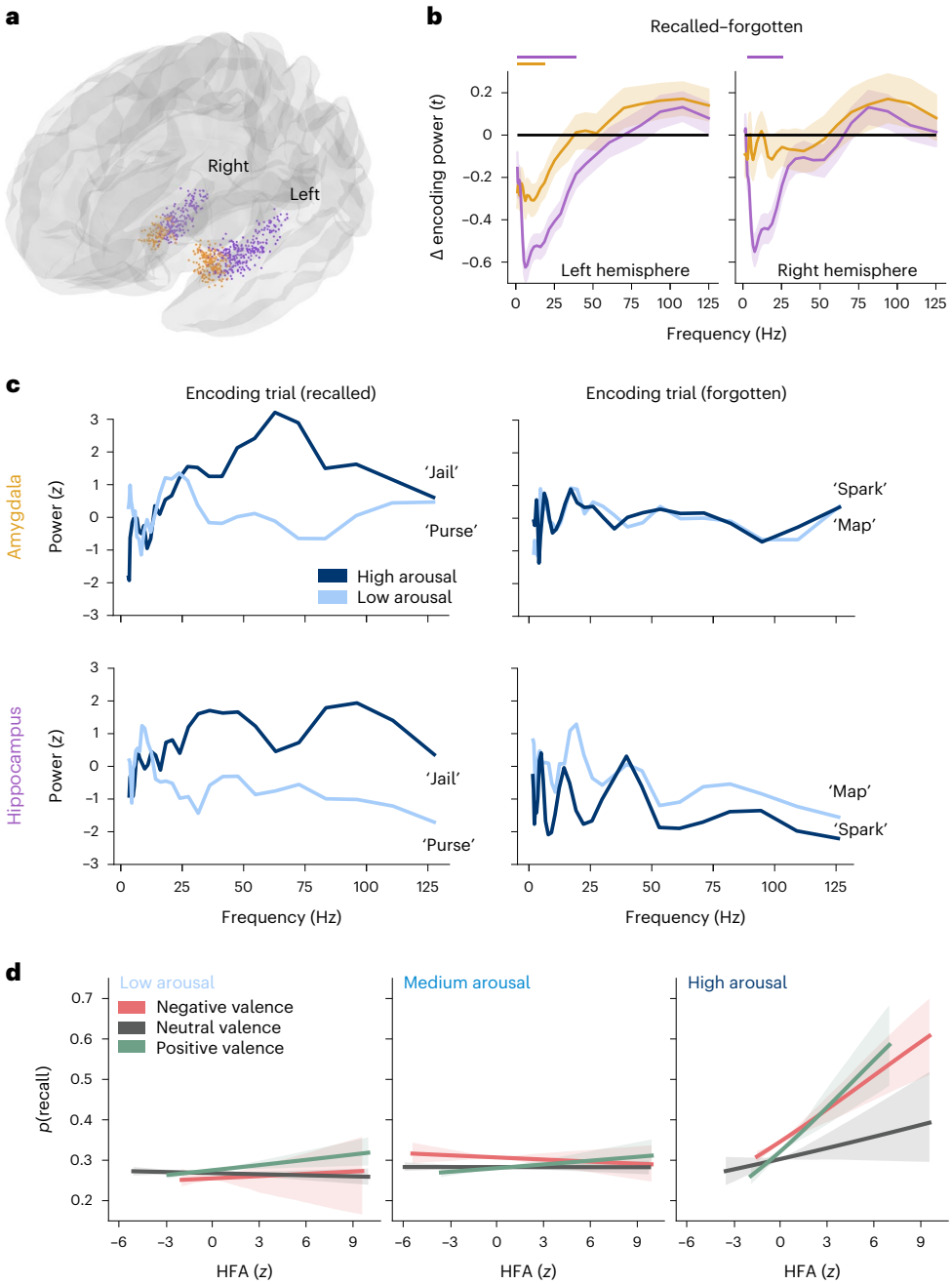

Fig. 2 | High-frequency activity predicts successful emotional memory encoding in the hippocampus and amygdala. a, Location of all 744 electrodes recorded across all participants. Purple circles indicate electrodes localized to the hippocampus, and orange circles indicate electrodes localized to the amygdala. **b**, Comparison of subsequent memory effect between the hippocampus (purple) and the amygdala (orange). Solid line denotes within-session *t*-statistic for comparison between remembered and forgotten trials, averaged over hippocampal and amygdala electrodes in the left and right hemispheres. Horizontal lines denote SMEs that significantly deviate from 0 for electrodes in the hippocampus ($t(1) < -2.1$, $P = 0.001$, Cohen's $d < -0.3$, two-sided cluster-based permutation test) and the amygdala ($t(1) < -2.4$, $P = 0.001$, Cohen's $d = -0.12$, two-sided cluster-based permutation test). Shading indicates standard deviation. **c**, Within-list *z*-scored power during example encoding trials from a single amygdala (top) and hippocampal (bottom) electrode in an example participant during memory encoding. Power during encoding of a high-arousal word from the list is depicted in dark blue, while power for a low-arousal word from the list is depicted in light blue. HFA increases during successful encoding (left) of high-arousal words versus low-arousal words, but not during failed encoding (right). **d**, Probability of recall as a function of HFA (*z*-scored), binned by valence and arousal for visualization, fit by a logistic regression model (solid line). As arousal increases, the slope indicating the relationship between HFA and recall probability increases in both regions. Shading indicates standard deviation of bootstrapped model fits.

To explain how stimulation specifically modulated the encoding of emotionally relevant stimuli associated with increased HFA, we compared spectral power in the hippocampus pre- versus post-stimulation (Fig. 3c). Stimulation caused a significant reduction in hippocampal HFA when applied to the hippocampus (post- versus pre-stimulation, $\beta = -0.11$, 95% HDI = [−0.18, −0.03], Supplementary Table 7), but not when applied to adjacent MTL-neocortical regions (Fig. 3c and Supplementary Table 7). Next, to assess the specificity of this effect to HFA, we tested whether hippocampal stimulation had a similar effect on power in other frequency bands including theta (2–8 Hz), alpha (8–13 Hz) and

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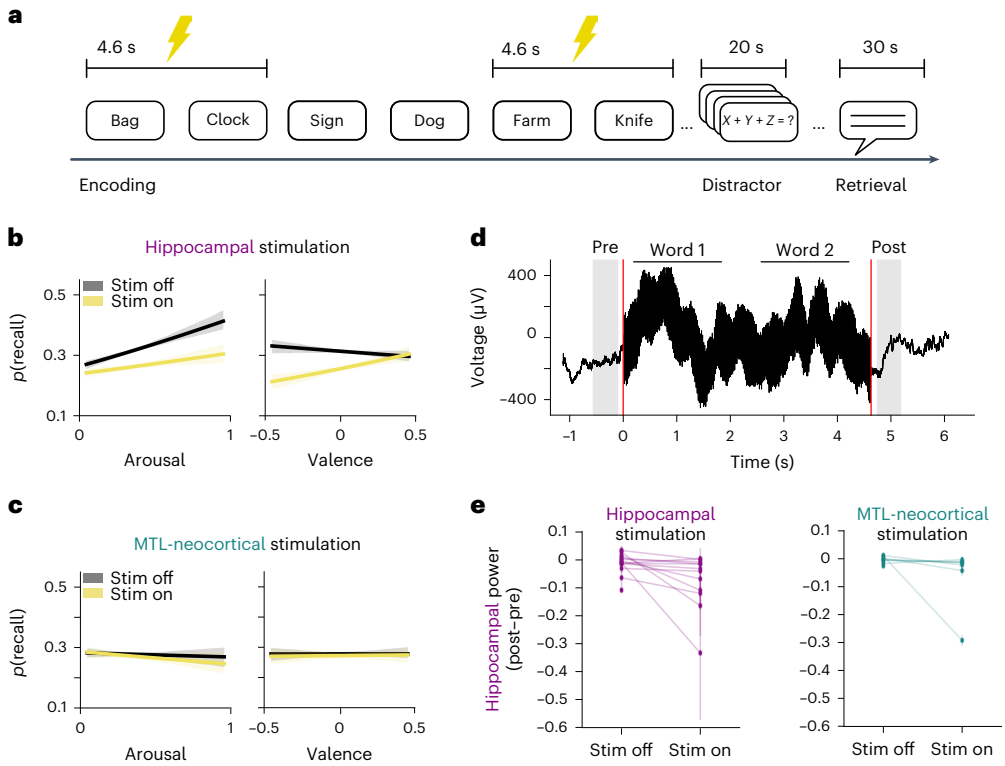

Fig. 3 | Direct stimulation of the hippocampus during encoding impairs emotion-mediated memory and decreases HFA. a, Schematic of task design showing the time intervals during direct brain stimulation. Stimulation was applied to alternating pairs of words in a list. **b**, Probability of recall as a function of arousal (left) and valence (right) for both the stimulation off (black) and on (yellow) conditions, in participants who underwent hippocampal stimulation, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. **c**, Probability of recall as a function of arousal for both the stimulation off (black) and on (yellow) conditions, in participants who underwent stimulation in nearby control regions, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. **d**, Single-trial example of LFP during stimulation of a word pair. Shaded regions indicate pre- and post-periods used for analysis. Word presentation is indicated by horizontal lines. Red lines indicate onset and offset of stimulation. **e**, Post–pre-hippocampal HFA, averaged across trials (dot) within participant ($n = 16$), when stimulation was off versus when stimulation was turned on. Colours denote stimulation region, and vertical lines denote standard deviation.

beta (13–30 Hz). Hippocampal stimulation did not significantly affect the hippocampal LFP in any of these frequency bands (Supplementary Table 8 and Extended Data Fig. 9), suggesting that hippocampal HFA, specifically, underlies the stimulation-induced disruption of emotional memory enhancement.

Depression impairs linkage between emotion, memory and HFA

A prominent theory of affective disorders hypothesizes that deficiencies in noradrenergic neurotransmission underlie symptoms of depression[32]. Therefore, we next assessed whether such disorders elicited concurrent changes in emotional memory performance and amygdalohippocampal HFA. We examined this by integrating psychometric information about the severity of affective disorders from a subset of the patients in our dataset who had completed the Beck Depression Inventory (BDI-II) and the Beck Anxiety Inventory (BAI). We found that only participants with higher depression scores (Fig. 4a) exhibited worse memory (BDI, $\beta = -0.05$, 95% HDI = [−0.08, −0.02]; Fig. 4b and Supplementary Table 9), as expected from earlier work[47]. We next examined how the memory encoding from individuals with depression correlated with the emotional features of each to-be-remembered word.

Notably, higher depression scores corresponded to diminished memory for arousing words (BDI:arousal, $\beta = -0.012$, 95% HDI = [−0.022, −0.001]; Supplementary Table 10). As seen in Fig. 4c, this means that the enhanced memory previously seen for arousing words was selectively disrupted in participants with higher depression scores. We assessed whether this decrease in emotion-mediated memory encoding was associated with changes to the observed increases in amygdalohippocampal HFA. In line with these behavioural effects, the strong positive relationship observed between HFA, arousal and memory (Fig. 2d) was abolished in participants with higher depression scores (BDI:HFA:arousal, $\beta = -0.017$, 95% HDI = [−0.029, −0.002]; Fig. 4d and Supplementary Table 11). This effect was specific to high-arousal words (Supplementary Fig. 3). In line with our initial analysis of HFA and memory, the effect of valence was more variable—higher depression scores only showed a trend towards diminishing memory for negative words (Extended Data Fig. 10a and Supplementary Table 10), while associated with a reversal in the relationship between HFA, valence and memory (BDI:HFA:valence, $\beta = 0.017$, 95% HDI = [0.003, 0.029]; Extended Data Fig. 10b and Supplementary Table 11). These results thus suggest that participants with higher depression scores may experience an overall decrease in emotional memory (particularly for highly arousing stimuli) associated with a concurrent degradation of the link between HFA, emotion and memory. Conversely, theta power did not show any correspondence with BDI, emotion and memory (Supplementary Table 12), suggesting that the mnemonic changes associated with depression may be tied specifically to the concurrent changes to amygdalohippocampal HFA.

Discussion

The emotional context of an event often determines how that event is remembered. Here, we investigate the neural basis of our enhanced memory for emotional events by using direct recordings, brain stimulation and psychometric assessment in human neurosurgical

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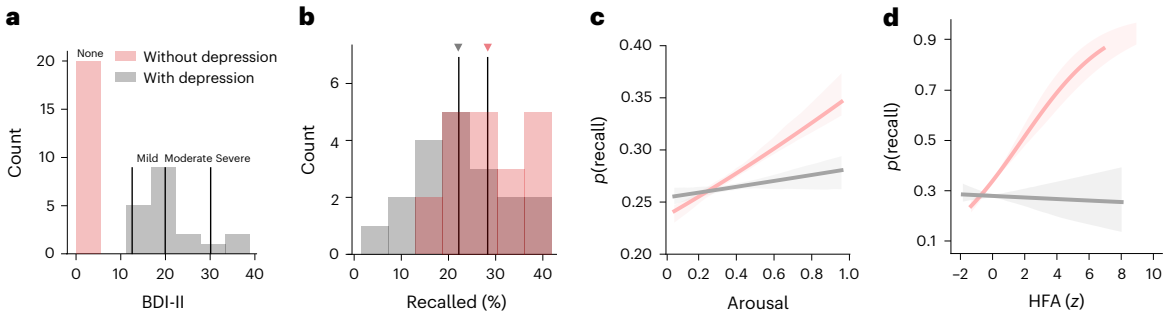

Fig. 4 | Participants with depression exhibit diminished arousal-mediated memory and HFA. a, Histogram of BDI-II scores for patients, split by depressive characterization. **b**, Distribution of recall performance across participnts as a function of depression rating. Participants with higher depression scores exhibited worse memory (BDI, $\beta = -0.05$, 95% HDI = [−0.08, −0.02]). **c**, Probability of recall as a function of arousal for both participants with or without depression, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. Higher depression scores corresponded to diminished memory for arousing words (BDI:arousal, $\beta = -0.012$, 95% HDI = [−0.022, −0.001]). **d**, Probability of recall as a function of HFA (*z*-scored), binned by depression level for visualization, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits.

participants. By directly examining human hippocampal and amygdalar electrophysiology from participants performing a memory task, we assessed the role of these two brain structures in encoding memories with emotional associations. In both the hippocampus and the amygdala, we found that HFA, a proxy for local neuronal spiking[29], correlated with stimulus-induced arousal during successful memory encoding. We found that this phenomenon is causally important because perturbations to this network, either through disruptive brain stimulation or symptoms of depression, selectively impaired the recall of emotional stimuli and the amygdalohippocampal HFA typically associated with their recall. These results (1) demonstrate that upregulation of amygdalohippocampal activity during encoding is correlated with enhancement of memory for emotionally engaging stimuli in humans and (2) show that modulating the activity within this circuit causally affects how the human brain prioritizes certain information for memory encoding, with relevance for psychiatric disorders, such as depression.

Substantial behavioural evidence has shown that the brain prioritizes the encoding of emotional content[1,25,26]. Here, we show that primarily high-arousal words are remembered better than other words, although the task word pool may have been too limited in highly positive or negative words to show a consistent effect of valence, alone, on recall. While lesion studies have demonstrated the importance of both the amygdala and the hippocampus to the enhancement of emotional memory, our findings show a causal mechanism underlying this effect: increased neuronal activity in the amygdalohippocampal circuit, as indexed by HFA, enhances memory for emotional information during memory encoding. This finding bridges evidence from iEEG studies of memory that implicated increased HFA with successful word recall[40] and aversive image viewing[48], with fMRI studies that have demonstrated increasing activation in the amygdala and hippocampus with recall of more emotional stimuli[7,10].

Furthermore, the results from our stimulation experiments indicate that hippocampal upregulation may be causally responsible for the emotional enhancement of memory, because stimulation reversed the memory enhancement and HFA increases associated with emotional context. The behavioural effect of stimulation was most clear for negative words, although the large (if inconsistent) deleterious effect of stimulation on arousal-mediated memory suggests that future stimulation studies with increased statistical power may demonstrate that stimulation alters memory for both arousing and negative words. Furthermore, future work should examine how the HFA we identified might propagate within the amygdalohippocampal circuit[49]. For example, stimulation studies with sufficient coverage of the anterior–posterior axis of the hippocampus should probe whether the relationship we observed between stimulation, valence and memory differs along this axis. Unlike previous work examining passive viewing[48], we did not observe significant cross-frequency coupling between the amygdala and the hippocampus conditional upon memory recall performance. It is possible that the reduction in low-frequency signals during successful memory diminishes true phase estimates and, consequently, cross-frequency coupling. Another possibility is that the phenomenon we observed may reflect awake ripple activity, which may play a role in cross-regional synchronization and subsequent consolidation[50].

While our study specifically examines the effects of direct stimulation of the hippocampus on affective memory processes, two recent studies are related to ours because they separately probed the effect of amygdala stimulation on memory and affective disorders. In one study, the authors[51] showed that amygdala stimulation enhanced memory overall, in contrast to our observed pattern of stimulation-induced memory impairment and HFA decreases. Two key methodological differences between the amygdala stimulation study and our work may explain the differing results. First, the stimuli used in the amygdala stimulation study were neutral stimuli, which probably did not engage the same emotional memory processes as the stimuli in our task. Second, whereas in our study retrieval occurred a few minutes after encoding, the amygdala stimulation study demonstrated memory enhancement one day after stimulation, suggesting that amygdala stimulation may have affected later memory consolidation processes rather than strictly modifying memory encoding. The second study assessed how amygdala stimulation modulated human depression symptoms, showing that amygdala HFA was a successful biomarker for high-efficacy closed-loop stimulation to treat major depressive disorder in a single participant[23]. Not only was bilateral amygdala HFA sufficient to classify depressive states but also stimulation induced a reduction in HFA that improved symptom severity. Our work provides a potential mechanistic explanation for these stimulation results by demonstrating that amygdalar and hippocampal HFA correlate with memory for emotional stimuli. We believe that future work will be able to establish that amygdala stimulation has similar effects to those we observed with hippocampal stimulation, specifically given previous evidence that amygdala stimulation selectively increases gamma frequency oscillations[52]. Future work should also assess whether stimulation that reduces symptoms of depression also modulates memory for emotional content.

Examining the link between emotional state and memory is particularly important given our results showing a direct relation between HFA, depression and the emotional enhancement of memory. We found that participants with depression had worse memory, driven by diminished recall of emotional words—particularly arousing words. This is potentially important because one prominent theory[53] suggested that valence-mediated memory is thought to engage prefrontal–hippocampal pathways, in contrast to arousal-mediated memory, which

is thought to rely more heavily on amygdalohippocampal interaction. This hypothesis is consistent with our finding that arousal-mediated memory and amygdalohippocampal HFA are disrupted by depression, as well as previous imaging work showing altered amygdalohippocampal activity in participants with depression[54]. Furthermore, previous research has demonstrated that cortisol, shown to enhance memory for arousing stimuli alongside noradrenergic activation of the amygdala[55], also rescues memory performance in participants with depression and alters hippocampal responses[56]. Our data thus suggest that disrupting amygdalohippocampal noradrenergic transmission is responsible for the differences we observed in both memory performance and HFA in participants with depression, in line with theories of depressive pathology[32]. Overall, our findings implicate HFA within the amygdala–hippocampus circuit in the emotional enhancement of memory in healthy individuals as well as its alteration in individuals with affective disorders, such as depression.

Although our study did not directly measure neuromodulatory signals, we believe that the emotion-related HFA signals we observed reflect neuromodulatory dynamics in the hippocampus and amygdala—in particular, noradrenergic drive from the locus coeruleus[24]. Norepinephrine release causes increases in HFA in many brain regions[20,57], including the hippocampus[58] and amygdala[59], and has also been linked to sharp-wave ripples in the hippocampus[60]. Consistent with our hypothesis of a link between HFA and norepinephrine, previous studies of human verbal memory have demonstrated that successful memory encoding positively correlated with HFA in the medial temporal lobe[40], as well as norepinephrine-related patterns, such as pupil dilation[28], and autonomic measures, such as heart rate and skin conductance[61]. In addition to explaining our HFA findings, noradrenergic transmission might also explain our stimulation results. Work in rodents has demonstrated that memory deficits induced by amygdala stimulation are mitigated in the absence of noradrenergic release, suggesting that norepinephrine is critical for amygdala stimulation to modulate memory[62]. How would noradrenergic release improve memory? One possibility is that the norepinephrine release facilitates hippocampal spike-timing-dependent plasticity, leading to enhanced memory[24,63,64]. This idea is supported by the fact that norepinephrine release alone is not sufficient to enhance memory unless it also elicits neuronal spiking in the amygdala[65] and that noradrenergic activation of basolateral amygdala, the primary subregion examined in this study, enabled selective memory enhancement for arousing experiences in rodents[55]. Overall, these data support the view that noradrenergic upregulation of neuronal spiking in the amygdalohippocampal circuit, reflected by increases in HFA, is a generalizable mechanism for the prioritization of information processing in the brain[66].

Emotional memories are some of the most valuable memories we have, and untangling the neural mechanisms underlying the relative robustness of such memories may prove critical to treating memory disorders[2]. Our work provides a bridge to basic science research in animals, providing new avenues for researchers to link midbrain noradrenergic transmission to electrophysiological correlates of memory in the amygdala and hippocampus, such as the HFA observed here. Furthermore, by demonstrating how activity in the amygdalohippocampal circuit supports the intersection of human memory and emotion, our findings provide mechanistic support to future therapeutic studies modulating this circuit to treat memory[51] and mood disorders[23]. Overall, our findings suggest that upregulation of neuronal activity within the amygdalohippocampal circuit during encoding may be a generalizable mechanism for the prioritization of information for memory encoding in humans.

Methods

Data recording and participants

We analysed publicly available data recorded from patients undergoing invasive iEEG monitoring in the course of their treatment for drug-resistant epilepsy. Patients were recruited to participate in a multicentre project, with data collected at Thomas Jefferson University Hospital, Mayo Clinic, Hospital of the University of Pennsylvania, Emory University Hospital, University of Texas Southwestern Medical Center, Dartmouth Hitchcock Medical Center, Columbia University Medical Center, National Institutes of Health and University of Washington Medical Center. Experimental protocol was approved by the Institutional Review Board at each institution, and informed consent was obtained from each participant. Data acquisition and storage was coordinated by the Data Coordinating Center at the University of Pennsylvania (Institutional Review Board protocol 820553). Electrodes were implanted using localized, penetrating depth electrodes (Ad-Tech Medical Instruments). Electrodes were spaced 10 mm apart, and data were recorded using either the Nihon Kohden EEG-1200, Natus XLTek EMU 128 or Grass Aura-LTM64. iEEG signals were sampled at either 500 Hz, 1,000 Hz or 1,600 Hz and referenced to an intracranial electrode or a contact on the scalp or mastoid process. Bipolar referencing was applied during post hoc analyses.

Statistical analysis

To determine the features predicting successful memory retrieval, we used a Bayesian mixed-effects logistic regression modelling framework[33]. Within this framework, we first assessed the influence of non-neural fixed effects by constructing models of the form

$$p(\text{recall} = 1) \sim X + (1|\text{subject}) \quad (1)$$

where the probability of recall is modelled as a logit-link binary outcome approximated (as indicated by the tilde) by X, which includes combinations of word features (arousal, valence, stimulation) and participant features (BDI score) depending on the specific question, while accounting for participant-level random effects. To ascertain the best formulation of the valence factor, we performed a model comparison between the basic recall model (depicted in Fig. 1c) utilizing valence and the same model utilizing squared valence and compared these models using the Watanabe–Akaike information criterion[67]. Because the model utilizing valence fared better, we retain that formulation throughout all subsequent models. We then assessed the influence of neural fixed effects by constructing models of the form

$$p(\text{recall} = 1) \sim X + (1|\text{subject}) + (1|\text{subject} : \text{electrode}) \quad (2)$$

where X includes combinations of word features, participant features, electrode features (hemisphere, region, stimulation site, recording site), and neural features (power), depending on the specific question, while accounting for participant-level and electrode-level random effects. We also utilized a similar Bayesian mixed-effects linear regression to analyse how stimulation modulated power, using a model of the form

$$\Delta\text{power}(\text{post} - \text{pre}) \sim X + (1|\text{subject}) + (1|\text{subject} : \text{electrode}) \quad (3)$$

where X includes electrode features (hemisphere, region, stimulation site, recording site) while accounting for participant-level and electrode-level random effects. Individual word features were not included because stimulation was applied continuously during pairs of word presentations. These models were fitted using the Python library Bambi[68], which generates weakly informative (broad) priors for all model variables[69] that are scaled to regularize the model rather than integrate domain knowledge. To fit models, we used 4 Markov chain Monte Carlo No-U-Turn (NUTS) samplers, drawing 1,500 samples from the posterior for each chain, after a minimum of 1,000 burn-in samples. All posteriors for independent variables were checked for convergence using the Gelman–Rubin statistic, which was less than 1.01 in all cases, indicating good convergence. We computed the 95%

HDI for each model parameter to quantify the uncertainty around the true value of the parameter[70]. We considered there to be significant evidence for the influence of a fixed effect if the 95% HDI did not include zero[71]. Interaction terms were included where sample size allowed.

Task

Participants participated in a delayed free recall verbal memory task. During this task, a 10 s countdown preceded each list of 12 words, which were presented for 1,600 ms each with interstimulus intervals randomly sampled from between 750 ms and 1,000 ms. Each list was followed by a math distractor task to prevent rehearsal, lasting at least 20 s, during which simple math problems were presented until a response was entered or recall began. A visual cue paired with an 800 Hz tone signalled the start of each recall period, and participants had 30 s to verbally recall as many words from the list of 12 words they had just seen, in any order. These vocal responses were recorded and annotated offline to assess recall accuracy. Participants encoded and recalled 25 lists in each session and did not see the same list twice across sessions.

Participants performed one or both versions of this task that differed in the semantic structure of the word lists. The uncategorized version of the task utilizes a word pool of 300 words, constructed by selecting words from the Toronto word pool with intermediate recall performance (after accounting for recall dynamics and clustering effects inherent to free recall). This word pool was split into lists of 12 words such that the mean pairwise semantic similarity within list was relatively constant across lists. For the categorized free recall task, the word pool was drawn from user-rated semantic categories (using Amazon Mechanical Turk). Words were sequentially presented as categorical pairs (drawn from the same category), and each list consisted of four words drawn from each of the three categories. Two pairs drawn from the same semantic category were never presented consecutively[72].

Characterizing emotional context during encoding

We utilized a publicly available rating scale, the National Research Council Lexicon[34], to quantify the emotional context of the words present in the word pool for each task. We selected this rating scale, as opposed to other commonly used rating scales, such as the Affective Norms for English Words database[73], because of the higher number of independent raters involved, higher split-half reliability for ratings (particularly for arousal ratings) and higher discriminant validity between valence and arousal ratings. In sum, 97% of the words tested had ratings in the National Research Council lexicon and were analysed in this study.

Electrode localization

To localize the depth electrodes to the different subregions of the amygdala, we used the CIT168 atlas[74]. Due to the bipolar reference scheme we utilized, we localized the resulting 'virtual' electrodes using the averaged Montreal Neurological Institute coordinates of the two referenced electrodes. Virtual electrodes were labelled according to the nearest subregion in the CIT168 atlas, within a 5 mm diameter (which corresponds to the inter-electrode distance).

Spectral analysis

All data were band-stop filtered around 60 Hz to minimize line noise, and data were bipolar referenced to eliminate reference channel artefacts and noise[40]. LFP data were downsampled to 256 Hz for analyses. Before analysis, we had excluded electrodes if an expert neurologist determined that the electrode had a damaged lead; was placed in white matter, a seizure onset zone, or lesioned brain tissue; or exhibited significant electrical or mechanical noise. We used a continuous wavelet transform (Morlet wavelets, wave number 6) with 30 log-spaced frequencies between 2 Hz and 128 Hz and 1,000 ms buffer windows to attenuate convolution edge effects. Spectral analysis was performed using the mne toolbox[75]. We averaged power into two bands: theta (2–8 Hz) and HFA (30–128 Hz). To assess the putative effect of spectral tilt, peak height and peak frequency, we utilized the 'Fitting Oscillations & One Over F' algorithm for parameterizing power spectra across trials, separately for all remembered and forgotten words in each session[76]. We restricted our analysis to frequencies below 32 Hz because only frequencies in this range were treated as potential narrowband oscillations. Furthermore, we restricted our analysis to no more than 4 peaks that were narrower than 4 Hz and at least 1 standard deviation above the detrended baseline. When testing for significant clusters (either across time or frequency), we utilized non-parametric cluster-based permutation tests[77] to compare between remembered and forgotten encoding trials.

Spectral connectivity

To compute the normalized coherence between the amygdala and hippocampus, we generated surrogate timeseries by swapping time blocks and then z-scored the true coherence estimate relative to the coherence computed for this surrogate distribution. We computed the phase–amplitude coupling (PAC) using the modulation index method[78]. We also normalized our PAC estimates using the same approach as for coherence and tested for significant PAC using a non-parametric cluster-based permutation test.

Stimulation during verbal free recall memory task

Stimulation was applied only after a neurologist determined safe amplitudes using an iterative mapping procedure, stepping up stimulation in 0.5 mA increments and monitoring for after-discharges. The maximum amplitude selected (1.5 mA) fell well below standard safety boundaries for charge density[79]. We applied stimulation in a bipolar configuration, with current passing through a single pair of adjacent electrodes. Stimulation consisted of charge-balanced biphasic rectangular pulses (width 300 μs) applied continuously at 50 Hz frequency for 4.6 s while participants encoded two consecutive words. Then, stimulation was paused for the following 2 words, and then applied again, for each list of 12 words. Stimulation began 200 ms before word presentation and lasted until 200–450 ms after the offset of the second word in the stimulated pair. We applied stimulation during 20/25 of the lists in a session, so participants were stimulated during encoding for 120 words and not stimulated for 180 words per session.

Directly stimulating the brain while simultaneously recording iEEG signals often results in the appearance of artefactual signals while stimulation is delivered and following stimulation offset. We thus analysed the effect of stimulation by assessing neural signals before and after the stimulation. Because the post-stimulation period of the second word in a pair overlapped with the pre-stimulation period of the first word in the subsequent pair, we only analysed the effect of stimulation on power before and after the second word in each pair. To measure true physiological signals before and after stimulation, we followed previous methods in implementing an artefact detection algorithm to identify trials and channels to exclude from analysis with either complete signal saturation or gradual post-stimulation artefact[44]. We assessed the effect of stimulation on HFA using a Bayesian mixed-effects linear regression model accounting for stimulation condition, stimulation location and LFP recording location as fixed effects while treating participant as a random effect.

Depression ratings

A subset of participants performed the BDI-II, a self-assessment rating scale for symptoms of depression[80]. We utilized the conventional scoring criteria to categorize participants as depressed or not depressed, as well as for the further categorization of depression severity. While we excluded participants with BDI-II scores between 6 and 13 to match the number of participants with depression ($n = 19$) to those without depression ($n = 20$) for direct visual comparisons between binned categories (as in Fig. 4a–c), all mixed-effects models utilized continuous BDI-II scores for all patients.

Reporting summary

Further information on research design is available in the Nature Portfolio Reporting Summary linked to this article.

Data availability

The raw electrophysiological data used in this study are available at http://memory.psych.upenn.edu/RAM. Word valence and arousal ratings are available at http://saifmohammad.com/WebPages/lexicons.html[34] and http://crr.ugent.be/archives/1003[73]. The CIT168 atlas is available at https://osf.io/r2hvk/[74].

Code availability

Custom analysis and modelling code is available at https://github.com/seqasim/NHB_EmotionMemory_Models.

References

1. Kensinger, E. A. & Corkin, S. Memory enhancement for emotional words: are emotional words more vividly remembered than neutral words? *Mem. Cogn.* **31**, 1169–1180 (2003).
2. Klein-Koerkamp, Y., Baciu, M. & Hot, P. Preserved and impaired emotional memory in Alzheimer's disease. *Front. Psychol.* **3**, 331 (2012).
3. Weiskrantz, L. Behavioral changes associated with ablation of the amygdaloid complex in monkeys. *J. Comp. Physiol. Psychol.* **49**, 381–391 (1956).
4. Poulin, S. P. et al. Amygdala atrophy is prominent in early Alzheimer's disease and relates to symptom severity. *Psychiatry Res.* **194**, 7–13 (2011).
5. Tulving, E. & Markowitsch, H. J. Episodic and declarative memory: role of the hippocampus. *Hippocampus* **8**, 198–204 (1998).
6. 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).
7. Canli, T., Zhao, Z., Brewer, J., Gabrieli, J. D. & Cahill, L. Event-related activation in the human amygdala associates with later memory for individual emotional experience. *J. Neurosci.* **20**, RC99 (2000).
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. Sharot, T. & Phelps, E. A. How arousal modulates memory: disentangling the effects of attention and retention. *Cogn. Affect. Behav. Neurosci.* **4**, 294–306 (2004).
10. Dolcos, F., LaBar, K. & Cabeza, R. Interaction between the amygdala and the medial temporal lobe memory system predicts better memory for emotional events. *Neuron* **42**, 855–863 (2004).
11. McGaugh, J. L. The amygdala modulates the consolidation of memories of emotionally arousing experiences. *Annu. Rev. Neurosci.* **27**, 1–28 (2004).
12. Atucha, E. et al. Noradrenergic activation of the basolateral amygdala maintains hippocampus-dependent accuracy of remote memory. *Proc. Natl Acad. Sci. USA* **114**, 9176–9181 (2017).
13. Cahill, L. & Alkire, M. T. Epinephrine enhancement of human memory consolidation: interaction with arousal at encoding. *Neurobiol. Learn. Mem.* **79**, 194–198 (2003).
14. Hurlemann, R. et al. Noradrenergic modulation of emotion-induced forgetting and remembering. *J. Neurosci.* **25**, 6343–6349 (2005).
15. Cahill, L., Prins, B., Weber, M. & McGaugh, J. L. Beta-adrenergic activation and memory for emotional events. *Nature* **371**, 702–704 (1994).
16. van Stegeren, A. H. The role of the noradrenergic system in emotional memory. *Acta Psychol.* **127**, 532–541 (2008).
17. Hagena, H., Hansen, N. & Manahan-Vaughan, D. β-adrenergic control of hippocampal function: subserving the choreography of synaptic information storage and memory. *Cereb. Cortex* **26**, 1349–1364 (2016).
18. Bacon, T. J., Pickering, A. E. & Mellor, J. R. Noradrenaline release from locus coeruleus terminals in the hippocampus enhances excitation–spike coupling in CA1 pyramidal neurons via β-adrenoceptors. *Cereb. Cortex* **30**, 6135–6151 (2020).
19. Haggerty, D. C., Glykos, V., Adams, N. E. & Lebeau, F. E. N. Bidirectional modulation of hippocampal gamma (20–80 Hz) frequency activity in vitro via alpha(α)- and beta(β)-adrenergic receptors (AR). *Neuroscience* **253**, 142–154 (2013).
20. Cape, E. G. & Jones, B. E. Differential modulation of high-frequency gamma-electroencephalogram activity and sleep–wake state by noradrenaline and serotonin microinjections into the region of cholinergic basalis neurons. *J. Neurosci.* **18**, 2653–2666 (1998).
21. Ridout, N., Astell, A., Reid, I., Glen, T. & O'Carroll, R. Memory bias for emotional facial expressions in major depression. *Cogn. Emot.* **17**, 101–122 (2003).
22. Pringle, A., McCabe, C., Cowen, P. J. & Harmer, C. J. Antidepressant treatment and emotional processing: can we dissociate the roles of serotonin and noradrenaline? *J. Psychopharmacol.* **27**, 719–731 (2013).
23. Scangos, K. W. et al. Closed-loop neuromodulation in an individual with treatment-resistant depression. *Nat. Med.* **27**, 1696–1700 (2021).
24. Mather, M., Clewett, D., Sakaki, M. & Harley, C. W. Norepinephrine ignites local hotspots of neuronal excitation: how arousal amplifies selectivity in perception and memory. *Behav. Brain Sci.* **39**, e200 (2016).
25. Madan, C. R. Exploring word memorability: how well do different word properties explain item free-recall probability? *Psychon. Bull. Rev* **28**, 583–595 (2020).
26. Aka, A., Phan, T. D. & Kahana, M. J. Predicting recall of words and lists. *J. Exp. Psychol. Learn. Mem. Cogn* **47**, 765–784 (2020).
27. Larsen, R. S. & Waters, J. Neuromodulatory correlates of pupil dilation. *Front. Neural Circuits* **12**, 21 (2018).
28. Kucewicz, M. T. et al. Pupil size reflects successful encoding and recall of memory in humans. *Sci. Rep.* **8**, 4949 (2018).
29. Manning, J. R., Jacobs, J., Fried, I. & Kahana, M. J. Broadband shifts in local field potential power spectra are correlated with single-neuron spiking in humans. *J. Neurosci.* **29**, 13613–13620 (2009).
30. Posner, J., Russell, J. A. & Peterson, B. S. The circumplex model of affect: an integrative approach to affective neuroscience, cognitive development, and psychopathology. *Dev. Psychopathol.* **17**, 715–734 (2005).
31. LaBar, K. S. & Cabeza, R. Cognitive neuroscience of emotional memory. *Nat. Rev. Neurosci.* **7**, 54–64 (2006).
32. Schildkraut, J. J. The catecholamine hypothesis of affective disorders: a review of supporting evidence. *J. Neuropsychiatry Clin. Neurosci.* **7**, 524–533 (1965).
33. Popov, V., Marevic, I., Rummel, J. & Reder, L. M. Forgetting is a feature, not a bug: intentionally forgetting some things helps us remember others by freeing up working memory resources. *Psychol. Sci.* **30**, 1303–1317 (2019).
34. Mohammad, S. M. Obtaining reliable human ratings of valence, arousal, and dominance for 20,000 English words. In *Proc. Annual Conference of the Association for Computational Linguistics,* 174–184 (ACL, 2018).
35. Long, N. M., Burke, J. F. & Kahana, M. J. Subsequent memory effect in intracranial and scalp EEG. *NeuroImage* **84**, 488–494 (2014).
36. Kramer, J. H. et al. Hippocampal volume and retention in Alzheimer's disease. *J. Int. Neuropsychol. Soc.* **10**, 639–643 (2004).

37. Paller, K. A. & Wagner, A. D. Observing the transformation of experience into memory. *Trends Cogn. Sci.* **6**, 93–102 (2002).
38. Prince, S., Daselaar, S. & Cabeza, R. Neural correlates of relational memory: successful encoding and retrieval of semantic and perceptual associations. *J. Neurosci.* **25**, 1203–1210 (2005).
39. Lega, B., Jacobs, J. & Kahana, M. Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus* **22**, 748–761 (2012).
40. Burke, J. F. et al. Human intracranial high-frequency activity maps episodic memory formation in space and time. *NeuroImage* **85**, 834–843 (2014).
41. Fellner, M.-C. et al. Spectral fingerprints or spectral tilt? Evidence for distinct oscillatory signatures of memory formation. *PLoS Biol.* **17**, e3000403 (2019).
42. Kucewicz, M. T. et al. High frequency oscillations are associated with cognitive processing in human recognition memory. *Brain* **137**, 2231–2244 (2014).
43. Long, N. M. et al. Contextually mediated spontaneous retrieval is specific to the hippocampus. *Curr. Biol.* **27**, 1074–1079 (2017).
44. Mohan, U. R. et al. The effects of direct brain stimulation in humans depend on frequency, amplitude, and white-matter proximity. *Brain Stimul.* **13**, 1183–1195 (2020).
45. Jacobs, J. et al. Direct electrical stimulation of the human entorhinal region and hippocampus impairs memory. *Neuron* **92**, 983–990 (2016).
46. Deese, J. & Kaufman, R. A. Serial effects in recall of unorganized and sequentially organized verbal material. *J. Exp. Psychol.* **54**, 180–187 (1957).
47. Ilsley, J. E., Moffoot, A. P. & O'Carroll, R. E. An analysis of memory dysfunction in major depression. *J. Affect. Disord.* **35**, 1–9 (1995).
48. Zheng, J. et al. Amygdala–hippocampal dynamics during salient information processing. *Nat. Commun.* **8**, 14413 (2017).
49. Costa, M. et al. Aversive memory formation in humans involves an amygdala–hippocampus phase code. *Nat. Commun.* **13**, 6403 (2022).
50. Zhang, H. et al. Awake ripples enhance emotional memory encoding in the human brain. Preprint at *bioRxiv* https://doi.org/10.1101/2021.11.17.469047 (2021).
51. Inman, C. S. et al. Direct electrical stimulation of the amygdala enhances declarative memory in humans. *Proc. Natl Acad. Sci. USA* **115**, 98–103 (2018).
52. Sendi, M. S. E. et al. Identifying the neurophysiological effects of memory-enhancing amygdala stimulation using interpretable machine learning. *Brain Stimul.* **14**, 1511–1519 (2021).
53. Kensinger, E. A. & Corkin, S. Two routes to emotional memory: distinct neural processes for valence and arousal. *Proc. Natl Acad. Sci. USA* **101**, 3310–3315 (2004).
54. Leal, S. L., Tighe, S. K., Jones, C. K. & Yassa, M. A. Pattern separation of emotional information in hippocampal dentate and CA3. *Hippocampus* **24**, 1146–1155 (2014).
55. 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).
56. Abercrombie, H. C. et al. Cortisol's effects on hippocampal activation in depressed patients are related to alterations in memory formation. *J. Psychiatr. Res.* **45**, 15–23 (2011).
57. Marzo, A., Totah, N. K., Neves, R. M., Logothetis, N. K. & Eschenko, O. Unilateral electrical stimulation of rat locus coeruleus elicits bilateral response of norepinephrine neurons and sustained activation of medial prefrontal cortex. *J. Neurophysiol.* **111**, 2570–2588 (2014).
58. Hajós, M., Hoffmann, W. E., Robinson, D. D., Yu, J. H. & Hajós-Korcsok, É. Norepinephrine but not serotonin reuptake inhibitors enhance theta and gamma activity of the septo-hippocampal system. *Neuropsychopharmacology* **28**, 857–864 (2003).
59. Headley, D. B. & Weinberger, N. M. Fear conditioning enhances γ oscillations and their entrainment of neurons representing the conditioned stimulus. *J. Neurosci.* **33**, 5705–5717 (2013).
60. Ul Haq, R. et al. Adrenergic modulation of sharp wave-ripple activity in rat hippocampal slices. *Hippocampus* **22**, 516–533 (2012).
61. Buchanan, T. W., Etzel, J. A., Adolphs, R. & Tranel, D. The influence of autonomic arousal and semantic relatedness on memory for emotional words. *Int J. Psychophysiol.* **61**, 26–33 (2006).
62. Bennett, C., Liang, K. C. & McGaugh, J. L. Depletion of adrenal catecholamines alters the amnestic effect of amygdala stimulation. *Behav. Brain Res.* **15**, 83–91 (1985).
63. Manns, J. R. & Bass, D. I. The amygdala and prioritization of declarative memories. *Curr. Dir. Psychol. Sci.* **25**, 261–265 (2016).
64. Liu, Y., Cui, L., Schwarz, M. K., Dong, Y. & Schlüter, O. M. Adrenergic gate release for spike timing-dependent synaptic potentiation. *Neuron* **93**, 394–408 (2017).
65. de Voogd, L. D., Fernández, G. & Hermans, E. J. Disentangling the roles of arousal and amygdala activation in emotional declarative memory. *Soc. Cogn. Affect. Neurosci.* **11**, 1471–1480 (2016).
66. Dahl, M. J., Mather, M. & Werkle-Bergner, M. Noradrenergic modulation of rhythmic neural activity shapes selective attention. *Trends Cogn. Sci.* **26**, 38–52 (2021).
67. Vehtari, A., Gelman, A. & Gabry, J. Practical Bayesian model evaluation using leave-one-out cross-validation and WAIC. *Stat. Comput.* **27**, 1413–1432 (2016).
68. Capretto, T. et al. Bambi: a simple interface for fitting Bayesian linear models in Python. *J. Stat. Software* **103**, 1–29 (2022).
69. Gelman, A., Jakulin, A., Pittau, M. G. & Su, Y.-S. A weakly informative default prior distribution for logistic and other regression models. *Ann. Appl. Stat.* **2**, 1360–1383 (2008).
70. Morey, R. D., Hoekstra, R., Rouder, J. N., Lee, M. D. & Wagenmakers, E.-J. The fallacy of placing confidence in confidence intervals. *Psychon. Bull. Rev.* **23**, 103–123 (2016).
71. Bartsch, L. M. & Oberauer, K. The effects of elaboration on working memory and long-term memory across age. *J. Mem. Lang.* **118**, 104215 (2021).
72. Weidemann, C. T. et al. Neural activity reveals interactions between episodic and semantic memory systems during retrieval. *J. Exp. Psychol. Gen* **148**, 1–12 (2019).
73. Warriner, A. B., Kuperman, V. & Brysbaert, M. Norms of valence, arousal, and dominance for 13,915 English lemmas. *Behav. Res. Methods* **45**, 1191–1207 (2013).
74. Pauli, W. M., Nili, A. N. & Tyszka, J. M. A high-resolution probabilistic in vivo atlas of human subcortical brain nuclei. *Sci. Data* **5**, 180063 (2018).
75. Gramfort, A. et al. MEG and EEG data analysis with MNE-Python. *Front. Neurosci.* **7**, 267 (2013).
76. Donoghue, T. et al. Parameterizing neural power spectra into periodic and aperiodic components. *Nat. Neurosci.* **23**, 1655–1665 (2020).
77. Maris, E. & Oostenveld, R. Nonparametric statistical testing of EEG- and MEG-data. *J. Neurosci. Methods* **164**, 177–190 (2007).
78. Tort, A. et al. Dynamic cross-frequency couplings of local field potential oscillations in rat striatum and hippocampus during performance of a T-maze task. *Proc. Natl Acad. Sci. USA* **105**, 20517 (2008).
79. Shannon, R. V. A model of safe levels for electrical stimulation. *IEEE Trans. Biomed. Eng.* **39**, 424–426 (1992).
80. Beck, A. T., Steer, R. A., Ball, R. & Ranieri, W. Comparison of beck depression inventories -IA and -II in psychiatric outpatients. *J. Pers. Assess.* **67**, 588–597 (1996).

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Author contributions
S.E.Q. conceived the study; S.E.Q. and U.R.M. analysed the data; J.M.S. processed neuroimaging data; all authors interpreted the results, and S.E.Q. and J.J. wrote the manuscript.

Competing interests
The authors declare no competing interests.

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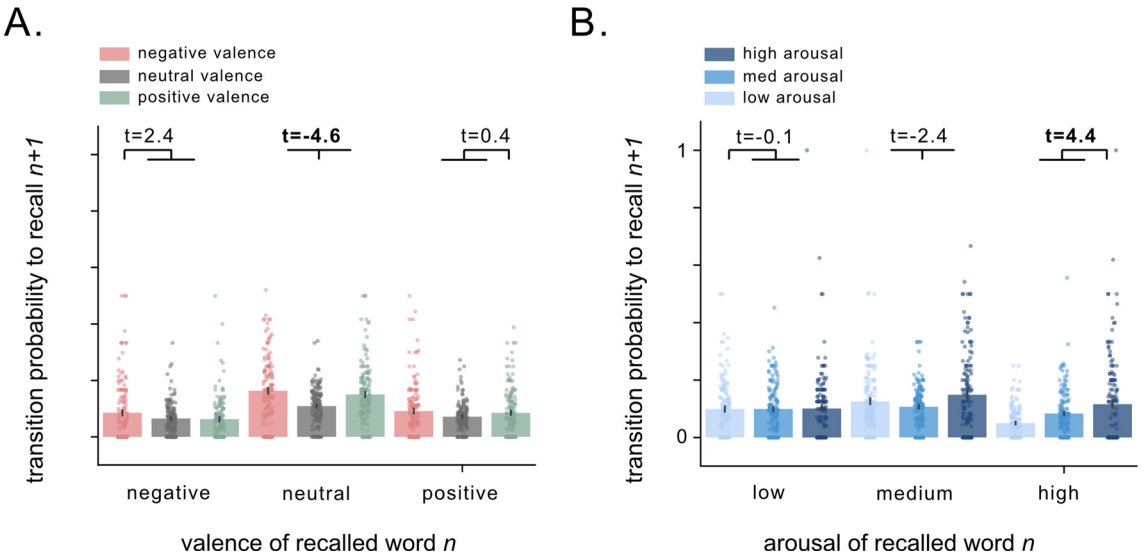

Extended Data Fig. 1 | Emotional context modulates recall dynamics. A) Conditional response probability based on valence, averaged across sessions for each participant (n=147). The height of each bar depicts the probability, averaged across participants, of making a transition to a particular valence word (denoted by the color of the bar) as a function of the just recalled word's valence (denoted by the x-axis label). Error bars denote standard deviation. T-statistics denote the relative proportion of within-valence transitions versus across-valence transitions, across participants. The largest t-statistic is bolded, denoting the relative prevalence of neutral-neutral transitions. B) Conditional response probability based on arousal, averaged across sessions for each participant (n=140). The height of each bar depicts the probability, averaged across participants, of making a transition to a particular arousal word (denoted by the color of the bar) as a function of the just recalled word's arousal (denoted by the x-axis label). Error bars denote standard deviation. T-statistics denote the relative proportion of within-arousal transitions versus across-arousal transitions, across participants. The largest t-statistic is bolded, denoting the relative prevalence of arousing-arousing transitions. Related to Fig. 1.

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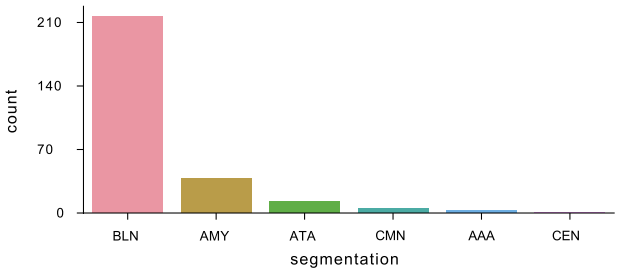

Extended Data Fig. 2 | Segmentation of electrodes to different amygdala nuclei. Count of electrodes categorized to different amygdala nuclei on the basis of post-implant imaging. BLN = basolateral nuclei, ATA = amygdala transition areas, AAA = anterior amygdala area, CMN = cortical and medial nuclei, CEN = central nucleus, AMY = could not be localized to specific subregion. Related to Fig. 2.

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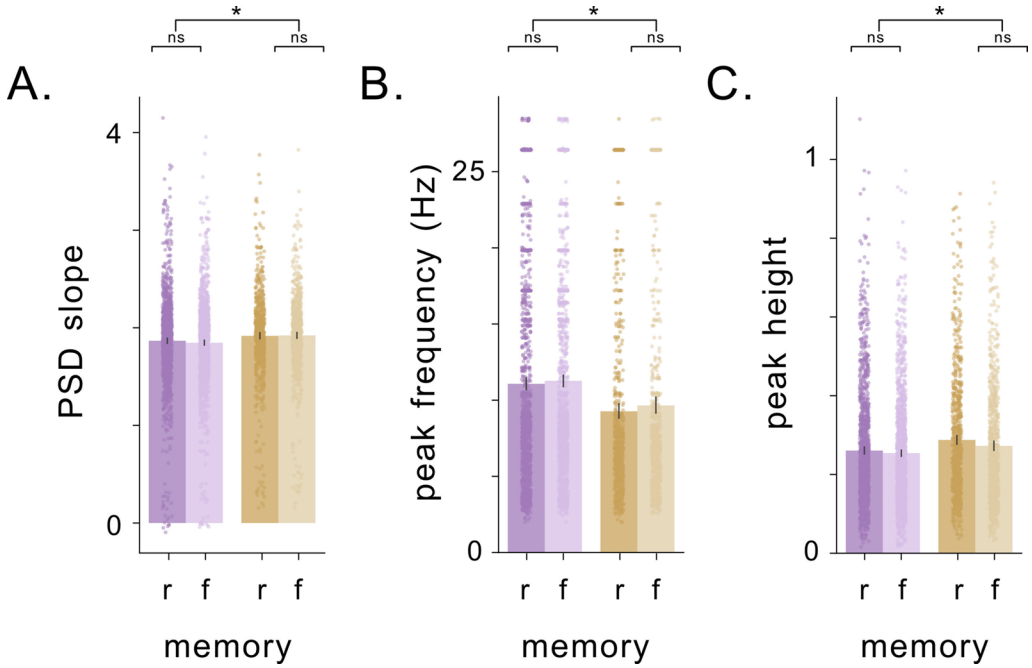

Extended Data Fig. 3 | Memory-related power changes are not due to changes in spectra characteristics. A) Power spectra slope across the entire session for both remembered (dark shade) and forgotten (light shade) trials in both hippocampus (purple) and amygdala (orange) for all participants (n=147). Asterisk denote significant difference ($t(3397) = 4.4$, $p = 1.1 \times 10^{-5}$, Cohen's $d = 0.14$, CI= [0.03, 0.09], two-sided t-test). Error bars denote standard deviation. B) Peak frequency across the entire session for both remembered and forgotten trials in both hippocampus and amygdala for all participants (n=147). Asterisk denote significant difference ($t(3262) = -7.6$, $p = 4.3 \times 10^{-14}$, Cohen's $d = -0.24$, CI= [-2.2, 1.3], two-sided t-test). Error bars denote standard deviation. C) Peak height across the entire session for both remembered and forgotten trials in both hippocampus and amygdala for all participants (n=147). Asterisk denote significant difference ($t(3030) = 4.6$, $p = 4 \times 10^{-6}$, $d = 0.15$, CI= [0.01, 0.03], two-sided t-test). Error bars denote standard deviation. Related to Fig. 2.

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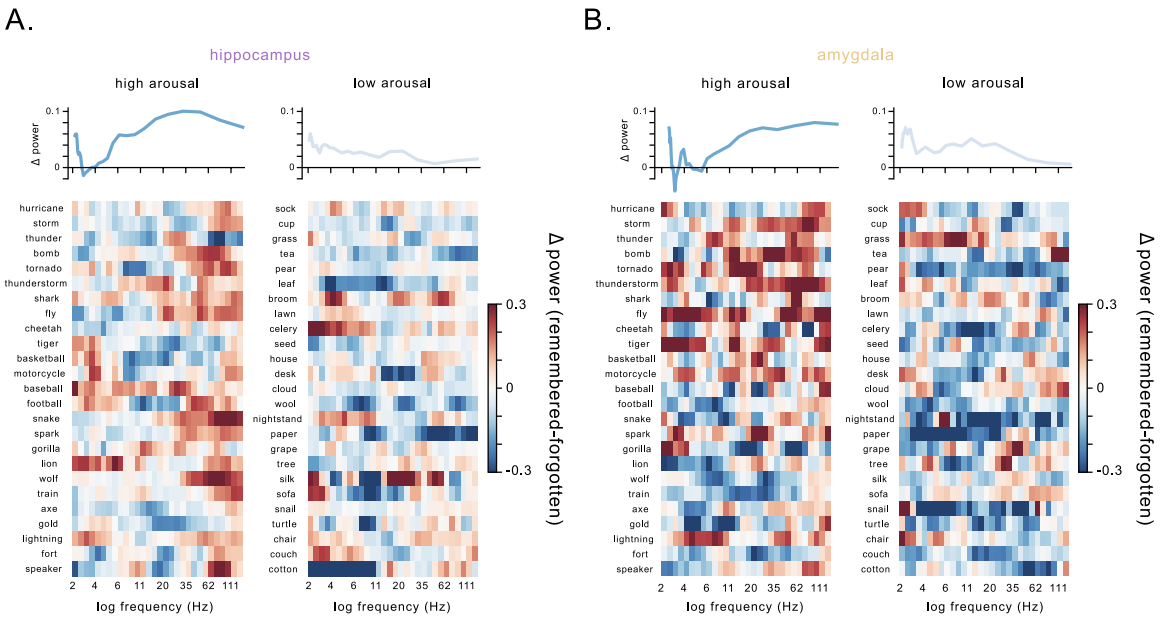

Extended Data Fig. 4 | Word-level SME for high arousal and low arousal words averaged across the population. A) Heatmaps of hippocampal power (z-scored within session) for specific words from the task wordpool, averaged across sessions and participants. Words were selected from the 30 words with the highest arousal ratings (left) or lowest arousal ratings (right). Warm colors indicate higher values while cool colors indicate lower values. Above each heatmap is the averaged z-scored power across the words in the heatmap. B) Same as panel A), but for amygdalar power. Related to Fig. 2.

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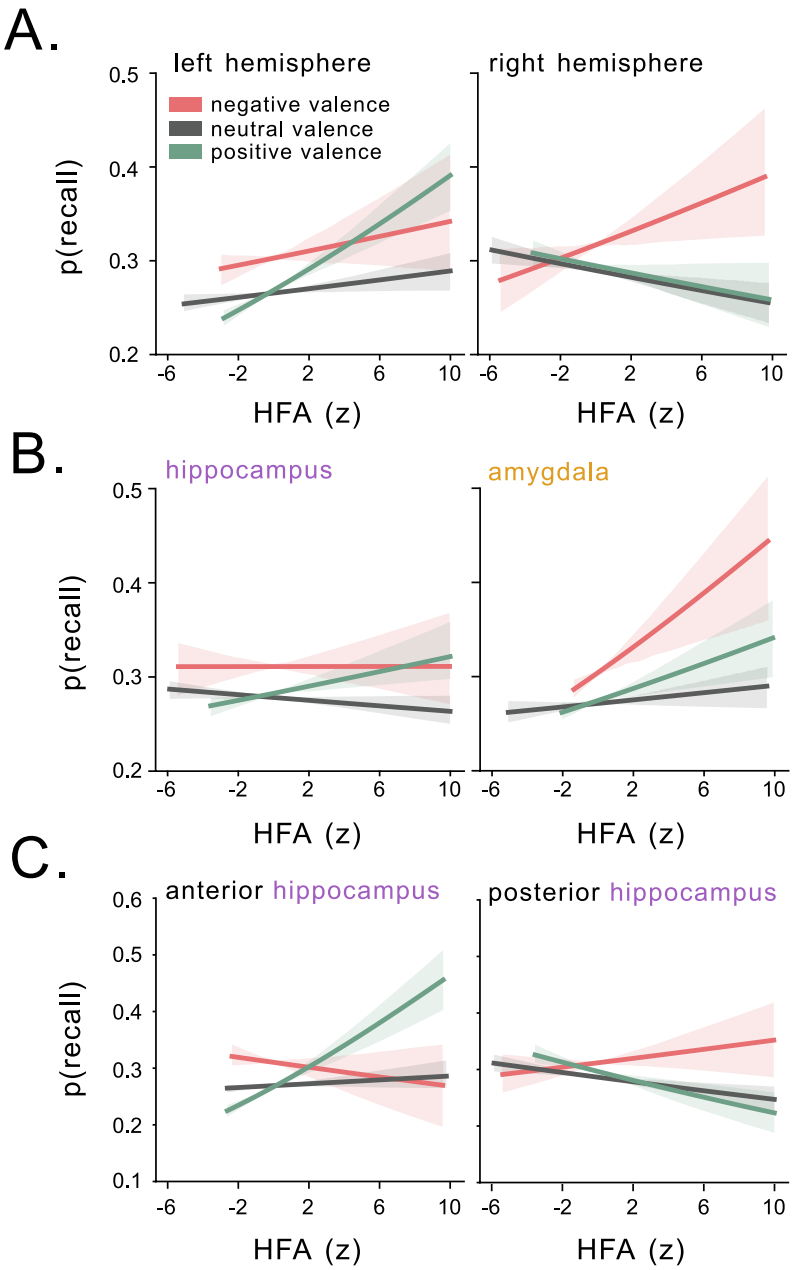
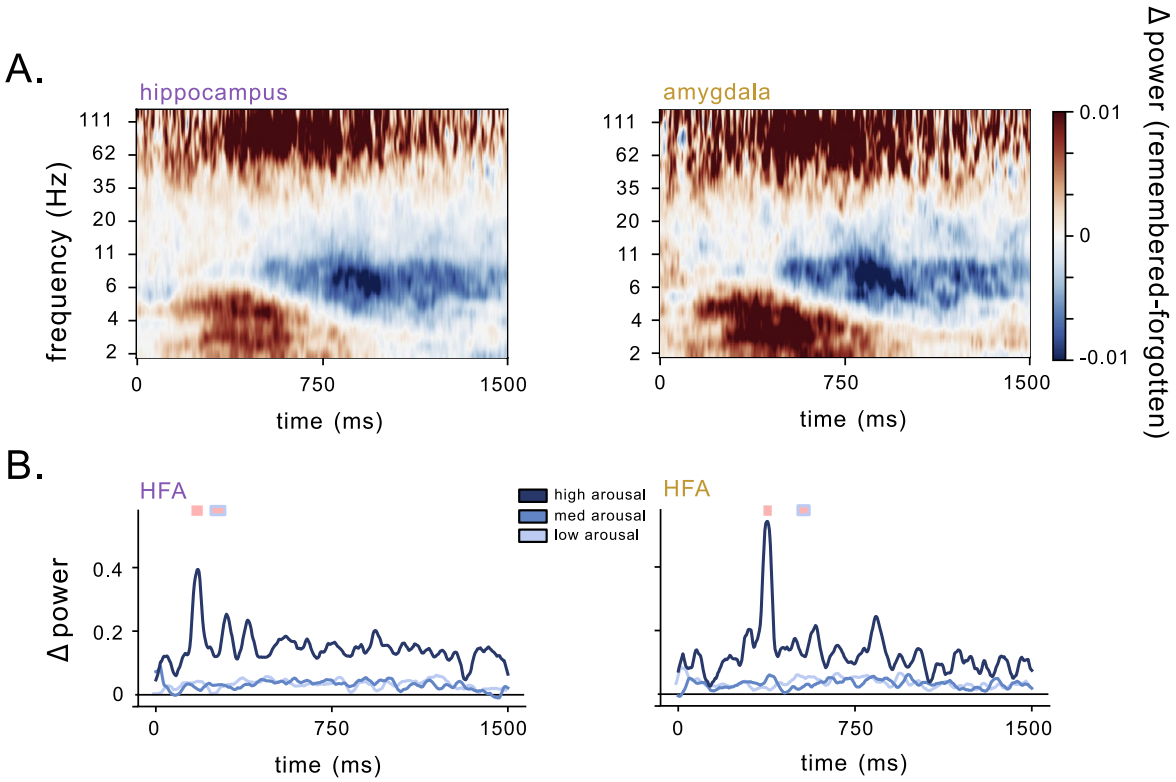


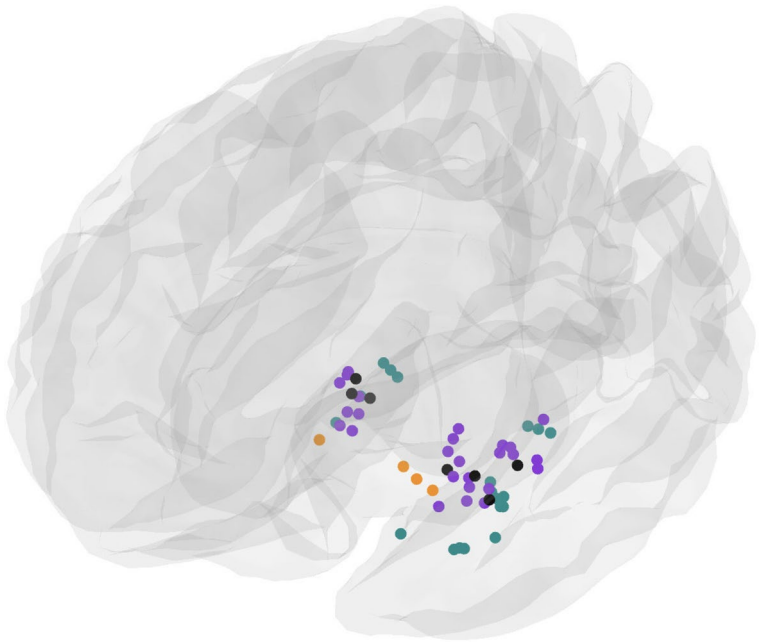
Extended Data Fig. 5 | Regional differences in the relationship between neuronal activity, memory and valence. A) Probability of recall as a function of HFA (z-scored) in the hippocampus and amygdala, binned by valence and split by hemisphere, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. B) Probability of recall as a function of HFA (z-scored), binned by valence and split by region, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. C) Probability of recall as a function of HFA (z-scored) in the hippocampus, binned by valence and split by longitudinal axis position, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. Related to Fig. 2.

https://doi.org/10.1038/s41562-022-01502-8



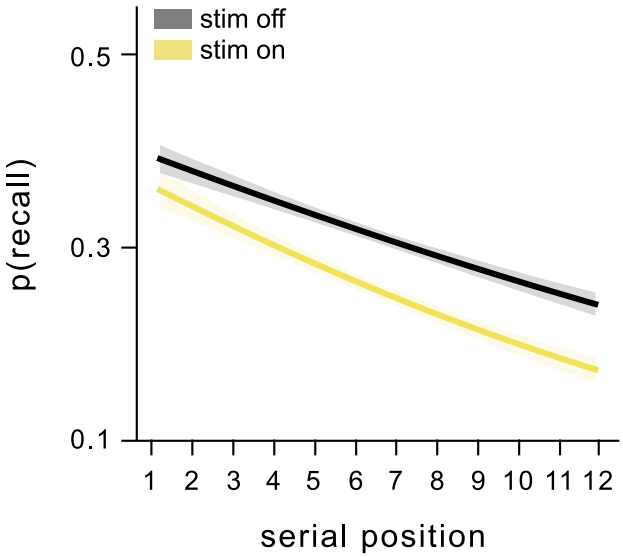
Extended Data Fig. 6 | Hippocampal and amygdalar spectrogram depicting difference in power between remembered and forgotten trials across all electrodes. A) Median z-scored spectrogram for hippocampal (left) and amygdalar (right) electrodes showing difference between remembered and forgotten words. Warm colors indicate an increase in power during encoding of remembered words, while cool colors indicate a decrease in power. B) Median HFA difference between remembered and forgotten words across all electrodes in the hippocampus (left) and amygdala (right), split by binned arousal rating. Horizontal bars indicate significant clusters of time-points when comparing remembered and forgotten high arousal words ($t(1)$'s > 2.5, p's < 0.05, Cohen's d's > 0.1, two-sided cluster-based permutation test). Related to Fig. 2.

https://doi.org/10.1038/s41562-022-01502-8



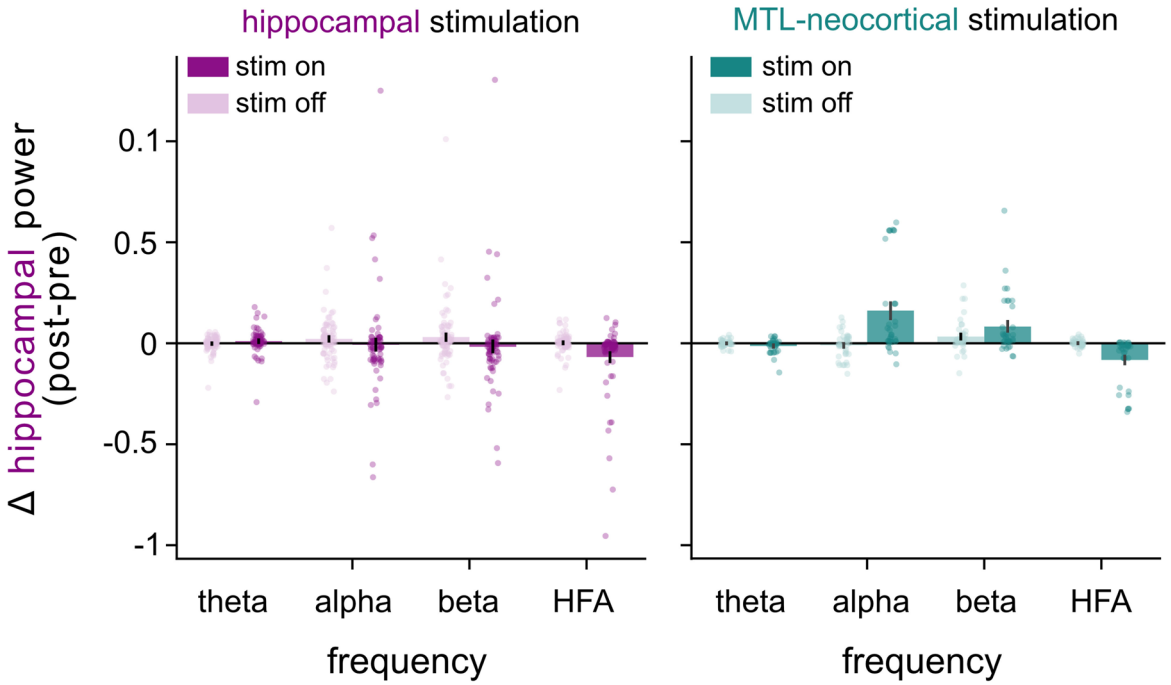
Extended Data Fig. 7 | Location of stimulation electrodes. Hippocampal electrodes (purple), amygdala electrodes (orange) and nonhippocampal MTL electrodes (teal) where direct stimulation was applied. Black electrodes were used for recording, only. Related to Fig. 3.

https://doi.org/10.1038/s41562-022-01502-8



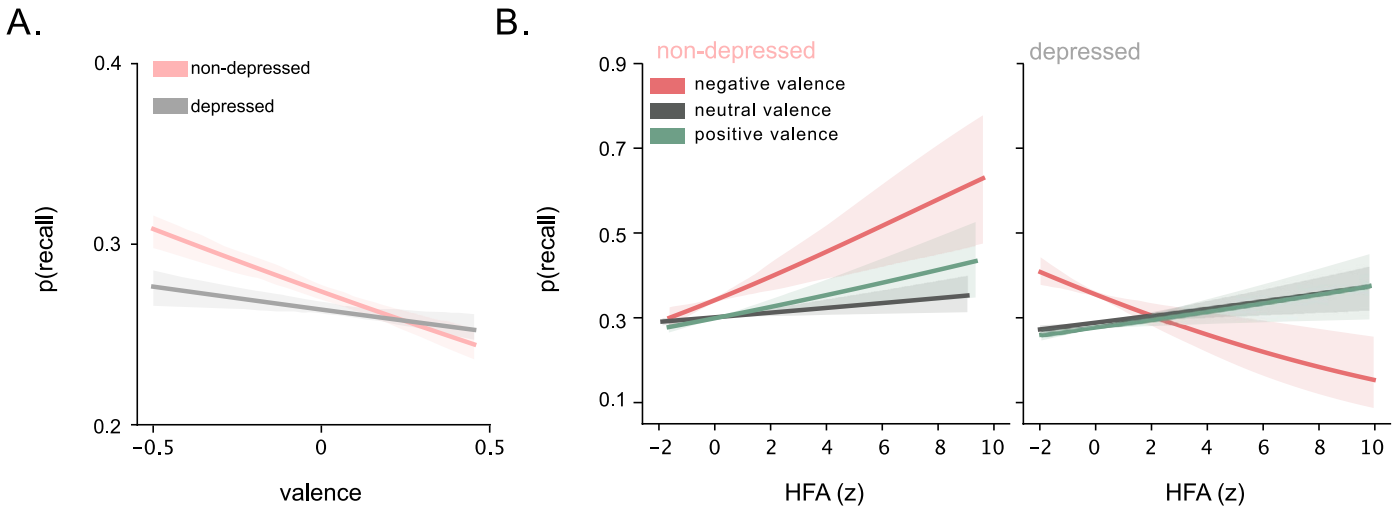
Extended Data Fig. 8 | Stimulation does not impair early-position words more than late-position words. Probability of recall as a function of serial position for both the stimulation off (black) and on (yellow) conditions, in participants who underwent hippocampal stimulation, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. Related to Fig. 3.

https://doi.org/10.1038/s41562-022-01502-8



Extended Data Fig. 9 | Hippocampal stimulation selectively decreases HFA. Change in hippocampal power (post–pre) when stimulation was applied to the hippocampus (left, averaged across n=16 electrodes) and nearby control regions (right, averaged across n=8 electrodes), compared between stimulation (dark) and no stimulation (light) conditions. Frequency bands are defined as follows: theta (2–8 Hz), alpha (8–13 Hz), beta (13–30 Hz) and HFA (30–128 Hz). Error bars denote standard deviation. Related to Fig. 3.

https://doi.org/10.1038/s41562-022-01502-8



Extended Data Fig. 10 | Depression reverses HFA-memory relationship for negative words. A) Probability of recall as a function of valence for both depressed and non-depressed participants, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. B) Probability of recall as a function of HFA (z-scored), binned by valence and depression level, fit by a logistic regression model (solid line). Shading indicates standard deviation of bootstrapped model fits. Related to Fig. 4.

nature portfolio

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Reporting Summary

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☐	☒	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☐	☒	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated

Our web collection on statistics for biologists contains articles on many of the points above.

Software and code

Policy information about availability of computer code

Data collection	No software was used for data collection.
Data analysis	Analysis was performed in Python (v. 3.9), using publicly available libraries such as mne (v. 0.23.0) and bambi (v. 0.8.0). Custom code is available at https://github.com/seqasim/NHB_EmotionMemory_Models.

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors and reviewers. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Portfolio guidelines for submitting code & software for further information.

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Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A description of any restrictions on data availability
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The raw electrophysiological data used in this study are available at http://memory.psych.upenn.edu/RAM. Word valence and arousal ratings are available at http://saifmohammad.com/WebPages/lexicons.html and http://crr.ugent.be/archives/1003. The CIT168 atlas is avilable at https://neurovault.org/images/56791/.

Human research participants

Policy information about studies involving human research participants and Sex and Gender in Research.

Reporting on sex and gender	Sex and gender were not relevant variables in our analysis; sex (as provided to clinical centers) is included in the demographic information provided in Table S1.
Population characteristics	All demographic information is detailed in Table S1 of the manuscript.
Recruitment	Data were drawn from a publicly available database, meaning active recruitment was not a part of this research. Details on subject recruitment are available in prior studies from the group that collected the data (ex. PMID: 29167419). In brief, subjects were recruited from pools of epilepsy patients between 18-65, with close to normal neuropsych evaluation, who were undergoing chronic implantation of subdural and/or intracortical electrodes with longterm EEG recording for clinical purposes.
Ethics oversight	Data was collected at Thomas Jefferson University Hospital, Mayo Clinic, Hospital of the University of Pennsylvania, Emory University Hospital, University of Texas Southwestern Medical Center, Dartmouth-Hitchcock Medical Center, Columbia University Medical Center, National Institutes of Health, and University of Washington Medical Center. Experimental protocol was approved by the IRB at each institution and informed consent was obtained from each participant. Data acquisition and storage was coordinated by the Data Coordinating Center (DCC) at the University of Pennsylvania (IRB protocol 820553).

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Field-specific reporting

Please select the one below that is the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/documents/nr-reporting-summary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	No statistical methods were used to determine sample size, as we utilized every sample in the database that featured electrodes in our regions of interest (amygdala and hippocampus). The resulting sample size is similar to prior work (ex. PMID 29167419).
Data exclusions	We removed electrodes from the neural analysis if an expert neurologist determined the electrode: had a damaged lead, was placed in white matter, a seizure onset zone, or lesioned brain tissue, or exhibited significant electrical or mechanical noise.
Replication	Findings are replicable across multiple subjects, and multiple sessions within some subjects, as subjects performed 2.4 ± 1.2 sessions of the task. While we did not perform replication of these results, data are publicly available enabling independent researchers to replicate these findings.
Randomization	Subjects were allocated into groups based on the availability of stimulation of psychometric data.
Blinding	Data collection and analysis were not performed blind to the conditions of the experiment. Blinding was not relevant to our study, and study authors did not perform data collection as data was pulled from a publicly available database.

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

n/a	Involved in the study
☒	☐ Antibodies
☒	☐ Eukaryotic cell lines
☒	☐ Palaeontology and archaeology
☒	☐ Animals and other organisms
☒	☐ Clinical data
☒	☐ Dual use research of concern

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☐	☒ MRI-based neuroimaging

Magnetic resonance imaging

Experimental design

Design type	MRI were acquired purely for clinical purposes to indicate electrode placement, and were not a part of the experiment.
Design specifications	MRI were acquired purely for clinical purposes to indicate electrode placement, and were not a part of the experiment.
Behavioral performance measures	MRI were acquired purely for clinical purposes to indicate electrode placement, and were not a part of the experiment.

Acquisition

Imaging type(s)	Structural MRI and CT
Field strength	3T MRI - before electrode implantation, 1.5 T MRI - after implantation
Sequence & imaging parameters	Sequence & imaging parameters: Imaging parameters varied somewhat among institutions in this multisite study. In general, sequences required for macroelectrode and microwire localization included 3D Tl-weighted with 1 mm or less isotropic resolution, coronal fast spin echo T2-weighted with 0.4 x 0.4 mm in-plane resolution and 2 mm slice thickness, and CT with less than 1 mm slice thickness. Representative examples are as follows: Pre-implant 3D Tl-weighted MPRAGE (TR 1900 ms, TE 2.52 ms, flip angle 9, 1 mm isotropic resolution, 216 x 256 x 174 matrix), pre-implant coronal FSE T2-weighted (TR 7200 ms, 76 ms, ETL 15, flip angle 139, 0.4 x 0.4 x 2 mm, 448 x 448 x 30), post-implant CT (0.5 x 0.5 x 0.625 mm, 512 x 512 x 384).
Area of acquisition	Tl - whole brain, T2 - temporal lobes spanning and oriented perpendicular to the hippocampal long axis

Diffusion MRI ☐ Used ☒ Not used

Preprocessing

Preprocessing software	Segmentations of amygdalar subfields were generated from 3D Tl-weighted and coronal T2-weighted images using ITK-SNAP software.
Normalization	Pre-implant MRI, post-implant CT, and when available post-implant MRI scans were all aligned to each other using rigid registration based on mutual information with Advanced Normalization Tools (ANTS) software.
Normalization template	Amygdala nuclei were delineated and parcel lated using the CIT168 human brain template.
Noise and artifact removal	No noise or artifact removal was used.
Volume censoring	No volume censoring was used.

Statistical modeling & inference

Model type and settings	No statistical modeling was used as MRI were acquired for clinical purposes to indicate electrode placement.
Effect(s) tested	No effects tested as MRI were acquired for clinical purposes to indicate electrode placement.

Specify type of analysis: ☐ Whole brain ☒ ROI-based ☐ Both

Anatomical location(s)	Amygdala nuclei were delineated and parcel lated using the CIT168 human brain template. This was conducted using a high-precision nonlinear volumetric coregistration of preoperative structural Tl and T2 imaging onto the template brain.
Statistic type for inference (See Eklund et al. 2016)	No inference was done as MRI were acquired for clinical purposes to indicate electrode placement.
Correction	No correction was used as MRI were acquired for clinical purposes to indicate electrode placement.

Models & analysis

n/a	Involved in the study
☒	☐ Functional and/or effective connectivity
☒	☐ Graph analysis
☒	☐ Multivariate modeling or predictive analysis