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Supplementary information

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Direct interactions between the human insula and hippocampus during memory encoding

In the format provided by the authors and unedited

SUPPLEMENTARY INFORMATION

Supplementary Methods

Analysis of Behavioral Data: Comparisons of behavior results were all conducted on subject level. To compare the behavior results (e.g., valence rating, memory performance) between pairs of conditions, Anderson-Darling tests were first deployed to examine the normality of samples and followed by paired-sample t-tests to examine the significance.

Comparisons of reaction time (RT) were performed after moving outliers. To identify outliers in RT, we applied the interquartile range (IQR) method on each participant's data separately. The IQR, representing the middle 50% of values, is calculated as the difference between the third quartile value (Q3) and the first quartile value (Q1). Outliers were defined as values falling below Q1 - 1.5 * IQR or above Q3 + 1.5 * IQR. Trials with an RT of less than 200 ms were also excluded from analysis.

To examine the potential primacy or recency effects (i.e., enhanced memory for words appearing early or late in a given encoding round), we divided the words into 10 groups based on their occurrence order in the encoding phase. Then, a Pearson's correlation analysis was performed to examine correlation between the recall rate of different groups at subject level and presented order of words. A linear mixed-effect model (LMM) with subject as a random effect was further deployed to measure the effect of presented position of words on memory performance (i.e. recall rate).

$$RecallRate \sim Position + (1|Subject)$$

Analysis of the Spectral Knee and Oscillation Power: The spectral knee and oscillation power were also measured using the FOOOF toolbox [1] during both the encoding phase (500ms to 2000ms relative to the stimulus onset) and the baseline (-500ms to -200ms prior to the stimulus onset) at the trial level. We first averaged the power spectrum of both INS_{DE} and INS_{IE} sites during the baseline and encoding phase for each trial and then obtained the knee frequency and power of oscillations for each time period. Paired-sample t-tests were then conducted to compare the changes of these parameters during the encoding phase from the baseline at the electrode level.

Analysis of Subtractive Approach: Considering the huge bias of sample numbers between high and low categories, we only included trials from the high categories to remove the intensity effect in the following analyses, as these high intensity ratings might also reflect the high confidence of their valence rating results.

To obtain the subtractive maps of memory effect and valence effect (*Supplementary Figure*

3a), we measured changes in the exponent of the aperiodic activity at the single trial basis and compared the measures of the exponent across two conditions of interest in two dimensions of memory and valence (originally rated), followed by a permutation test for p-value adjustment (5000 permutations) for each single insular site. In this analysis we used balanced number of trials across the two conditions of interest. Specifically, in each permutation, we randomly selected the maximum number of trials to balance the number between conditions (recalled vs. non-recalled, positive vs. negative). Then, a two-sample t-test was performed to obtain the real t-value. Subsequently, we randomly shuffled the labels of two conditions and obtained the pseudo t-value. After 5000 permutations, we averaged the real t-value across permutations and got the final real t-value and built a null distribution based on 5000 pseudo t-values. The site was considered significant if the final real t-value exceeded 95% of the null distribution.

To address the combination of memory and valence effects, a LMM was performed with one factor as main effect and the other as a covariate (*Supplementary Figure 3b*) on each single insular site. In this analysis, as we had to consider both memory and valence effects, we included all trials regardless the unequal number of samples between conditions.

$$Exponent \sim beta_0 + beta_1 * memory + beta_2 * valence$$

Exponent Analysis of the Hippocampal iEEG Signals: To compare changes of the exponent between recalled and non-recalled conditions in hippocampus during the encoding phase, a paired-sample t-test was performed on the electrode-level exponent at each time point with -500ms to 2500ms time periods relative to the stimulus onset; all p-values were adjusted using cluster-based permutation tests with randomly shuffled labels of conditions. More specifically, a cluster was defined as a group of contiguous significant time points. The total t-value within a cluster represented the real t-value of that cluster. Then, a cluster-based correction was adopted to define whether the real t-value was significant. The data were randomly shuffled 5000 times, and, for each shuffle, the total t-value of the largest significant cluster was entered into the distribution of the null hypothesis. The real data cluster was considered significant if the real cluster t-value exceeded 95% of the null distribution.

Supplementary Results

Behavior Results:

Valence Judgment Ratings

Word stimuli in this experiment have been used and validated in several previous investigations of memory encoding[2,3]. For each study list, words were balanced according to their original valence ratings, with 50% positive (5 words) and 50% negative (5 words) presented in random order. After viewing each word for 2000ms, participants were asked to rate how negatively or positively they evaluated the word, using a scale of -3 to +3. Words that were rated as -3, -2, or -1 were categorized as *negative valence*; similarly, words that were rated as +3, +2, or +1 were rated as *positive valence* (participants rated some words as "0" even though all words, selected from a previous dataset, were originally rated as either negative or positive). Further, we labeled words that were rated as +3, -3, +2, or -2 as *high intensity* and words that were rated as +1, -1, or 0 as *low intensity*.

Participants rated 48.63±5.64% (range: 40.00-61.11%) of the words they saw as positive and 42.41±8.30% (range: 27.78–60.00%) of the words they saw as negative, and they rated 8.95±6.91% (range: 0-24.67%) of the words they saw as "0". Across participants, there was no significant difference in the percentage of words rated as positive vs. negative ($t(15)=2.0088$, $p=0.0629$). Comparing participants' valence ratings with the original valence ratings of the words revealed that participants judged as positive 89.11±10.19% (range: 60.00%-98.89%) of words originally rated as 'positive,' and as negative 79.78±17.58% (range: 55.56%-100.00%) of the words originally rated as 'negative' ($t(15)=2.5356$, $p=0.0228$). Finally, participants rated 80.16±9.84% (range: 62.50-96.67%) of the words they saw as high intensity.

Memory Performance

Participants successfully recalled 31.80±12.38% of the words they encoded (range of 10.00–50.67%, *Supplementary Table S3*). We analyzed memory performance using paired-sample t-tests on subject level. We found that recall rates did not significantly differ between words that were originally rated as positive (32.18±14.91%, range: 11.11–53.33%) vs. negative (31.45±11.55%, range: 8.89–48.00%; $t(15)=0.2933$, $p=0.7733$), or between words that participants rated as positive (33.57±15.17%, range: 12.73–58.33%) vs. negative (30.57±11.99%, range: 4.00–53.33%; $t(15)=1.1503$, $p=0.2680$). Recall rates were also similar for high vs. low intensity words [high (32.44±13.31%, range: 9.59–56.36%); low (30.85±18.21%, range: 0–

66.67%), (t(15)=0.3708, p=0.7160)]. Thus, recall performance did not differ as a function of either stimulus valence or intensity.

To examine potential primacy or recency effects (i.e., better memory for words appearing early or late in a given encoding round, respectively), we calculated the serial position function (i.e., recall rate as a function of the word's position in the series of 10 items). LMM analysis with subject as a random effect yielded a significant effect of presented position of words on memory performance (df = 135, F=3.229, p=0.0013). Participants demonstrated better recall for words that were presented later in the list (i.e., a recency effect; *Supplementary Figure S1*, Pearson's ρ=0.227, p=0.004). Similarly, we examined the primacy effect and recency effect by comparing the performance of position 1 or position 10 with the middle positions (5 and 6). Paired sample t-tests revealed a significant recency effect (t(15)=3.0109, Bonferroni corrected p=0.0176), but not a primacy effect (t(15)=0.8605, Bonferroni corrected p=0.8062).

Reaction Times

As noted, participants viewed each word for a fixed window of 2000ms; thus, the encoding time window was equal for all words. However, the valence judgement phase was self-paced. We tested whether reaction times (RTs) during the judgment trials differed as a function of valence, intensity, and/or subsequent memory. Applying an interquartile range (IQR) analysis for each participant, we removed trials with extreme RT values (e.g., <200 ms, 8.94±8.71%, range: 2.05-34.00%). Mean RT on the remaining trials was 2.42±1.22s (range of mean: 0.53-5.15s). RTs did not differ between words rated originally (t(15)=-1.5742, p=0.1363) or by the participants (t(15)=-1.5419, p=0.1439) as positive vs. negative, or between subsequently recalled vs. non-recalled words (t(15)=-0.3319, p=0.7445); however, RTs were longer for low- than for high-intensity words (low: 3.13±1.74 s; high: 2.26±1.12 s; t(15)=-4.2930, p=0.0006).

Analysis of Subtractive Approach: We statistically compared exponent changes across pairs of conditions in two domains of interest: memory (subsequently recalled vs non-recalled) and valence (words originally rated as positive vs negative). Considering the marked difference in the trial counts between participant-rated high and low intensity words, we only included trials from the high-intensity category to remove the intensity effect in the following analyses. We found significant changes of activity only in a minority of recording sites per domain – i.e., when a pair of conditions of interest were compared independently (Details in *Supplementary Figure 3a*).

We appreciate that the activity of a given insular site during encoding of words could be affected by a *combination* of conditions rather than by a single condition alone. This could be

problematic if within condition A (e.g., recalled words) the shift in the exponent changes in the opposite direction across trials with different values of condition B (e.g., positive or negative valence). As such, contrasting recalled vs non-recalled trials on their own may not provide the best approach to identify insular sites that are implicated in memory encoding. Therefore, we conducted a linear mixed-effect model (LMM) to measure the memory effect and valence effect with the other as a covariate. We found that sites that showed a significant memory effect did not meaningfully change by adding valence as a covariate; however, the number of sites showing a significant valence effect decreased from 20 to 9 when memory was included as a covariate (*Supplementary Figure 3b*).

Nonetheless, these analyses could be problematic because measuring the exponent of aperiodic activity - at the trial-by-trial level - may not reflect the actual profile of change occurring at a given recording site. For instance, the exponent change may be too subtle to be detected at the single-trial level, even when the directions of these subtle changes are consistent enough to be detected at the level of analysis averaging all trials together.

Analysis of Low Frequency Oscillations: We examined the true oscillatory changes captured by the FOOOF algorithm in the LFA range which spanned the conventional boundaries of delta and theta bands (center frequency = 3.40 ± 0.91 Hz, bandwidth = 5.56 ± 1.67 Hz). For the INS_{DE} sites, low-frequency oscillations were detected in only 16.55% ± 14.16% of trials during the encoding phase, compared to 19.35% ± 7.80% of trials during the baseline period. There was no significant difference in the percentage of trials with low-frequency oscillations between the encoding and baseline periods (paired-sample t-test, $t(24) = -1.3437$, $p = 0.1916$). Additionally, the oscillation power during the encoding phase (0.1057 ± 0.1013 unit) did not significantly differ from the baseline period (0.0759 ± 0.0409 unit) (paired-sample t-test, $t(24) = 1.2257$, $p = 0.2322$). Similarly, for the INS_{IE} sites, low-frequency oscillations were detected in only 12.50% ± 11.45% of trials during the encoding phase, compared to 18.76% ± 6.36% of trials during the baseline period. While fewer trials with oscillations were detected during the encoding phase compared to the baseline (paired-sample t-test, $t(25) = -3.2372$, $p = 0.0034$), the average power was comparable between the two periods (encoding phase: 0.0664 ± 0.0752 unit; baseline: 0.0849 ± 0.0233 unit; paired-sample t-test, $t(25) = -1.2601$, $p = 0.2193$).

We also examined the true oscillatory changes focusing only on recalled trials. For the INS_{DE} sites, LF oscillations were detected in 21 of the 25 sites during both encoding and baseline. Within those sites, LF oscillations were detected in 17.13% ± 15.48% of trials during the encoding phase, compared to 20.41% ± 11.03% of trials during the baseline period. There was no significant difference in the percentage of trials with LF oscillations between the encoding and baseline periods (paired-sample t-

test, t(24) = -1.2944, p = 0.2079). Additionally, the oscillation power during the encoding phase (0.1226 ± 0.1488 unit) did not significantly differ from the baseline period (0.0931 ± 0.0727 unit) (paired-sample t-test, t(20) = 1.1549, p = 0.2617). Similarly, for the INS_{IE} sites, LF oscillations were detected in 19 of the 26 sites during both the encoding and baseline. Within those sites, LF oscillations were detected in only 11.73% ± 13.57% of trials during the encoding phase, compared to 21.12% ± 10.00% of trials during the baseline period. While fewer trials with oscillations were detected during the encoding phase compared to the baseline (paired-sample t-test, t(25) = -3.6114, p = 0.0013), the average power was comparable between the two periods (encoding phase: 0.0938 ± 0.0967 unit; baseline: 0.0944 ± 0.0421 unit; paired-sample t-test, t(18) = -0.2048, p = 0.8400).

***Analysis of the Aperiodic Offset and Spectral Knee*:** We performed a retrospective analysis of the offset (y-intercept) and spectral knee based on the selectively identified insular sites (i.e., INS_{DE} and INS_{IE}). We first calculated the offset time series, which was subsequently segmented into epochs using windows of -500 ms to 2500 ms relative to stimulus onset. Our analysis revealed that the offsets were highly correlated with the exponents. For trial-level analysis on each electrode, we computed the average Pearson's correlation coefficient between the offset and exponent time series across all trials. To assess statistical significance, we conducted a 1000-permutation test by randomly shuffling the time series between trials and calculating 1000 pseudo-average correlation coefficients. The p-value was determined as the percentage of pseudo-average coefficients greater than the true correlation coefficient. The results demonstrated that all 217 insular sites exhibited a significant correlation between offset and exponent time series ($p < 0.05$), with an average Pearson's correlation coefficient of 0.9524 ± 0.0186. Furthermore, at the electrode level, changes in the offset during the encoding phase (compared to the baseline) were also strongly correlated with changes in the exponent (Supplementary Figure S4, n = 217, Pearson's $\rho = 0.971$, $p < 0.0001$).

We also analyzed the knee frequency during both the encoding phase and the baseline period for each experimental trial. For INS_{DE} sites, the knee frequency was significantly lower during the encoding phase (4.67 ± 2.31 Hz, range: 1.41–12.42 Hz) compared to the baseline period (5.38 ± 2.48 Hz, range: 2.73–12.72 Hz) (electrode-level paired-sample t-test, t(24) = -4.6606, $p < 0.0001$). Similarly, for INS_{IE} sites, the knee frequency was significantly lower during the encoding phase (4.20 ± 1.49 Hz, range: 1.86–7.42 Hz) compared to the baseline (5.80 ± 1.58 Hz, range: 3.68–8.87 Hz) (electrode-level paired-sample t-test, t(25) = -10.3899, $p < 0.0001$).

Analysis of Exponent with Different Length of Sliding Window Used for Aperiodic Calculation: To explore whether the sliding window used for the aperiodic calculation affects the exponent sequences during memory task, we recalculated the exponent sequences of selective insular sites

(INS_{IE} and INS_{DE}) using sliding windows of different lengths (100 ms, 200 ms, and 1000 ms). The results, shown in Supplementary Figure S6, indicate that longer sliding windows yield smoother exponent sequence curves, while shorter windows produce more fluctuations. However, regardless of the window length chosen, the overall trend remains unchanged; the differences are primarily in the degree of smoothing.

***Analysis on the Exponent of Insula Based on List/Session/Subject Level Baseline Correction*:** We re-analyzed our comparison between the post-stimulus exponent and the list/session/subject-level baseline to identify selective insular sites, and also conducted a linear mixed model (LMM) analysis to assess memory and valence effects after subtracting the list/session/subject-level baseline.

1) Using list-level-averaged baseline correction, we identified 33 INS_{IE} sites and 28 INS_{DE} sites (Supplementary Figure S5a-upper panels). Among 51 insular sites selected by the original method, 47 of them (92.16%) were still selective. We then conducted an LMM on these 51 sites based on the recorrected baseline exponents (Supplementary Figure S5b&c-upper panels). The result revealed a significant interaction between recording site type and task conditions (LMM, df = 147.000, F=10.2945, p=0.0016). Specifically, there was a significant interaction between recording site type and subsequent memory (df = 147.000, F=5.7804, p=0.0175). Changes of the aperiodic exponent in the INS_{DE} sites were greater (i.e., more decreased) for subsequently recalled than non-recalled words (df = 89.275, F=5.0019, p=0.0278); by contrast, the exponent changes in the INS_{IE} sites did not differ between subsequently recalled and non-recalled words (df = 95.011, F=1.2536, p=0.2657). Additionally, although there was not an interaction between recording site type and valence (df = 147.000, F=2.1235, p=0.1472), the exponent changes in the INS_{IE} sites were significantly different between positive and negative words (df = 95.011, F=4.4802, p=0.0369), whereas there was no significant difference in the exponent changes in INS_{DE} sites as a function of valence (df = 88.275, F=0.0031, p=0.9555).

2) Using session-level-averaged baseline correction, we identified 35 INS_{IE} sites and 31 INS_{DE} sites (Supplementary Figure S5a -middle panels). Among 51 insular sites selected by the original method, 47 of them (92.16%) were still selective. We then conducted an LMM on these 51 sites based on the recorrected baseline exponents (Supplementary Figure S5b&c-middle panels). The result revealed a significant interaction between recording site type and task conditions (LMM, df = 147.000, F=7.2338, p=0.0080). Specifically, there was a significant interaction between recording site type and subsequent memory (df = 147.000, F=8.1465, p=0.0049). Changes of the aperiodic exponent in the INS_{DE} sites were greater (i.e., more decreased) for subsequently recalled than non-recalled words (df = 89.232, F=6.3237, p=0.0137); by contrast, the exponent changes in the INS_{IE} sites did not differ between subsequently recalled and non-recalled words (df = 94.990, F=2.2205, p=0.1395). Additionally, although there was not an interaction between recording site type and valence (df =

147.000, F=3.8694, p=0.0511), the exponent changes in the INS_{IE} sites were significantly different between positive and negative words (df = 94.990, F=5.3443, p=0.0230), whereas there was no significant difference in the exponent changes in INS_{DE} sites as a function of valence (df = 88.232, F=0.3432, p=0.5595).

3) Using subject-level-averaged baseline correction, we identified 34 insular LF sites and 30 insular HF sites (Supplementary Figure S5a&b-below panels). Among 51 insular sites selected by the original method, 47 of them (92.16%) were still selective. We then conducted an LMM on these 51 sites based on the recorrected baseline exponents (Supplementary Figure S5b&c-below panels). The result revealed a significant interaction between recording site type and task conditions (LMM, df = 147.000, F=7.2242, p=0.0080). Specifically, there was a significant interaction between recording site type and subsequent memory (df = 147.000, F=8.1465, p=0.0049). Changes of the aperiodic exponent in the INS_{DE} sites were greater (i.e., more decreased) for subsequently recalled than non-recalled words (df = 89.232, F=6.3366, p=0.0136); by contrast, the exponent changes in the INS_{IE} sites did not differ between subsequently recalled and non-recalled words (df = 94.990, F=2.2166, p=0.1398). Additionally, although there was not an interaction between recording site type and valence (df = 147.000, F=3.8710, p=0.0510), the exponent changes in the INS_{IE} sites were significantly different between positive and negative words (df = 94.990, F=5.3419, p=0.0230), whereas there was no significant difference in the exponent changes in INS_{DE} sites as a function of valence (df = 88.232, F=0.3442, p=0.5589).

Analysis on the "Task Silent" Insular Sites: We examined the power changes of 166 "task-silent" insular sites with no significant changes in the exponent (i.e., neither INS_{DE} nor INS_{IE} sites) during the encoding phase relative to the baseline. LMM analyses of band power yielded no significant differences in the changes of theta band power (df = 165, F = 0.3477, p = 0.5562), gamma band power (df = 165, F = 6.6051, Bonferroni-corrected p = 0.0663), or HFA power (df = 165, F = 3.1864, Bonferroni-corrected p = 0.4565). We also conducted the LMM on the electrode-level exponent of these "task silent" insular sites (see Methods, same as the previous analysis on INS_{DE} or INS_{IE} sites) to investigate the main effects and interaction between subsequent memory (recalled vs. non-recalled) and valence rating (positive vs. negative). The exponent changes did not significantly differ between subsequently recalled and non-recalled words (df = 495, F = 1.8546, p = 0.1739), nor between positive and negative words (df = 495, F = 2.6049, p = 0.1072).

Analysis of Memory and Valence Effects Using All Insular Sites: We conducted an LMM on the exponent data from all 217 insular sites to investigate the main effects and interactions between subsequent memory (recalled vs. non-recalled) and valence rating (positive vs. negative). As expected, pooling data from all sites did not reveal significant differences in exponent changes between subsequently recalled and non-recalled trials (df = 648, F = 2.4726, p = 0.1163) or between positive and negative words (df = 648, F = 3.7313, p = 0.0538). This further underscores the importance of respecting the heterogeneity of functional responses at the mesoscale level, and pooling data from all recording sites indiscriminately may not be appropriate.

Analysis at Subject Level: We analyzed the memory effect in the hippocampus at subject level by averaging the indexes from all hippocampal sites for each subject, respectively. In the pre-onset period, theta power did not differ subsequently recalled compared to non-recalled words (t(15) = 0.9514, p = 0.3565) – possibly due to insufficient power / small sample size. By contrast, in the peri-offset period, HFA power (t(15) = 2.1766, p = 0.0459) and gamma band power (t(15) = 2.1708, p = 0.0464) were significantly greater for subsequently recalled compared to non-recalled words. Time histograms of hippocampal ripples revealed a higher ripple rate for words that were subsequently recalled than words subsequently not recalled in the peri-offset time window (1910 ms to 2095 ms relative to stimulus onset, n= 16, p =0.0090; cluster-based permutation test).

We also analyzed the power of CCEP at subject level. Specifically, the N1 power of INS_{DE} →HPC was significantly higher than the opposite direction (pair-sample t-test, t(5) = 3.5817, p = 0.0158), while the N1 power of INS_{IE} →HPC did not differ from the opposite direction (paired-sample t-test, t(3) = 0.5218, p = 0.6379).

Analysis of the Insular-Hippocampal Coactivation at Trial Level: We also conducted the exponent sequence for each insular site time-locked to ipsilateral hippocampal ripple events at the trial level. The results validated the coactivation between hippocampal and INS_{DE} sites (Cluster-based permutation test: n = 4399, -305ms to 450ms time-locked to peak of ripples, p = 0.0040; LMM: df = 4315, F = 14.729, p = 0.0001), but not for the INS_{IE} sites (LMM, df = 5524.7, F = 0.301, p = 0.5836).

Analysis of Exponent of the Hippocampus: We examined changes of the exponent in all available hippocampal sites during the viewing and encoding of the words (from -500ms to 2500ms window locked to the stimulus onset). We compared the exponent between recalled and non-recalled conditions at each time point for a given site. During this period, we found a

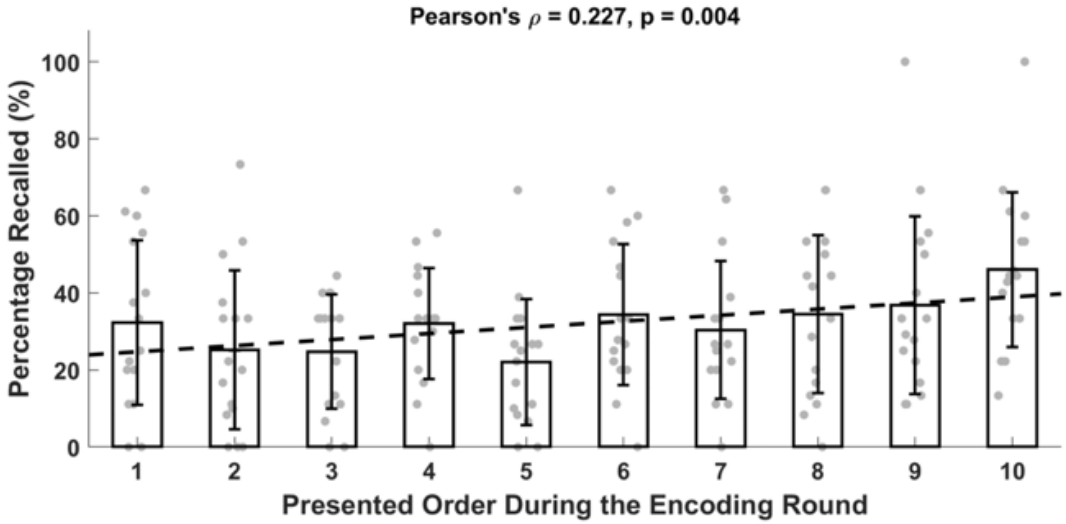
significantly lower exponent around the time of word offset for recalled compared to non-recalled words (1955ms to 2255ms relative to the stimulus onset, n = 131, p = 0.0260, cluster-based permutation test). Notably, this is the same time window where we observed both electrode level and subject level significant changes in the ripple rate for recalled words.

Analysis of the Hippocampal Ripples Using a Complementary Ripple Detection Routines: We also conducted the ripple detection pipeline based on another ripple detection method[4,5], which applies a bandpass filter restricted to the range of 80 to 120 Hz. The findings obtained were consistent with those reported in the initial submission.

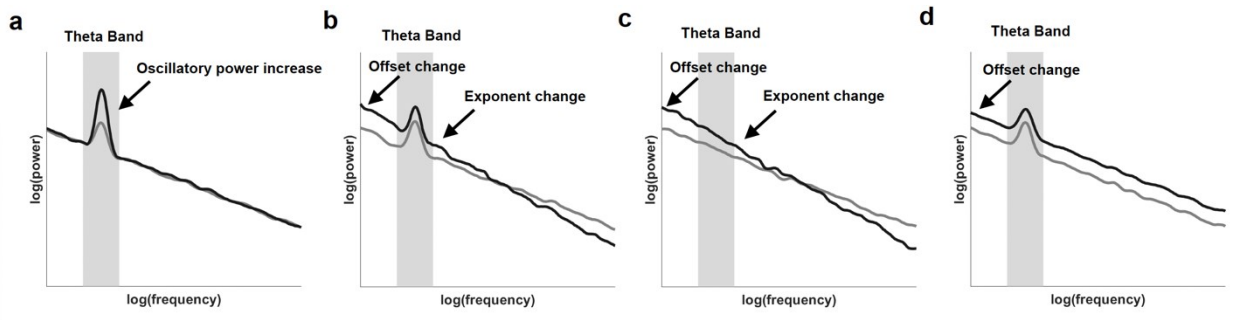
Time histograms revealed that the ripple rate was significantly higher for words that were subsequently recalled compared to non-recalled words in the peri-offset time window (1870 ms to 2500 ms relative to stimulus onset) (Supplementary Figure S6a, n = 131, p < 0.001, cluster-based permutation test). When focusing on the 1-second window surrounding the stimulus offset (1500 ms to 2500 ms), the ripple rates were significantly higher for recalled trials compared to non-recalled trials (LMM, df = 245.77, F = 7.6702, p = 0.0060).

Additionally, we found that the aperiodic exponent changes in the INS_{DE} sites were time-locked to the peak ripple activity in the hippocampus of the same hemisphere for both trial-averaged analysis (-345ms to 680ms time-locked to peak of ripple activity, cluster-based permutation test: p<0.001, n = 149) and trial-level analysis (-345ms to 90ms time-locked to peak of ripple activity, cluster-based permutation test: p=0.0080, n(recalled) = 2488, n(non-recalled) = 3956). We also conducted LMM on the INS_{DE} exponent in a 100-ms time window preceding the peak hippocampal ripples and found consistent results (Trial-averaged: LMM, df = 286.69, F = 18.898, p <0.0001; Trial-level: LMM, df = 6203.0, F = 10.931, p = 0.0010).

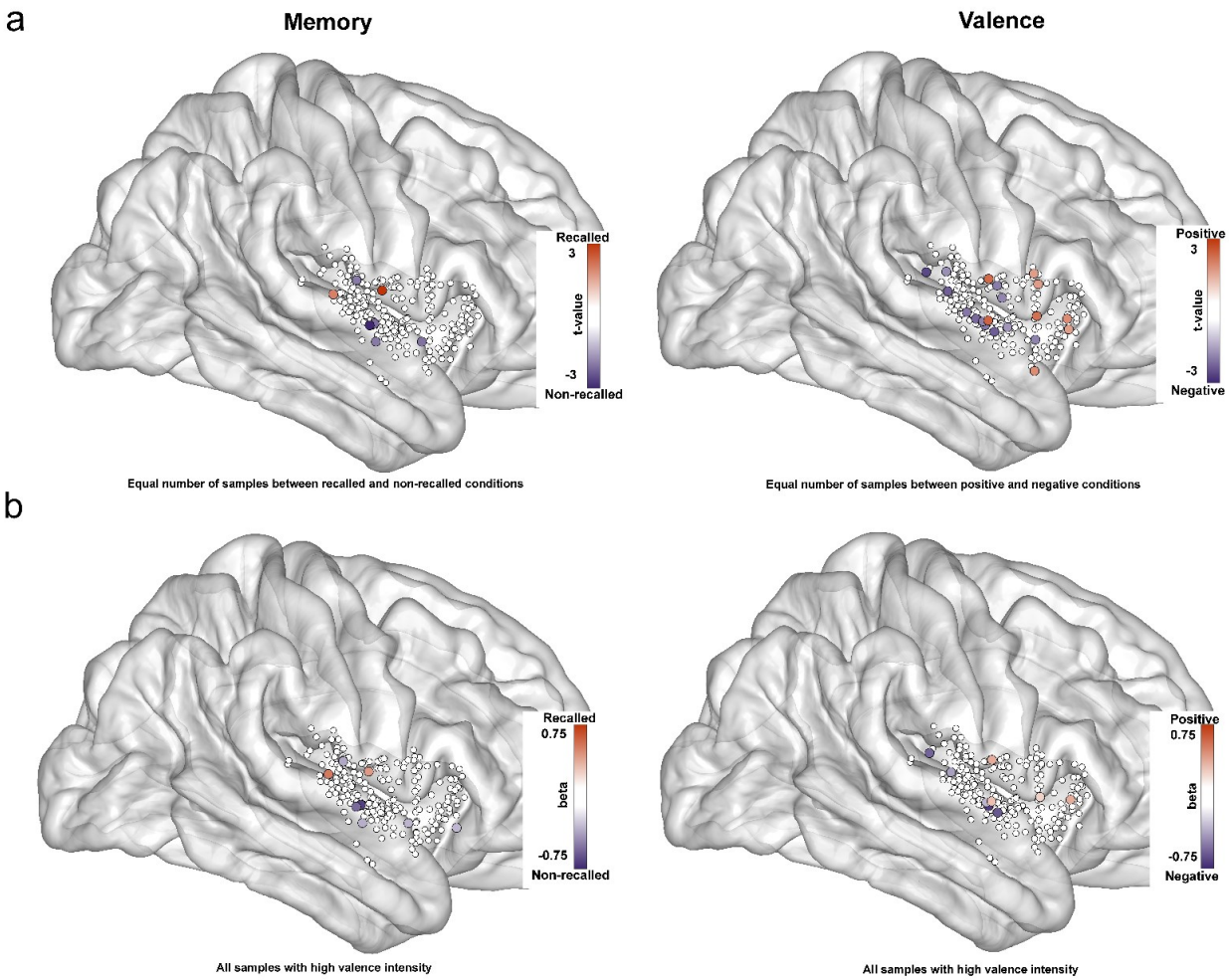
Supplementary Figures



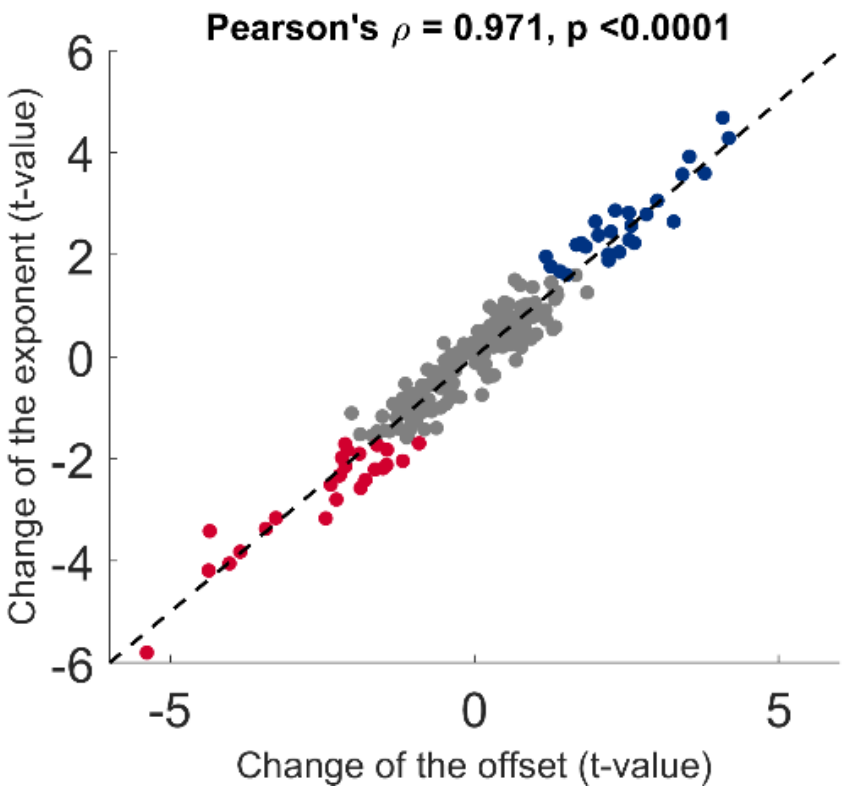
Supplementary Figure S1. Recall as a Function of Serial Position. The bar plots show the mean percentage of recalled words (n=16 subjects) as a function of presented order (i.e., serial position). Dots denote mean for individual participants, and the whiskers are proportional to ± 1 SD.



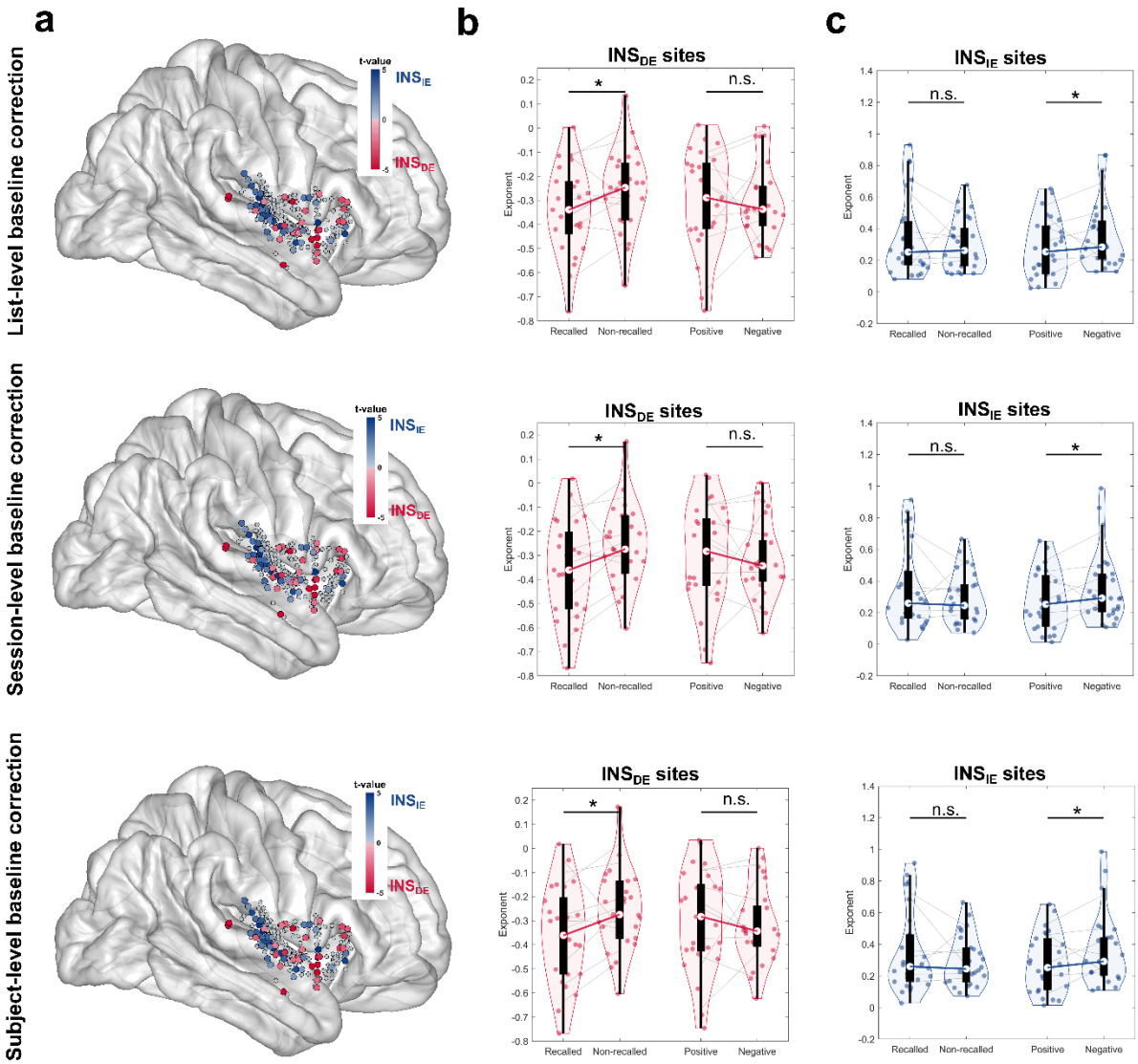
Supplementary Figure S2. Illustration of Aperiodic Exponent. The aperiodic property of neural signals is characterized by a 1/f-like *exponential* decline in the power spectrum where higher power at the lowest frequencies falls off as frequency increases. A true oscillatory activity often is manifested as a significant bump on the power-law slope. The exponential decay of 1/f-like power distribution, when plotted in a log-log space, can be shown as a line with a specific *slope*, which is an index for the degree of exponent of 1/f like power law distribution. When the exponent decreases, the spectrum slope shifts in a direction where the high-frequency power increases and the low-frequency power decreases. By contrast, as shown here, when the exponent increases, the spectrum slope shifts in a direction where the low-frequency power increases and high-frequency power decreases. We emphasize that this is an over-simplification, and the plots presented here are not from real iEEG signals. With real iEEG signals, the exponent is more affected by changes in the lower (than higher) frequencies. For instance, a greater increase in low frequency power can tilt the exponent curve upward with or without decreases (or even with a small but statistically significant increase) in the high frequency activity. The most important point here is that power changes in a given arbitrary band of iEEG signal *cannot* be directly attributed to changes in the physiological activities corresponding to that narrowband alone, or to an oscillatory activity in that range per se. For instance, power increase in the theta band range (grayed area) can be due to mechanistically different physiological processes including (a) true oscillatory activity in this narrow band range, (b) exponent change plus theta oscillations, (c) a change in the slope of the exponent without a band-limited change of power or narrowband oscillations, or (d) simply a change in offset (Y-intercept). We emphasize that the analysis of aperiodic activity in our approach was necessary given that we had no a priori hypotheses regarding the presence or absence of true oscillations - or changes of power - within specific bands of iEEG signal within the insula, nor did we have specific predictions about the interactions between the insula and the hippocampus falling within a specific band.



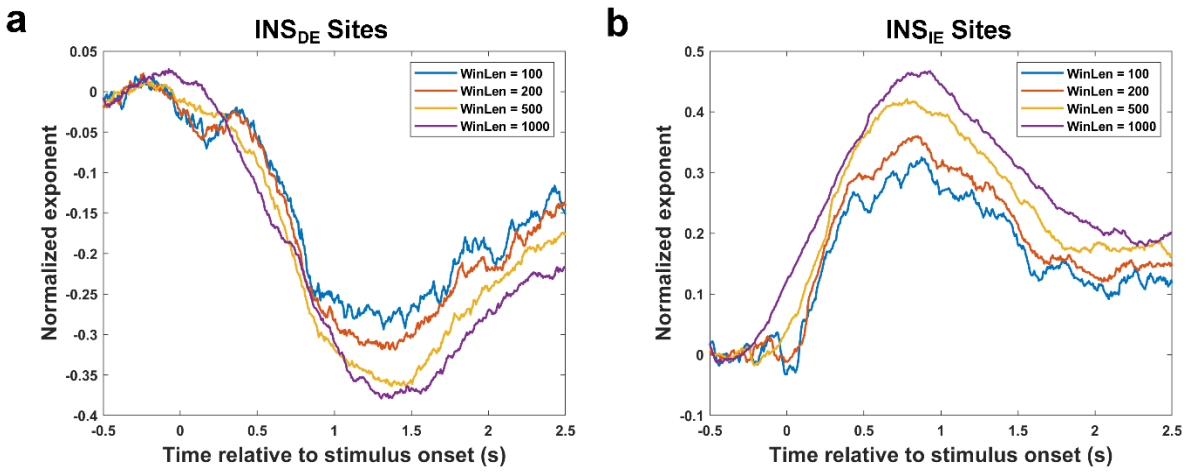
Supplementary Figure S3. Subtractive Analysis of the Exponent of Aperiodic Activity. (a) In each recording site, we measured changes in the exponent of the aperiodic activity at the single trial basis and compared the measures of the exponent across two conditions of interest per domain (memory and originally rated valence). In this analysis we used balanced number of trials across the two conditions of interest. As noted, an equal number of originally-rated positive and negative words were selected. However, the proportion of trials that were recalled vs. non-recalled was remarkably unbalanced in each participant. Thus, we subsampled the number of recalled trials to match the number of non-recalled trials. We are mindful that reducing the total number of trials entering the analysis reduced the statistical power of this analysis (note the fewer number of significant sites in the memory contrast). **(b)** LMM analysis at single-trial level for memory or valence effect with the other factor as covariate. Gray and colored circles represent recording sites without and with statistically significant changes in either direction. Sites from both hemispheres, and across all participants, are plotted on the right insula while keeping the right brain transparent.



Supplementary Figure S4. Correlation between the Aperiodic Exponent and Offset. The change of the offset strongly positively correlates with the change of the exponent at the electrode level (n= 217). In the figure, each dot represents a unique electrode, with red dots indicating INS_{DE} sites and blue dots indicating INS_{IE} sites.



Supplementary Figure S5. Exponent Analyses on the Insula Based on List/Session/Subject Level Baseline Correction. The results based on list-level, session-level and subject-level baseline, are displayed on the upper panels, middle panels and below panels, respectively. **(a)** Recording sites from both hemispheres, and across all participants, are plotted on the right insula. The red sites are the location of insular neuronal populations whose aperiodic activity changed during the encoding phase and correlated significantly with the participants' subsequent memory (INS_{DE} sites). The activity of blue sites did not correlate with the subsequent memory but varied significantly between words with positive vs. negative valence conditions (INS_{IE}). **(b and c)** Significant interactions between site type (INS_{DE} vs. INS_{IE}), subsequent memory (recalled vs. non-recalled trials) and valence (positive vs. negative trials) in exponent during the encoding phase. In the violin plots, lower and upper edges of the boxplots show the 25th and 75th percentiles of the data. The white dot within the black boxes shows the median of the data and the whiskers indicate the range within 1.5x interquartile range below 25th percentile or above 75th percentiles. The dots within the violin plot denote unique recording sites, grey lines show individual subject averages, and colored lines connect the median value across recording sites. (* $p<0.05$, LMM, see the supplementary information for full statistics).



Supplementary Figure S6. Exponents sequence with different length of sliding window used for aperiodic calculation. The exponent sequence of **(a)** INS_{DE} sites (n=25) **(b)** INS_{IE} sites (n=26) time locked to stimulus onset during the encoding phase. Colorful lines represent the mean exponent sequences of selective insular sites calculated by sliding windows of different lengths (100 ms, 200 ms, 500ms, and 1000 ms). Longer sliding windows yield smoother exponent sequence curves, while shorter windows produce more fluctuations. However, regardless of the window length chosen, the overall trend remains unchanged.

Supplementary Tables

Table S1: Demographics

#	ID	Sex	Age	Race	Handedness	IQ	Total number of recording sites	Seizure onset zone
1	S172	M	47	A	R	NA	172	Bilateral Medial Temporal Cortex
2	S175	M	29	W	R	110	156	Left frontal
3	S176	F	35	W	R	99	156	Left Medial Temporal Cortex
4	S177	M	19	W	R	NA	168	Right Medial Temporal Cortex
5	S178	M	28	W	R	118	252	Bilateral Medial Temporal Cortex
6	S183	M	33	W	R	114	174	Right Medial Temporal Cortex
7	S185	F	36	W	R	100	142	Left Medial Temporal Cortex
8	S190	F	50	W	R	NA	116	Right Primary Sensory Cortex
9	S191	F	25	H	R	85	110	Right Medial Temporal Cortex
10	S199	M	36	W	R	103	178	Right Lateral Temporal Cortex
11	S201	M	27	H	R	NA	188	Bilateral Medial Temporal Cortex
12	S202	F	48	A	R	110	194	Left Medial Temporal Cortex
13	S205	F	48	W	R	102	184	Right Medial Temporal Cortex
14	S207	F	67	W	R	113	112	Left Medial Temporal Cortex
15	S211	F	32	ME	R	119	198	Right Lateral Temporal Cortex
16	S212	M	35	H	R	92	218	Undetermined

A: Asian; H: Hispanic; ME: Mixed Ethnicity; W: White.

Table S2. Participants' sEEG electrode coverages

Participant #	Number of recording sites in the insula			Number of recording sites in the hippocampus		
	All	Left	Right	All	Left	Right
1	14	12	2	11	9	2
2	9	9	0	9	4	5
3	12	12	0	4	4	0
4	5	2	3	18	12	6
5	7	3	4	9	5	4
6	24	2	22	8	3	5
7	20	19	1	9	5	4
8	3	0	3	4	0	4
9	18	0	18	11	6	5
10	22	4	18	4	2	2
11	23	12	11	7	4	3
12	2	2	0	7	7	0
13	18	2	16	8	2	6
14	5	5	0	5	5	0
15	27	2	25	7	4	3
16	8	3	5	10	4	6
SUM	217	89	128	131	76	55

Table S3. Individual Recall Rates

Participant	Percent Recalled	Number of trials		Percent Recalled for Each Condition			
		Recalled	Non-recalled	Positive	Negative	High	Low
1	40.00%	60	90	41.67%	38.10%	38.30%	66.67%
2	20.00%	36	144	19.05%	15.79%	17.33%	33.33%
3	31.11%	28	62	30.56%	32.69%	28.17%	42.11%
4	22.50%	27	93	22.64%	27.08%	28.00%	13.33%
5	43.84%	64	82	52.78%	32.20%	43.64%	44.44%
6	34.17%	82	158	32.52%	35.14%	33.77%	41.67%
7	10.00%	9	81	12.73%	4.00%	9.59%	11.76%
8	41.67%	75	105	46.15%	30.99%	42.75%	38.10%
9	43.33%	13	17	58.33%	33.33%	50.00%	30.00%
10	16.67%	15	75	15.22%	22.22%	17.28%	11.11%
11	15.33%	23	127	18.31%	13.73%	17.54%	8.33%
12	40.00%	12	18	42.86%	40.00%	41.38%	0.00%
13	44.44%	40	50	44.90%	42.50%	41.89%	56.25%
14	23.76%	24	77	18.75%	33.33%	22.78%	27.27%
15	50.67%	76	74	54.05%	53.33%	56.36%	35.00%
16	31.33%	47	103	26.56%	34.69%	30.28%	34.15%
mean	**31.80%**	**39.44**	**84.75**	**33.57%**	**30.57%**	**32.44%**	**30.85%**
SD	**12.38%**	**24.87**	**38.78**	**15.17%**	**11.99%**	**13.31%**	**18.21%**

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