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Multiple memory systems for efficient temporal order memory

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Abstract

We report distinct contributions of multiple memory systems to the retrieval of the temporal order of events. The neural dynamics related to the retrieval of movie scenes revealed that recalling the temporal order of close events elevates hippocampal theta power, like that observed for recalling close spatial relationships. In contrast, recalling far events increases beta power in the orbitofrontal cortex, reflecting recall based on the overall movie structure.

Remembering the order of event occurrence is fundamental to episodic memory. Converging evidence suggests that at least two copies of events are encoded in parallel in distinct brain regions during memory formation¹⁻³. One system retains events with high fidelity and is hippocampal-dependent. The other system encodes schematic information and engages the prefrontal cortex. At recall, memories are reconstructed when we combine our understanding of the unfolding of events in time with episodic information⁴. Episodic memory, especially recalling the temporal order of events, requires the hippocampal network, evident from the behavior of patients with hippocampal lesions who have impairments in recalling past events in the same order as they were encountered^{5,6}. Functional MRI and lesion studies suggest that in addition to the hippocampus (HPC), the orbitofrontal cortex (OFC) is also involved in successful temporal order recall^{7,8}. However, the neural mechanisms by which the HPC and the OFC support temporal order memory are unclear.

Temporal memory, shaped by the relatedness of the sequence of events, can be studied as the absolute time relative to salient event boundaries⁹ or as the recency of events relative to each other^{10,11}. At encoding, both the OFC and HPC track the temporal relatedness of events¹², and the left HPC is known to represent the temporal approximation of events¹³. Temporal order recall is easier for events with distinct contexts occurring far apart

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in time¹⁰. This suggests that the temporal context of far events enables temporal order judgment without the need to recall the episodic details of an event's recency. Recalling memories with high precision engages the HPC¹⁴, however, tracking the temporal order of long sequences of events with high fidelity would require substantial HPC resources. Accordingly, we hypothesized that memory systems utilize OFC for recalling the temporal order of far events, while HPC retrieves the episodic details necessary for recalling the temporal order of close events.

We investigated the neural dynamics within the HPC and the medial OFC in the left hemisphere that support recognition of the temporal order of events from long-term memory. Epileptic patients undergoing seizure monitoring (n=8, 3 female, Table 1) watched a novel animated movie and, after brief delay including a 2-min rest period, determined the order of movie frames that were presented in pairs (Figure 1a and 1b). Subjects performed equally well in recalling close and far events (paired t-test $t(7) = 1.7$, $p = 0.86$). However, response times were longer for close events compared to far events (paired t-test $t(7) = 2.64$, $p = 0.03$; Figure 1c), indicating that temporal order judgement was more demanding for the close events.

We compared the power spectral density (PSD) for correct temporal judgement of close and far events during the 2 seconds after the probe onset (i.e., prior to the cue for response selection). At a group-level analysis, we compared the coefficients of the contrast between close and far correct temporal judgments against zero (for no differences) in a mixed effect model due to unequal number of regional contacts across the patients. The results showed that theta power was higher for recalling the order of close events than for far events in the HPC (n = 7; 4-8 Hz, peaking at 6.5 Hz, $p < 0.001$). This effect was also observed in two additional peaks in a narrow band at 32-42 Hz and a broader high frequency band of 100-170 Hz ($p < 0.001$). By contrast, beta power in the left OFC was higher for recalling the order of far compared to close events (n = 6; 20-25 Hz, peaking at 22.5 Hz, $p = 0.012$, with no differences observed in frequencies above 30Hz; Figure 2).

Although we observed significant group differences across conditions and contacts, within-contact contrasts differences were not statistically significant. A power calculation based on these data recommends at least 50 trials for detecting within-contact differences with 0.9 power, which was more than was feasible in the time available with each participant. An advantage of the adopted group-level experimental design is that, despite a low number of trials, the experimental effects can be evaluated across participants. A limitation of the study is that we are not able to evaluate single trial and single contact responses. The overall results suggest enhanced theta/alpha-band, low gamma-band, and high frequency power in the HPC is associated with successful retrieval of episodic information in temporal order recall, whereas enhanced beta-band power in the OFC supports the temporal order recall of far events.

The hippocampus (HPC) is connected to the medial OFC both directly and indirectly through the entorhinal cortex and para-hippocampus gyrus¹⁵. The entorhinal cortex - specifically the lateral entorhinal cortex along with the neighboring perirhinal cortex - has been implicated in the precision of recalling the time of an event relative to the task

onset (a salient event boundary)¹⁶ and these cortical regions have direct connections to both HPC and the OFC¹⁵. Far events are more likely to have an intervening salient event boundary during encoding, raising the possibility that the order of far events can be inferred relative to the event boundaries and the gist of the movie structure without the need for hippocampal input. However, HPC is essential for temporal order memory of close events that are not anchored to the boundaries of a sequence¹⁷. In the spatial domain, the absence of fine-resolution para-hippocampal representation disturbs the resolution of hippocampal spatial representation for places that are away from the salient boundaries¹⁸. Similarly, we hypothesize that, in parallel to the spatial neural mechanism, input from the entorhinal cortex to HPC may support recalling the temporal order of close events in fine detail. The present study did not include eye-tracking data but, given the known relationship between saccadic eye-movements and hippocampal activity^{19,20}, an interesting area of future study would be to examine hippocampal theta-band oscillations and eye movements during the recall of close vs far events.

The OFC represents the gist structure of the flow of events that strengthens with consolidation²¹, such as learning a reward value that follows an event²². In contrast, HPC activity corresponds to the detailed order of events that closely follow each other^{23,24}. We propose that at retrieval, HPC provides a signal of the temporal order of close events following the top-down signal from the OFC, congruent with reports from rodents²⁵. Given the known role of hippocampal-cortical interaction in support of memory consolidation, an interesting area for future study would be to examine changes in these temporal memory signals with longer retrieval delays, such as after a night of sleep. Converging evidence suggests that the existence of multiple traces of memory benefits long-term memory consolidation¹⁻³. Here, we show that, in a short time after encoding, multiple memory traces in HPC and OFC support efficient temporal order memory, enabling recall of far events with the support of the OFC and close events with hippocampal activity.

Methods and methods:

The study protocol was approved by the Office for the Protection of Human Subjects of the University of California, Berkeley, the University of California, Irvine, and Stanford University. All patients provided written informed consent before participating and all methods were performed in accordance with the relevant guidelines and regulations. The movie and the data that support the findings of this study are openly available in OSF.IO at DOI [10.17605/OSF.IO/932A5](https://doi.org/10.17605/OSF.IO/932A5).

Participants

Eight participants (3 female, 5 right-handed, mean age = 38.8, sd = 14.3, range = 20-58) were implanted stereotactically with depth electrodes to localize the seizure onset zone for subsequent surgical resection (Table 1). All participants had normal or corrected normal vision. No seizures occurred during task administration. The signal for the epochs with interictal epileptiform activity was discarded. Only 3 of the participants had coverage for simultaneous recording from the general OFC and the HPC areas, which is too limited for conclusive across regions connectivity analysis.

Experimental design

Participants were instructed to carefully watch a short mute animation (around 3 minutes long) knowing that we would ask questions about the movie (Jafarpour et al, 2019 JoCN; available in OSF.IO at DOI [10.17605/OSF.IO/932A5](https://doi.org/10.17605/OSF.IO/932A5)). Then, after a brief delay of 3-5 minutes with distractions, the participants were instructed to perform a temporal order recognition test. This test required the participants to determine the order of two movie frames that were shown side by side. Each test trial started with a fixation point for two seconds, then two scenes of the movie were shown side by side for 3 sec. Right after, a probe appeared on top of the two frames, asking which frame occurred *earlier* or *later* (Figure 1). The probe was selected pseudo-randomly so that in half of the trials the earlier scene asked for the earlier scene. The test consisted of 35 trials that were split into an approximately equal number of trials with far and close probes (table 2). Participants used left or right arrow keys and had 4 sec available to respond. The experiment was designed to separate the process of retrieving the temporal order of events from picking an answer. The tested movie scenes were between 1.6 to 60 seconds apart allowing us to study the differences between temporal order recognition of events that were close in time and those that were far apart. The accuracy of temporal order recognition for three people who did not watch the movie and guessed the order showed that an accurate performance required watching the movie. The close probes were less than 11 seconds apart (table 2). An independent group of (n= 80) people determined the event boundaries in the movie, meaning when a new event started. The number of determined events in between the movie frames reflects the distinctness of the movie frames¹². In this task, the number of determined event boundaries between the close probes (M = 0.45, SD = 0.45) was less than between the far probes (M = 2.6, SD = 1; $t(33) = 7.1, p < 0.001$), as defined by an independent larger non-patient group.

EEG data collection and preprocessing

Intracranial EEG data were acquired using the Nihon Kohden recording system, analog-filtered above 0.01 Hz, and digitally sampled at 5 kHz or 10 kHz. A photodiode was recorded to track the flow of the experiment as it appeared to the participant. All EEG analyses were run in Matlab 2014a, EEGLAB, and Fieldtrip offline. Fieldtrip was used for electrode localization²⁶. The electrodes' anatomical locations were determined by a neurologist's team in the native space. The EEG recorded during the retrieval was de-trended (i.e., the mean value of the entire signal at each contact was subtracted for the value at each time point). Then the EEG was high-pass filtered at 0.5 Hz using a zero-phase delay finite impulse response filter with Hamming window, and then down-sampled to 1 KHz using Matlab's `resample()` function. Independent component analysis of the signal of all recording channels with neuronal data was used for removing the common noise²⁷ – akin to a weighted common average re-referencing. The EEG was cropped around the onset of the probes when two movie frames were shown side by side with no instruction. Trials with the interictal epileptiform that a neurologist identified were discarded (Table for the number of trials per participant).

Power Spectral Density

We contrasted the power spectrum density (PSD) of signals that were elicited by the far versus close probe onset. The power spectrum density was summarized after transformation of the signal round the probe onset into time and frequency 3 to 30 Hz with steps of 0.5 Hz using Morlet wavelet with 7 cycles. The power at every frequency was averaged for the first two seconds after the probe onset and contrasted between far and close trials using a linear regression. The coefficient of the contrast (Beta values) of each electrode in one region were pooled and averaged to have one value per region and patient for every frequency. The coefficients of the contrasts (beta-coefficients) of each electrode in one region were pooled. The aggregated coefficients were then compared against zero using a mixed-effect model with the patient number as a random factor. The p-values were adjusted to account for the False Discovery Rate (FDR) related to multiple comparisons of far and close trials at every frequency²⁸. We accepted $p < 0.025$ because we repeated the comparison in two regions. We only reported the FDR-corrected p-values. Although the analysis is done in high frequency resolution, for visualization purposes, Figure 2 shows a summary of the relative power differences in a frequency band, formulated as $(close - far)/(close + far)$.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments:

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Data Availability Statement:

The movie and the data that support the findings of this study are openly available in OSF.IO at DOI [10.17605/OSF.IO/932A5](https://doi.org/10.17605/OSF.IO/932A5).

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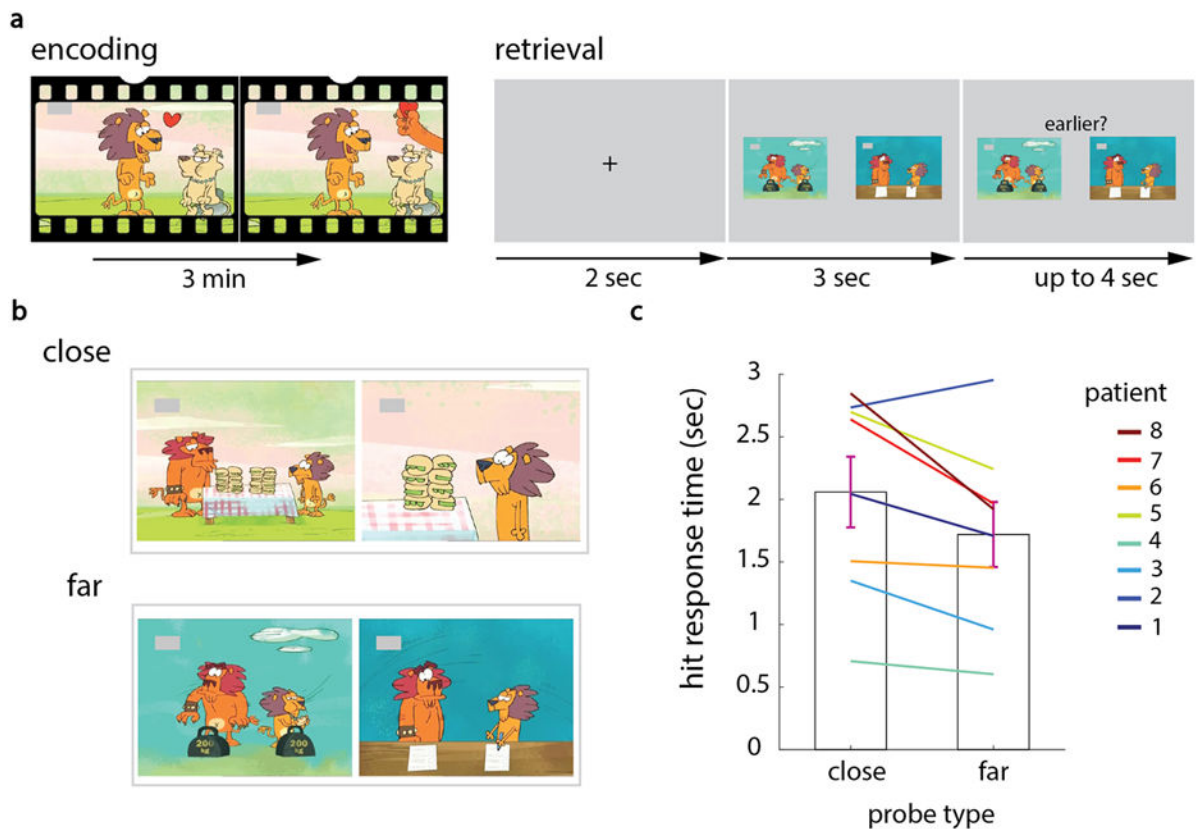


Figure 1. Experimental design and behavior.

(a) At encoding, participants watched a novel animation (3 minutes long) and were informed that memory would be assessed. At retrieval, participants performed a temporal order recognition task. Each temporal order retrieval trial started with a fixation point to draw attention to the middle of the screen. Then, two frames of the movie were shown side by side. After 3 seconds, an instruction appeared asking about the order of the probes. Pseudo-randomly, the instruction was split to ask for selection of the earlier or later frame. This design allowed us to study the neural mechanism of memory recall that is separate from preparing for the response. (b) An example of the *close* (top) and *far* (bottom) prompts. The close probes were neighboring movie frames that were visually distinct, while the far probes were between 12 to 60 seconds apart and were more contextually distinct than the close events (see the supplemental methods). (c) It took longer to correctly recall the temporal order of close events than far events. Patients' responses are color-coded and numbered according to (table S1). The error bars show S.E.M.

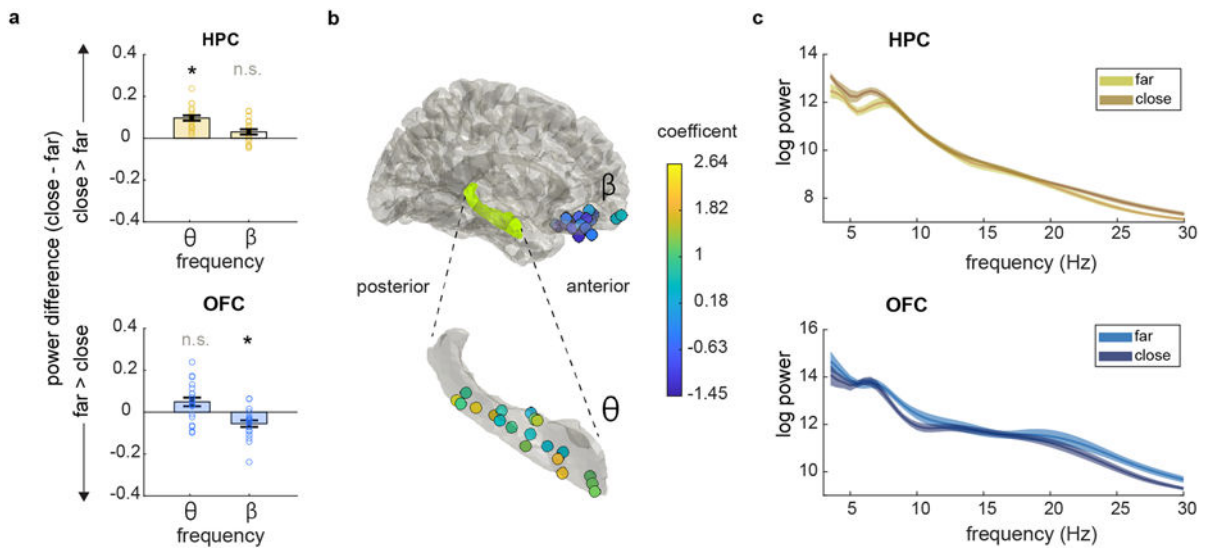


Figure 2. Hippocampal and OFC power differences between close and far events.

(a) HPC theta-band (4-8 Hz) power was higher for close compared to far temporal memory recall (top). This effect was reversed for beta-band power in the OFC (20-25 Hz; bottom).

* $p < 0.005$ and n.s. for $p > 0.05$. Error bars indicate S.E.M. (b) The coefficient for the comparison between recalling close and far events shown in the HPC (in theta-band) and in the OFC (in beta-band). A positive coefficient supports higher power in recalling close compared to far events; whereas a negative coefficient supports higher power in recalling far compared to close events. (c) Example of the PSD in one contact in the OFC (top) and one contact in the HPC (bottom). The shaded area shows S.E.M.

Table 1:

The demography diagnosis and the number of trials and contacts per patient. The table includes the age, gender, and dominant hand, as well as the diagnosed seizure onset zone. The diagnosis for the seizure onset zone was at L (left), R (right), or B (bilateral) temporal lobe; N/A is for not available. The table also includes the number of contacts in the HPC and mOFC and the number of trials that were contributed by each patient.

patient	Age (year)	gender	dominant hand	diagnosis	Number of contacts	
					HPC	mOFC
1	50	M	R	RTL	7	
2	20	M	R	N/A		8
3	40	F	L	RTL	2	2
4	58	F	R	LTL	3	2
5	31	M	L	N/A		4
6	34	M	R	BTL		1
7	55	F	L	RTL	2	
8	23	M	R	RTL	6	3

Table 2:

The table lists the number and the temporal distances of far and close probes, as well as the hit rate after discarding epileptic epochs. All participants had a hit rate higher than the 50% chance as calculated both before and after cleaning.

patient	Hit rate	Number (and the percentage) of responded trials		Averaged (and the standard deviation) of the probe temporal distance in seconds	
		far	close	far	close
1	69%	17 (94%)	16 (94%)	34 (16)	4 (4)
2	85%	16 (89%)	15 (88%)	34 (16)	4 (4)
3	80%	18 (100%)	17 (100%)	34 (15)	4 (4)
4	60%	17 (94%)	13 (76%)	34 (16)	5 (4)
5	67%	7 (39%)	9 (53%)	27 (10)	5 (4)
6	70%	6 (33%)	9 (53%)	39 (13)	3 (2)
7	70%	10 (56%)	13 (76%)	43 (14)	4 (8)
8	96%	15 (83%)	11 (65%)	34 (17)	3 (3)