Neural Mechanisms of Episodic Memory formation

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Neural Mechanisms of Episodic Memory formation

Abstract
In order to remember what you had for breakfast today, you must rely on episodic memory, the memory for personal events situated within a spatiotemporal context. In this dissertation, I use electroencephalographic (EEG) recordings to measure the neural correlates of successful episodic memory formation. The recorded EEG 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 which are thought to reflect the concerted activity of neuronal populations. I collected EEG recordings while participants engage in free recall, an episodic memory task during which participants must study and then recall a list of items. In the first chapter, I compare the spectral correlates during encoding of items later remembered to those later forgotten using two separate recording modalities, scalp and intracranial EEG. I find that memory formation is characterized by broad low frequency spectral power decreases and high frequency power increases across both datasets, suggesting that scalp EEG can resolve high frequency activity (HFA) and that low frequency decreases in intracranial EEG are unlikely due to pathology. In the next chapter, I connect these HFA increases to memory-specific processes by comparing study items based on how they are recalled, not whether they are recalled. I find increased HFA in left lateral cortex and hippocampus during the encoding of subsequently clustered items, those items recalled consecutively with their study neighbors at test. The precise time course of these results suggests that context updating mechanisms and item-to-context associative mechanisms support successful memory formation. In the third chapter, I measure how the formation of these episodic associations is modulated by pre-existing semantic associations by including a semantic orienting task during the encoding interval. I find that semantic processing interferes with the formation of new, episodic memories. In the final chapter, I show that the memory benefit for emotionally valenced items is better explained by a contextual mechanism than an attentional mechanism. Together, my work supports the theory that contextual encoding associative mechanisms, reflected by HFA increases in the memory network, support memory formation.

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NEURAL MECHANISMS OF EPISODIC MEMORY FORMATION

Nicole Marie Long

A DISSERTATION

in

Psychology

Presented to the Faculties of the University of Pennsylvania

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Nicole Marie Long
To Jonathan.
First, I would like to thank my advisor, Mike Kahana. It has been through Mike’s guidance and support that I have become the researcher that I am today. Mike has taught me both how to critically evaluate the details of my work and how to take a step back and view my work in the context of the larger literature. I would also like to thank my previous mentors, Lila Davachi and David Badre, who gave me support and encouragement when I was just learning about memory and neuroscience research.

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ABSTRACT

NEURAL MECHANISMS OF EPISODIC MEMORY FORMATION

Nicole Marie Long
Michael J. Kahana

In order to remember what you had for breakfast today, you must rely on episodic memory, the memory for personal events situated within a spatiotemporal context. In this dissertation, I use electroencephalographic (EEG) recordings to measure the neural correlates of successful episodic memory formation. The recorded EEG 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 which are thought to reflect the concerted activity of neuronal populations. I collected EEG recordings while participants engage in free recall, an episodic memory task during which participants must study and then recall a list of items. In the first chapter, I compare the spectral correlates during encoding of items later remembered to those later forgotten using two separate recording modalities, scalp and intracranial EEG. I find that memory formation is characterized by broad low frequency spectral power decreases and high frequency power increases across both datasets, suggesting that scalp EEG can resolve high frequency activity (HFA) and that low frequency decreases in intracranial EEG are unlikely due to pathology. In the next chapter, I connect these HFA increases to memory-specific processes by comparing study items based on how they are recalled, not whether they are recalled. I find increased HFA in left lateral cortex and hippocampus during the encoding of subsequently clustered items, those items recalled consecutively with their study neighbors at test. The precise time course of these results suggests that context updating mechanisms and item-to-context
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Contents

Acknowledgments iv
Abstract vi
Contents viii
List of tables x
List of figures xi

1 Introduction 1
  1.1 Spectral signals of episodic memory encoding 2
  1.2 Retrieved context theory 6
  1.3 Semantic memory in the context of episodic memory 8
  1.4 Overview 9

2 Subsequent memory effect in intracranial and scalp EEG 10
  2.1 Abstract 10
  2.2 Introduction 11
  2.3 iEEG Methods 13
  2.4 Scalp Methods 15
  2.5 Results 21
2.6 Discussion ................................................................. 27

3 Contextual encoding mechanisms in hippocampus and prefrontal cortex support successful memory formation. 33
3.1 Abstract ................................................................. 33
3.2 Introduction ............................................................. 34
3.3 Materials and Methods .................................................. 36
3.4 Results ................................................................. 40
3.5 Discussion ............................................................... 43

4 Modulation of task demands suggests that semantic processing interferes with the formation of episodic associations 48
4.1 Abstract ................................................................. 48
4.2 Introduction ............................................................. 49
4.3 Results ................................................................. 51
4.4 Discussion ............................................................... 57
4.5 Materials and Methods .................................................. 61

5 Recall dynamics reveal the retrieval of emotional context 65
5.1 Abstract ................................................................. 65
5.2 Introduction ............................................................. 66
5.3 Norming study ........................................................... 69
5.4 Free recall study ......................................................... 71
5.5 Results and Discussion .................................................. 75
5.6 Supplemental ............................................................ 78

6 General discussion ...................................................... 82
6.1 Summary ................................................................. 82
6.2 Future Directions .................................................. 85
6.3 Concluding remarks ........................................... 87

References ................................................................. 89
List of tables

2.1 Subsequent memory effect in iEEG and scalp EEG studies . . . . . . 22
# List of figures

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.1</td>
<td>Maps of <em>a priori</em> selected regions of interest.</td>
<td>19</td>
</tr>
<tr>
<td>2.2</td>
<td>Frequency analysis of the subsequent memory effect</td>
<td>25</td>
</tr>
<tr>
<td>2.3</td>
<td>Time-frequency analysis of the subsequent memory effect</td>
<td>32</td>
</tr>
<tr>
<td>3.1</td>
<td>Behavioral measures of recall performance</td>
<td>41</td>
</tr>
<tr>
<td>3.2</td>
<td>Subsequent memory and clustering effects</td>
<td>41</td>
</tr>
<tr>
<td>3.3</td>
<td>Clustering effects across time</td>
<td>43</td>
</tr>
<tr>
<td>3.4</td>
<td>Relation between hippocampal activation and temporal difference score</td>
<td>44</td>
</tr>
<tr>
<td>4.1</td>
<td>Methods and behavioral results</td>
<td>51</td>
</tr>
<tr>
<td>4.2</td>
<td>Subsequent clustering effects</td>
<td>54</td>
</tr>
<tr>
<td>4.3</td>
<td>HFA as a function of clustering and list type</td>
<td>55</td>
</tr>
<tr>
<td>4.4</td>
<td>Subsequent memory effect for semantically isolated items</td>
<td>57</td>
</tr>
<tr>
<td>5.1</td>
<td>Conditional response probability based on valence</td>
<td>77</td>
</tr>
<tr>
<td>5.2</td>
<td>Semantic-valence CRP</td>
<td>80</td>
</tr>
</tbody>
</table>
Chapter 1

Introduction

Our memories are composed of personal experiences as well as knowledge for facts. The distinction between these types of memories was formalized by Endel Tulving (Tulving, 1972) when he coined the term “episodic memory”. Episodic memories are unique to an individual; many people know that Paris is the capital of France, but only I can re-experience the night when I was visiting Paris and was faced with the dilemma: nutella crêpe or jam crêpe? (The answer is get one, and once you’ve walked one block to the next crêpe stand, get the other flavor.) This experiential quality, the ability to perform a sort of mental time travel when retrieving a memory, is one of the major features that dissociates episodic from semantic memory, the memory for facts or knowledge devoid of such contextual details.

Episodic memory can be measured in the laboratory through the free recall paradigm. In free recall, a participant studies a list of items, typically words or nameable objects, and either immediately after study or after a brief delay, must recall any items from the preceding list. Each item is considered an “episode” and the ability to retrieve an item is based on the success of reinstating the spatiotem-
poral context in which that episode was first experienced. As there are no external cues available during test, free recall mirrors aspects of real-world retrieval.

Our understanding of episodic memory processes has greatly benefited from behavioral studies utilizing free recall; however, behavioral studies cannot disentangle successful encoding from successful retrieval processes as the behavioral data collected during retrieval may reflect success during encoding, retrieval, or both. In order to understand the mechanisms that support successful episodic encoding, we utilize neuro-imaging methods to measure neural signals while participants study lists of items. This enables the comparison between encoding items that are subsequently remembered and subsequently forgotten. This subsequent memory effect (SME) analysis is a classic technique in the study of memory encoding.

1.1 Spectral signals of episodic memory encoding

Researchers began studying memory encoding processes through electroencephalographic (EEG) recordings using electrodes placed on the scalp. EEG recordings measure voltage potentials across the brain. Whereas an event related potential (ERP) analysis can reveal voltage differences between conditions of interest and was one of the earliest measures used to study encoding processes (Sanquist et al., 1980; Paller et al., 1987, 1988), EEG data contains other dimensions of information. Specifically, any given voltage trace is composed of a series of sine waves of particular frequencies, amplitudes and phase characteristics. Unlike ERP analyses, where the interpretation of polarity is unclear, these rhythmic signals directly reflect the concerted activity of groups of neurons or cell assemblies (Lachaux et al., 2003). These oscillatory or spectral signals arise due to modulations in neuronal excitabil-
ity that affect the likelihood of spike output and sensitivity to synaptic input and are considered the dominant communication mechanism of the brain (Fries, 2005; Schnitzler & Gross, 2005; Jacobs & Kahana, 2010).

The power, or squared amplitude, of a spectral signal reveals how much energy of a particular frequency is contained in an EEG trace. Decades of research, beginning with Berger (1929) has shown that fluctuations in power at specific frequency bands correlate with a wide array of cognitive, perceptual, and motor processes. Although the exact definitions tend to vary, there are five commonly measured frequency bands which include delta (2 - 4 Hz), theta (3 - 8 Hz), alpha (8 - 14 Hz), beta (16 - 26 Hz), and gamma (> 30 Hz).

Across these five bands, two frequencies have emerged as critical players in the service of memory: theta and gamma. As theta represents the “on-line” mode of the hippocampus (Buzsáki, 2002) and hippocampus is essential for episodic memory (Scoville & Milner, 1957), it would appear that theta is critical for memory. However, theta fluctuations can be observed across a variety of processes, including, but not limited to, arousal, anxiety, olfaction, motivation, and movement. Indeed, theta is so ubiquitous that, in the words of Gyorgy Buzsaki (2005),

The only firm message that can be safely concluded ... is that in an immobile animal no theta is present, provided that no changes occur in the environment (and the animal is not “thinking”).

It is thus clear that theta does not map onto a single cognitive process. Instead, it likely represents a cellular or biological signal which gives rise to all of these processes. One hypothesis is that theta is directly related to long term potentiation (LTP), the cellular mechanism of memory formation (Kandel, 2001). In LTP, neighboring neurons that successively discharge action potentials (APs) within 10
to 30 ms of one another will be more likely to fire synchronously in the future, due to a cascade of protein changes enhancing the connection between those neurons. Stimulation at the peak of the theta rhythm will induce LTP (Axmacher et al., 2006; Fell & Axmacher, 2011). Furthermore, the peak and trough of the theta phase in dentate gyrus/CA1 may correspond to memory encoding and retrieval processes, respectively (Hasselmo, 2005; Hasselmo & Stern, 2014). Outside of the hippocampus, theta directs passage of information around multiple cortical loops and may underlie top-down control of the hippocampus via prefrontal cortex (T. Mitchell et al., 2008; Nyhus & Curran, 2010; Fell & Axmacher, 2011).

Despite this evidence suggesting that theta power should increase for memory formation, theta increases have been consistently demonstrated in studies of human memory. Although researchers have observed theta increases for subsequently remembered relative to forgotten items (Klimesch, Doppelmayr, Russegger, & Pachinger, 1996; Sederberg, Kahana, Howard, Donner, & Madsen, 2003), there is comparable evidence for theta power decreases (Sederberg et al., 2003, 2006; Guderian, Schott, Richardson-Klavehn, & Duzel, 2009; Lega, Jacobs, & Kahana, 2011). This discrepancy might result from differences in methodology and/or data analytic methods. For instance, it appears that post-stimulus theta fluctuations may be dependent on the level of pre-stimulus theta fluctuations (Guderian et al., 2009; Fell et al., 2011). Thus, among other parameters, how data are baseline corrected could alter the observed theta results.

Somewhat less controversial is the finding that gamma or high frequency activity (HFA, 30 - 200 Hz) increases for successful memory formation (Sederberg et al., 2003; Gruber, Tsivilis, Montaldi, & Müller, 2004; Osipova et al., 2006; Sederberg et al., 2006). Like theta, gamma is not specific to any single cognitive process, but fluctuates across a range of behaviors including attention, visual search, ob-
ject recognition, learning, language processing and emotional evaluation (Engel et al., 2001). Changes in gamma likely reflect one of two signals. First, gamma oscillations can induce LTP by synchronizing pre- and post-synaptic activity; the window during which two spikes must co-occur to induce LTP precisely matches the interval of the gamma oscillation (Axmacher et al., 2006; Jensen et al., 2007; Nyhus & Curran, 2010; Jutras & Buffalo, 2010). Alternatively, broad asynchronous increases in HFA positively correlate with neuronal firing (Manning et al., 2009), which may reflect large scale increases in multi-unit activity (Burke et al., 2015) and may index cortical network processing (Ray et al., 2008; Jacobs & Kahana, 2009; Canolty & Knight, 2010; Lachaux et al., 2012).

The critical issue that arises with HFA is not whether it increases for successful memory formation, but more broadly, whether high frequency signals can be detected using scalp EEG. Unlike intracranial EEG (iEEG) which measures signals directly from the surface of the brain and magnetoencephalography (MEG) which measures magnetic signals, high frequency signals in scalp EEG may be attenuated by the skull. Specifically, volume conduction through the skull results in a low pass spatial filtering (Nunez & Srinivasan, 2006). A recent study failed to find gamma effects in scalp EEG, despite finding evidence for such effects in iEEG (Morton et al., 2013). Additionally, there is evidence that gamma responses observed through scalp EEG are artifactual and the result of saccades (Yuval-Greenberg et al., 2008).

In sum, the extant literature paints a complicated picture as to how theta and gamma support memory formation. Given its role in LTP and communication across the brain, theta power is expected to increase during successful memory formation. However, such results are not found consistently across studies. And although gamma increases are consistently observed across studies utilizing iEEG and MEG, there are more broad concerns about the ability of scalp EEG to resolve
high frequency signals. With a diversity of recording modalities and analysis methods, it is unclear whether these discrepancies are due to selection of analysis parameters or actual differences in recording methods. In Chapter 2, I directly address this question by analyzing the SME using matched data analytic methods in intracranial and scalp EEG datasets.

**Convergent evidence from functional Magnetic Resonance Imaging** HFA is positively related to both spiking activity and the BOLD effect in functional Magnetic Resonance Imaging (fMRI, Logothetis et al., 2001; Logothetis, 2003; Mukamel et al., 2005; Niessing et al., 2005; Lachaux et al., 2007; Ojemann et al., 2013), greatly facilitating comparisons across recording modalities, in particular between fMRI and iEEG, the latter of which has more precise spatial resolution than scalp EEG. fMRI studies have consistently shown that increased activation in left prefrontal cortex (PFC) and medial temporal lobe cortex is predictive of subsequent memory (Wagner et al., 1998; Brewer, Zhao, Desmond, Glover, & Gabrieli, 1998; Fernández et al., 1998; Fernandez, Brewer, Zhao, Glover, & Gabrieli, 1999; Strange, Otten, Josephs, Rugg, & Dolan, 2002; Kim, 2011).

PFC activity is thought to reflect control mechanisms which guide encoding and retrieval processes (Blumenfeld & Ranganath, 2007; Hayama & Rugg, 2009; Thompson-Schill et al., 1997, 2005; Badre et al., 2005; Badre & Wagner, 2007) whereas hippocampus engages in relational processing which binds information into a single, contextually rich, “high-resolution” representation (Paller & Wagner, 2002; Hwang & Golby, 2006; Mayes, Montaldi, & Migo, 2007; Brewer et al., 1998; Eichenbaum, 2004; Brassen, Weber-Fahr, Sommer, Lehmanbeck, & Braus, 2006; Staresina & Davachi, 2006; Shrager, Kirwan, & Squire, 2008; Yonelinas, 2013). Furthermore, PFC directly interacts with hippocampus through reciprocal connections.
(Hwang & Golby, 2006; Dickerson et al., 2007) and PFC may use top-down processing to guide or bias encoding and retrieval in hippocampus (Simons & Spiers, 2003; Preston & Eichenbaum, 2013).

These same regions have been identified in an iEEG study examining the SME using HFA (Burke, Long, et al., 2014), providing convergent evidence that a specific network supports successful encoding. However, it is unclear whether the SME reflects memory-specific processing per se. As items may be forgotten due to failures of any number of processes, including inattention, the contrast comparing remembered and forgotten items cannot distinguish memory-specific encoding processes from a mnemonic attentional signal. To overcome this limitation, it is necessary to measure differences at encoding based on how items are remembered, not whether they are remembered. To define how items are remembered, I turn to retrieved context theory.

1.2 Retrieved context theory

Retrieved context theory originated with Estes’ (1955) stimulus sampling model. In brief, the theory posits the existence of a context representation which is an amalgamation of internal states and external stimuli (McGeoch, 1942; Underwood, 1957; Bower, 1972). By simulating a slowly updating context representation which is reinstated and used as a cue during retrieval, computational models of memory (Howard & Kahana, 2002a; Sederberg et al., 2008; Polyn et al., 2009a; Lohnas et al., in press) can capture many of the behavioral phenomena observed during free recall tasks.

Retrieved context theory can account for the robust behavioral finding that participants temporally cluster their recalls: when asked to recall items in any
order, participants typically consecutively recall study neighbors (Kahana, 1996; Howard & Kahana, 1999; Sederberg et al., 2010). The phenomenon of temporal clustering arises because during study, neighboring items will be associated to similar context representations. Therefore, when a given context representation is reinstated at test, it will be likely to cue both a given item and that item’s neighbors. Importantly, the degree to which an item is associated to its context can vary, determining the likelihood that a given item will be clustered with its neighbors at recall.

Recent neuro-imaging studies have provided evidence corroborating the existence of a context representation. By measuring the similarity of encoding and retrieval patterns, researchers have shown that the retrieval pattern of item $i$ is most similar to the encoding patterns of item $i$’s neighbors and that this similarity decreases as a function of lag (Manning et al., 2011; Yaffe et al., 2014).

How does the presence of this contextual representation relate to the SME? Behavioral evidence has shown that recall success is positively related to the amount of temporal clustering exhibited across participants (Sederberg et al., 2010), suggesting that associating items to their context promotes successful memory formation. Thus, the SME may reflect contextual processing mechanisms. However, clustering could be the result of retrieval, rather than encoding, mechanisms and the SME could reflect non-specific attentional signals. In Chapter 3, I investigate the neural correlates of clustering in order to elucidate the ambiguous findings from the SME analysis.
1.3 Semantic memory in the context of episodic memory

All of the studies discussed thus far have endeavored to understand the neural mechanisms of episodic memory. However, it is clear that no participant enters a laboratory experiment with a blank slate. Instead, a participant comes to the study with a large body of knowledge and pre-existing associations which are likely to influence the formation of new episodic associations. The distributed-plus-hub theory of the organization of semantic memory suggests that the basis of semantic memory extends across a wide range of cortex (Martin, 2007; Patterson et al., 2007, though see Caramazza & Shelton, 1998; Tyler & Moss, 2001). These same cortical regions show reactivation during retrieval of episodic memories (Polyn et al., 2005; Rissman & Wagner, 2012), suggesting that these two systems are intimately connected.

In free recall, semantic clustering, or consecutive recall of semantic associates, is a robust finding (Bousfield, 1953; Long et al., 2010). Like temporal clustering, semantic clustering can be explained by retrieved context theory whereby semantic information is incorporated into the slowly updating context representation. In fact, retrieved context theory can account for clustering along a variety of dimensions including categorical clustering, consecutively recalling items from the same category, as well as spatial clustering, consecutively recalling items studied in nearby spatial locations (Manning et al., 2012; Morton et al., 2013; J. F. Miller et al., 2012; J. F. Miller, Neufang, et al., 2013). Such a mechanism could also explain memory benefits for emotionally valenced items, if emotional items tend to be clustered at recall (LaBar & Cabeza, 2006).

Critically, though these results illustrate the presence of semantic information
during episodic tasks, they do not address how semantic associations influence the formation of episodic memories. In Chapters 4 and 5, I will address how semantic memory and emotional valence interact with episodic encoding.

1.4 Overview

In this thesis, I will attempt to address outstanding questions about the neural mechanisms that support memory formation and what cognitive processes those signals represent. Chapter 2 identifies the spectral correlates of successful memory formation across both intracranial and scalp EEG studies. Chapter 3 extends these findings using cognitive theory to relate contextual processing signals to the traditional subsequent memory effect. Chapter 4 measures the impact of semantic knowledge on the formation of episodic associations. Chapter 5 investigates whether retrieved context theory can account for the memory benefit observed for emotionally valenced items.
Chapter 2

Subsequent memory effect in intracranial and scalp EEG

Nicole M. Long, John F. Burke, & Michael J. Kahana
NeuroImage, 84, 488–494

2.1 Abstract

Successful memory encoding is marked by increases in 30-100 Hz gamma-band activity in a broad network of brain regions. Activity in the 3-8 Hz theta band has also been shown to modulate memory encoding, but this effect has been found to vary in direction across studies. Because of the diversity in memory tasks, and in recording and data-analytic methods, our knowledge of the theta frequency modulations remains limited. The difference in the directionality of these theta effects could arise from a distinction between global cortical and deeper subcortical effects. To address this issue, we examined the spectral correlates of successful memory encoding using intracranial EEG recordings in neurosurgical patients and
scalp EEG recordings in healthy controls. We found significant theta (3-8 Hz) power modulations (both increases and decreases) and high gamma (44 - 100 Hz) power increases in both samples of participants. These results suggest that (1) there are two separate theta mechanisms supporting memory success, a broad theta decrease present across both the cortex and hippocampus as well as a theta power increase in the frontal cortex, (2) scalp EEG is capable of resolving high frequency gamma activity, and (3) iEEG theta effects are likely not the result of epileptic pathology.

2.2 Introduction

Memory processes during encoding that give rise to successful retrieval are collectively termed subsequent memory effects (SMEs, Paller & Wagner, 2002) and have been characterized using scalp electroencephalography (EEG, Paller et al., 1987; Klimesch et al., 1997; Sederberg et al., 2006), magnetoencephalography (MEG, Osipova et al., 2006; Guderian et al., 2009), and intracranial EEG recorded in neurosurgical patients undergoing treatment for intractable epilepsy (iEEG, Fernandez, Effern, et al., 1999; Fell et al., 2001; Sederberg et al., 2003). Whereas these recording modalities have millisecond temporal resolution, scalp EEG is limited by poor spatial resolution and may not reveal changes in high frequency activity due to muscle and eye movement artifacts that generate their own high frequency electrical signals (Yuval-Greenberg et al., 2008; Muthukumaraswamy, 2013). In comparison, iEEG offers subcentimeter range spatial resolution and the ability to directly record from deep brain structures. However, iEEG can only be recorded in neurosurgical patients leading some to question the generalizability of these results to neurologically healthy individuals.

Both iEEG and scalp EEG have been effectively used to study the spectral
correlates of memory encoding. Although most studies show gamma (30 - 100 Hz) power increases for subsequent memory (Gruber et al., 2004; Sederberg et al., 2006; Osipova et al., 2006; Serruya et al., 2014), direct comparisons cannot be easily made because of differences in experimental and data analytic methods. For example, Morton et al. (in press) measured category-specific oscillatory patterns and found that high gamma was more informative in iEEG than scalp EEG. However, the scalp study included a preliminary session in which participants rated the familiarity of the experimental stimuli. As gamma effects are often observed for primacy items (Sederberg et al., 2006; Serruya et al., 2014), pre-exposure to the items may have dampened potential scalp gamma effects.

Theta frequency (3-8 Hz) activity has exhibited both increases and decreases during successful memory formation (Burgess & Gruzelier, 1997; Klimesch, 1999; Sederberg et al., 2003, 2006; Osipova et al., 2006; Guderian et al., 2009; Lega et al., 2011; Hanslmayr & Staudigl, 2013). The inconsistent patterns observed in the theta band could arise from a number of factors including the task parameters and the brain regions, time windows, and frequencies analyzed. For example, there may be differential effects of theta power based on anatomical location, with the hippocampus showing an increase in theta power and neocortical regions showing decreases (Lisman & Jensen, 2013).

Our goal here is to compare the spectral SMEs measured using both intracranial and scalp EEG by controlling as many of these variables as possible. Using identical data analytic methods and roughly corresponding brain regions, we analyzed data from neurosurgical patients (n=93) and healthy participants (n=102) who participated in a free recall study. To foreshadow our results, we found very similar patterns of results in both iEEG and scalp EEG indicating that memory effects observed in iEEG can be directly translated to healthy individuals and that
high frequency effects can be detected by scalp EEG.

2.3 iEEG Methods

Participants

98 participants with medication-resistant epilepsy underwent a surgical procedure in which electrodes were implanted subdurally on the cortical surface as well as deep within the brain parenchyma. In each case, the clinical team determined the placement of the electrodes so as to best localize epileptogenic regions. Demographic and electrode information are described in publications on the same dataset (Burke et al., 2013).

Data were collected at 4 hospitals: Children’s Boston (Boston, MA), Hospital of the University of Pennsylvania (Philadelphia, PA), Freiburg University Hospital (Freiburg, Germany), and Thomas Jefferson University Hospital (Philadelphia, PA). The research protocol was approved by the IRB at each hospital and informed consent was obtained from the participants and their guardians. We restricted our analysis to include only those patients (n=93) who were left-hemispheric language dominant, as assessed by either the patients’ handedness or a clinically administered intracarotid injection of sodium amobarbital (Wada test). As the electrode placements in these 93 patients were clinically determined, each patient did not have electrodes in all of our regions of interest (see Methods, below). Therefore, the total number of patients per region of interest varied as a function of electrode placement and the total number of patients for a given region of interest ranged from 29 (left inferior prefrontal cortex) to 55 (non-hippocampal medial temporal lobe cortex).
Experimental paradigm

Each patient participated in a delayed free-recall task in which they were instructed to study lists of words for a later memory test; no encoding task was used. Lists were composed of either 15 (67/93 patients) or 20 common nouns, chosen at random and without replacement from a pool of high frequency nouns (either English or German, depending on the subject’s native language; http://memory.psych.upenn.edu/WordPools). Each sequentially presented word remained on the screen for 1600 ms, followed by a randomly jittered 800-1200 ms blank inter-stimulus interval (ISI).

Immediately following the final word in each list, participants were given a distraction task designed to attenuate the recency effect (Kahana, 2012). The distraction task was a series of arithmetic problems of the form A+B+C=??, where A, B and C were randomly chosen integers ranging from 1-9. The distraction interval lasted at least 20 sec, but patients were allowed to complete any problem that they started resulting in a variable distraction interval (average duration, 25 sec).

Following the distraction period, participants were given 45 seconds to freely recall as many words as possible from the list in any order. Vocalizations were digitally recorded and subsequently manually scored for analysis. On average, patients participated in two sessions yielding an average total of 14 lists. Any session in which probability of recall was less than 15% was excluded from the final analysis, resulting in an average of one session per patient.

Electrophysiological recordings and data processing

iEEG data were recorded using a Bio-Logic, DeltaMed, Nicolet, GrassTelefactor, or Nihon Kohden electroencephalogram (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.

2.4 Scalp Methods

Participants

102 (60 female) paid volunteers (ages 18 - 29), were recruited via fliers posted around the University of Pennsylvania campus. Participants were provided with a base monetary compensation plus an additional performance-based monetary incentive to ensure full effort. Our research protocol was approved by the Institutional Review Board at the University of Pennsylvania, and informed consent was obtained from all participants.

Experimental paradigm

The data reported in this manuscript were collected as part the Penn Electrophysiology of Encoding and Retrieval Study, involving three experiments that were sequentially administered. The data reported here come from participants who took part in Experiment 1. The methods are briefly summarized below, and complete description of the methods can be found in (Lohnas & Kahana, 2013; J. F. Miller et al., 2012).

Each session consisted of 16 lists of 16 words presented one at a time on a computer screen. Each study list was followed by an immediate free recall test.

The study also included an encoding task manipulation: some lists were encoded freely (no task lists) whereas other lists were encoded using a size or animacy task (e.g. will the item fit in a shoebox? Is it living or non-living?). To facilitate com-
parison between scalp EEG and iEEG studies, we only considered the “no-task” lists in these analyses.

Words were drawn from a pool of 1638 words (http://memory.psych.upenn.edu/WordPools). Each item was on the screen for 3000 ms, followed by jittered 800 - 1200 ms inter-stimulus interval. After the last item in the list, there was a 1200 - 1400 ms jittered delay, after which a tone sounded, a row of asterisks appeared, and the participant was given 75 s to attempt to recall any of the just-presented items.

To maintain consistency with the iEEG dataset, we only analyzed the first 1600 ms of word presentation. As the scalp paradigm utilized immediate free recall, to further constrain the comparison, we excluded words from late serial positions (13 - 16) to minimize effects of recency. Additionally, each participant completed seven experimental sessions; however, to more closely match the iEEG dataset and reduce the influence of practice effects, we only analyzed the first 4 sessions. It was with this number of sessions that iEEG and scalp EEG datasets had on average an equal number of recall events.

Electrophysiological recordings and data processing

EEG measurements were recorded using Geodesic Sensor Nets (GSN; Netstation 4.3 acquisition environment, from Electrical Geodesics, Inc.). The GSN provided 129 standardized electrode placements across participants. All channels were digitized at a sampling rate of 500 Hz, and the signal from the caps was amplified via either the Net Amps 200 or 300 amplifier. Recordings were initially referenced to Cz and later converted to an average reference. Channels that demonstrated high impedance or poor contact with the scalp were excluded from the average reference.
To identify epochs contaminated with eyeblink and other movement artifacts, electrooculogram (EOG) activity was monitored bipolarly using right and left electrode pairs (electrodes 25, 127 and 8 and 126 on the GSN). An individual word presentation event was rejected from subsequent analyses if the weighted running average for either the right or the left EOG pair exceeded a 100 µV threshold. Additionally, events were excluded on a per channel basis for each participant if the voltage on a particular event/channel pair exceeded a pre-determined threshold. The threshold was set as 4.5 times the standard deviation of the mean voltage calculated across all electrodes (excluding those on the eyes, face and neck, electrodes F10, 8, FPZ, 17, FPZ, 25, F9, T9, 56, 63, 99, 107, 113, T10, 126, 127) for a single session for each participant.

Analysis of iEEG and scalp EEG data

Behavioral analysis We calculated probability of recall as well as the number of intrusions, or incorrect recalls, for participants in both datasets. Intrusions were measured for each participant and each list by calculating the number of incorrect words recalled (words not from the preceding study list) as a proportion of the total number of words recalled. Values were then averaged across lists for each participant.

Oscillatory analysis To minimize confounds resulting from volume conduction and saccades, we analyzed both the iEEG and scalp EEG with bipolar referencing (Nunez & Srinivasan, 2006; Kovach et al., 2011). We defined the bipolar montage in our dataset based on the geometry of the iEEG and scalp EEG electrode arrangements. For each participant and electrode, the raw EEG signal was first 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. We isolated pairs of immediately adjacent electrodes and found the difference in voltage between them (Burke et al., 2013). The resulting bipolar signals were treated as new virtual electrodes and are referred to as such in the remainder of the text. The Morlet wavelet transform (with a wave number of 6) was used to compute spectral power as a function of time for all EEG signals during word presentation (0 - 1600 ms) and a 1000 ms buffer was included on both sides of the data to minimize edge effects. Frequencies were sampled logarithmically at 46 intervals between 2 and 100 Hz. Power values were then down-sampled by taking a moving average across 100 ms time windows from stimulus onset and sliding the window every 50 ms, resulting in 31 total time windows with 16 non-overlapping time windows. Log transformed power values were then Z-transformed to normalize power within participants. Power was Z-transformed according to the mean and standard deviation of the power across all events within a session, separately for each participant, electrode and frequency.

**ROI selection and analysis** iEEG ROIs were selected *a priori* by Brodmann area or gyrus. We were interested in regions most commonly associated with memory encoding and retrieval (Wagner et al., 1998; Blumenfeld & Ranganath, 2007; Sederberg, Schulze-Bonhage, Madsen, Bromfield, McCarthy, et al., 2007; Shrager et al., 2008; Kim, 2011), and therefore chose the following eight ROIs: bilateral inferior temporal cortex (BA 20, 21), bilateral inferior frontal cortex (IFC, BA 45, 47), bilateral dorsolateral prefrontal cortex (DLPFC, BA 46, 9), bilateral hippocampus and parahippocampal cortex. Localizations were radiologically determined by a neurologist at each of the four hospitals. The number of participants with at least one electrode in each of these regions is in parentheses in Table 2.1A. Scalp
ROIs were selected \textit{a priori} (Weidemann et al., 2009) to loosely match the cortical iEEG ROIs with bilateral anterior superior (AS, corresponding to DLPFC), bilateral anterior inferior (AI, corresponding to IFC), and bilateral posterior inferior (PI, corresponding to inferior temporal). Figure 2.1 shows both iEEG and scalp EEG topographies for the current study.

\textbf{Frequency effects across time} The data were split into five distinct bands, theta (3 to 8 Hz), alpha (10 to 14 Hz), beta (16 to 26 Hz), low gamma (28 to 42 Hz) and high gamma (44 to 100 Hz), by taking the mean of the Z-transformed power in each frequency band. Z-transformed power was filtered into the conditions being analyzed (e.g. subsequently recalled and subsequently forgotten events) and an unpaired t-test was run comparing the two sets of events separately for each participant, electrode and frequency band across the 1600 ms duration of encoding word presentation. T-statistics were then averaged across electrodes within an ROI. Averaging t-statistics means that only signals that are consistent across an ROI will appear significant, as opposing effects will be cancelled out. We chose this method as we were interested in general effects across an ROI and not regional differences within an ROI. This averaging step yielded a single t-statistic for each participant and frequency band for a given ROI. Within an ROI and for a particular frequency band, an unpaired t-test was calculated across the participant
t-statistics. All resultant t-statistics are presented in Table 2.1.

In cases in which we ran post-hoc tests on z-scored power to determine the laterality of frequency effects, we used a Bonferroni corrected $p$ value.

**Time-frequency analysis**  We used a modified version of the bootstrap method detailed in previous studies (Sederberg et al., 2006; Serruya et al., 2014). We corrected for comparisons across 16 time windows and 46 frequencies.

For each participant, electrode, time window and frequency a t-statistic was generated through an unpaired t-test comparing the z-scored power of subsequently recalled to not recalled items. These t-statistics were averaged across electrodes within an ROI, creating a single t-statistic for each participant, time window and frequency for one ROI. The distribution of participant t-statistics were compared to zero using an unpaired t-test, resulting in a single across participant t-statistic for each time window and frequency. To correct for multiple comparisons, we ran a bootstrap procedure in which we generated a null distribution of across participant t-statistics. For the bootstrap analysis, we followed the same procedure as above, however, the tests were carried out on shuffled data, such that the labels of subsequently recalled and not recalled were randomly assigned to events. Instead of a single across participant t-statistic being generated, 1,000 null across participant t-statistics were generated from 1,000 iterations of the bootstrap procedure. Finally, all null t-statistics from the 16 time windows and 46 frequencies were concatenated into a single distribution of 736,000 values. To determine which real t-statistics, and thus time windows and frequencies, were significant at a $p = .05$ level corrected for multiple comparisons, we found the top and bottom 2.5% of the null distribution. Any real t-statistics which exceeded those values were labeled significant and the corresponding z-scored power differences (subsequently recalled - not recalled)
appear in the time frequency plots in Figure 2.3.

In cases in which we ran post-hoc tests on z-scored power to determine the temporal or regional specificity of frequency effects, we used a Bonferroni corrected $p$ value.

2.5 Results

Before examining the spectral components of the subsequent memory effect we report the basic behavioral data for the two studies. In the scalp EEG study, participants recalled an average of 68% of the studied items ($SD=14\%$) and committed an average of .31 recall errors (0.12 prior list intrusions [$SD = .09$] and 0.19 extra list intrusions [$SD = .17$]) on each list. Neurosurgical patients who participated in the iEEG study recalled an average of 24% of studied items ($SD = 9\%$) and committed an average of 4.2 recall errors (0.64 prior list intrusions [$SD = .63$] and 3.57 extra list intrusions [$SD = 3.58$]) per list. The finding of substantially lower recall and higher intrusion rates in the iEEG study was to be expected both because the task was inherently more difficult (delayed free recall for the iEEG participants vs. immediate free recall for the scalp EEG participants) and because of the obvious differences in the populations being studied (a community sample of neurosurgical patients with medial temporal lobe epilepsy vs. an elite college population). We also obtained a measure of general intelligence (Wechsler Adult Intelligence Scale) for 77 of the scalp EEG participants and 74 of the iEEG participants. As expected IQ scores for the scalp EEG participants ($M = 128, SD = 10$) were substantially higher than for the iEEG participants ($M = 98, SD = 14$).

We characterized the spectral components of the SME by comparing power in five frequency bands (theta, alpha, beta, low and high gamma) across items subse-
<table>
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<tr>
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<tr>
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Table 2.1: Subsequent memory effect in iEEG and scalp EEG studies T-statistics for the comparison of z-scored power for recalled - not recalled items, across the five frequency bands and for (A) iEEG cortical, (B) Scalp, and (C) iEEG subcortical ROIs. Numbers in parentheses denote number of participants with electrodes in each region. * p < .05, ** p < .01
quently recalled and subsequently forgotten across the presentation interval (1600 ms). The comparison of subsequently recalled minus not recalled items revealed low frequency power decreases and high frequency power increases (Figure 2.2A-C). We found significant theta and alpha power decreases across all ROIs with the exception of a nonsignificant alpha effect in RIFC (Table 2.1A-C). Beta power was significantly decreased across most ROIs except right DLPFC, bilateral PI, and parahippocampus.

Gamma effects were less widespread with significant high gamma increases predominantly localized to the left hemisphere, including left DLPFC and left inferior temporal cortex (Figure 2.2A). Gamma effects were also evident in both hippocampal and parahippocampal ROIs, as well as scalp bilateral AS and PI (Figure 2.2B,C). To test the apparent gamma laterality in iEEG we ran paired t-tests comparing high gamma power across the three pairs of left and right ROIs in those participants with at least one electrode in each ROI. Gamma power in left DLPFC was significantly more increased than in

Figure 2.2: Z-scored power for recalled minus not recalled items for all frequencies (3 to 100 Hz) and collapsed across 1600 ms for (A) iEEG Cortical, (B) scalp, and (C) iEEG Subcortical ROIs. Shaded regions around each curve are Loftus Masson 95% confidence intervals.
the right \( t(17) = 3.4, p = .004; \) critical \( p \)-value set at 0.02; Bonferroni corrected 0.05/3).

**Temporal dynamics of the subsequent memory effect**

One of the main benefits of EEG data is its high temporal resolution. Subtle effects that may exist on smaller time scales could be obscured by collapsing data across large time intervals (as above). Though not observed when time intervals were collapsed, when examining 100 ms windows between 0 and 1600 ms, we found significant theta power increases in left DLPFC, bilateral AI, and right PI around 500 ms (Figure 2.3A-B). This theta power increase was not specifically left- or right-lateralized for either iEEG or scalp ROIs, as revealed by paired t-tests comparing theta power differences from 400 - 600 ms in left and right DLPFC and PI in those participants with at least one electrode in each ROI \( ts < 2, ps > .1 \) critical \( p \)-value set at 0.03; Bonferroni corrected 0.05/2).

All ROIs, including hippocampus, showed late theta decreases (Figure 2.3A-C).
We ran a 6 x 2 repeated measures ANOVA on the scalp EEG z-scored theta power comparing all 6 ROIs and 2 time windows (early, 0 - 500 and late, 1000 - 1500 ms). This analysis revealed no main effect of ROI (F(5,505) = 1.6, p = .2), a main effect of time window (F(1,101) = 19.5, p < .0001), and no interaction (F(5,1111) = 2.2, p = .06). A post-hoc t-test of z-scored theta power averaged across all ROIs revealed that theta power was significantly decreased in the late time window relative to the early time window (t(101) = 4.4, p < .0001). To assess the temporal dynamics of z-scored theta power in the iEEG dataset we ran paired t-tests comparing theta power from 0 - 500 ms and 1000 - 1500 ms in each ROI, as not all participants contributed electrodes to all ROIs. Theta was significantly decreased in the late time window for all ROIs (t(s) > 3.0, ps < .005, critical p-value set at .006, Bonferroni corrected .05/8) except left DLPFC (t(30) = 2.4, p = .02).

Increased temporal precision showed that gamma power increases were present both in iEEG and scalp EEG (Figure 2.3A-C). We ran a 6 x 2 repeated measures ANOVA on the scalp EEG z-scored gamma power comparing all 6 ROIs and 2 time windows (early, 0 - 500 and late, 1000 - 1500 ms). This analysis revealed no main effect of ROI (F(5,505) = .91, p = .48), a main effect of time window (F(1,101) = 19.0, p < .0001), and no interaction (F(5,1111) = 1.9, p = .1). A post-hoc t-test of z-scored gamma power averaged across all ROIs revealed that gamma power was significantly increased in the early time window relative to the late time window (t(101) = 4.4, p < .0001). To assess the temporal dynamics of z-scored gamma power in the iEEG dataset we ran paired t-tests comparing gamma power from 0 - 500 ms and 1000 - 1500 ms in each ROI, as not all participants contributed electrodes to all ROIs. Gamma was significantly increased in the late time window for left DLPFC and left IFC (t(s) > 3.5, ps < .006, critical p-value set at .006, Bonferroni corrected .05/8). There was no significant difference in gamma power for the remaining ROIs.
(right DLPFC, right IFC, bilateral IT, hippocampus or PHC $t < 2.5$, $p > .03$).

2.6 Discussion

Memory formation elicited a remarkably similar pattern of results across scalp and iEEG recordings. Across the encoding interval a general pattern of low frequency decreases and high frequency increases was present in both datasets. While theta power decreases and gamma power increases were evident across the encoding interval, a more precise examination of the temporal dynamics revealed theta increases in addition to the decreases. iEEG and scalp EEG showed significant theta increases around 500 ms post stimulus onset. That both effects predominantly localized to the frontal region suggests that they may reflect the ‘frontal mid-line (FM) theta’ pattern often observed during cognitive tasks (for a comprehensive review, see D. Mitchell et al., 2008). The origin of FM theta in human EEG recording is unclear; midline frontal areas, such as the anterior cingulate cortex (ACC), are most commonly cited as potential sources (Gevins, Smith, McEvoy, & Yu, 1997; Sauseng, Hoppe, Klimesch, Gerloff, & Hummel, 2007) and might explain the lack of a laterality effect in the current study. Additionally, there is evidence that though generated in medial PFC, frontal midline theta extends outward into a network of regions encompassing lateral PFC (Mizuhara et al., 2004). Our results show that these theta increases are conserved across both iEEG and scalp EEG and are consistent with other scalp EEG studies showing theta power increases (Klimesch et al., 1997, 1998; Hanslmayr et al., 2011).

In addition to very circumscribed theta power increases in frontal cortex, we also observed broad theta power decreases across iEEG and scalp EEG, including hippocampus. There are two hypotheses to explain the decreases in theta power.
First, it has been suggested (Stoller, 1949) that theta decreases in iEEG reflect decreases in alpha power as the alpha rhythm may be slowed in epileptic brains. However, we found highly similar theta power decreases in healthy controls in the scalp study, suggesting that theta power decreases in iEEG are not an artifact of the patient population. A second hypothesis is that theta power decreases and increases are separate properties of the neocortex and the hippocampus, respectively (Lisman & Jensen, 2013). However, we observe the same decreases across both neocortical and hippocampal ROIs, which runs counter to this hypothesis. Previous work using a subset of the data presented here (Lega et al., 2011) has shown theta power increases in the hippocampus for subsequently remembered items. While the current study does not show this effect, it is likely due to the fact that Lega et al. (2011) specifically regressed out broadband shifts in spectral power in order to detect oscillations. As broadband activity is known to correlate with local field potentials (Manning et al., 2009) and could potentially be related to memory signals, we did not wish to bias ourselves to only detecting oscillations. Additionally, while Lega et al. (2011) specifically focused on theta power increases, they also observed significant theta power decreases that occurred roughly twice as often as theta power increases (cf Figures 2A and 3 in Lega et al.), consistent with the results reported here.

We hypothesize that these conflicting results of theta power increases and decreases reflect two competing effects: shifts in broadband power and narrow-band theta oscillations, leading to subsequent memory effects characterized either by theta power decreases or increases, respectively. Furthermore, broadband power shifts appear to be much larger than narrow-band changes, resulting in the overall decrease in theta power reported here and in other studies (Sederberg, Schulze-Bonhage, Madsen, Bromfield, McCarthy, et al., 2007; Guderian et al., 2009; Burke et
al., 2013). However, when these broadband power changes are removed, as in Lega et al. (2011), increases in theta power are more readily observed. Consistent with the hypothesis of two separate theta effects, Burke et al. (2013) recently found that theta synchrony, presumably a more specific marker of theta oscillatory activity, exhibits both increases and decreases during memory formation.

One limitation of the current study is the use of a single task, free recall, to measure encoding processes. It is possible that the effects observed may be specific to free recall and thus may not be observed across other memory paradigms or with an analysis comparing different sets of events as opposed to subsequently recalled and not recall items (Hanslmayr & Staudigl, 2013). However, there is some evidence that theta power decreases and gamma power increases are task independent memory signals as this pattern has been observed in a subsequent memory study utilizing recognition (Matsumoto et al., 2013). Our results provide compelling evidence to motivate future memory studies and to investigate the role of theta power in memory processes.

Although we have presented topographies of the subsequent memory effect across scalp and intracranial datasets for roughly corresponding regions of interest, we fully recognize that scalp EEG does not permit the identification of signal generating sources with anywhere near the precision of subdural electrode recordings. Indeed, given the difference in timing of memory-related gamma-band activity (discussed below), frontal gamma effects in scalp are potentially more related to activity in the medial temporal lobe.

In addition to late low frequency decreases, both iEEG and scalp EEG showed high frequency increases. In iEEG, significant gamma power increases were evident across the encoding interval for left cortical and all subcortical ROIs. The time frequency analysis revealed that these effects were present across the 1600
ms encoding interval for all ROIs with the exception of left DLPFC and left IFC which showed significantly greater gamma power in the late (1000 - 1500 ms) time window. In comparison, significant gamma effects were not present across the encoding interval for the scalp EEG dataset, although gamma effects were typically in the positive direction. The time frequency analysis revealed significant gamma effects across all ROIs for the early (0 - 500 ms) time window.

As gamma is considered a mapping signal related to the BOLD activation observed with fMRI (Crone et al., 2011; Lachaux et al., 2012; Burke et al., 2013), we would expect that the gamma effects in iEEG would closely mirror the subsequent memory effects observed with fMRI. Scalp EEG, due to its low spatial resolution, would be less likely to map directly onto the signals observed in fMRI and iEEG. The significant gamma results in scalp EEG suggest that despite concerns about interference from eye and muscle movement (Yuval-Greenberg et al., 2008; Muthukumaraswamy, 2013), which may still be present here, as well as general attenuation of spectral power due to the skull (Voytek et al., 2010), scalp EEG is able to resolve high frequency gamma effects, at least up to 100 Hz.

It is clear from our results that across both intracranial and scalp EEG the dominant electrophysiological effect of successful memory encoding is an overall skew in power toward higher-frequencies at the expense of lower-frequencies. The meaning of this pattern vis-a-vis episodic memory is an open question, but we note that a similar pattern of results is found across a wide variety of electrophysiological recordings during behaviors ranging from motor movement (K. J. Miller et al., 2007; Crone et al., 1998a, 1998b), to auditory tone perception (Crone et al., 2001), among others. Indeed, this pattern is consistent with the event-related synchronization/desynchronization (ERS/ERD) processes that have been described outside of the memory literature (see Pfurtscheller & Lopes Da Silva, 1999 for
a review). Furthermore, recent studies have found that this pattern of spectral changes correlates well with the fMRI BOLD signal (Kilner et al., 2005; Niessing et al., 2005). Our results show that this pattern is fairly conserved across the brain, for both iEEG and scalp EEG, given that low frequency power decreases and high frequency power increases are observed with slight variation across all ROIs. It is therefore possible that the spectral content of both iEEG and scalp EEG during memory formation may not reflect a memory specific signal per se, but rather may indicate a more non-specific underlying process of general cortical activation and that it is the precise intersection of timing and spatial location of these effects that is important.

Beyond this characterization of memory processes, these results suggest that while data from individual patients might not be reflective of normal functioning, the average effects across a large patient population are representative of the general population. Additionally, these results suggest that, despite its limited spatial resolution and potential muscle artifacts, scalp EEG measures qualitatively similar physiological processes as more precise yet more invasive recording techniques.
Chapter 3

Contextual encoding mechanisms in hippocampus and prefrontal cortex support successful memory formation.

Nicole M. Long & Michael J. Kahana

3.1 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 intracra-
nially 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. Crit-
ically, the magnitude of this effect was largest for those recalled items that were
also subsequently clustered. HFA temporally dissociated across regions, with in-
creases 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 spatiotem-
poral context underlie the traditionally observed subsequent memory effect and
support successful memory formation.

3.2 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. Neuro-imaging studies investigating these sub-
sequent memory effects (SMEs) have revealed that increased activation in a network
of temporal and prefrontal cortical regions predict subsequent memory (Wagner
et al., 1998; Kim, 2011; Burke, Long, et al., 2014). However, these changes in ac-
tivation might be due to any number of processes, including increased attention,
use of elaborative strategies, or the formation of item-to-context associations. For-
going 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.

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.

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. The timing of this effect dissociated across regions: LIFG clustering related increases in HFA preceded those in hippocampus. Together, these results suggest that prefrontal context updating mechanisms which precede item-to-context binding processes in the hippocampus are reflected in the SME and drive successful memory formation.

3.3 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 was ranged from 60 (left inferior frontal gyrus) to 86 (left inferior
temporal cortex). 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).

**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. 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 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 & 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 spaces 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 was 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.

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.

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.

**ROI 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, Long, 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).

**Peak time analysis**

Using previous methods (Burke, Long, et al., 2014), we analyzed the temporal specificity of the subsequent clustering effect. Within each ROI and each participant, we found the time point of the maximum (peak) difference in Z-power between subsequently clustered and non-clustered items. As the resulting distributions of peak times was not normally distributed (see Results), we compared peak times across ROIs using a non-parametric Wilcoxon rank sum test.

### 3.4 Results

Before examining the spectral components of the subsequent memory and clustering effects, we report the basic behavioral data. Participants recalled on average 23% of studied items (SD = 10%). Participants were more likely to make recall transitions between neighboring study items than between non-neighboring study items (Figure 3.1A), replicating the lag contiguity effect (Kahana, 1996). We quantified this tendency to cluster with a temporal difference score: the probability of making a transition of absolute lag of 1 minus the average probability of making a transition of absolute lag of 3 through 5. The average temporal difference score .13 was significantly greater than zero (t(135) = 14.0, p < .01) and was positively correlated with probability of recall (r = .19, p = .03, Figure 3.1B), replicating previous findings (Sederberg et al., 2010). These results show that iEEG patients, like healthy controls, cluster their recalls and that the tendency to cluster is positively related to overall performance.
We characterized the spectral components of the subsequent memory and clustering effects by comparing Z-power across items subsequently recalled and forgotten (SME) or items subsequently clustered and not clustered (SCE). Clustered items were recalled either preceding or following the recall of a study neighbor. Non-clustered items were recalled preceding and following the recall of a non-neighboring study item. We ran a paired t-test comparing Z-power across the encoding interval (0-1600 ms) in six 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) for each contrast.

The subsequent memory analysis revealed high frequency activity (HFA, 44 - 100 Hz) increases and low frequency activity decreases in left inferior frontal gyrus (LIFG), left inferior temporal lobe (LIT), and hippocampus ($ts > 2.0, ps < .05$; Figure 3.2A), replicating previous results (Burke, Long, et al., 2014; Long et al., 2014). The subsequent clustering analysis revealed HFA increases in LIFG ($t(54) = 2.0, p = .053$), LIT ($t(79) = 2.2, p = .03$), and hippocampus ($t(60) = 2.3, p = .02$; Figure 3.2B).

We have shown that subsequent clustering is characterized by HFA increases in the SME network. Although we hypothesize that these signals reflect contextual
encoding, they could instead be driven by a mnemonic attentional signal that is not memory specific. Such an attentional signal would likely be present throughout the encoding period, including the pre-stimulus interval (Osipova et al., 2006). In contrast, a memory specific signal should be restricted to the post-stimulus interval, especially if this signal reflects the formation of a bound item-to-context representation. Therefore, we tested the post-stimulus specificity of the SCE in our ROIs. Using a paired t-test, we compared pre-stimulus (-300 to 0 ms) to post-stimulus (0 to 1600 ms) HFA differences between subsequently clustered and non-clustered items. Pre- and post-stimulus intervals did not differ in LIFG ($t(54) = .68, p = .50$) or LIT ($t(79) = .38, p = .70$), but the SCE was significantly greater in the post- than pre-stimulus interval in hippocampus ($t(60) = 3.1 p < .01$).

We have identified an SCE characterized by HFA increases across our three ROIs during the post-stimulus interval. Figure 3.3 illustrates the time course of that effect in each region. Because LIFG has been hypothesized to play a critical role in retrieval and selection processes (Thompson-Schill et al., 1997, 2005; Gold et al., 2006; Badre & Wagner, 2007; Blumenfeld & Ranganath, 2007), and because these processes, which may update context (Polyn & Kahana, 2008), have to unfold prior to hippocampally-mediated item-to-context binding in order to support subsequent clustering, we hypothesized that clustering-related activity in LIFG should precede activity in hippocampus.

To test this hypothesis, for each participant and ROI we identified the time interval during which the SCE was maximal (see Methods). We observed that the median peak interval in hippocampus (900 - 1000 ms) was reliably later than the median peak interval in LIFG (600 - 700 ms; non-parametric Wilcoxon rank sum test ($z = -2.27, p = .02$). There was no reliable difference in peak time between hippocampus and LIT (median peak time in LIT, 500 - 600 ms; $z = 1.65, p = .10$) or
between LIFG and LIT ($z = -0.66, p = .51$).

![Figure 3.2: Subsequent memory and clustering effects.](image)

**Figure 3.2: Subsequent memory and clustering effects.** The figure shows average across participant Z-power difference for six 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) and three regions of interest (ROI; left inferior frontal gyrus, LIFG; left inferior temporal lobe, LIT, and hippocampus). Z-power values were generated by comparing the frequency band-specific spectral power of two conditions and averaging those difference values across electrodes within an ROI. Errorbars are standard errors of the mean. Asterisks denote power differences that significantly differed ($p < .05$) from zero. (A) Subsequent memory effect, comparison of subsequently remembered and forgotten items. (B) Subsequent clustering effect, comparison of subsequently clustered and non-clustered items, where items recalled preceding or following a study neighbor (+/- 1 lag) are considered clustered and all others are not clustered.

We have shown that the peak LIFG SCE precedes the peak hippocampal SCE, supporting the hypothesis that hippocampus drives item-to-context binding. If hippocampal HFA is indicative of such a process, then the amount of late HFA in the hippocampus should directly relate to behavioral measures of clustering. We selected the modal hippocampal peak time (1300 - 1400 ms, Figure 3.3) as our interval of interest. For each participant, we extracted hippocampal HFA during
this interval across all encoding trials and correlated the average signal with each participant’s temporal difference score. We found a significant positive correlation \((r = .38, p = .002)\) whereby increased HFA in the hippocampus was associated with increased temporal clustering (Figure 3.4). There was no correlation with the median peak time \((r = .03, p = .83)\).

**Figure 3.3: Clustering effects across time.** The figure shows average high gamma Z-power across the -300 to 1600 ms presentation interval where 0 is when the word is presented on screen, separately for each ROI. Z-power values are plotted separately for clustered (black), not clustered (dark gray) and not recalled (light gray) conditions. Error bars are standard error of the mean. Below each time course is a box-and-whisker plot showing the interquartile range of peak SCE time intervals. For each participant, we found the time interval during which the HFA difference between subsequently clustered and subsequently non-clustered items was maximal. The solid black circle is the mode peak time interval and the white circle is the median peak time interval. For LIT, the median and mode peak time intervals were the same.

### 3.5 Discussion

The goal of the current study was to measure the neural correlates of memory encoding as they relate to subsequent clustering. Our study demonstrates three key findings. First, there is a subsequent clustering effect (SCE) whereby high frequency activity (HFA) in left inferior frontal gyrus (LIFG), left inferior temporal lobe (LIT), and hippocampus is greater for subsequently clustered compared to subsequently recalled, but not clustered items. Second, clustering related HFA increases in LIFG precede those hippocampus, and the hippocampal SCE is specific to the post-
stimulus interval. Finally, HFA in the hippocampus during the late interval (1300 - 1400 ms) across all encoding trials positively correlates with behavioral measures of clustering. Together, these results suggest that the core memory network is not simply driven by a mnemonic attentional signal and that item-to-context binding in the hippocampus supports successful memory formation.

We found increased HFA across the core memory network (Kim, 2011) for the encoding of items subsequently clustered compared to items subsequently recalled but not clustered. Though classic memory analyses (Wagner et al., 1998; Kim, 2011; Burke, Long, et al., 2014) have shown region-specific activation increases by comparing subsequently remembered and forgotten items, this activation need not be a memory signal per se. By directly comparing items based on how they were recalled, instead of whether they were recalled, we were able to relate the SME to a memory-specific mechanism of contextual encoding. Although there is a wealth of evidence showing that

![Figure 3.4: Relation between hippocampal activation and temporal difference score.](image)

For each participant, we calculated the average high gamma Z-power across all encoding trials specifically for the late, 1300 - 1400 ms post-stimulus interval in hippocampus, as this interval was the modal peak time across participants (see Results and Figure 3). We found a significant positive correlation between late hippocampal activation and temporal difference score (each point is a participant).
hippocampus is involved in both associative (Davachi & Wagner, 2002; Kirwan & Stark, 2004; Mayes et al., 2007; K. J. Mitchell & Johnson, 2009) and order memory (Jenkins & Ranganath, 2010; Ezzyat & Davachi, 2014; Davachi & DuBrow, 2015), previous studies have assessed encoding differences between items by explicitly manipulating task demands at either encoding or retrieval. An open question is whether the same mechanisms support memory formation when there are no requirements to encode or retrieve associations, as such demands could induce explicit strategy use which might obscure other processes (Carr et al., 2010). Without using an associative encoding or retrieval task, our results show that HFA in the SME network increases with effective contextual encoding, suggesting that hippocampus may readily associate items and contexts even in the absence of explicit task demands (Eichenbaum, 2004).

We found evidence that clustering related HFA increases in LIFG precede those in hippocampus. Substantial evidence has shown that LIFG engages in controlled retrieval, semantic elaboration and selection processes (Demb et al., 1995; Thompson-Schill et al., 1999; Badre & Wagner, 2007; Martin, 2007). Furthermore, communication between prefrontal and medial temporal lobe cortex has been shown to support memory formation (Dickerson et al., 2007; Preston & Eichenbaum, 2013). In our study, an encoding item’s pre-existing associations could be retrieved by LIFG and integrated with the current context representation. This context representation would then be bound to the current encoding item by the hippocampus (Polyn & Kahana, 2008). Although we found early LIFG HFA increases, previous work (Burke, Long, et al., 2014) has suggested that late HFA increases in LIFG might retrieve or select stimulus-relevant information in the service of item memory (Blumenfeld & Ranganath, 2007; Kim, 2011). Therefore, the relative time course of LIFG and hippocampus may dictate whether or not an item
is bound to its spatiotemporal context.

Finally, late hippocampal HFA is associated with the degree to which a participant will consecutively recall study neighbors during test. If late HFA in hippocampus is indicative of item-to-context binding, as we inferred from the time course of the SCE, then the amount of late hippocampal HFA should directly relate to participants’ tendency to cluster responses during recall. We found that increases in late (1300 - 1400 ms) hippocampal HFA are positively correlated with temporal difference scores. This finding, coupled with the temporal dissociation of SCE across regions, suggests that hippocampus engages in item-to-context associative processes during encoding.

Two major questions not addressed by the present work include the role of theta in contextual encoding and how HFA is modulated during contextual retrieval. One may have made the a priori prediction that theta (3 - 8 Hz) would show a reliable clustering effect. Theta may signal the on-line state of the hippocampus (Buzsáki, 2002), the theta phase relates to long term potentiation and may provide a temporal context for events (Buzsáki, 2005; Hasselmo & Stern, 2014), and theta has been implicated in tasks which manipulate context (Summerfield & Mangels, 2005; Staudigl & Hanslmayr, 2013). Theta effects in the current study may be obscured by broad asynchronous power fluctuations. The most consistent pattern associated with the SME is increased HFA coupled with decreased low frequency activity (Burke, Long, et al., 2014; Long et al., 2014); a somewhat similar pattern is present in the SCE as well (see Figure 3.2). Such a pattern may be indicative of a “general activation” mechanism as it is observed outside of the memory domain (Crone et al., 2001; K. J. Miller et al., 2007; Jerbi et al., 2009) and may obscure narrowband theta signals. A promising future direction will be to investigate not only narrowband effects, but to also assess the role of theta phase in contextual
encoding (Canolty et al., 2006; Axmacher et al., 2006; Nyhus & Curran, 2010; Rutishauser et al., 2010; Lega et al., in press).

Additionally, the current study focused on contextual processing as an indicator of effective encoding based on predictions of context models (Howard & Kahana, 2002a; Polyn et al., 2009a). Context models also posit that context is reinstated during retrieval, a prediction supported by recent neuro-imaging work showing evidence for content and context reinstatement (Polyn et al., 2005; Manns et al., 2007; Manning et al., 2011, 2012; Morton et al., 2013; J. F. Miller, Neufang, et al., 2013; Yaffe et al., 2014). A critical open question is how the univariate HFA increases observed here manifest during retrieval and how HFA increases interact with multivariate representations of items and context. One prediction is that HFA may increase prior to clustering at retrieval, and that HFA signals may correlated with the amount of similarity between encoding and retrieval patterns.

3.5.1 Conclusion

We have demonstrated that HFA increases as a function of effective contextual encoding, whereby subsequently clustered items show the greatest HFA. Additionally, we have shown that the SCE dissociates across time and regions with the SCE in LIFG preceding the SCE in hippocampus. This result supports the hypothesis that prefrontal cortex retrieves or selects contextual information and that the hippocampus associates items with this contextual representation. Finally, we have shown that late hippocampal HFA correlates with participants’ tendency to consecutively recall study neighbors. Together, these results suggest that HFA increases observed in the SME network are likely the result of contextual encoding and that this contextual encoding directly supports successful memory formation.
Chapter 4

Modulation of task demands suggests that semantic processing interferes with the formation of episodic associations

Nicole M. Long & Michael J. Kahana

4.1 Abstract

Although episodic and semantic memory share overlapping neural mechanisms, it remains unclear how our pre-existing semantic associations modulate the formation of new, episodic associations. When freely recalling recently studied words, people rely on both episodic and semantic associations, shown through temporal and semantic clustering of responses. We asked whether orienting participants toward semantic associations interferes with or facilitates the formation of episodic
associations. We compared electroencephalographic (EEG) activity recorded during the encoding of subsequently recalled words that were either temporally or semantically clustered. Participants studied words with or without a concurrent semantic orienting task. We identified a neural signature of successful episodic association formation whereby high frequency EEG activity (HFA, 44 - 100 Hz) overlying left prefrontal regions increased for subsequently temporally clustered words, but only for those words studied without a concurrent semantic orienting task. To confirm that this disruption in the formation of episodic associations was driven by increased semantic processing, we measured the neural correlates of subsequent semantic clustering. We found that HFA increased for subsequently semantically clustered words only for lists with a concurrent semantic orienting task. This dissociation suggests that increased semantic processing of studied items interferes with the neural processes that support the formation of novel episodic associations.

4.2 Introduction

Episodic memory, the memory for contextually rich personal experiences, is typically distinguished from semantic memory, the memory for general knowledge and facts (Tulving, 1972). Despite this qualitative distinction, it is clear that semantic and episodic memory interact (Tulving, 1983; Squire & Zola, 1998; McClelland & Rogers, 2003), given that episodic retrieval leads to activation of the same neural substrates which support semantic memory (Martin et al., 1995; Polyn et al., 2005; Martin, 2007; Patterson et al., 2007; Binder & Desai, 2011; Rissman & Wagner, 2012). Although these lines of evidence show a broad interaction between semantic and episodic memory systems, it remains unclear how pre-existing semantic
knowledge impacts the formation of new, episodic associations.

The goal of the current study was to measure the influence of semantic associations during the encoding of items in a free recall task (Figure 4.1A). In free recall, participants study a list of items and, either immediately or after a brief delay, must recall those items in any order. Participants often consecutively recall study neighbors, a phenomena known as temporal clustering (Kahana, 1996; Sederberg et al., 2010), which may be the result of an association formed between a study item and a slowly updating context representation, as posited by retrieved context theory (Howard & Kahana, 2002a; Sederberg et al., 2008; Polyn et al., 2009a; Lohnas et al., in press). Semantic processing could either facilitate or interfere with the formation of these episodic associations. Semantic processing could be facilitative by creating a richer context representation, in line with the levels of processing theory (Craik & Tulving, 1975). In this view, any information, including semantic, which creates a more elaborate memory trace will provide a better retrieval cue. Behavioral evidence has shown enhanced priming for items that are both semantically and episodically related (McKoon & Ratcliff, 1979) and increased probability of transitioning between these items during free recall (Howard & Kahana, 2002b). Alternatively, if semantic and episodic associations compete for position in the context representation, increased semantic processing will interfere with the formation of episodic associations. The context maintenance and retrieval model of Polyn et al., (2009a) inversely weights the input of semantic and episodic associations in context, which predicts that each will interfere with the other.

We measured the spectral correlates of subsequent temporal clustering, a proxy of episodic association formation, using scalp electroencephalographic (EEG) recordings. These EEG signals can be analyzed in terms of specific time-varying oscillatory or spectral components of neural activity. High frequency activity (HFA, 44 -
Figure 4.1: Methods and behavioral results. (A) Methods. During the encoding period, participants viewed words presented for 3000 ms and separated by a variable interstimulus interval. Following the last item on the list, participants recall the study items in any order. A subset of study items were semantic associates, e.g. cat and dog in this figure. Semantic relatedness was determined using Word Association Space (WAS) values (see Methods). Encoding items were divided into four conditions based on how they were recalled: temporally clustered (C_t, black) or recalled preceding or following a study neighbor, e.g. tree and lime; semantically clustered (C_s, dark grey) or recalled preceding or following a semantic associate; not clustered (NC, light grey) or recalled preceding and following non-neighboring and non-semantically related items; or not recalled (NR, white). (B) Behavioral results. Participants show a tendency to both temporally and semantically cluster their recalls. The lag contiguity analysis (first panel) shows that participants are more likely to make transitions between study neighbors, those items separated by a lag of +/- 1, than between non-neighboring study items. Likewise, the semantic contiguity analysis (second panel) shows that participants are more likely to make transitions between semantically associated items, where increased association corresponds to increased WAS values. These effects are consistent for both no-task (blue) and task (orange) lists. The third panel shows the quantification of these contiguity effects. Temporal clustering scores are reliably greater on no-task compared to task lists, whereas semantic clustering scores do not vary as a function of list type. (C) Regions of interest. We analyzed three a priori defined ROIs, left Anterior Superior (AS), left Anterior Inferior (AI) and left Posterior Inferior (PI).
100 Hz) in particular may reflect general cortical activation (Manning et al., 2009; Jacobs & Kahana, 2009; Burke et al., 2015) and shows reliable increases during successful memory formation (Sederberg et al., 2003; Long et al., 2014; Burke, Long, et al., 2014).

We sought to assess the impact of semantic processing on the formation of episodic associations by measuring these spectral signals. To manipulate semantic processing, we included lists with and without a semantic orienting task (henceforth task and no-task lists). We predict that HFA will increase during the encoding of subsequently temporally clustered items and that this HFA increase will vary as a function of orienting task. If semantic processing is facilitative, these effects should be greater for task lists than no-task lists, as the semantic processing on task lists should enhance contextual encoding. If semantic processing interferes with episodic processing, subsequent temporal clustering effects should be greater for no-task lists, as semantic processing will disrupt episodic processes specifically on task lists.

4.3 Results

The goal of our study was to assess the influence of semantic processing on episodic memory formation. We first measured the tendency of participants to temporally and semantically cluster their recalls (Figure 4.1B) separately for task and no-task lists. Difference in serial position, or lag, determined temporal relatedness. Word Association Space (WAS) values (Steyvers et al., 2004), determined semantic relatedness. Participants recalled on average 66% (SD = 13%) of studied items on no-task lists and 58% (SD = 11%) of studied items on task lists. Participants were more likely to make recall transitions between neighboring than distal study items
(Figure 4.1B, first panel) and were more likely to make recall transitions between semantically related study items than non-semantically related study items (Figure 4.1B, second panel). We quantified the tendency to cluster study neighbors with a *temporal clustering (tc) score*: the probability of making a transition of absolute lag of 1 minus the average probability of making a transition of absolute lag of 3 through 5 (Kahana, 1996). Likewise, we quantified the tendency to cluster semantic associates with a *semantic clustering (sc) score*: the probability of making a transition to another item with a WAS value of .4 or greater minus the average probability of making a transition to an item with a WAS value less than .4. Across both list types, tc and sc scores were reliably greater than zero (Figure 4.1B, third panel, \( t_s > 13.0, p_s < .001 \)). tc scores reliably differed between no-task and task lists (\( t(151) = 6.3, p < .001 \)), but sc scores did not (\( t(151) = 1.0, p = .32 \)).

The behavioral results suggest that the semantic orienting task might interfere with episodic encoding as temporal clustering was reliably decreased in task lists. However, clustering is likely the result of both encoding and retrieval processes, thus the decrease in temporal clustering might be due to interference at retrieval. As behavioral measures alone cannot dissociate these two processes and our goal was to measure how semantic processing impacts episodic association formation, we turn to the neural data to measure the processes at encoding. We extracted spectral signals across six frequency bands, low theta (3-4 Hz), high theta (6-8 Hz), alpha (10-14 Hz), beta (16-26 Hz), low gamma (28-42 Hz) and high gamma (44-100 Hz) and three regions of interest (ROIs), left Anterior Superior (AS), left Anterior Inferior (AI) and left Posterior Inferior (PI; Figure 4.1C). We made comparisons across items subsequently temporally clustered, but not semantically clustered \((C_t)\), items subsequently semantically clustered, but not temporally clustered \((C_s)\), and items subsequently recalled, but not clustered \((NC)\) separately for no-task and
task lists. C\textsubscript{t} items were recalled preceding or following a study neighbor, C\textsubscript{s} items were recalled preceding or following a semantic associate, and NC items were recalled preceding and following non-neighboring and non-related study items. Semantic associates were pairs of study list items with WAS values of .4 or greater.

Our first goal was to identify a neural subsequent temporal clustering effect. In a previous study (Long & Kahana, submitted) we found that high frequency activity (HFA, 44 - 100Hz) increases as a function of subsequent temporal clustering; however, as we did not control for semantic relatedness among study words, temporally clustered words could also have been clustered based on semantic associations. Therefore, we were unable to dissociate the contributions of episodic and semantic processing. To measure the signals unique to episodic association formation, we analyzed the subsequent temporal clustering effect (SCE\textsubscript{t}) by comparing C\textsubscript{t} items to NC items on no-task lists. All semantically clustered items were excluded. This SCE\textsubscript{t} analysis revealed several power increases across ROIs (Figure 4.2, top row, blue line). Beta power increases were significant in all ROIs (AS, \(t(151) = 3.0, p < .01\); AL, \(t(151) = 2.8, p < .01\); PI, \(t(151) = 2.3, p = .02\)). Low and high gamma power increases were significant in AS (low gamma, \(t(151) = 2.7, p < .01\); high gamma, \(t(151) = 2.0, p = .04\)). These results suggest that the formation of episodic associations is characterized by increases in HFA over left prefrontal regions.

Next, we sought to test the hypothesis that orienting participants to semantic associations could facilitate or interfere with the formation of episodic associations. If semantic processing facilitates episodic memory formation, we should observe an increased SCE\textsubscript{t} on task relative to no-task lists. Semantic processing may increase contextual encoding by creating a more elaborative encoding context (Craik & Tulving, 1975). Alternatively, if semantic processing interferes with episodic memory formation, we should observe a decreased SCE\textsubscript{t} on task relative to no-task
lists. The task may decrease contextual encoding by directing processing toward semantic associations at the expense of episodic associations. We tested these competing hypotheses by comparing C̄ and NC items on task lists. This SCE analysis revealed no consistent effects in our ROIs (Figure 4.2, top row, orange line) and specifically no significant HFA effects ($t < 1.5, p > .10$).

Our results suggest that semantic processing interferes with episodic encoding mechanisms. However, this interpretation assumes that the semantic orienting task fully focuses processing on semantic features. Although there is a decrease in temporal clustering for task lists, there is not concurrent increase in semantic clustering. It is thus unclear whether the task increases semantic processing. If the semantic orienting task directs resources away from episodic association formation in favor of semantic processing, there should be a neural

**Figure 4.2: Subsequent clustering effects.** The top panel shows the subsequent temporal clustering effect (SCE$_t$) and the bottom panel shows the subsequent semantic clustering effect (SCE$_s$) for no-task (blue) and task (orange) lists. Each line shows the difference in Z-Power between subsequently clustered and subsequently recalled, but not clustered, items, for 6 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). Z-Power is averaged across the encoding interval (0 - 3000 ms). Errorbars are standard error of the mean.
subsequent semantic clustering effect for task lists. To test this hypothesis, we analyzed the subsequent semantic clustering effect (SCE$_s$) by comparing C$_s$ and NC items exclusively for task lists. All temporally clustered items were excluded. This SCE$_s$ analysis revealed broad increases in power across both anterior ROIs (Figure 4.2, bottom row, orange line). High theta increases were significant in AS ($t(148) = 2.1, p = .03$) and beta increases were significant in AI ($t(148) = 2.0, p = .04$). Low and high gamma increases were significant in both AS (low gamma, $t(148) = 2.3, p = .02$; high gamma, $t(148) = 2.7, p < .01$) and AI (low gamma, $t(148) = 2.3, p = .02$; high gamma, $t(148) = 2.9, p < .01$).

We have shown that for task lists the SCE$_t$ decreases whereas the SCE$_s$ increases, suggesting that participants are processing semantic features during the orienting task. However, participants may process those semantic features regardless of the orienting task. Indeed, the behavioral results suggest that semantic clustering is matched for both no-task and task lists. If semantic processing interferes with episodic encoding, a reliable SCE$_t$ should not co-occur with a SCE$_s$. To test this hypothesis, we measured the SCE$_s$ for no-task lists. This SCE$_s$ analysis revealed no consistent effects in our ROIs (Figure 4.2, bottom row, orange line). Subsequent temporal and semantic clustering effects (SCE$_t$ and SCE$_s$) separately for no-task (blue) and task (orange) lists. Each bar shows the difference in high frequency activity between subsequently clustered (temporal or semantic) and subsequently recalled, but not clustered words. There is a reliable interaction in AS and AI such that the SCE$_t$ is specific to no-task lists and the SCE$_s$ is specific to task lists. Error bars are standard errors of the mean.
bottom row, blue line) and specifically no significant HFA effects ($t < 2, p > .05$). Although we see behavioral evidence for semantic clustering, this may be driven by the use of semantic associations exclusively during retrieval. As our neural results suggest that semantic processing interferes with episodic processing, we should observe an interaction between the type of clustering effect and the list type. We compared HFA for the $SCE_t$ and $SCE_s$ for no-task and task lists (Figure 4.3) using a 2 × 2 repeated measures ANOVA and found a reliable clustering effect type × list type interaction in AS ($F(1,143) = 14.5, p < .001$) and AI ($F(1,143) = 11.7, p < .001$), but not PI ($F(1,143) = .85, p = .36$).

The dissociation in clustering effect type and list type suggests that semantic processing interferes with episodic processing. As HFA increases for both of these processes, it might reflect a control mechanism which biases retrieval of task-relevant features. Although HFA increases are typically associated with successful memory formation (Sederberg et al., 2003; Burke, Long, et al., 2014; Long et al., 2014), an implication of such a control mechanism is that when task-relevant associations are incongruent with episodic memory demands, HFA should be negatively related to memory performance. We can test this prediction by measuring the encoding activity of semantic isolated items, those items with no semantic neighbors on the study list (pairs of study list items with WAS values < .4, see Methods). Increased semantic processing of these items, reflected through increases in HFA, should be detrimental to their subsequent recall, as no other semantic associate will be available as a retrieval cue, and the necessary episodic associations will not have been formed. We measured HFA during the encoding of semantically isolated items which were later recalled or not recalled, for both task and no-task lists. This analysis revealed a negative subsequent memory effect exclusively for task lists (Figure 4.4). We ran a 2 × 2 repeated measures ANOVA comparing recall
status (recalled or not recalled) and list type (no-task or task) to test the significance of this result. We found a reliable recall status \times list type interaction in AS (F(1,151) = 6.4, p = .01), but not AI or PI (AI, F(1,151) = 1.8, p = .19; PI, F(1,151) = .79, p = .37).

4.4 Discussion

The goal of the current study was to measure the contribution of semantic associations to the formation of episodic associations. Our study demonstrates three key findings. First, there is a subsequent temporal clustering effect (SCE$_t$), characterized by increased high frequency activity (HFA, 44 - 100 Hz) over left prefrontal (PFC) regions, specific to lists without a concurrent semantic orienting task (no-task lists). Second, there is a subsequent semantic clustering effect (SCE$_s$), characterized by increased HFA over left PFC, specific to lists with a concurrent semantic encoding task (task lists). Finally, during task lists, semantically isolated items show a negative subsequent memory effect (SME). That is, HFA over PFC was greater for subsequently forgotten compared to subsequently recalled items, specifically for items which were only weakly semantically related to other study list items. These results suggest that orienting processing toward pre-existing semantic associations, as in the task lists, interferes with the formation of new, episodic associations.

We found increased HFA over left PFC regions during the encoding of subsequently temporally clustered items, specifically for no-task lists. Retrieved context theory posits that clustering is the result of items forming associations with a slowly updating context representation (Howard & Kahana, 2002a; Polyn et al., 2009a; Lohnas et al., in press). This context representation is a weighted sum of both pre-experimental semantic associations and newly formed episodic associations. We hypothesize that increased HFA over PFC reflects a cognitive control mechanism
which determines the relative weight of each of these associations. Specifically, PFC may alternate between maintaining the previously studied items or retrieving semantic associations. Substantial evidence has shown that PFC is critical for a variety of control processes, including maintenance and manipulation of information in working memory (Petrides, 2000; Howard et al., 2003; Hazy et al., 2006; Chatham et al., 2014) as well as controlled retrieval and selection processes (Thompson-Schill et al., 1998; Thompson-Schill, 2003; Bunge et al., 2005; Badre & Wagner, 2007; Rodd et al., 2012). Our finding that the SCE, is specific to no-task lists suggests that HFA increases on no-task lists might reflect maintenance of previous study list items and that the orienting task interferes with this process.

HFA over left PFC increased during the encoding of subsequently semantically clustered items specifically for task lists. This result confirmed that during encoding, the semantic orienting task increased semantic processing relative to the no-task lists. Furthermore, this result is consistent with the interference hypothesis, as we would not expect to concurrently observe both an SCE, and an SCE, on no-task lists. That the SCE, and SCE, both show increased HFA over left PFC suggests a control

Figure 4.4: Subsequent memory effect for semantically isolated items. Semantically isolated items are those items which do not have a strong semantic study associate (WAS > .4). The figure shows HFA for semantically isolated items that are subsequently recalled (R₅₀, black) or subsequently not recalled (NR₅₀, white), separately for no-task and task lists. There is a reliable interaction in AS such that HFA is increased for NR₅₀ relative to R₅₀ items specifically for task lists. Error bars are standard errors of the mean.
mechanism which directs processing based on task demands. This interpretation is consistent with previous work showing that left PFC can bias content-specific processing in posterior regions (E. K. Miller & Cohen, 2001; Thompson-Schill, 2003; Noppeney et al., 2006; Bedny et al., 2008; Kuhl et al., 2013).

The dissociation of subsequent clustering effect and list type suggests that the processing of semantic and episodic associations may be inversely related as predicted by retrieved context models (Polyn et al., 2009a). However, one might have predicted that semantic associations would facilitate the formation of episodic associations, as there is evidence that items related both episodically and semantically show the most facilitative priming (McKoon & Ratcliff, 1979). Our experiment was ideally suited to test these competing hypotheses as the design intentionally included semantically isolated items, items paired with a study list item of low semantic similarity (WAS < .4). According to the facilitative hypothesis, increased semantic processing should always benefit a given study item, whether or not that item is semantically isolated. Alternatively, according to the interference hypothesis, increased semantic processing of a semantically isolated item should diminish its probability of being recalled. That is, semantic processing is not beneficial because no other items can cue retrieval of the semantic isolate. It is furthermore detrimental because it prevents episodic association formation. Our results support the latter hypothesis. We found increased HFA for subsequently forgotten relative to recalled semantically isolated items, specifically for task lists. Although HFA increases typically predict successful memory formation (Sederberg et al., 2003; Burke, Long, et al., 2014; Long et al., 2014), when task demands emphasize stimulus features that will not be useful at retrieval, HFA increases could predict memory failures (Blumenfeld & Ranganath, 2007). Thus, left PFC biased processing towards task-relevant information that was both not beneficial for later memory
and impaired processing that was necessary for later memory. Together our results show that accessing semantic associations can interfere with the formation of episodic associations.

Although the majority of our effects occurred in the high frequency range, we might have expected to observe both theta (3 - 8 Hz) and beta (16 - 26 Hz) effects. Evidence has shown that theta increases during order and contextual processing (Hsieh et al., 2011; Staudigl & Hanslmayr, 2013). We did not find theta effects, outside of a single contrast in a single ROI. As appears to be the case with HFA, variations in task demands, e.g. explicitly encoding item order, may modulate theta effects. Also, recent work has suggested that beta decreases reflect semantic processing (Hanslmayr et al., 2009). We found beta increases for both subsequent temporal and semantic clustering. This discrepancy could be the result of differences in encoding single items as opposed to pairs of items or associations (Hanslmayr et al., 2012). It is also possible that the increases we observed reflect broadband asynchronous high frequency effects (Manning et al., 2009; Burke et al., 2015) that obscure narrowband effects.

Since the term “episodic memory” was coined by Endel Tulving, researchers have endeavored to understand how the episodic and semantic memory systems interact. A critical question has been how our pre-existing associations influence our ability to form new episodic associations. By measuring the impact of a semantic orienting judgment in an episodic task, we have provided evidence suggesting that the processing of semantic associations interferes with the formation of episodic associations. An important future question to address is how semantic and episodic processes interact during retrieval. Although we did not observe encoding activity related to semantic clustering in no-task lists, there was still behavioral evidence for semantic clustering. Unlike episodic information, semantic information does not
need to be accessed during encoding in order to be available at retrieval. Thus, there could be an interaction between episodic and semantic processing during recall as well, potentially explaining how the most likely recall transitions are to those items that are both semantically and episodically related (Howard & Kahana, 2002b). An additional critical next step will be to understand how our univariate results relate to recent multivariate work showing that episodic and semantic information is present in context representations during encoding and retrieval (Manning et al., 2011, 2012). Univariate HFA increases should correlate with the degree to which patterns reflect episodic vs. semantic associations and such an effect should be modulated by task demands, given our conclusion that processing semantic associations can interfere with the formation of episodic associations.

4.5 Materials and Methods

Participants

152 (86 female) paid volunteers (ages 18 - 29) were recruited via fliers posted around the University of Pennsylvania campus. Participants were provided with a base monetary compensation plus an additional performance-based monetary incentive to ensure full effort. The Institutional Review Board at the University of Pennsylvania approved our research protocol, and informed consent was obtained from all participants.

Free recall task

The data reported in this manuscript were collected as part the Penn Electrophysiology of Encoding and Retrieval Study (PEERS), involving three multi-session
experiments that were sequentially administered. The data reported below are from Experiment 1.

Participants performed an immediate free recall experiment consisting of seven sessions of 16 lists of 16 words presented one at a time on a computer screen (Figure 4.1). Each word was drawn from a pool of 1638 words taken from the University of South Florida free association norms (Nelson et al., 2004, available at http://memory.psych.upenn.edu/files/wordpools/PEERS_wordpool.zip). Semantic relatedness was determined using the word association space (WAS) model (Steyvers et al., 2004). WAS similarity values were used to group words into four similarity bins (high similarity, \( \cos \theta > 0.7 \); medium-high, \( 0.4 \) \( < \) \( \cos \theta < 0.7 \); medium-low, \( 0.14 \) \( < \) \( \cos \theta < 0.4 \); low similarity, \( \cos \theta < 0.14 \)). Two pairs of items from each of the four groups were arranged such that one pair occurred at adjacent serial positions and the other pair was separated by at least two other items. All randomly generated word lists conformed to this structure. The same word was not repeated in a session.

Words were presented concurrently either with a task cue, indicating the judgment that the participant should make for that word, or with no encoding task. The two encoding tasks were a size judgment (“Will this item fit into a shoebox?”) and an animacy judgment (“Does this word refer to something living or not living?”), and the current task was indicated by the color and typeface of the presented item. There were four no-task (control) lists (participants did not have to perform judgments with the presented items), six single-task lists (all items were presented with the same task, three of each task), and six task-shift lists (items were presented with either task). List and task order were counterbalanced across sessions and participants.

For each list, there was a 1500 ms delay before the first word appeared on the
Each item was on the screen for 3000 ms, followed by a jittered 800 to 1200 ms interstimulus interval (uniform distribution). After the last item in the list, there was a 1200 to 1400 ms jittered delay, after which a tone sounded, a row of asterisks appeared, and the participant was given 75 s to attempt to recall any of the just-presented items.

To minimize recency effects (Murdock, 1962) and to facilitate comparison with our previous analyses (Long et al., 2014, Long & Kahana, submitted), we excluded all recency items (serial positions 13 - 16), all task-shift lists, and the last three sessions from our analyses.

Electrophysiological recordings and data processing

EEG measurements were recorded using Geodesic Sensor Nets (GSN; Netstation 4.3 acquisition environment, from Electrical Geodesics, Inc.). The GSN provided 129 standardized electrode placements across participants. All channels were digitized at a sampling rate of 500 Hz, and the signal from the caps was amplified via either the Net Amps 200 or 300 amplifier. Recordings were initially referenced to Cz and later converted to an average reference. Channels that demonstrated high impedance or poor contact with the scalp were excluded from the average reference. For each participant and electrode, a fourth order 2 Hz stopband butterworth notch filter was applied to the raw EEG signal at 60 Hz to eliminate electrical line noise.

To identify epochs contaminated with eyeblink and other movement artifacts, electrooculogram (EOG) activity was monitored bipolarly using right and left electrode pairs (electrodes 25, 127 and 8 and 126 on the GSN). An individual word presentation event was rejected from subsequent analyses if the weighted running average for either the right or the left EOG pair exceeded a 100 µV threshold.
Data analyses and spectral power

We applied the Morlet wavelet transform (wave number 6) to all electrode EEG signals from 500 ms preceding to 3000 ms following word presentation, across 46 logarithmically spaces 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 69 time intervals (35 non-overlapping) from -500 ms to 3000 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 and across the 0 to 3000 ms presentation interval.

We defined four conditions of interest (Figure 4.1), items subsequently recalled and temporally clustered ($C_t$), items subsequently recalled and semantically clustered ($C_s$), items subsequently recalled and not clustered (NC), and items subsequently not recalled (NR). $C_t$ items were study items recalled either preceding or following the recall of a study neighbor (absolute lag between serial position of items was 1), but not recalled preceding or following a semantic associate. $C_s$ items were study items recalled either preceding or following the recall of a semantic associate (WAS value for the pair of items was $\geq .4$), but not recalled preceding or following a study neighbor. NC items were study items recalled preceding and following non-neighboring and non-semantically associated study items. We analyzed these conditions separately for control lists (no encoding task performed).
and task lists (single encoding task, either animacy or size judgment, performed for all items in a list).

**ROI selection and analysis**

Z-power values were averaged 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 condition for each ROI. Our three ROIs (Figure 4.1 were selected *a priori* based on previous scalp EEG studies (Weidemann et al., 2009; Long et al., 2014) and were intended to cover left prefrontal (Anterior Superior, AS; Anterior Inferior, AI) and left temporal cortex (Posterior Inferior, PI). Conditions were compared across participants within an ROI and frequency using a paired t-test.
5.1 Abstract

Memory is often better for emotional rather than neutral stimuli. The benefit for emotional items could be the result of an associative mechanism whereby items are associated to a slowly updating context. Through this process, emotional features are integrated with context during study, and are reactivated during test. The presence of emotion in context would both provide a stronger retrieval cue, enhancing memory of emotional items, as well as lead to emotional clustering, whereby emotionally similar items are recalled consecutively. To measure whether associative mechanisms can explain the enhancement for emotional items, we conducted a free recall study in which most items were emotionally neutral to minimize effects.
of mood induction and to more closely reflect naturalistic settings. We found that emotional items were significantly more likely to be recalled than neutral items and that participants were more likely to transition between emotional items rather than between emotional and neutral items. Together, these results suggest that contextual encoding and retrieval mechanisms may drive the benefit for emotional items both within and outside the laboratory.

5.2 Introduction

Both the emotional quality of an item and the emotional state of an individual can impact how an item is remembered. Emotional items are typically better remembered than neutral items (Dolcos et al., 2004; LaBar & Cabeza, 2006; Kuhbandner & Pekrun, 2013) and emotional states can enhance memory for both neutral and emotional items (Bower, 1981; Eich, 1995; Maratos & Rugg, 2001; Erk et al., 2003). The associative network theory of emotion (Bower, 1981) suggests that emotional information is associated with concurrently presented stimuli and is part of the retrieval cue. If emotion enters into such associations, then the effects of emotion on memory should extend beyond the “macro” scale of experiment level mood effects and be present on the “micro” scale of individual items. Despite this, associative network theory has not been extended to explain the benefit for individual emotional items in neutral contexts. Additionally, there has been conflicting evidence as to whether emotion enhances (Doerksen & Shimamura, 2001) or impairs (Kensinger, 2009; Maddock & Frein, 2009) associative memory.

Enhanced memory for items presented during a specific mood may be driven by associations between items and context (Bower, 1981; Lewis & Critchley, 2003). The term context here describes a mental representation, which reflects both e-
ternal stimuli, such as the color of the computer screen, the experiment room, and the internal state of the individual, including his or her mood and associations automatically retrieved in response to external stimuli. The inclusion of emotion in context can provide a cue for retrieving neutral items associated with the same emotional context during encoding (mood dependent memory effect) or for retrieving emotional items that match the current emotional context (mood congruent memory effect). A natural extension of this mechanism is that individual emotional items should impart their emotional features to context. This emotional information should then be present in the retrieval cue and lead to enhanced memory for emotional items.

Alternatively, the salience theory suggests that enhanced memory for emotional items is the result of more resources dedicated to processing emotional items. Neuro-imaging evidence has shown that emotional items recruit attentional and motivational networks (Dolcos et al., 2004; Kissler et al., 2006; Liu et al., 2012), potentially due to modulatory signals from the amygdala. This modulation hypothesis suggests that the amygdala enhances processing of emotional stimuli in other brain networks (Anderson & Phelps, 2001; Pessoa & Adolphs, 2010). Consistent with this theory, increased amygdala activation correlates with better memory for emotional, but not neutral, items (Canli et al., 2000).

Both salience and context theories derive support from experiments using many emotional stimuli or an emotional orienting task. Although such a design provides ample statistical power, it does not mirror natural encounters with emotional stimuli. Having many emotional stimuli or an emotional orienting task could induce explicit strategy use or mood induction, both of which may interfere with typical organizational tendencies.

The goal of our study was to investigate memory for emotional items in a
largely neutral context. To accomplish this, we used a largely neutral word pool where only a small subset of words were emotional (see below). If with such a design, memory is still enhanced for emotional relative to neutral items, this enhancement could be explained by two alternative hypotheses. First, if emotional items activate emotion features in context during study, and those features are reactivated during retrieval, then recall of an emotional item should be followed by consecutive recall of other emotional items, since they have similar contexts as the result of their shared emotional features. Such an “emotional” clustering effect falls naturally out of retrieved context theories (Howard & Kahana, 2002a) and is in line with other clustering phenomena, whereby individuals organize their memories by semantic, episodic and spatial associations (Bousfield, 1953; Kahana, 1996; J. F. Miller, Lazarus, et al., 2013). Previous work has suggested that emotional clustering only occurs when participants are explicitly oriented to the emotionality of items (Siddiqui & Unsworth, 2011); however, the use of many emotional items may have altered participants’ strategies and interfered with a context mechanism. Alternatively, if emotional features are not represented in context, then there should be no consecutive recall of emotional items. Instead, the benefit for emotional items may be due to increased attentional processing which does not necessarily lead to emotional clustering.

To assess the interaction of emotion and context, we measured memory success for emotional and neutral items in a free recall task. In free recall, participants study and recall a list of items with no external cues, and thus, must rely on contextual information to generate cues. To quantify emotion, we conducted an independent experiment in which a separate group of participants rated each word for emotional valence. The words had originally been selected to be predominantly neutral and there was no emotion-related orienting task. We measured both memory for
emotional and neutral items, as well as the tendency of participants to consecutively recall items of similar valence.

5.3 Norming study

Methods

We conducted a norming experiment using Amazon's Mechanical Turk (MTurk, Mason & Suri, 2012). MTurk is a crowdsourcing website used for the mass collection of data via the internet. The Institutional Review Board at the University of Pennsylvania approved our research protocol, and informed consent was obtained from all participants. The norming study consisted of two parts: a qualifier test to screen for high-performing participants, and the main study in which participants normed the free recall study word pool.

247 participants completed the qualifier study in which they rated the emotional valence of 100 words drawn from the Affective Norms for English Words (ANEW) dataset (Bradley & Lang, 1999). None of these words appeared in the free recall study. Participants were asked to rate words on an emotional sliding scale ranging from unpleasant to pleasant. Though not shown to the participants, these ratings corresponded to a numerical value from 1 to 9, with 1 being unpleasant and 9 being pleasant. The instructions and scale were identical to those used in the ANEW study. Each of the 100 words was presented twice, and in random order, to measure internal consistency. Participants were compensated $0.30 for completing the qualifier survey.

Qualification for the main study was determined through internal consistency, external consistency, and response distribution. Internal consistency was measured
using the correlation between an individual participant’s ratings of the first and second presentations of the same word. External consistency was measured using the correlation between a participant’s average rating of a word and the ANEW ratings. To qualify, both internal and external values had to exceed .7 (Cicchetti, 1994). Additionally, participants were required utilize the full range of responses (1-9). 173 participants qualified for the main study.

120 participants completed the main study in which they rated the emotional valence of 1638 words from the free recall study (see below). The rating procedures were identical to the qualifier task. Participants were compensated $15. Twenty participants did not rate all of the words and were therefore excluded from further analysis. Ratings were averaged across the 100 participants who completed the study. Each word was then assigned a status of negative (ratings 1-4), neutral (ratings 4-6), or positive (ratings 6-9) valence (Baran et al., 2012).

Results and Discussion

Of the 1638 words, 140 were negative (9%), 1073 were neutral (65%), and 425 were positive (26%). There is evidence that word properties, including word frequency, imageability, concreteness, and semantic relatedness, can influence memory performance and vary as a function of valence (Glanzer & Adams, 1990; Talmi & Moscovitch, 2004; Bennion et al., 2013). Therefore, we attempted to simultaneously control for these factors across our three valence categories. We matched average word frequency between positive and neutral words, and negative and neutral words. We calculated which word pool (either positive or neutral, or negative or neutral) had the higher average word frequency. We then removed from this pool the word with the highest frequency. We repeated this procedure iteratively until the word pools did not significantly differ in word frequency using an un-
paired t-test (the $p$ value had to exceed 0.10 to be considered non-significant). With this new word pool, we then controlled for imageability, concreteness and semantic relatedness with the same procedure. Imageability and concreteness ratings were only available for 984 of the 1638 words (Wilson, 1988). Semantic relatedness was measured using average word association space (WAS) values (Steyvers et al., 2004). The distributions of semantic relatedness values were compared across word pools and were not reliably different (see Supplemental Information). It is important to note that we matched each valence pool (negative, positive) to the neutral pool. It was impossible to directly match negative and positive pools and still have sufficient words for analysis. Additionally, although we collected arousal data (see Supplemental Information) and found that, on average, negative items had higher arousal than positive items, we could not simultaneously control for all factors and still retain a sufficient number of words for analysis.

After applying the exclusion criteria, 1268 words were available for the free recall analyses, 66 negative (5%), 981 neutral (77%) and 221 positive (17%).

Recently published valence ratings are available for 1555 of our 1638 words (Warriner et al., 2013). We used this dataset to test the reliability of our ratings. We found that though their valence ratings were slightly more positive ($t(3191)=2.5, p = .01$), both ratings were significantly positively correlated ($\rho = .9, p < .0001$). We used our ratings for the free recall study as values were available for all 1638 words.
5.4 Free recall study

Methods

152 (86 female) paid volunteers (ages 18 - 29) were recruited via fliers posted around the University of Pennsylvania campus. Participants were provided with a base monetary compensation plus an additional performance-based monetary incentive to ensure full effort. The Institutional Review Board at the University of Pennsylvania approved our research protocol, and informed consent was obtained from all participants.

Experimental Paradigm

The data reported in this manuscript were collected as part of the Penn Electro-physiology of Encoding and Retrieval Study (PEERS), involving three multi-session experiments that were sequentially administered. The data reported below come from participants who completed all three experiments. Additional methodological details can be found in the supplemental information.

Experiment 1  Participants performed an immediate free recall experiment consisting of seven sessions of 16 lists of 16 words presented one at a time on a computer screen. Each word was drawn from a pool of 1638 words taken from the University of South Florida free association norms (Nelson et al., 2004, available at http://memory.psych.upenn.edu/wordpools/PEERS_wordpool.zip). Semantic relatedness was determined using the WAS model (Steyvers et al., 2004). WAS similarity values were used to group words into four similarity bins (high similarity, $\cos \theta > 0.7$; medium-high, $0.4 > \cos \theta < 0.7$; medium-low, $0.14 > \cos \theta < 0.4$; low similarity, $\cos \theta < 0.14$). Two pairs of items from each of the four groups were
arranged such that one pair occurred at adjacent serial positions and the other pair was separated by at least two other items. All randomly generated word lists conformed to this structure. The same word was not repeated in a session.

Words were presented concurrently either with a task cue, indicating the judgment that the participant should make for that word, or with no encoding task. The two encoding tasks were a size judgment ("Will this item fit into a shoebox?") and an animacy judgment ("Does this word refer to something living or not living?"), and the current task was indicated by the color and typeface of the presented item. There were four no-task lists (participants did not have to perform judgments with the presented items), six single-task lists (all items were presented with the same task, three of each task), and six task-shift lists (items were presented with either task). List and task order were counterbalanced across sessions and participants. The task manipulation was included to assess the effect of task switching on clustering during recall (Polyn et al., 2009b) and was not considered here.

For each list, there was a 1500ms delay before the first word appeared on the screen. Each item was on the screen for 3000ms, followed by jittered 800 to 1200ms interstimulus interval (uniform distribution). If the word was associated with a task, participants indicated their response via a keypress. After the last item in the list, there was a 1200 to 1400ms jittered delay, after which a tone sounded, a row of asterisks appeared, and the participant was given 75s to attempt to recall any of the just-presented items.

Experiment 2  Experiment 2 was identical to Experiment 1 except as described below. There were either 7 (N = 92) or 9 (N = 60) experimental sessions of 12 study lists of 16 words. Experiment 2 included a mix of immediate recall lists, delayed recall lists (the final word was followed by a distractor), and continual
distractor lists (each word was followed by a distractor). Distractor tasks consisted of answering math problems of the form \( A + B + C = ? \), where \( A, B, \) and \( C \) were positive, single-digit integers, and participants typed the sum as quickly as possible. Participants performed free recall with five possible time durations for the between-item and end-of-list distractor tasks. As listed here, the first number indicates the between-list distractor duration and the second number indicates the end-of-list distractor duration, both in seconds: 0-0 for immediate (identical to Experiment 1), 0-8 or 0-16 for delayed, and 8-8 or 16-16 for continual distractor recall. The distractor manipulation was included to attenuate between-item and end-of-list rehearsal (Lohnas & Kahana, 2014) and was not considered here.

**Experiment 3**  For 92 participants, Experiment 3 used the externalized recall (ER) procedure (Zaromb et al., 2006) to measure participants’ tendency to commit intrusions during recall. Participants were instructed to say aloud every time a specific, salient word came to mind while performing free recall and to press the spacebar immediately following recall of an intrusion or repetition. Participants performed 6 experimental sessions with methods identical to Experiment 1 with ER-specific instructions. For the remaining 60 participants, Experiment 3 consisted of 4 sessions completely identical to Experiment 1.

**Conditional Response Probability Analysis**  The order in which items are recalled is not random; each retrieval event is influenced by items already recalled. To determine if valence drives recall order, we can measure participants’ tendency to recall an item of a given valence conditionalized on the prior recall item’s valence. We evaluated recall transitions as a function of valence to measure this tendency. For each list, separate transition probabilities were calculated for each of 9 valence
combinations (negative to negative, negative to positive, etc.). To account for the low likelihood of same valence transitions, we calculated the number of actual transitions as a function of possible transitions, based on the study items in the list and the items that had already been recalled. Therefore, the number of possible transitions could range from 0 to 15. The likelihood of a transition was calculated by dividing the number of actual transitions by the number of possible transitions. The number of actual transitions was always 0 or 1. In this way we accounted for the lower proportion of emotional items, and less likely transitions were given a greater value. If a neutral-neutral transition was made, and there were 7 available neutral items, the score for that transition would be 1/7. If a negative-negative transition was made and there were 2 available negative items, the score for that transition would be 1/2. Lists which had no positive or negative items, thus precluding any relevant transitions, were excluded from all analyses (on average 202 lists), resulting in on average 83 lists per participant. Probabilities were averaged across lists within participants and then across participants.

5.5 Results and Discussion

We measured probability of recall as a function of valence. On average, participants recalled 61% of negative words, 60% of neutral words, and 62% of positive words. We ran a one-way repeated measures ANOVA comparing valence conditions and found a significant interaction (F(2, 302) = 11.5 p < .01; $\eta^2_p = .03$). Post-hoc comparisons using the Tukey HSD test indicated that the probability of recall differed significantly between both negative (M = .61, SD = .14) and neutral words (M = .60, SD = .14) as well as between positive (M = .62, SD = .14) and neutral words (M = .60, SD = .14). There was no difference in probability of recall for negative and
positive words.

We observed reliably greater recall for both positive and negative items, which is consistent with previous work (Dolcos et al., 2004; Kensinger & Schacter, 2006). There is some evidence that memory is differentially enhanced for positive or negative items (Erk et al., 2003; Bennion et al., 2013). Such findings may be the result of task design as many highly emotional items could drive unintended mood changes in participants. By using a small proportion of emotional items, our study avoided this possible confound and showed a benefit for both positive and negative items. However, the small proportion of emotional items might make those items more distinctive and thus easier to remember than neutral items. To account for this possibility, we re-analyzed the data using equally distinctive emotional and neutral items (see Supplemental Information) and found that emotional items were still remembered better than neutral even when controlling for distinctiveness.

Memory enhancement for positive and negative items might be driven by contextual or salience mechanisms. If emotional features are integrated with context and used as a retrieval cue, then recall outputs should be clustered by valence, akin to various clustering phenomena whereby participants organize their recalls according to semantic, episodic and spatial associations (Bousfield, 1953; Kahana, 1996; J. F. Miller, Lazarus, et al., 2013). To explore whether participants emotionally cluster their retrievals during recall, we calculated the likelihood of transitioning between words as a function of valence. Participants were more likely to transition between same valence items than different valence items and this tendency was greater than would be expected by chance as measured by repeatedly shuffling recall order and calculating transition probabilities on this permuted data (Figure 5.1). To test the significance of this valence clustering effect, we ran a 3×3 repeated measures ANOVA comparing valence of item transitioned from (positive, neutral, neutral,
or negative) and valence of item transitioned to (positive, neutral, or negative). We found a main effect of item transitioned to (F(2, 302) = 18.8, p < .01; η² = .09) and an interaction effect (F(4, 302) = 28.2, p < .01; η² = .18). Post-hoc comparisons revealed that negative to negative transitions were significantly more likely than negative to neutral transitions (t(151) = 4.0, p < .01; Cohen’s d = .46) and positive to positive transitions were significantly more likely than positive to neutral transitions (t(151) = 2.8, p < .01; Cohen’s d = .30; Bonferroni corrected for 2 tests, p = .025). This valence clustering effect was not driven by within list semantic similarity, as confirmed by a combined semantic-valence conditional response probability analysis (see Supplemental Information).

Together, these results suggest that contextual encoding and retrieval mechanisms may explain increased memory for emotional items. Previous research has suggested that contextual mechanisms may drive mood dependent and mood con-
gruent memory effects (MDM, MCM; Bower, 1981; Lewis & Critchley, 2003), but MCM and MDM effects might represent a special case only relating to the mood-induction paradigm (Eich, 1995). Alternatively, the use of many emotional items could induce explicit strategy use that interferes with or overrides a natural context mechanism. Existing research has provided conflicting evidence as to whether emotion enhances (Doerksen & Shimamura, 2001) or impairs (Kensinger, 2009; Maddock & Frein, 2009; Madan et al., 2012) associative memory. Furthermore, a related study on the organizational effects of emotion on memory (Siddiqui & Unsworth, 2011) showed emotional clustering only when a valence orienting task (pleasantness judgment) was used. Together, these results suggest that a large percentage of emotional items might create subjective and variable strategies, which may interfere with the associative mechanisms that support emotional clustering.

In the current study, we found enhanced emotional memory and emotional clustering, both of which are consistent with predictions of retrieved context models (Howard & Kahana, 2002a) and suggest that emotional information is incorporated into a slowly updating context representation during study and is used to cue retrieval of items at test. That this result occurs in the absence of mood induction suggests a general mechanism by which emotional items are better remembered than neutral items.

A leading theory of emotional memory enhancement suggests that emotional items receive increased attentional processing (Dolcos et al., 2004). It is possible that there are, in addition to the context effects observed here, independent attentional effects that increase the strength of the item. These attentional effects may be more directly related to arousal than valence (Kensinger, 2009). Alternatively, attention could interact with context by promoting item-to-context binding or increasing the salience of emotional features in context.
5.5.1 Conclusions

The current study suggests that enhanced emotional memory is due to an associative mechanism by which items, including emotional features, are associated to a slowly updating context representation. Through a free recall task with few emotional items, we have shown that participants recall emotional items more often than neutral items and that participants consecutively recall or cluster items of the same emotional valence. These benefits are unlikely to be driven by mood induction or explicit strategy use that may arise when many emotional items are present or when an emotion-orienting task is used. Such a contextual mechanism provides a framework by which emotional memory may be enhanced in situations outside the laboratory.

5.6 Supplemental

Free recall study methods

The first session of each experiment was a practice session to familiarize participants with the task. All sessions ended with a recognition test. Half of the sessions (randomly chosen) included a final free recall test before recognition in which participants recalled words from any of the lists from the session. The recognition and final free recall manipulations are not considered here.

Based on the results of a prior norming study, only words that were clear in meaning and that could be reliably judged in the size and animacy encoding tasks were included in the pool. There were three conditions: no-task lists (participants did not have to perform judgments with the presented items), single-task lists (all items were presented with the same task), and task-shift lists (items were presented
with either task). The first two lists were task-shift lists, and each list started with a different task. The next 14 lists contained four no-task lists, six single-task lists (three of each task), and four task-shift lists.

The math distraction task was self-paced, such that a participant may have been presented with, but not responded to, a problem at the end of the distraction interval. Participants were given a monetary bonus based on the speed and accuracy of their responses.

**Controlling semantic relatedness at the word list level**

We compared the distribution of negative-negative WAS or LSA (Latent Semantic Analysis) semantic similarity values to the distribution of negative-neutral WAS or LSA values using a two-sample Kolmogorov-Smirnov test. Negative-negative similarity was not reliably larger than negative-neutral similarity (WAS, ks = .0047, p = .95; LSA, ks < .01, p = .59). Positive-positive similarity was reliably larger than positive-neutral similarity only for WAS (WAS, ks = .05, p < .01; LSA, ks < .01, p = .99).

While we controlled for semantic relatedness at the level of word pools, we did not control for semantic relatedness at the list level. To address this potential confound, we ran a combined semantic-valence CRP analysis. The semantic-valence CRP (Figure 5.2) shows the likelihood of a particular transition, where there are four valence transitions (negative-negative, negative-neutral, positive-neutral, positive-positive) and either five semantic bins (WAS, [-.15 to .08, .08 to .31, .31 to .54, .54 to .77, .77 to 1]) or three semantic bins (LSA, [-.2 to .2, .2 to .6, .6 to 1]). Different numbers of bins were used because there were no negative-negative transitions for LSA bins > .7. For each transition within each list, we calculated the number of actual and possible transitions in a given bin (e.g. negative-negative, semantic bin > .7).
Importantly, as each of these calculations occurred within list, it accounts for any imbalance in within-list semantic similarity. If negative-negative transitions were driven exclusively by semantic relatedness, we would predict that high-semantic negative-negative transitions would be equally likely as high-semantic negative-neutral transitions. We found that even when controlling for semantic relatedness within list, same valence transitions were more likely than different valence transitions. These results argue against a within-list semantic relatedness effect.

**Distinctiveness**

By virtue of being a small proportion of the total items presented, emotional items might have been more distinctive than neutral items. To assess this possibility, for each study list we calculated the average number of semantic neighbors for positive, neutral and negative items. Semantic neighbors were any other items presented on the same list with a WAS value of .2 or greater. The assumption is
that items with more neighbors are less distinctive and that neutral items will tend to have more neighbors. Therefore, we iteratively removed non-distinct neutral items until neutral items had on average .21 neighbors per list, which did not differ from the average number of list neighbors for negative items, .20 (t(151) = 1.6, p = .12). Positive items had on average .24 neighbors per list, which was significantly greater than the number of neutral item neighbors (t(151) = 8.9 p < .01), leaving neutral items more distinctive than positive items. When controlling for distinctiveness in this manner, probability of recall was still greater for emotional than neutral items (negative vs. neutral, t(151) = 2.2, p = .03; positive vs. neutral t(151) = 4, p < .01). Likewise, transitions between same-valence items was still more likely than transitions between different-valence items (negative-negative vs. negative-neutral, t(151) = 5.1, p < .01, positive-positive vs. positive-neutral, t(151) = 7.5, p < .01).
Chapter 6

General discussion

6.1 Summary

In the previous chapters, I examined the neural mechanisms of episodic memory formation using the free recall paradigm coupled with electroencephalographic (EEG) recordings. My results suggest that episodic memory formation is driven by contextual encoding processes which are supported by high frequency activity (HFA) increases in the memory network.

In Chapter 2, I measured the spectral correlates of episodic memory formation using matched data analytic methods in a scalp EEG and an intracranial EEG (iEEG) study. I analyzed the subsequent memory effect (SME) by comparing the encoding signals of items subsequently recalled to those subsequently forgotten. Although theta (3 - 8 Hz) and gamma (> 30 Hz) signals often vary during memory formation (Nyhus & Curran, 2010; Johnson & Knight, 2015), the specific pattern of power increases and decreases in these frequencies has been unclear (Klimesch, 1996; Sederberg et al., 2003; Gruber et al., 2004; Sederberg et al., 2006; Guderian et al., 2009; Burke, Long, et al., 2014). This discrepancy in findings may be the result
of differences in recording modalities (Stoller, 1949; Yuval-Greenberg et al., 2008) or differences in the choice of analysis parameters. Using matched data analytic methods, I found that broad HFA increases and LFA decreases are associated with successful memory formation in both iEEG and scalp EEG, suggesting that theta effects in iEEG are not likely the result of pathology and that scalp EEG is capable of resolving HFA signals. As this pattern of HFA increases and LFA decreases has been observed across domains outside of memory (Crone et al., 2001; Jerbi et al., 2009; K. J. Miller et al., 2007) and correlates with the BOLD effect in fMRI (Mukamel et al., 2005; Niessing et al., 2005), this pattern may not reflect a memory specific signal per se, but rather may indicate a more non-specific underlying process of general cortical activation and that it is the precise intersection of timing and spatial location of these effects that is important.

Next, I connected HFA increases in the SME to contextual encoding. HFA increases in the memory network which were observed in Chapter 2 might reflect memory-specific processing or a more general mnemonic attentional signal. Although the SME analysis is a classic approach to understanding memory formation (Wagner et al., 1998; Brewer et al., 1998), it is a coarse measure as an item may be forgotten due to reasons unrelated to memory processing. In Chapter 3, I defined items based on how they were recalled, by comparing subsequently clustered and not clustered items, where clustered items are those recalled preceding or following a study neighbor. I used clustering as a proxy for contextual encoding, as retrieved context theory (Howard & Kahana, 2002a; Sederberg et al., 2008; Polyn et al., 2009a) suggests that clustering arises due to the existence of a slowly updating context representation that is associated to items at encoding and is used as a retrieval cue during test. I found that HFA increases in the memory network track contextual encoding and that the time course of HFA increases varies across
brain regions. Specifically, HFA increases in left prefrontal cortex (PFC) preceded those in hippocampus. These late hippocampal clustering signals positively correlated with behavioral measures of clustering. These results suggest that control processes in left PFC coupled with associative processes in hippocampus underlie contextual encoding processes that support successful memory formation.

In Chapter 4, I measured the influence of semantic processing on the formation of episodic associations. By including a semantic orienting task on a subset of study lists, I was able to compare the effects of subsequent temporal clustering with and without a task that oriented participants to the semantic associations among items. I found increased HFA over left prefrontal regions for subsequently temporally clustered items only for no-task lists, those without a semantic orienting task. I also found increased HFA over left prefrontal regions for subsequently semantically clustered items on for task lists. These results suggest a dissociation between semantic and episodic processing during encoding. I further confirmed this dissociation by comparing the encoding patterns of subsequently recalled and not recalled semantically isolated items. HFA during task lists for semantically isolated items, those study items paired with a low semantic associate, was increased when those items were subsequently not recalled. These left prefrontal HFA effects are likely to reflect a control mechanism which biases processing in posterior regions according to task demands. The results I have observed suggest that semantic processing interferes with the formation of episodic associations.

In Chapter 5, I used retrieved context theory to account for the memory benefit observed for emotionally valenced items. Positively and negatively valenced items are remembered better than items with a neutral valence (LaBar & Cabeza, 2006), which may be because valenced items receive more attentional processing than neutral items. Alternatively, if emotional features, like semantic and temporal
features, are incorporated into the context representation, memory for emotional items will be enhanced due to the presence of emotional features in the contextual retrieval cue at test. Of these two hypotheses, only retrieved context theory predicts that recalls should be clustered by valence. I measured recall and transition probabilities for items of positive, negative, and neutral valence. I found that both positive and negative items were more likely to be recalled than neutral items and that participants were more likely to make transitions between same valence items than differently valenced items. These results suggest that emotional features are represented in context and provide a mechanism by which emotions might be processed outside the laboratory.

These studies broadly provide evidence in support of a contextual encoding mechanism whereby items are associated to a slowly updating context representation in service of memory formation. Although I consistently found high frequency effects, there are likely other signals associated with contextual encoding. Furthermore, as my work has been focused on encoding, a critical next step will be uncovering the contributions of contextual processing during retrieval. Similarly, to have a complete understanding of contextual processes, we must integrate the univariate findings I present here with the multivariate patterns that represent contextual encoding and retrieval patterns. I discuss each of these in turn below.

6.2 Future Directions

Theta and phase

The research that I have presented in this thesis shows that contextual processing is most clearly represented by changes in HFA. However, other studies have shown
theta increases associated with contextually mediated memories (Hanslmayr & Staudigl, 2013). The majority of theta effects I observe are theta decreases, rather than increases. These are likely broadband, asynchronous effects which could potentially mask transient narrowband effects.

Where theta might prove to be critical is in the phase, rather than the amplitude domain. Stimulation during the peak of a theta oscillation can induce LTP (Axmacher et al., 2006) and phase locking of single unit activity to theta oscillations is increased during successful memory formation (Rutishauser et al., 2010). Phase reset of theta oscillations during memory formation is negatively correlated to theta power (Rizzuto et al., 2003), as are memory related phase-synchrony increases (Burke et al., 2013), providing compelling evidence that the power decreases I observe may co-occur with phase changes. Also promising is the finding of phase-amplitude coupling (PAC) between theta phase and gamma amplitude during memory formation (Canolty et al., 2006; Jensen et al., 2007; Lega et al., in press). The HFA increases I have observed might be coupled to a particular theta phase, suggesting that contextual encoding might be supported by both of these frequency bands.

Retrieval

The goal of my thesis was to elucidate the neural correlates of episodic memory formation. However, as stated in the introduction, successful memory is based on success during encoding as well as retrieval. Contextual encoding is only effective insofar as context is reinstated at test. EEG analyses of retrieval has revealed HFA increases preceding successful recall (Sederberg, Schulze-Bonhage, Madsen, Bromfield, Litt, et al., 2007; Lega et al., 2011; Burke, Sharan, et al., 2014) which could reflect controlled memory search processes or the reinstatement of memories.
I have identified two potentially distinct signals of contextual encoding, a control mechanism supported by left prefrontal cortex and an associative mechanism supported by hippocampus. Given fMRI results connecting left prefrontal cortex to controlled retrieval processes (Badre et al., 2005; Badre & Wagner, 2007), one might predict that left prefrontal HFA increases should be observed during the retrieval of clustered compared to not clustered items. However, fMRI evidence suggests that there may be a dissociation between encoding and retrieval such that items which received strong associative processing during encoding might require less controlled retrieval during test (Long et al., 2010). Thus a critical next step will be to detail exactly when and where in the brain we observe HFA increases during the retrieval of clustered and non-clustered items.

**Multivariate analyses and patterns**

The work in my thesis used univariate analyses to elucidate the neural correlates of episodic memory formation. However, multivariate analyses of patterns of brain activity have proven to be incredibly fruitful for addressing questions about memory formation and retrieval (Rissman & Wagner, 2012). The patterns of activity during encoding are reinstated during retrieval (Polyn et al., 2005) and the strength of reinstatement predicts memory success (Kuhl et al., 2012). Multivariate analyses of the similarity between encoding and retrieval patterns have suggested the existence of a slowly drifting context representation (Manning et al., 2011, 2012; Morton et al., 2013). Specifically, the similarity between encoding and retrieval patterns increases as a function of temporal or semantic similarity between stimulus items and predicts the degree to which participants will cluster their recalls.

My research has identified the control and associative processes which might enable items to interact with context. The next step will be to measure these
univariate signals in tandem with the multivariate contextual signals. Changes in HFA should predict the degree of pattern similarity between items at encoding and at retrieval.

6.3 Concluding remarks

The work in my thesis provides a substantial contribution to our understanding of episodic encoding mechanisms. Knowing that memory formation is driven by contextual processing, we can move beyond free recall, to explain findings in recognition, interference and inference tasks. Extending my work to other paradigms and questions will bring us closer to a unified theory of memory function.
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