Power Shifts Track Serial Position and Modulate Encoding in Human Episodic Memory

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The first events in a series exert a powerful influence on cognition and behavior in both humans and animals. This is known as the law of primacy. Here, we analyze the neural correlates of primacy in humans by analyzing electrocorticographic recordings in 84 neurosurgical patients as they studied and subsequently recalled lists of common words. We found that spectral power in the gamma frequency band (28–100 Hz) was elevated at the start of the list and gradually subsided, whereas lower frequency (2–8 Hz) delta and theta band power exhibited the opposite trend. This gradual shift in the power spectrum was found across a widespread network of brain regions. The degree to which the subsequent memory effect was modulated by list (serial) position was most pronounced in medial temporal lobe structures. These results suggest that globally increased gamma and decreased delta–theta spectral powers reflect a brain state that predisposes medial temporal lobe structures to enhance the encoding and maintenance of early list items.

Introduction

In both humans and animals, the first events in a series exert a more powerful influence on behavior and cognition than do subsequent events. This law of primacy (Tulving 2007) is particularly striking in learning and memory tasks, where the first few items are better recalled and recognized than subsequent list items (e.g., Wright et al. 1985; Neath et al. replication study).

Because remembering an item reflects the complex interplay of encoding and retrieval processes (Kahana 2012), neural recordings taken during the encoding phase of a learning task can be used to identify differences in the way the brain processes of early and later list items.

Recent human neuroimaging and electrophysiological recording studies have shed considerable light on the neural correlates of memory encoding in general. By comparing the encoding of items later recalled (or recognized) with those items that are not recalled (or recognized), researchers have helped to characterize the neural networks involved in memory storage. Functional magnetic resonance imaging (fMRI) has localized metabolic activity associated with effective memory encoding to prefrontal and medial temporal lobe structures (Paller and Wagner, 2002; Davachi et al. 2001; Strange et al. 2002; De Zubicaray et al. 2005). Electrophysiological recordings have identified a similar network of brain areas (e.g., Sederberg et al. 2007a, b) with these regions, exhibiting increases in gamma power (28–100 Hz) and decreases in power at lower frequencies (4–14 Hz) during good encoding (Miltner et al. 1999; Fell et al. 2001; Sederberg et al. 2007a, b; Jutras et al. 2009). The detection of increased

4–8-Hz theta power with successful encoding has also been observed in the hippocampus and some regions of the temporal and frontal cortices (Sederberg et al. 2003; Hanslmayr et al. 2009; Lega et al. 2012).

We sought to address the question of whether neural activity differed for the encoding of early (primacy) items when compared with later list items. Such a difference would be a candidate neural correlate of the ubiquitous primacy effect observed in so many cognitive tasks. To address this question, we analyzed intracranial electroencephalographic (iEEG) recordings taken as neurosurgical patients studied the lists of common nouns and then freely recalled the list items following a delay period during which they performed a mental arithmetic task. This delayed-free recall task typically exhibits robust primacy effects (Postman and Phillips 1965), while the end-of-list distractor task greatly attenuates the recency effects that are observed in immediate-free recall.

Sederberg et al. (2006) carried out a similar experiment using scalp EEG recordings in healthy volunteers. During the encoding of early list items, they found increased gamma activity for those items that were subsequently recalled. However, during the encoding of midlist items, they found decreased low-frequency (4–14 Hz) power for those items that were subsequently recalled. In general, they found that over the course of list presentation, gamma activity decreased while power at lower frequencies increased. They interpreted these findings as suggesting that increased gamma and decreased lower frequency activity reflect focused attention on early list items that boosted encoding efficacy relative to the midlist items.

The present analysis of iEEG recordings from 84 neurosurgical patients enables us to identify the unique contributions of medial temporal lobe structures that are believed to be critical for memory encoding. In addition, data from indwelling electrodes are not susceptible to the skull's filtering of higher frequencies, thus enabling us to better identify the gamma correlates of memory encoding. This is important because previous work has shown that gamma power correlates with selective attention (Fries et al. 2001; Ossandon et al. 2012), top-down attention (Engel et al. 2001; Jutras et al. 2009), and the maintenance of behaviorally relevant information (Sauseng et al. 2008; Haegens et al. 2010; van Vugt et al. 2010). The 10–30-ms processing time window imposed by the gamma rhythm has been proposed to be the mechanism by which attention can facilitate the processing of selected information represented by synchronized activity, and it matches the time constant at which activity-dependent modification occurs at synapses (Tallon-Baudry 2009). If intracranial recordings were to confirm that enhanced gamma activity accompanies the encoding of early items, this might imply that

early items are encoded better because they receive greater attention.

Materials and Methods

Participants
We analyzed data from 84 patients undergoing invasive monitoring as the treatment for drug-resistant epilepsy. During their 1–3-week invasive monitoring periods, these patients volunteered to participate in our cognitive testing in their free time between clinical procedures. Each patient participated in 1–10 testing sessions. Our research protocol was approved by the appropriate institutional review boards at the Hospital at the University of Pennsylvania (PA, United States of America), Thomas Jefferson University Hospital (PA, United States of America), Children's Hospital of Philadelphia, University Clinic (Freiburg, Germany), Children's Hospital (Boston), and Brigham and Women's Hospital (Boston). Informed consent was obtained from patients (or their guardians, in the case of children). Some of these datasets have been previously examined (e.g., Sederberg et al. 2003; Sederberg et al. 2007a, b; Manning et al. 2011), but the data analyses described here are novel. Demographic data are summarized in Table 1.

Electrophysiology
For each participant, we analyzed iEEG recordings from 19 to 126 electrodes. Clinical teams positioned electrodes to identify seizure foci and functional brain regions to guide potential resective surgery. As a result, most electrodes were usually placed in the temporal cortex, but many electrodes were also placed in the hippocampi, frontal, occipital, and parietal cortices. Because the clinical procedure of identifying seizure foci entails placing electrodes in any region that is potentially epileptogenic, the majority of recordings come from brain regions outside the area that is eventually determined to be involved in seizures (Sederberg et al. 2003). Recording electrodes consisted of 2 arrangements: Grid and strip electrodes, which are placed on the surface of the neocortex, and depth electrodes, which penetrate through the cortex and record from the hippocampus and overlying regions. Electrodes were made of platinum (3 mm diameter) with an interelectrode spacing of 1 cm (for subdural electrodes) or 8 mm (for depth electrodes). Electrode locations were identified by coregistering a computed tomography (CT) scan with a higher-resolution postoperative magnetic resonance image (MRI), or if a postoperative

image was not available, then a preoperative MRI. These images were then normalized to a standardized brain, and each electrode's lobe and Brodmann Area were determined using Talairach coordinates (Talairach and Tournoux 1988; Lancaster et al. 2000). We used brain images from the WFU PickAtlas for data visualization (Maldjian et al. 2003). For depth electrodes implanted in the temporal lobe, a clinician experienced in neuroanatomical localization manually labeled each electrode by reviewing CT and MRIs. For the purposes of these investigations, the term "parahippocampal gyrus" can be understood broadly to include the entire rostrocaudal extent of the gyrus. In certain cases, an electrode could be confidently identified within the entorhinal cortex (i.e., in the depth of the collateral sulcus).

iEEG activity was recorded at a sampling rate of 200–2000 Hz using Bio-Logic, XLTek, Neurofile, DeltaMed SA, Nicolet, or Nihon-Koden recording systems, depending on the amplifier. The online filter settings ranged from a lower cutoff of 0.1–0.3 Hz to an upper cutoff of 60–100 Hz. These recordings were synchronized with measurements of the patient's behavior in the task through optically isolated synchronization pulses received from the testing computer on an additional recording channel. The recording from each electrode was rereferenced to the weighted average of all the patient's electrodes, weighted such that each grid, strip, or depth probe contributed equally.

Task
We recorded iEEG from patients, while they studied and recalled lists of words in a delayed-free recall task. The lists were composed of 15 or 20 common nouns, chosen at random and without replacement from a pool of high-frequency words (either English or German, depending on the subject's native language; mean frequency 49.0, http://memory.psych.upenn.edu/wordpools.php, Friendly et al. 1982). Twenty-four subjects received 20-item lists, and the remaining 60 subjects received 15-item lists.

A computer controlled stimulus presentation and recorded participants' responses. At the beginning of each trial, a plus sign appeared for 1600 ms at the center of the screen to alert the participants to upcoming word presentations at that location on the screen. The plus sign was followed by an 800–1200-ms blank interstimulus interval (ISI). The computer next displayed each list item in capital letters for 1.6 s, followed by an 800–1200-ms blank ISI. This temporal jitter served to decorrelate the physiological responses from successive word presentations. To minimize artifacts, we asked participants to avoid blinking and remain motionless during word presentations. To encourage elaborative encoding, participants were encouraged to say each word as it was presented, either to out loud or to themselves. Experimenters were with the patients at all times during the experiment to encourage attention to the task.

Immediately after each list presentation, participants were given a series of simple arithmetic problems. This end-of-list distractor task served to reduce the large advantage accorded to the end-of-list items during recall. Each problem took the form of $A + B + C$, where A, B, and C were randomly chosen one-digit positive integers. Participants were asked to respond by typing the answer into the keyboard. Immediate feedback was given in the form of a high-pitched tone for correct entries and a low-pitched tone for incorrect answers. After 20 s of arithmetic problems, participants were shown a row of asterisks accompanied by a 300-ms tone signaling the start of the recall period. Participants were given 45 s to recall items aloud from the current list in any order (standard-free recall instructions).

Data Processing
Vocal responses were digitally recorded and scored for analysis following each session (Sederberg et al. 2003; Solway et al. 2010). iEEG signal was extracted from the 500 ms before to the 2500 ms after each word was presented on the screen. Data were notch-filtered online at 50 or 60 Hz with a Butterworth filter with zero-phase distortion, to eliminate electrical line and equipment noise, and were downsampled to 256 Hz. We used the Morlet wavelet transform (with a wave number of 6) to compute spectral power at 46 logarithmically spaced

Table 1
Participant demographics and electrode coverage

Participant demographics		
Age (years)	Range 8–56, mean 30.9 ± std 12.5	
Gender	50 male, 34 female	
Handedness	20 left-handed, 63 right-handed, 1 ambidextrous	
Electrode coverage		
Region	Number of Participants	Number of Electrodes
Amygdala	36	86
Hippocampus	49	317
Entorhinal cortex	11	15
Parahippocampal gyrus	21	86
Lateral temporal cortex	84	2178
Dorsolateral prefrontal cortex	58	420
Frontal lobe	75	2199
Occipital lobe	53	277
Parietal lobe	64	655
Temporal lobe	84	2685
Left hemisphere	67	3330
Right hemisphere	65	3583
Whole brain	84	6913

Age, gender, and handedness are described. Hemispheric lateralization determination by Wada or fMRI was not performed on all participants; in those that did undergo one of these procedures, all but 2 exhibited language dominance in the left hemisphere. Electrode coverage is presented by the region: Electrodes from either hemisphere of the homologs structure are included except for the penultimate entries that tally the number of electrodes in each hemisphere separately.

intervals between 2 and 98 Hz as a function of time, with bands defined as delta (1–4 Hz), theta (4–8 Hz), alpha (10–14 Hz), beta (16–26 Hz), low gamma (28–42 Hz), and high gamma (44–98 Hz). For each encoding event, first and last 500 ms were subsequently cut off to remove edge artifacts. The remaining power signal was then log-transformed. We next Z-transformed power for each encoding event, at each electrode, based on the mean and standard deviation of wavelet-computed power for all events within a given experimental session that the participant completed. The frequency band cutoffs, and the time windows (0–1000 ms, 1000–2000 ms, and 0–2000 ms), were chosen to match those used in Sederberg et al. (2006) to facilitate comparison between the studies. The log and Z-transformation were performed before binning.

Visualizing Oscillatory Power as a Function of Serial Position

To visualize how oscillatory power varied as a function of serial position, the mean Z-scored power for subsequently recalled word events, subsequently not-recalled words, and for all words regardless of recall, for each serial position, was calculated at each electrode at each frequency band for each time window. The resulting averages per channel were then averaged across all channels within a particular subject, localized to a particular region. The intrasubject per region averages were then averaged again across all subjects to generate a grand per region oscillatory power, with error bars calculated across participants.

Statistical Significance of Encoding at Primacy and Later Positions

To assess how signals recorded at each electrode varied as a function of subsequent recall, a t-statistic was calculated comparing the distribution of mean Z-transformed wavelet power for all events where the word was subsequently recalled and the distribution of powers for the presentation of words that were not subsequently recalled. This "subsequent memory effect" (SME) analyses were performed for all items (regardless of serial position) and then separately for primacy items (the first 5 words presented), and for midlist items (the second 5 words presented). The delineation of primacy versus middle list positions around item 5 was chosen to be consistent with the prior analysis of Sederberg et al. (2006) to facilitate the comparison of the 2 studies. In addition to the SME, the effect of the position regardless of recall was also examined: Namely a t-test between all early words and all midlist words. The statistical comparisons were made separately for each electrode and at each frequency band. An identical analysis using a nonparametric (Wilcoxon-rank sum) test yielded very similar results.

Because the large sample of electrodes provided an extensive coverage of the most brain regions, we were able to aggregate data across both subjects and electrodes to ascertain if there was a statistically significant effect within a given brain region (Sederberg et al. 2007a). We calculated between-subjects statistics within each Brodmann area (BA), as determined with the Talairach Daemon (Lancaster et al. 2000), and for the left and right medial temporal subregions, as determined by the clinical team.

To evaluate the results in terms of region, t-statistics were first averaged across all electrodes in that region within a subject. The mean t-statistics per region were then summed across all subjects who had at least 1 electrode in that region. We confined our analysis of regions to those that comprised data from at least 5 different participants. Summing the average t-statistics ensured that participants were weighed equally regardless of the number of electrodes they contributed to any particular region. To calculate the significance of these resulting summed t-statistics, a permutation procedure was used to allow us to control for the multiple comparisons while maintaining a fixed Type I error rate (Efron 1979; Gibbons and Shanken 1987). The permutation procedure involved a generation of the bootstrap distribution of 1000 iterations. Namely, the t-test was repeated 1000 times on a channel-by-channel basis, for every given time window and frequency band, with the "recalled" and "nonrecalled" labels shuffled randomly for each t-test. The bootstrap distributions were then averaged across channels within a region for the particular participant, and these per participant mean-bootstrap distributions were summed

across all participants contributing electrodes to a given region, both in the same way the t-statistics were combined for the original non-shuffled data.

We determined a single significance threshold by means of the false-discovery rate method (with $\alpha = 0.05$), and then applied this threshold to all regions (Genovese et al. 2002). Using this procedure, we were able to determine significant interactions for the 4 t-tests discussed (SME for all positions, early SME for first 5 words, middle SME for the midlist words, and early vs. middle regardless of subsequent recall).

Because we were interested in the interaction between encoding and serial positions, we also calculated the difference in the t-statistics generated for the early item encoding comparison and for the midlist encoding comparison (namely, early SME–middle SME); we performed the same difference operation on the bootstrap distributions. This "difference SME" procedure was adapted directly from our prior scalp EEG analysis (Sederberg et al. 2006).

Results

Participants recalled approximately one-fourth of the words on each list (60 participants studied lists of 15 words recalling an average of 26%; 24 participants studied lists of 20 words, recalling an average of 19%). Because the basic behavioral and electrophysiological findings were qualitatively similar across the 2 list length conditions, we report data from the pooled sample. Although recall performance for these lists is lower than one would obtain with healthy young adults (Sederberg et al. 2006), performance is surprisingly good when one considers that our participants have a history of refractory epilepsy and that they are being tested in the days immediately following the surgical implantation of the large arrays of electrodes. Demographic and electrode coverage data are provided in Table 1.

Figure 1 shows how recall probability varied with list (serial) position. As expected, early serial positions exhibited the standard primacy effect, while the end-of-list distractor greatly reduced the recency effect normally seen in free recall studies. The trends apparent in Figure 1 were verified by conducting a paired-sample t-test on the proportion of items recalled from early (positions 1–5) to middle list positions
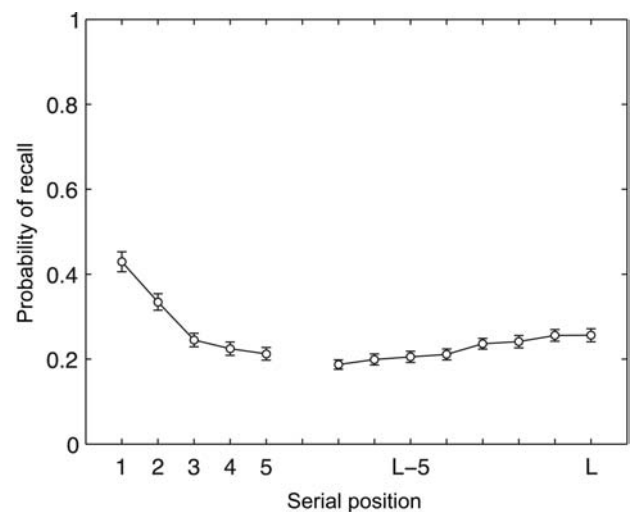

Figure 1. Recall probability as a function of serial position. "L" represents the last item, which could be 15 or 20 depending on the list length for a particular participant. Error bars represent ±1 standard error of the mean.
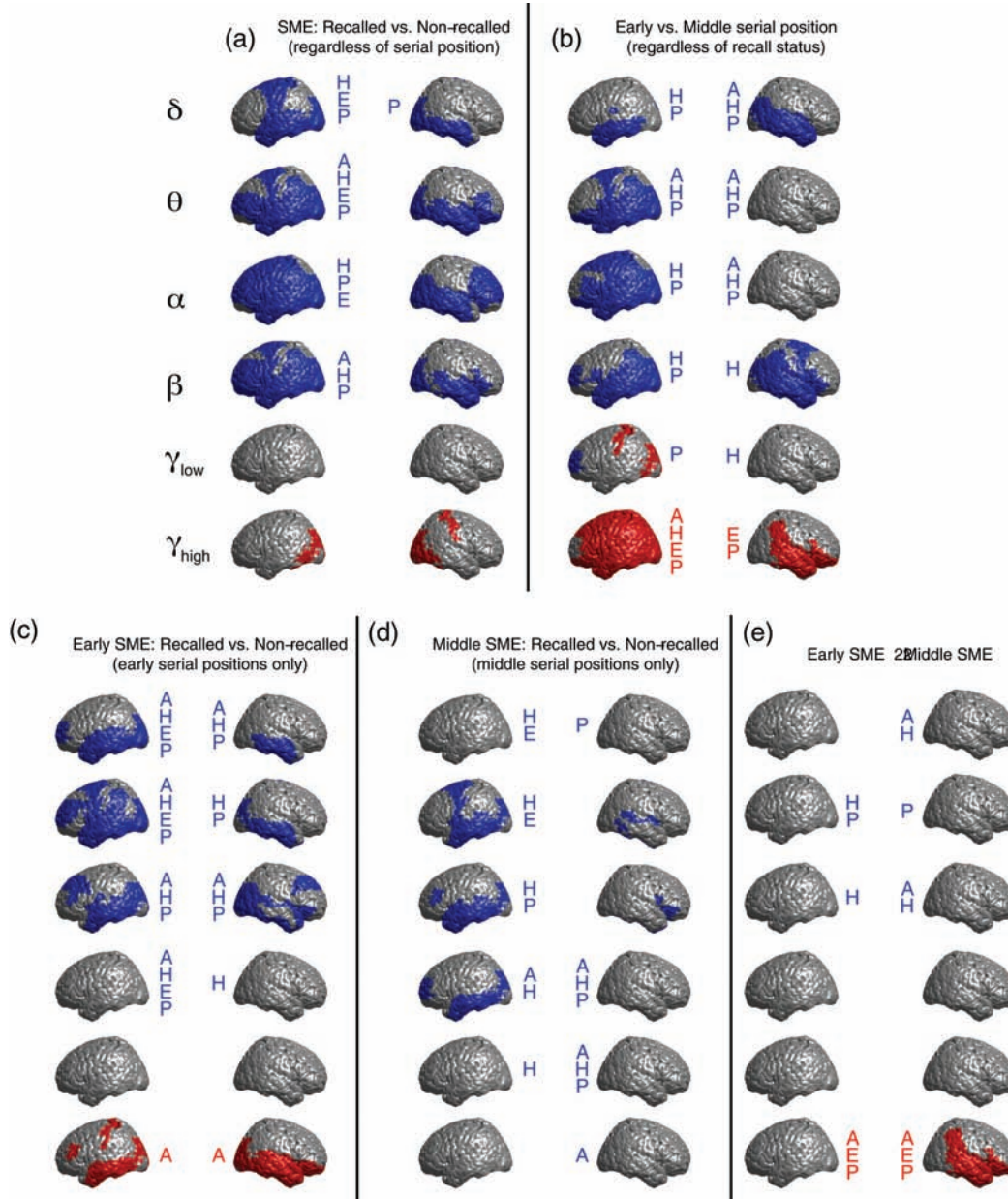
Figure 2. Topography of significant memory, position, and memory–position interaction effects. Each pair of cortical surface topographies illustrates the regions exhibiting a significant interaction between subsequent recall and serial position for 1 of 6 distinct frequency bands; medial temporal lobe structures are denoted by capital letters: A for the amygdala, H for the hippocampus, E for the entorhinal cortex, and P for the parahippocampal gyrus. Positive interactions where the difference in power was greater for the first condition in each pair are in red, while negative interactions are in blue. *A* shows the standard SME, namely the comparison of oscillatory power during the encoding of items that were subsequently recalled versus during the encoding of items that were not: Increased gamma and decreased low-frequency, power are the hallmarks of successful encoding. *B* demonstrates the effect of serial position independent of subsequent recall; early items are associated with diffuse enhancement of high-frequency, and attenuation of low-frequency activity. *C* and *D* show the results of comparing recalled and nonrecalled encoding events at just early (early SME) or just middle list positions (middle SME), respectively. *E* shows the results of taking the difference between the early and middle SMEs and hence reveals the interaction of serial position and encoding: Red indicates the difference in power being greater for early SME than for middle SME, while blue indicates the opposite. A false-discovery rate of 10% was used as a cutoff for significance. Greek letters refer to each frequency band: Delta (1–4 Hz), theta (4–8 Hz), alpha (10–14 Hz), beta (16–26 Hz), low gamma (28–42 Hz), and high gamma (44–100 Hz). The time window 0–2 s after word presentation was used to calculate power.

(6–10) across all participants; this difference was statistically significant ($t(83) = 5.4$, $P < 0.001$).

Before determining the joint effects of subsequent recall and serial position on spectral power during encoding (Fig. 2), we first compared the mean Z-scored power during the presentation of words that were subsequently recalled to the mean Z-scored power during the presentation of words

that were not subsequently recalled; this comparison identifies the well-known SME (panel *a* of Fig. 2) in which low-frequency power is suppressed diffusely throughout the brain, and gamma activity is enhanced in a subset of areas (Sederberg et al. 2007a, b). For this comparison, and all others displayed in Figure 2, only the colored regions exhibited a statistically significant result (defined as a *P*-value less

than the value generated by applying the false-discovery rate of 0.05 to a 1000-sample bootstrap distribution).

To examine the neural correlates of primacy, we compared the *Z*-scored power during the presentation of any word from the first part of the list (regardless of whether it was later recalled) to the *Z*-scored power during the presentation of any word from the middle part of the list (regardless of whether that word was later recalled; panel *b* of Fig. 2). Consistent with Sederberg et al.'s (2006) analysis of scalp EEG during memory encoding, we found that the enhancement of gamma activity and the suppression of low-frequency activity distinguished early from middle items in a number of brain regions, regardless of recall.

If the primacy effect arises due to mechanisms unique to the encoding of early (primacy) and not subsequent items, we would expect that the neural correlate of encoding (SME) would vary with list position. We therefore examined the "SME" separately for early (Fig. 2c) and middle list items (Fig. 2d) and found that the enhancement of gamma activity (28–100 Hz), primarily in the temporal lobes, distinguished the successful versus unsuccessful encoding of items at early (Fig. 2c), but not middle list position items (Fig. 2d).

To quantify the overall interaction between encoding (SME) and serial positions, beyond establishing the relative increases or decreases in power for early and middle SMEs (Fig. 2c,d), we computed the significance of the "difference" in the *t*-statistics generated for the early SME minus the middle SME analyses. As shown in Figure 2e, positive interactions (shown in red) where the difference in power was greater for the early SME than for the middle SME were significant only in the high-gamma band. We found that this effect extended to medial temporal lobe structures, including the amygdala, entorhinal cortex, and parahippocampal gyrus. In addition, for low-frequency activity in medial temporal lobe regions, we noted a negative interaction (shown in blue typeface), where the difference in mean power between successfully and unsuccessfully encoded items was greater for middle list items (middle SME) than for early list items (early SME). The early and middle SMEs were examined individually in order to allow interpretation of a difference of differences. In both the hippocampus and amygdala, the low-frequency position–recall interaction was driven by a significant strong negative early SME when compared with a still negative and significant but attenuated middle SME, in both cases significant.

To visualize the timing of the significant results, the spectral power within the time scale of individual events was plotted. Figure 3, in the left most column, shows the difference in the mean *Z*-scored power across all 6913 electrodes outside the seizure focus of all 84 participants, for all subsequently recalled minus not-recalled words, regardless of serial position. The right column of Figure 3 shows the difference in mean *Z*-scored power across the same electrodes for all early minus middle list items, regardless of recall status. We had chosen to focus our analysis on the 0–2-s window after word presentation to be consistent with prior primacy analysis (Sederberg et al. 2006). In keeping with the previously characterized SME (Sederberg et al. 2007a, b), the spectral power during encoding of subsequently recalled items was accompanied by a diminution of lower frequency, and enhancement of higher frequency, activity when compared with the presentation of items that are not subsequently

recalled. These effects appeared qualitatively throughout the 2-s interval.

Having visualized the spectral energy within an individual event, we next sought to display how spectral energy of neural activity evolved in the course of the list of items (Fig. 4). Gradual shifts in power as a function of serial position were seen at all spatial scales, from the entire brain to individual BAs. Whereas gamma power generally decreased with serial position, oscillatory power at lower frequencies showed the opposite trend, increasing with serial position. As shown in Figure 4, the tendency for power to shift in the course of the list occurred regardless of whether an item at each particular serial position was subsequently recalled (in red) or not (in blue); however, delta power tended to be more suppressed, and gamma power enhanced for subsequently recalled items at the start of the list. These gradual shifts in spectral power were found to be qualitatively similar in all participants and all brain regions examined.

Having identified areas exhibiting significant encoding and position effects (Fig. 2), we next sought to clarify the relative magnitude of *Z*-scored power for recalled versus nonrecalled and early versus middle events. To render this analysis tractable given the large number of regions, we defined 3 regions of interest (ROIs) known to be involved in memory: Medial temporal cortex, lateral temporal cortex, and dorsolateral prefrontal cortex (Strange et al. 2002; Sederberg et al. 2007b; Axmacher et al. 2009). ROIs were defined bilaterally: Hence, a participant could contribute electrodes to the right, left, or both homologs of a structure to be included in the analysis. The medial temporal cortex included entorhinal and parahippocampal cortices because these cortical areas had shown interaction effects in our earlier analysis (Fig. 2e). To reduce the number of comparisons, we a priori confined this analysis to the theta and high-gamma frequency bands, both known to exhibit memory-related effects in our prior analysis (Fig. 2) and the broader literature. Whereas the summed *t*-statistic methodology used in our previous analyses is appropriate for testing an effect in a given focal brain region, that method is less well suited for quantitative comparisons between regions. As such, we adopted the conventional approach for estimating the interaction between serial position and subsequent recall status for each participant and then estimating the standard error of these effects across participants with electrodes in those ROIs. For each of these 3 broad ROIs, at each of 2 frequency bands (theta and high gamma), we performed a 2-factor repeated-measures analysis of variance (ANOVA), with SME (subsequently recalled or not recalled) and POS (early or middle list position) as the 2 factors. The significance threshold was determined by applying a false-discovery rate with $\alpha = 0.05$ to the distribution of all *P*-values of all ANOVA repetitions. Our question was whether the general patterns seen in Figure 2 were reliably present in specific ROIs when equally weighting data across participants.

Based on the previous analyses, we would expect to see a general pattern of higher gamma and lower theta for primacy items (when compared with middle list items), and this is precisely what we found (Fig. 5). This effect of primacy (POS) was significant in medial temporal cortex (degrees of freedom, DOF = 115; $F = 4.03$ in the theta band), lateral temporal cortex (DOF = 319, $F = 18.48$ for theta, $F = 12.05$ for high gamma), and dorsolateral prefrontal cortex (DOF = 215, high-gamma band, $F = 12.39$). We also expected that
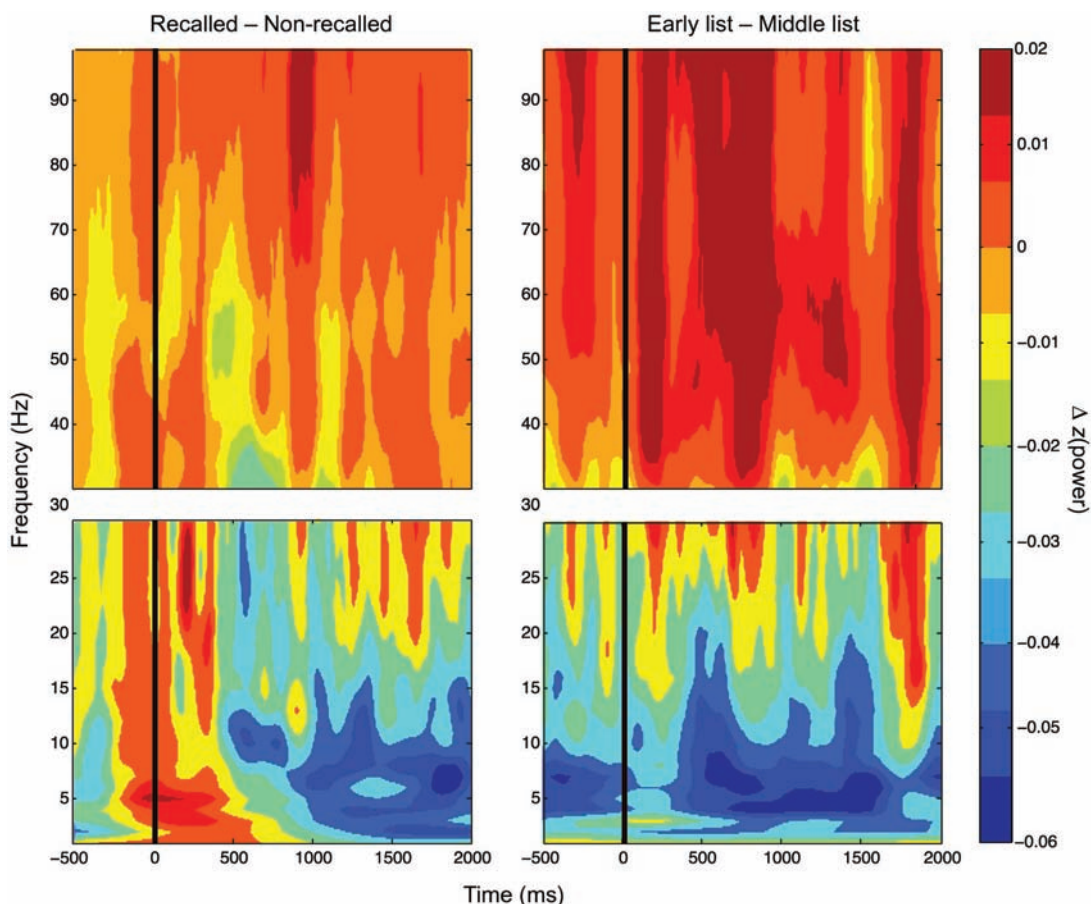
Figure 3. Power spectrographic signatures of encoding and position. Power was averaged across all electrodes within a subject, and then across all 84 subjects, for events indicated. In the leftmost column, the left panels indicate the difference spectrogram generated by subtracting the mean spectrogram for all subsequently not-recalled events from the mean spectrogram for all subsequently recalled events. This pattern of enhanced high-frequency activity and attenuated low-frequency activity during the encoding of subsequently recalled words is termed a SME. The right panels represent the difference spectrogram generated by subtracting the mean spectrogram for all middle events from the mean spectrogram for all early events. Power was as computed in the −500 to 2000 ms following word presentation. Color bars represent difference in Z-scored power.
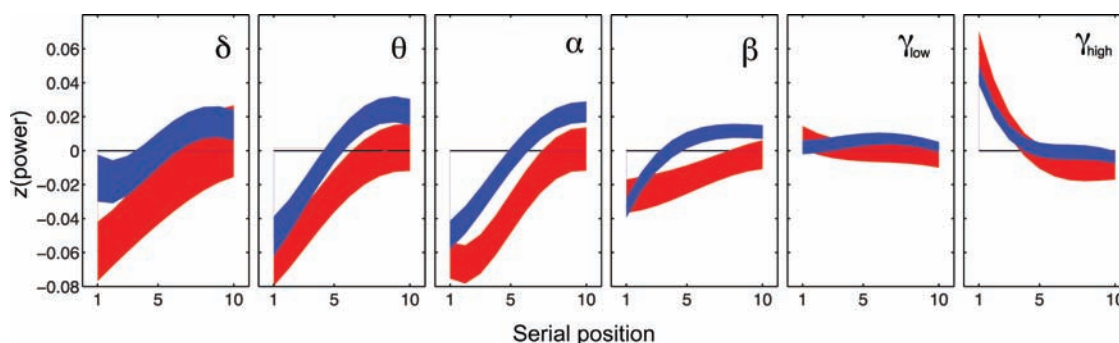

Figure 4. Oscillatory power gradients vary with serial position broadly throughout the brain. Whereas the Z-transformed oscillatory low gamma (28–42 Hz) and high-gamma (44–100 Hz) powers generally decrease with serial position, mirroring the behavioral primacy effect seen in Figure 1, oscillatory power at lower frequencies, such as delta (1–4 Hz) and theta (4–8 Hz), show the opposite trend, increasing with serial position. Power was as computed in the 0–2000 ms following word presentation at each of the first 10 positions, regardless of subsequent recall, averaged across all electrodes within a participant then across all participants ($n = 84$). The red areas represent the power derived only from events where the word was subsequently recalled; whereas the blue areas represent power derived only from events where the word was not recalled; the shaded areas encompass ±1 standard error of the mean.

subsequently recalled (when compared with not-recalled) items would be associated with higher gamma and lower theta (with the comparison denoted SME in Fig. 5). While Z-scored theta power was indeed significantly lower for subsequently recalled items in all 3 ROIs ($F = 14$, 33, and 8 for

medial temporal, lateral temporal, and dorsolateral prefrontal cortices, respectively), a relative increase in high gamma was not observed (similar to the limited scope of gamma increases seen in Fig. 2a). Although the main effects of primacy and encoding were not observed in the medial temporal cortex in
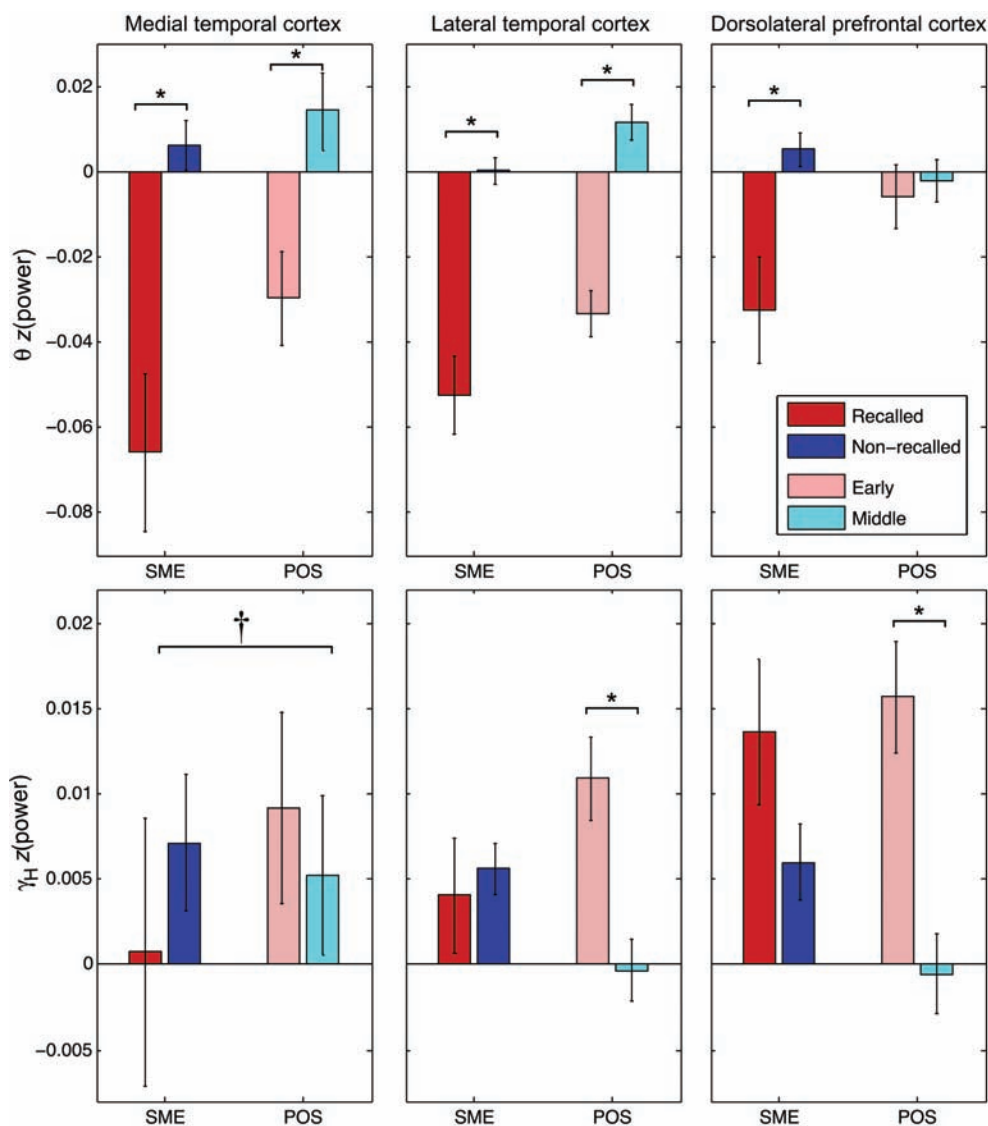
Figure 5. Theta and high-gamma powers vary with encoding and position in broad cortical areas related to episodic memory. The distributions of Z-transformed theta (4–8 Hz) and high-gamma (44–100 Hz) power in the 0–2 s after word presentation, taken across participants, for 3 cortical areas thought to be involved in memory (medial temporal cortex, lateral temporal cortex, and dorsolateral prefrontal cortex), vary as a function of whether the word is subsequently recalled (SME) and the position when a word is encountered in the list (POS). For each of 3 areas, a 2-factor repeated-measures ANOVAs (with recall status and position as the 2 factors) were performed separately for the theta and gamma bands. The significance P-value threshold was determined by applying a false-discovery rate with $\alpha = 0.05$ (significant main effects meeting this criterion are indicated with an asterisk). Theta power was significantly lower for subsequently recalled, when compared with subsequently not recalled, items in all 3 cortical regions; no significant SME effects was found in the high gamma band. Theta power was lower for the encoding of early, when compared with middle list, items in all 3 cortical regions: This effect was significant in temporal cortices. Likewise, high-gamma power was increased for primacy items: This effect was significant in the lateral temporal and dorsolateral prefrontal cortices. A significant interaction between encoding and primacy was noted only in the high-gamma band in the medial temporal cortices (denoted by dagger symbol in the bottom left panel). Error bars represent ±1 standard error of the mean.

the high-gamma band, this was the one case where a significant "interaction" between primacy and encoding was observed ($F = 6.67$; indicated by a dagger symbol in the lower left panel of Fig. 5).

To determine the anatomical specificity of these interactions, we conducted a 3-way ANOVAs on each pair of ROIs, with serial position, recall status, and ROI as factors. We repeated this ANOVA for all 3 possible pairs of ROIs and at the 2 frequency bands (theta and high gamma). To minimize Type I error, the significance threshold was determined by applying a false-discovery rate with $\alpha = 0.05$ to the distribution of P-values generated for all repeated comparisons. To visualize the relative magnitude of the position–recall interaction,

we calculated a "difference of differences" for each region. We did this by calculating a "recalled difference" (Z-scored power during early subsequently recalled items minus Z-scored power during middle subsequently recalled items) and a "not-recalled difference" (Z-scored power during early subsequently not-recalled items minus Z-scored power during middle subsequently recalled items), and then calculated the difference between these differences. While no significant 3-way interactions were found in the theta band, significant 3-way interactions were found when comparing medial temporal cortex with lateral temporal cortex (DOF = 435, $F = 5.54$), or to dorsolateral prefrontal cortex (DOF = 331, $F = 4.63$), in the high-gamma band. As shown in Figure 6, the

relative magnitude of the difference of difference Z-scored power was greater for the medial temporal cortex than the other 2 ROIs.

Discussion

This study explored the anatomical and electrophysiological basis of the primacy effect in order to better elucidate the fundamental mechanisms of human memory. The large primacy effect seen in our data (Fig. 1) is commonly found in intentional learning tasks and may reflect the participants' use of elaborative rehearsal strategies to help associate items and encode them into memory (Craik and Tulving 1975). Our previous work found that early items exhibited enhanced gamma power, while the encoding of items in the middle of the list was accompanied by increased low-frequency power (Sederberg et al. 2006). As in that scalp EEG study, these power shifts were found to be steady gradients (Fig. 4) rather than abrupt shifts in power. Whereas prior work had shown evidence for gradients in scalp-recorded event-related potential amplitudes (Azizian and Polich 2007), our results reveal that different frequency bands exhibit distinct trends, with lower-frequency oscillatory power gradually increasing with serial position and higher-frequency power decreasing. This general trend was found in all brain regions examined, in all 84 participants, in both hemispheres, and extended to medial temporal lobe structures (Figs 2 and 4).

By evaluating the difference between spectrographic correlates of subsequent recall in early versus in middle list items, we identified areas that showed an interaction between encoding efficacy and when that word was encountered in the list (Fig. 2e). This interaction could also be seen in our power trend plots: Although power during encoding changed as a gradient steadily throughout each list regardless of subsequent recall, early recalled items exhibited additional power in the high-gamma band and middle list recalled items exhibited increased power in the lower-frequency bands (Fig. 3). As shown in Figure 2e, the primacy–recall interaction was particularly strong in medial temporal lobe structures. Furthermore, the magnitude of the encoding–position interaction was more pronounced in the medial temporal cortices when directly compared with other cortical areas known to play a role in memory, such as the lateral temporal cortex and dorsolateral prefrontal cortex (Fig. 6).

While our current finding that intracranial high-gamma activity exhibited a significant interaction effect between subsequent memory and serial position was similar to what we observed in the scalp data (see Fig. 4 in Sederberg et al. 2006), the previously identified interactions in lower frequencies (4–26 Hz) were not detected here in any cortical region. The presence of this negative position–recall interaction does not appear to have a correlate in the Sederberg et al. (2006) scalp study (the absence of "blue" areas in Fig. 4 in Sederberg et al. 2006). On the contrary, here, we found that medial temporal lobe regions exhibited an opposite trend, with a greater difference in lower-frequency power for middle list items. Prior iEEG work suggests that low-frequency power might correlate directly with interference between items encoded at different times (Axmacher et al. 2009; van Vugt et al. 2010) and generally decreased information processing capacity (Hanslmayr et al. 2012). In light of this, our data might imply greater interference for items encoded later in the list. More generally, the detection and direction of theta SME may be affected by different techniques (e.g., magnetoencephalography vs. scalp EEG), tasks (word recognition vs. free recall), or encoding strategy (e.g., semantic vs. nonsemantic; Hanslmayr et al. 2009) and certain narrow-band SMEs might be more spatially confined anatomically or participant-specific. For example, positive SMEs are often found at individual channels (Sederberg et al. 2003; Osipova et al. 2006) and may be averaged out when areas are defined more broadly and across more participants as in this study. Furthermore, the detection of a positive low-theta SME drawing upon the same data set used here was found only after subtracting out broadband power (Lega
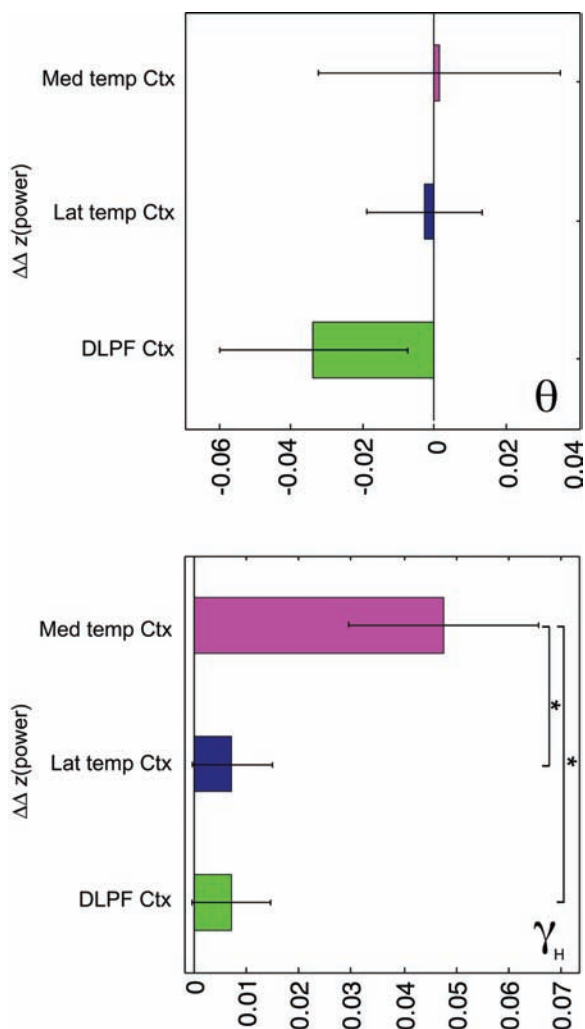

Figure 6. The magnitude of the encoding–position interaction in theta and high-gamma power is greater in the medial temporal cortex when compared with lateral temporal and dorsolateral prefrontal cortices. Bars represent the difference of the recalled difference in Z-scored power (early recalled minus middle recalled) minus the nonrecalled difference (early not-recalled minus middle not-recalled). A 3-way ANOVAs (with recall status, early versus middle list position, and region as factors) were performed for each pair of regions, separately at the theta and high-gamma bands; the significance P threshold was determined by applying a false-discovery rate with $\alpha = 0.05$. Though the magnitude of this difference of differences appeared greater in the medial temporal cortex than the other areas (upper panel), the 3-way interactions were not significant. In the high-gamma band, however, significant 3-way interactions were observed when comparing the medial temporal cortex with the other cortical areas (lower panel). The position–recall difference of differences in Z-scored power was greatest in the medial temporal cortices. Error bars represent ±1 standard error of the mean.

et al. 2012), an additional analysis beyond the scope of the present one.

The waxing of low-frequency activity concomitant with the waning of high-frequency activity in the course learning a list of words (a process modulated by the success of encoding at each word) raises the outstanding question of whether the low and high-frequency changes are manifestations of 2 distinct oscillators or a shift in power spectral energy of a single broadband process (Kilner et al. 2005; Martuzzi et al. 2009; Miller et al. 2009). The gradual, time-locked, and ubiquitous nature of this power spectral ebb and flow was unexpected, and the experiment was not designed to elucidate its mechanism. If this gradual pivot of the entire spectrum was a single broadband process (Fig. 4; with the fulcrum in the beta to gamma 20–40 Hz band) of deactivation (with a gradual increase in low relative to high frequencies), one would predict concomitant attenuation in a BOLD signal if participants were imaged with fMRI (Kilner et al. 2005). Inasmuch as the shifts in gamma activity seen here arise from broadband fluctuations, they may in fact be driven by multiunit activity rather than a distinct oscillating network (Buzsaki et al. 2012).

If we view the gradual power shifts as separate oscillations, then early high gamma could be a manifestation of top-down undivided attention phenomena specific to the gamma band (Engel et al. 2001; Sederberg et al. 2006; Jutras et al. 2009), and the waxing low-frequency activity of an interference process specific to delta–theta (Axmacher et al. 2009). Prior work has shown that gamma activity with complex temporal dynamics is spatially confined to areas most related to the particular task (e.g., primary visual cortex for visual processing), while an increasingly broader range of lower frequencies ripples outwards to higher-order and more frontal areas (Martuzzi et al. 2009). As seen in other studies (Sederberg et al. 2003; Chalk et al. 2010), we found that activity in various frequency bands is dissociable and their inter-relationship can vary significantly depending on both subsequent memory and brain region (e.g., in Figs 2 and 5, areas showing significant position or encoding effects are not precise mirror inverses of each other as one goes from lower to high frequencies).

Though different oscillations in the power spectra may indeed arise from distinct mechanisms or processes, this would not preclude them from being intertwined. Prompted by work in both macaque cortex and human iEEG indicating that delta activity-indexed gamma oscillations (Whittingstall and Logothetis 2009; Voytek et al. 2010), recent analysis using part of the same dataset investigated here showed that the human brain, when engaged in active behavioral processing, exhibits a variety of phase-amplitude couplings (van der Meij et al. 2012). While ongoing work will be needed to separate out the relative contributions of oscillators from broadband shifts, and the precise mechanisms underlying each, one can safely assume that activity in a given frequency band is a complex summation of different processes ranging from volume-averaged postsynaptic potentials and ephaptic effects to the envelope of multiunit activity (Buzsaki et al. 2012).

The primacy effect, in which people remember items studied earlier in a list better than later items, is a robust phenomenon in human learning (Jenkins and Dallenbach 1927; Murdock 1962). Early items may be better encoded because they benefit from additional rehearsals (Rundus 1971; Tan and Ward 2000), lack predecessors and thus perceptually distinctive or free from interference (Murdock 1962;

Underwood 1975; Cowan et al. 2002), or because they receive greater and more focused attention or activity-dependent encoding energy (Atkinson and Shiffrin 1968; Neath and Crowder 1990; Page and Norris 1998; Brown et al. 2000; Tulving and Rosenbaum 2006). The current experiment was not designed to dissociate the roles of attention, rehearsal, perceptual salience, semantic clustering, or other effects. The fact that power shifts occur throughout the entire brain and operate at a time scale of seconds, does, however, place constraints on mapping encoding-related processes onto their neural substrates.

The neural power gradients, which we found occurring throughout the entire cortex and mesial structures, may reflect the effects of a global modulatory circuit such as the ascending reticular activating system (Mesulam 2010), dopaminergic midbrain nuclei such as the substantia nigra (Morris et al. 2006) or cholinergic forebrain nuclei (Baxter and Chiba 1999). These gradients might also represent an "attentional resource" that is gradually depleted as items are studied. A gradual depletion might be consistent with the camatosis hypothesis (Tulving and Rosenbaum 2006), which posits neural assemblies "fatigue" with the "effort" of encoding information. Consequently, camatosis predicts less efficient encoding for subsequent stimuli until a suitable amount of time has passed to allow the system to recover (e.g., for the next list of words). Studies that explicitly vary attentional demand and the salience of individual items at various list positions will be necessary to address these possibilities.

The same global, gradual shifts in power occurring throughout the brain may cause diverse effects in particular regions, whereas increased gamma activity may facilitate selective attention in primary visual cortices (Engel et al. 2001; Fries et al. 2001; Jutras et al. 2009), it may enhance the encoding of early list items when acting at synapses in the entorhinal cortex and the hippocampus. Just as a rising tide lifts all boats, the power shifts that track serial position are manifest throughout the cortex and in the medial temporal lobe. Like a tug boat buoyed by this tide to perform its job more efficiently, these memory hub structures appear to ride this wave of enhanced gamma, and attenuated slow oscillations, to more efficiently encode early list items in a manner that we speculate contributes to the ubiquitous primacy effect in human memory.

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