Supplementary Information: Gamma oscillations distinguish true from false memories

Per B. Sederberg[1], Andreas Schulze-Bonhage[2], Joseph R. Madsen[3], Edward B. Bromfield[4], Brian Litt[1], Armin Brandt[2] & Michael J. Kahana[1]

1. University of Pennsylvania, Philadelphia, Pennsylvania 19104, USA
2. University Hospital of Freiburg, Freiburg, Germany
3. Children's Hospital Boston, Massachusetts 02115, USA
4. Brigham & Women's Hospital, Boston, Massachusetts 02115, USA

Supplementary Methods

Participants

We tested 52 patients (ages 8 to 53, 22 female) with drug-resistant epilepsy who had arrays of subdural and/or depth electrodes surgically implanted for one to two weeks to localize the site or sites of seizure onset (See Supp. Tab. 2). Subsets of these patients were included in prior studies of subsequent memory effects (Sederberg, Kahana, Howard, Donner, & Madsen, 2003; Sederberg et al., in press). The clinical team determined the placement of these electrodes with the goal of localizing suspected epileptogenic foci and identifying functional regions to be avoided in surgery.

Our research protocol was approved by the appropriate institutional review boards at the University Clinic in Freiburg, Germany, Children's Hospital Boston, Brigham and Women's Hospital in Boston, and Hospital of the University of Pennsylvania in Philadelphia. Informed consent was obtained from the subjects and their guardians.

Behavioral methods

Subjects studied lists of words for a delayed free-recall task. Lists were composed of 15 or 20 common nouns, chosen at random and without replacement from a pool of either English or German high-frequency nouns (http://memory.psych.upenn.edu/wordpools.php), depending on the subject's native language. 21 subjects received 20-item lists, while the remaining 31 subjects received 15-item lists. Over the course of 1 to 5 sessions, subjects received between 9 and 60 study-test lists (the number of trials completed depended on the patient's interest and availability for testing). A computer controlled the stimulus presentations and recorded subjects' responses. At the start of each trial, a plus sign appeared at the center of the screen to alert subjects to the upcoming word presentation and to encourage them to fixate on the center of the screen. The plus sign appeared for 1600 ms, followed by an 800 to 1200 ms blank inter-stimulus interval (ISI). The computer then displayed each list item in capital letters for 1600 ms, and was followed by an 800 to 1200 ms blank ISI. This temporal jitter served to decorrelate the physiological responses from successive word presentations. To ensure that each word was attended to, we asked subjects to read each word aloud as soon as it appeared.

Immediately after each list presentation, subjects were given a series of simple arithmetic problems. Each problem took the form of $A + B + C =?$, where A, B, and C were randomly chosen positive or negative integers from the set 1–9. Subjects were asked to respond vocally as soon as they knew the answer, and the experimenter typed their answer into the keyboard. After subjects solved arithmetic problems for ~ 18 s, a row of asterisks, accompanied by a tone, signaled the start of the recall period. Subjects were given 45 s to recall list items in any order. Vocal responses, digitally recorded during the trial, were scored for analysis following each session (Sederberg et al., 2003, 2006, in press).

For comparisons between successful and unsuccessful encoding, we categorized all word presentation events based upon whether they were subsequently recalled or not recalled. The 52 subjects recalled $23.2 \pm 1.2\%$ of the words on each list. To compare true and false memories, we separated correct from incorrect responses. After removing repetitions of correct responses,

subjects made correct responses $72.9 \pm 2.4\%$ of the time, while the remaining incorrect responses were either words from prior lists or words that were not presented. For EEG analysis, any response that occurred within 2 s of a prior response was discarded to avoid overlap with the prior vocalization. After applying the above criteria, any subject who did not make at least 6 incorrect responses was discarded from the EEG retrieval analysis. The remaining 32 subjects made correct recalls $67.0 \pm 2.4\%$ of the time. Note that 67% correct recalls refers to the percentage of responses that were correct out of the total number of responses, not the percentage of words on the list that were correctly recalled.

iEEG recordings

The iEEG signal was recorded from either subdural grids or depth electrodes. The signal was recorded by means of a Bio-Logic, XLTek, Neurofile, or Nicolet EEG system. Depending on the amplifier, the signals were sampled at 200, 256, 500, 512, or 1024 Hz and band-pass-filtered between 0.3 and 70 Hz or between 0.1 and 100 Hz. Data were subsequently notch-filtered with a Butterworth filter with zero phase distortion at 50 or 60 Hz to eliminate electrical line and equipment noise. Individual word presentation and retrieval events were scanned for artifacts (e.g., spikes) and were discarded if the kurtosis of the amplitude distribution of the signal exceeded a threshold of 5 (Delorme, Makeig, & Sejnowski, 2001).

To synchronize the electrophysiological recordings with behavioral events, the experimental computer sent pulses through the parallel or USB port via an optical isolator into an unused recording channel or digital input on the amplifier. The time stamps associated with these pulses aligned the experimental computer's clock with the iEEG clock to a precision well under the sampling interval of the iEEG recording (< 4 ms). For all subjects, the locations of the electrodes were determined by means of coregistered post-operative CTs and pre-operative MRIs, or from post-operative MRIs, by an indirect stereotactic technique and converted into Talairach coordinates.

Data analysis

After down-sampling the data to 200 Hz, we used the Morlet wavelet transform (with a wave-number of 6) to compute spectral power as a function of time for all our EEG signals. For encoding events, wavelet power was calculated from -500 to 2000 ms around the onset of each word presentation. At retrieval, wavelet power was calculated from -1000 to 500 ms around the onset of each response vocalization. For all wavelet transformations we added a 1 s window on either side of the events to avoid edge artifacts. We then log-transformed and down-sampled the power to 50 Hz. Frequencies were sampled logarithmically at 46 intervals between 2 and 100 Hz and split into six distinct bands— 2 to 4 Hz (delta), 4 to 8 Hz (theta), 10 to 14 Hz (alpha), 16 to 26 Hz (beta), 28 to 42 Hz (low gamma), and 44 to 100 Hz (high gamma)— by taking the mean of the log-transformed power in each frequency band.

A Wilcoxon rank sum test was then used for the two comparisons: between recalled and not recalled encoding events and between correct and incorrect recall events. At encoding, we tested for differences in the mean log-transformed wavelet power during the period from 0 to 2000 ms after presentation onset. At retrieval, we tested for differences in mean log-transformed wavelet power in the 500 ms prior to a response. These comparisons were made separately for each electrode and at each frequency.

We used a permutation procedure to generate an unbiased empirical estimate of the Type I error rate (Efron, 1979; Sederberg et al., 2003). First, we generated 1,000 random samples of the experimental data by randomly swapping items from each condition (for example, in the retrieval comparison, we swapped correct and incorrect recalls, keeping the number in each condition constant). Next, we performed the Wilcoxon rank sum test on the 1,000 random shuffles of data. To account for correlations between electrodes we used the same 1000 permutations for all electrodes within a single subject.

To calculate the significance of the power differences aggregated across subjects for specific regions, we performed region of interest (ROI) analyses that combined the significance values for all electrodes in a region. First, cortical electrodes were categorized into Brodmann areas

by means of the Talairach Daemon (Lancaster et al., 2000) and hippocampal electrodes were identified via CT scans and MRIs by the clinical team. For a region to exhibit an aggregate effect across subjects, we required that at least 5 subjects contribute electrodes to that region. We next applied the inverse normal transformation (Z score) to both the p value obtained by comparing the actual events from each condition and the distribution of p values from the permutation test (Gibbons & Shanken, 1987). This was done at each frequency and for each electrode in a region. To ensure that each subject contributed equally to the aggregate significance value, we calculated the mean of the within-subject Z scores across all of their electrodes in a particular region, and then summed the mean Z scores across subjects, thus producing a summed Z score and an empirically determined random distribution of summed Z scores of what would have been expected by chance in that region. The point at which a summed Z score fell within the empirical distribution of summed Z scores provided the p value for the significance of that region. To correct for multiple comparisons we determined a p value threshold for each frequency band to apply to each region by means of the false discovery rate method with $\alpha = .1$ (Genovese, Lazar, & Nichols, 2002). Thus, we determined a p value threshold that would guarantee that no more than 10.0% of the regions that exceeded that threshold for that comparison were not significant.

To visualize the results of the ROI analysis, we overlaid the Brodmann areas defined by the Talairach Daemon on the standard MNI brain by using information in the WFU PickAtlas toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003).

To determine the correlation between the power differences between successful and unsuccessful encoding and the differences between correct and incorrect responses, we first determined a p value, defined as the point where the summed Z scores fell in the distribution of empirical summed Z scores, quantifying the significance of the encoding and retrieval effects for each region. Next, we calculated a Pearson's correlation, across all regions with electrodes from greater than 5 subjects, between the inverse normal of the p values at encoding to the p values at retrieval. To test for differences between correlations of different frequency bands, we

performed a Fisher's two-tailed test for the difference between two independent correlations with an alpha value of .05.

To illustrate the timing of the significant differences between conditions for individual regions, we plotted mean power as a function of time across all electrodes in a region for each condition. To normalize power values to combine across subjects for presentation purposes, we smoothed the power over time with a low-pass filter set at 5 Hz and Z-transformed the power of a subject's events at each electrode, based on the mean and standard deviation of either the subject's encoding or retrieval events.

To determine the significance at each point in time, we performed a permutation test as described above, but with 250 shuffles of the data at each time point. Thus, for each region of interest we had a summed Z score and an empirical distribution of summed Z scores at each point in time, which we then converted to p values based on where the actual summed Z fell into the empirical distribution. We then applied a threshold of $p <= .025$ to determine significant time-points for each comparison.

Supplementary Results

	Left		**Right**	
	# Elec.	**# Subj.**	**# Elec.**	**# Subj.**
Hippocampal	100	20	86	19
Frontal	654	28	616	29
Temporal	891	36	808	35
Parietal	143	16	241	20
Occipital	50	11	88	15

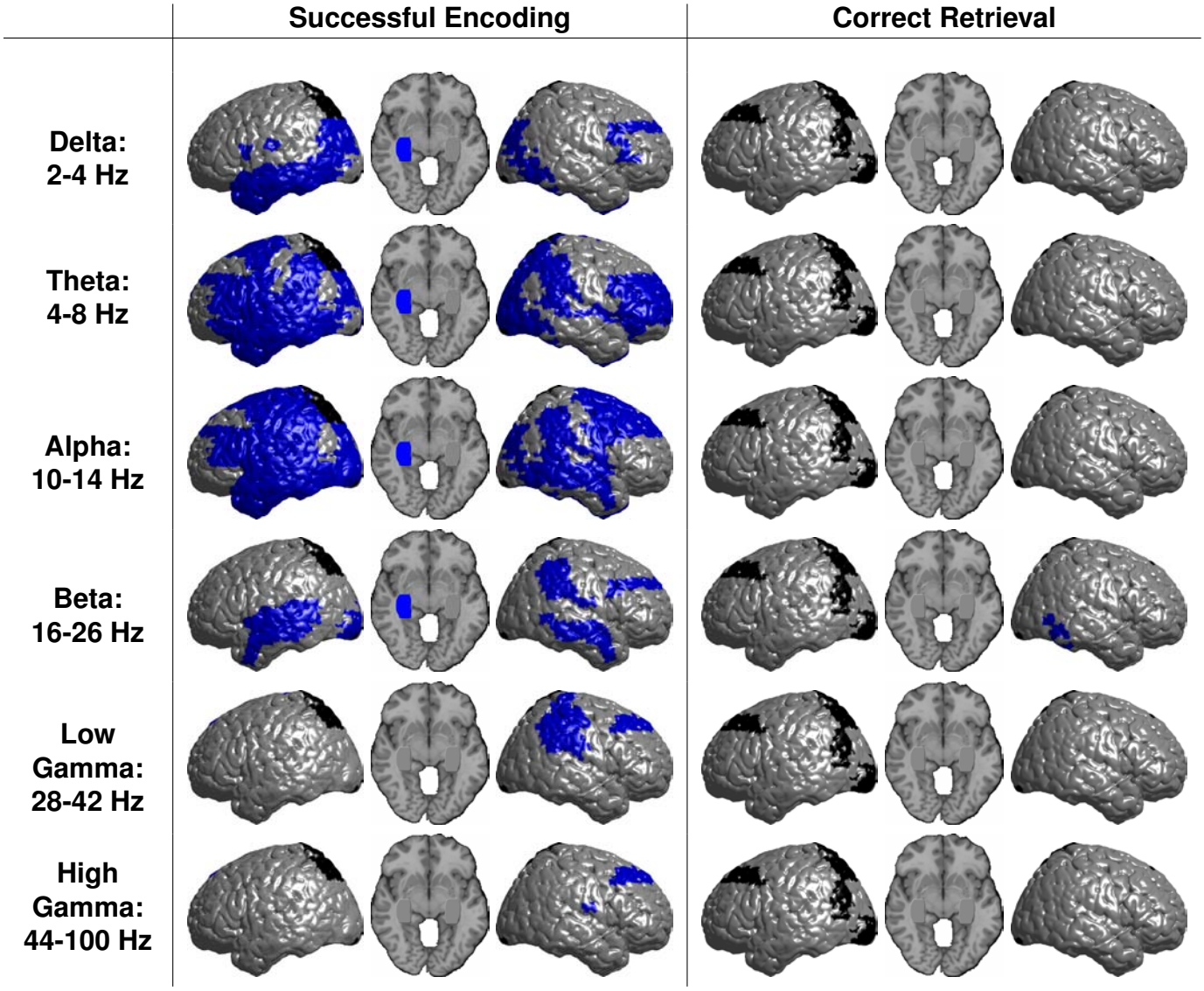
Supp. Table 1: **Total electrodes and number of subjects by hemisphere and lobe.**

Id.	Age	Gender	Handed./Lang.	% Rec.	# Elec.	Resection Area
1	33	F	R Hand.	19.6	58	R Temporal
2	51	F	R Hand.	22.0	40	None
3	32	M	R Hand.	36.2	32	R Anterior Temporal
4	40	M	R Hand.	28.8	93	R Frontal
5	44	M	R Hand.	20.4	16	None
6	27	M	R Hand.	26.7	64	R Inferior/ Posterior Temporal
7	13	F	R Hand.	24.6	63	L Amygdala/ Anterior Hippocampus
8	12	F	R Hand.	16.2	102	R Motor-Sensory Transection
9	17	M	R Hand.	19.8	63	L Inferior/ Medial Temporal
10	15	M	R Hand.	28.7	122	L Anterior Frontal
11	11	M	R Hand.	17.9	101	R Angular Gyrus
12	14	F	R Hand.	34.7	71	L Temporal
13	8	F	R Hand.	26.7	78	R Temporal
14	17	M	R Hand.	11.5	82	L Temporal
15	20	F	R Hand.	33.0	127	L Frontal
16	14	M	R Hand.	24.1	89	R Temporal/ Occipital
17	19	F	R Hand.	18.4	115	None
18	16	M	R Hand.	31.7	153	L Frontal
19	12	M	L Hand.	23.1	80	L Temporal
20	13	M	R Hand.	33.3	71	L Anterior Temporal
21	33	M	R Hand.	23.9	94	None
22	25	M	R Hand.	25.0	82	R Temporo-Parietal
23	31	M	L Lang.	13.3	55	Selective L Amygdala/ Hippocampus
24	41	F	R Hand.	16.4	62	R Pre-central
25	34	F	L Lang.	27.1	38	L Temporal
26	45	F	L Lang.	16.9	99	L Frontal
27	46	F	L Lang.	16.7	14	None
28	20	M	R Hand.	16.2	82	R Temporo-Occipital
29	53	F	L Lang.	16.3	40	Radiation of L Hippocampal Sclerosis
30	50	M	R Hand.	20.0	67	L Temporal
31	28	M	L Lang.	14.2	108	L Frontal & L Posterior Temporal
32	37	F	L Lang.	21.7	30	Selective R Amygdala/ Hippocampus
33	18	M	L Lang.	40.3	29	Selective R Amygdala/ Hippocampus
34	23	M	L Lang.	34.5	56	None
35	21	M	L Lang.	32.7	76	R Temporal
36	35	F	L Lang.	21.2	120	R Frontal
37	37	F	L Lang.	32.5	42	None
38	19	M	L Lang.	37.0	72	L Temporal
39	41	F	R Hand.	14.1	28	None
40	21	F	R Hand.	23.8	63	R Central
41	43	F	R Hand.	11.0	55	R and L Temporal

Continued on next page. . .

Id.	Age	Gender	Handed./Lang.	% Rec.	# Elec.	Resection Area
42	19	M	R Hand.	32.0	29	None
43	21	M	R Hand.	51.7	69	None
44	35	F	R Hand.	19.6	56	L Temporal
45	25	M	R Hand.	33.3	82	L Frontal
46	45	F	R Hand.	31.9	88	R Temporal
47	38	M	R Hand.	22.5	60	R Temporal
48	30	M	R Hand.	18.9	85	None
49	43	M	R Hand.	17.2	64	None
50	36	M	R Hand.	15.6	81	L Anterior Temporal
51	25	M	R Hand.	22.5	57	R Temporal
52	18	F	R Hand.	23.1	74	None

Supp. Table 2: **Patient demographics.** This table provides the patients' age, gender, handedness or language mapping, percent recalled on the free-recall task, number of electrodes included in the analyses, and subsequent resection information. The 52 patients contributed 3,677 total electrodes and had 23.2% mean recall performance.



Supp. Figure 1: **Cortical and hippocampal regions exhibiting decreases in oscillatory activity that predicted successful encoding and correct recall.** The left column illustrates regions exhibiting significant decreases (blue) in mean power for successful relative to unsuccessful encoding. The right column indicates regions exhibiting significant decreases (blue) in mean power prior to correct versus incorrect recalls. Each row indicates a distinct frequency band: 2 to 4 Hz (delta), 4 to 8 Hz (theta), 10 to 14 Hz (alpha), 16 to 26 Hz (beta), 28 to 42 Hz (low gamma), and 44 to 100 Hz (high gamma). For each comparison we show left and right cortical views with regions defined as Brodmann areas (left and right), and a brain slice with regions indicating the significance of the left and right hippocampus (center). Nonsignificant regions are shown in grey. Regions containing electrodes from fewer than 5 subjects are shown in black. Note that fewer subjects were included in the retrieval than in the encoding analysis, giving rise the discrepancy in regions with fewer than 5 subjects.

References

Delorme, A., Makeig, S., & Sejnowski, T. (2001). Automatic artifact rejection for EEG data using high-order statistics and independent component analysis. In *Proceedings of the Third International ICA Conference.* San Diego.

Efron, B. (1979). Bootstrap methods: Another look at the jackknife. *Annals of Statistics*, *7*(1), 1–26.

Genovese, C. R., Lazar, N. A., & Nichols, T. E. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*, *15*, 870–878.

Gibbons, M. R., & Shanken, J. (1987). Subperiod aggregation and the power of multivariate tests of portfolio efficiency. *Journal of Financial Economics*, *19*, 389-394.

Lancaster, J. L., Woldorff, M. G., Parsons, L. M., Liotti, M., Freitas, C. S., Rainey, L., et al. (2000). Automated Talairach atlas labels for functional brain mapping. *Human Brain Mapping*, *10*, 120–131.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003, Jul). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. *Neuroimage*, *19*(3), 1233–1239.

Sederberg, P. B., Gauthier, L. V., Terushkin, V., Miller, J. F., Barnathan, J. A., & Kahana, M. J. (2006). Oscillatory correlates of the primacy effect in episodic memory. *NeuroImage*, *32*(3), 1422–1431.

Sederberg, P. B., Kahana, M. J., Howard, M. W., Donner, E. J., & Madsen, J. R. (2003). Theta and gamma oscillations during encoding predict subsequent recall. *Journal of Neuroscience*, *23*(34), 10809–10814.

Sederberg, P. B., Schulze-Bonhage, A., Madsen, J. R., Bromfield, E. B., McCarthy, D. C., Brandt, A., et al. (in press). Hippocampal and neocortical gamma oscillations predict memory formation in humans. *Cerebral Cortex*.