



# Successful memory formation is driven by contextual encoding in the core memory network



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## ABSTRACT

To understand how memories are successfully formed, scientists have compared neural activity during the encoding of subsequently remembered and forgotten items. Though this approach has elucidated a network of brain regions involved in memory encoding, this method cannot distinguish broad, non-specific signals from memory specific encoding processes, such as associative encoding. Associative encoding, which is a key mechanism of learning, can be seen in the tendency of participants to successively recall, or cluster, study neighbors. We assessed the electrophysiological correlates of associative processing by comparing intracranially recorded EEG activity during the encoding of items that were subsequently recalled and clustered; recalled and not clustered; or not recalled. We found that high frequency activity (HFA) in left prefrontal cortex, left temporal cortex and hippocampus increased during the encoding of subsequently recalled items. Critically, the magnitude of this effect was largest for those recalled items that were also subsequently clustered. HFA temporally dissociated across regions, with increases in left prefrontal cortex preceding those in hippocampus. Furthermore, late hippocampal HFA positively correlated with behavioral measures of clustering. These results suggest that associative processes linking items to their spatiotemporal context underlie the traditionally observed subsequent memory effect and support successful memory formation.

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## Introduction

To investigate the neural mechanisms of successful memory formation, scientists compare brain activity measured during the encoding of subsequently remembered and subsequently forgotten items. Neuroimaging studies investigating these subsequent memory effects (SMEs) have revealed that increased activation in a network of temporal and prefrontal cortical regions predict subsequent memory (Wagner et al., 1998; Paller and Wagner, 2002; Kim, 2011; Burke et al., 2014). However, these changes in activation might be due to any number of processes, including increased attention, use of elaborative strategies, or the formation of item-to-context associations. Forgetting an item could be caused by failures of any of these processes. Therefore, to establish whether the SME is driven by memory-specific processes or a mnemonic attentional signal, it is necessary to use a more fine-grained contrast comparing items that vary in *how* they are remembered, not *whether* they are remembered.

In a free recall task, items that are effectively encoded in relation to their context exhibit strong temporal clustering, being recalled in close proximity to their study-list neighbors (Kahana, 1996). By comparing brain activity during the encoding of items that are subsequently clustered with those that are not clustered (defined here as the

subsequent clustering effect, SCE), we can isolate the neural correlates of effective item-to-context associative memory encoding. To identify the memory-specific neural mechanisms supporting memory formation, we compared the SCE and SME. We hypothesized two potential outcomes. First, the SCE may be a component of the SME. Activation in the SME might be driven by items that are subsequently clustered, a prediction supported by behavioral evidence showing that increased clustering correlates with high recall success (Sederberg et al., 2010). Alternatively, the SCE and SME may be independent and while clustering may correlate with probability of recall, both may be moderated by a third unknown variable (Brown et al., 1991). In this case, the SME might instead be driven by attentional mechanisms. Elevated attention across a subset of items could enhance recall for those items, but, as clustering arises predominantly from cue dependent retrieval processes (Schwartz et al., 2005; Howard et al., 2008), enhanced attention would be unlikely to give rise to the substantial clustering effects that are typically observed.

We analyzed intracranial electroencephalographic (iEEG) data from neurosurgical patients participating in a free recall task. The recorded iEEG signals simultaneously sample local field potentials throughout the brain, and can be analyzed in terms of specific time-varying oscillatory or spectral components of neural activity. Using brain regions selected *a priori* based on previous subsequent memory studies, we measured the spectral signals during encoding of words that were later clustered; later recalled and not clustered; or later forgotten.

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To foreshadow our results, we found that high frequency activity (HFA, 44–100 Hz) in the memory network tracked effective contextual encoding with greater HFA for subsequently clustered compared to subsequently recalled non-clustered items. Furthermore, we found that the timing of this effect dissociated across regions: left prefrontal cortex clustering related increases in HFA preceded those in hippocampus and late hippocampal HFA was correlated with the behavioral tendency to cluster responses.

## Materials and methods

### Participants

136 participants (58 female; age range: 8–57, mean = 33) with medication-resistant epilepsy underwent a surgical procedure in which electrodes were implanted subdurally on the cortical surface and deep within the brain parenchyma. In each case, the clinical team determined electrode placement so as to best localize epileptogenic regions. Data were collected as part of a long-term multicenter study; data were collected at Boston Children's Hospital, Hospital of the University of Pennsylvania, Freiburg University Hospital, and Thomas Jefferson University Hospital. The institutional review board at each hospital approved the research protocol. We obtained informed consent from the participants or their guardians. Participants were left-hemispheric language dominant as assessed by either the participants' handedness or a clinically administered intracarotid injection of sodium amobarbital (Wada test). Clinical need determined the electrode placements and the total number of participants contributing to each region of interest ranged from 60 (left inferior frontal gyrus) to 86 (left inferior temporal cortex). Although portions of this dataset were previously reported (Burke et al., 2014; Long et al., 2014), all of the analyses and results described here are novel. The raw, de-identified data as well as the associated codes used in this study can be accessed at the Cognitive Electrophysiology Data Portal ([http://memory.psych.upenn.edu/Electrophysiological\\_Data](http://memory.psych.upenn.edu/Electrophysiological_Data)).

### Intracranial recordings

iEEG data were recorded using a Bio-Logic, DeltaMed, Nicolet, GrassTelefactor, or Nihon Kohden EEG system. Depending on the amplifier and the discretion of the clinical team, the signals were sampled at 256, 400, 500, 512, 1000, 1024, or 2000 Hz. Signals were referenced to a common contact placed either intracranially or on the scalp or mastoid process. Contact localization was accomplished by co-registering the post-op CTs with the MRIs using FSL Brain Extraction Tool (BET) and FLIRT software packages. Contact locations were then mapped to both MNI and Talairach space using an indirect stereotactic technique. Depth electrodes were manually localized by a neuroradiologist experienced in neuroanatomical localization utilizing post-operative MRIs and CT images in order to accurately identify all depth contacts located within the hippocampus. For each participant and electrode, the raw EEG signal was downsampled to 200 Hz and a fourth order 2 Hz stopband butterworth notch filter was applied at 50 or 60 Hz to eliminate electrical line noise.

### Free recall task

Participants studied lists of 15 or 20 high-frequency nouns for a delayed free recall task (Fig. 1A). The computer displayed each word for 1600 ms, followed by an 800 to 1200 ms blank interstimulus interval. Immediately following the final word in each list, participants were given a series of arithmetic problems of the form  $A + B + C = ??$ , where A, B and C were randomly chosen integers ranging from 1–9. This distractor interval lasted at least 20 s, but participants were allowed to complete any problem that they started resulting in an average retention interval of 25 s. After the distractor, participants had 45 s to freely

recall as many words as possible from the list in any order. Vocalizations were digitally recorded and later manually scored for analysis. On average, participants participated in two sessions.

### Data analyses and spectral power

Two concerns when analyzing bivariate interactions between closely spaced intracranial contacts are volume conduction and confounding interactions with the reference line. We used bipolar referencing to eliminate such confounds when analyzing the neural signal (Nunez and Srinivasan, 2006). We found the difference in voltage between pairs of immediately adjacent electrodes (Burke et al., 2013). The resulting bipolar signals were treated as new virtual electrodes and are referred to as such throughout the text. Analog pulses synchronized the electrophysiological recordings with behavioral events.

We applied the Morlet wavelet transform (wave number 6) to all bipolar electrode EEG signals from 300 ms preceding to 1600 ms following word presentation, across 46 logarithmically spaced frequencies (2–100 Hz). We included a 1000 ms buffer on both sides of the data to minimize edge effects. After log transforming the power, we downsampled the data by taking a moving average across 100 ms time windows and sliding the window every 50 ms, resulting in 31 time intervals (16 non-overlapping) from –300 ms to 1600 ms surrounding stimulus presentation. Power values were then Z-transformed within session by subtracting the mean and dividing by the standard deviation power. Mean and standard deviation power were calculated across all encoding events and time points in a session for each frequency. We split the Z-transformed power into six distinct frequency bands ( $\theta_L$ , 3–4 Hz;  $\theta_H$ , 6–8 Hz;  $\alpha$ , 10–14 Hz;  $\beta$ , 16–26 Hz;  $\gamma_L$ , 28–42 Hz;  $\gamma_H$ , 44–100 Hz; Sederberg et al., 2006), by taking the mean of the Z-transformed power in each frequency band. We included two theta bands as there is evidence for distinct slow and fast theta bands (Lega et al., 2011).

Our conditions of interest were subsequently recalled clustered items, study items recalled either preceding or following the recall of a study neighbor (absolute lag between serial position of items was 1), subsequent recalled non-clustered items, study items recalled preceding and following the recall of a non-neighboring study item (absolute lag between serial position of items was 2 or greater), and subsequently not recalled items. Across participants there were on average 44 clustered items, 56 non-clustered items, and 358 not recalled items. A participant had to have a minimum of 5 items per condition to be included in the analysis, 126 participants met this criterion.

Our two contrasts were between subsequently recalled and forgotten items and between subsequently clustered and non-clustered items. For each contrast of interest and for each participant, electrode and frequency band, we calculated Z-transformed power in each of two conditions. We averaged Z-power values across electrodes within a region of interest (ROI) as we were interested in effects consistent across an ROI and not regional differences within an ROI. Therefore, each participant contributed a single Z-power value for each of two conditions for each ROI. Conditions were compared across participants within an ROI and frequency using a paired *t*-test.

### Region of interest selection and analysis

The three ROIs were derived from several recent large scale studies suggesting that these are core regions in the memory network (Kim, 2011; Burke et al., 2014; Long et al., 2014). We defined ROIs using Brodmann area or neuroradiological localization and included left inferior frontal gyrus (LIFG, BA 45/47, N = 60), left inferior temporal lobe (LIT, BA 20/21, N = 86) and hippocampus (N = 64). Each participant had at least two electrode pairs in a given ROI.

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