BRAIN OSCILLATORY DYNAMICS OF LEXICAL-SEMANTIC PROCESSING

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By

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Neuropsychological and imaging studies have shown that anterior and posterior brain areas are involved in the retrieval and selection of semantic representations, but it is not known how these areas dynamically interact during semantic processing. A candidate mechanism is through the synchronization of neuronal oscillations as they are likely involved in the creation of local and long-range functional neuronal networks. We hypothesized that low frequency coherence would reflect the coupling of anterior and posterior brain areas and examined the oscillatory dynamics of lexical-semantic processing using two paradigms, a semantic priming paradigm and a semantic ambiguity paradigm, which recruit this global network. For the first experiment, high density EEG was recorded while subjects read semantically-related or unrelated word pairs. Time-frequency analysis revealed facilitation of semantic processing for Related compared to Unrelated conditions, which resulted in shorter response times, reduced N400 amplitude, and reduced gamma (45-50 Hz) power from 150-450 ms. Moreover, reduced theta (4-7 Hz) coherence for Related compared to Unrelated conditions was observed between left anterior and posterior electrodes over the time windows 150-425 ms and 600-900 ms. We suggest that while gamma power reflects activation of local functional networks supporting semantic representations, the anterior-posterior topography of theta coherence indicates dynamic
coupling of anterior and posterior areas for retrieval and post-retrieval processing of these semantic representations. This coupling appears much greater when retrieval demands are high and top-down retrieval is needed. In the second experiment, subjects read word pairs in which the first word biases the second, an ambiguous word, to either the dominant or subordinate meaning. When selecting the subordinate meaning over the prepotent, dominant meaning, selection demands are higher which slows response time and engages a similar anterior-posterior semantic network for top-down selection processing. We observed both increased reaction time and increased anterior-posterior theta coherence over 100-1000ms for the Subordinate condition compared with the Dominant condition. Thus we suggest that theta coherence reflects coupling within the anterior-posterior semantic selection network for selecting the subordinate meaning. These experiments provide converging evidence that theta coherence may serve as a mechanism for creating dynamic large-scale semantic networks.
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Introduction

How is it that we understand the world around and within us? How do we attach meaning not only to objects, words, and pictures, but also to feelings and more abstract concepts? Incredibly, meaning can be conveyed through the simple lines and curves of written words – symbols that invoke an internal world of understanding, for instance, when reading a good book. Artists, philosophers, and scientists have pondered these mysteries for centuries, and these questions are far from trivial. This is due not only to the difficulty of probing the great organ that decodes and interprets meaning, that is, the brain, but also because meaning itself is changing. Meaning is dynamically constructed – rapidly on an individual basis during our childhoods and slowly over generations as humankind probes the nature of this world. Even within the psychological and neuroscience literatures, words such as thinking, decision-making, motivation, and attention lack definite, universally agreed upon meanings, and consensus may never be achieved. So meaning is a quintessential element of our lives in both an everyday sense and through our desire to further basic human understanding of the brain and the world.

Psychologists, linguistics, and neuroscientists have pursued the study of meaning or “semantics” more methodically in the past century with increasingly sophisticated tools. While this field is vast, we hope to address one aspect of how semantics is neutrally implemented. In this thesis, we ask “how are local and large-scale brain networks created when retrieving multiple possible meanings of a word and selecting the appropriate one?”
Chapter 1

1.1 Semantic Networks

In order to understand and interact with the world around us, our brains must store information about all of the objects, concepts, and beings we encounter. These so-called “semantic representations” are essential to our lives, as evidenced by the severe disability caused by disorders that degrade these representations or impair access to them (e.g., Damasio et al. 2004; Rogers & Friedman, 2008). As such, much effort has appropriately been put towards investigating how the brain stores semantic representations and how we retrieve the correct representation in a given situation from among the many competing ones. Lexical-semantics, the study of meaning as denoted by words (as opposed to pictures or symbols), is often used as a convenient way to probe semantic representations in the brain. Evidence suggests that the conceptual knowledge underlying word and object comprehension is similar though some differences in the routes of access and extent of perceptual representation activation exist (Binder et al., 2009). We have chosen to use words in our studies to focus on the processing of concepts rather than percepts.

Evidence suggests that there is a widespread network of brain areas responsible for storage and retrieval of semantic representations divided grossly into posterior and anterior regions, respectively (for reviews, see Binder et al., 2009; Bookheimer, 2002; Lau et al., 2008). These regions also tend to be lateralized to the left-hemisphere though there is some bilateral representation in posterior areas. In general it is thought that parts of the temporal and parietal...
lobes are heteromodal cortex mainly involved in the storage of these representations while the left inferior frontal gyrus (LIFG) is involved in top-down retrieval and manipulation of semantic information.

1.1.1 Posterior cortices

The left posterior temporal cortex including the middle temporal gyrus (MTG), superior temporal sulcus (STS), and inferior temporal cortex (IT) have been shown to be involved in long-term storage of lexical-semantic representations. For example, a single-word reading study with aphasia patients bearing lesions in these areas showed that they have difficulty with semantic comprehension at the superordinate, equivalence, and subordinate levels of meaning (Hart & Gordon, 1990). Functional magnetic resonance imaging (fMRI) activation studies using semantic categorization or judgment tasks on words also consistently show activation in MTG (for a review, see Lau et al., 2008). Semantic priming, which is thought to ease retrieval of stored representations, has repeatedly shown facilitated retrieval of a word preceded by a semantically related word and a corresponding suppression of fMRI activity in the MTG (Devlin et al., 2004; Gold et al., 2006; Rissman et al., 2003; Wible et al., 2006).

Information about more specific semantic properties or features of a word or object may reside in sensorimotor cortices. Several studies suggest that the representation for a particular property is stored in brain regions active during the perception of that property. Naming the color of objects v. naming the same objects themselves elicited activity in occipital regions active during passive color viewing (Chao & Martin, 1999), while retrieving object color but not object motion information activates the region of the fusiform gyrus implicated in color perception
(Simmons et al., 2007). Other sensory- and motor-based properties are also partially stored in their respective cortices. Goldberg et al. (2006) had subjects answer written questions about the visual, sound, touch, and taste properties associated with objects and observed activation in the brain regions associated with the sensory processing of these specific properties. Similar evidence was also found using words. Hauk and colleagues (2004) showed that reading words associated with the movement of certain body parts activated the same regions in premotor cortex that were active when actually making the respective movements. Such observations reflect the greater concept of embodied cognition, but for our purposes they demonstrate that semantic representations may be stored not just in posterior temporal cortex but more broadly in sensorimotor cortices.

A recent meta-analysis of 120 fMRI studies investigating lexical-semantic processing clearly demonstrates that MTG activity extends more anteriorly also (Binder et al., 2009). Neuropsychological studies have shown that damage to the anterior temporal lobe from herpes simplex encephalitis or semantic dementia results in loss of semantic knowledge (e.g., Lambon Ralph et al., 2007; Noppeney et al., 2007) though this may be related to loss of connectivity with posterior temporal lobe regions as patients with semantic dementia have shown reduced posterior IT activation during semantic tasks (Mummery et al., 1999). fMRI studies also show greater activation in anterior temporal lobe when listening to sentences compared with well-controlled word lists (Friederici et al., 2000; Humphries et al., 2006) suggesting that this area may be more involved in combinatorial or syntactic processing. Binder et al. (2009) also present accumulated evidence for involvement of the left angular gyrus (AG) and supramarginal gyrus (SMG) in semantic processing. Notably, imaging studies have shown modulation of AG activity for
semantically incongruent words within a sentence (Ni et al., 2000) or only when words within the sentence could be integrated into a coherent meaning (Humphries et al., 2007). Thus the AG may play more of a role in integration of complex information such as integration of semantic information into a sentence. Overall evidence suggests that the storage of lexical-semantic representations seems largely to be held in posterior temporal cortex and posterior sensory areas.

1.1.2 Left inferior frontal gyrus and connectivity

Semantic cognition relies not only on the storage of semantic representations but also on the controlled use and application of this semantic knowledge in appropriate conditions. The brain area largely responsible for this controlled or top-down semantic processing is the left interior frontal gyrus (LIFG). The LIFG is involved in a number of language processes including semantic, syntactic, and phonological processing, and these processes may partially occupy separate subspaces within LIFG (Devlin et al., 2003; Friederici et al., 2000; Vigneau et al., 2006). Broadmann areas 45 (“pars triangularis”) and 47 (“pars orbitalis”) have both been implicated in semantic processing of a more top-down or controlled nature (defined as attentional or strategic processing) and may also have separate functions. Evidence suggests that anterior LIFG (aLIFG, BA47) supports controlled retrieval of semantic representations when retrieval is semantically demanding, while posterior LIFG (pLIFG, BA45) supports selection of a semantic representation from a competing set and inhibition of the competitors (for a review, see Lau et al., 2008). Interestingly patients with lesions to LIFG don’t always show unambiguous deficits in semantic processing (Hagoort et al., 1996; Milberg et al., 1995) and TMS to these areas only slows RT during semantic tasks (Devlin et al., 2003). Thus these areas may not be
crucial to complete tasks but are involved in semantic processing and the efficiency of that processing in the healthy brain (Price et al., 1999).

For the semantic network to be more than a collection of separate brain areas, the anatomically distant areas involved in semantic processing must be anatomically and/or functionally connected. Classically, it has been shown that Broca’s area (encompassing BA 45 and 47) and Wernicke’s area (encompassing posterior superior temporal gyrus and pMTG) are connected through the arcuate fasciculus, although diffusion tensor imaging (DTI) has demonstrated that other dorsal and ventral tracts also exist (for a review, see Friederici, 2009). Evidence from tracing provides more precise evidence than DTI, and a recent study indicates that the macaque monkey homologue of BA 45 is anatomically connected via the extreme capsule to association cortex in the superolateral temporal lobe and via the superior longitudinal fasciculus to the inferior parietal lobe and adjacent STS (Petrides & Pandya, 2009). Additionally, there is evidence for functional connections between these anterior and posterior regions. Resting-state fMRI BOLD correlations suggest that BA 45 and 47 are functionally connected with posterior temporal gyrus as well as AG and adjacent parietal areas (Xiang et al., 2010), while task-related BOLD correlations suggest connectivity between LIFG and posterior temporal gyrus (Bokde et al., 2001).

Even with this ample evidence, our understanding of semantic networks is still incomplete. fMRI activation essentially identifies local circuits or nodes of the networks while tracing and DTI detects anatomical connections or edges of the networks. Notably, fMRI has excellent spatial resolution but relatively poor temporal resolution while DTI and tracing provide static data only. Thus these methods are unable to provide us with a fully dynamic account of
networks, i.e., how networks perform in real time. Importantly, anatomical connections do not promote constant functional interaction between brain areas. So while we have a good understanding of the brain areas involved in semantic processing, it is not yet known how these anterior and posterior areas are dynamically recruited or can dynamically interact during retrieval of these semantic representations.

1.1.3 Investigating semantics using ERPs

The dynamics of lexical-semantics are frequently investigated using electroencephalography (EEG) as it measures real-time changes in the scalp electrical potentials coming from the brain. The most commonly used electrical marker of lexical-semantics is the N400 event-related potential (ERP) component (for a review, see Kutas & Federmeier, 2011). The N400 is a negative-going deflection of the electrophysiological signal spanning 300-500 ms after stimulus presentation and peaking around 400 ms. Initially discovered to have an increased amplitude when reading incongruent words within a sentence (Kutas & Hillyard, 1980), the N400 has been found to be sensitive to word- and sentence-level variables (such as word frequency, repetition, and congruity) and also influenced by non-lexical processes such as attention. Though classically semantic processing is thought to occur within this window of 300-500 ms, other ERP/ERF (ERF is the magnetic equivalent of the ERP) evidence points to aspects of semantic processing being involved as early as 100-200 ms (Pullvermuller et al., 2001; Segalowitz & Zheng, 2009; Sereno et al., 2003) and lasting until 900-1000 ms (for a review, see Van Petten & Luka, 2012) based on context and task demands.
While the N400 has helped elucidate many aspects of semantic processing, ERP analysis is unable to take full advantage of the rich dynamic information present in the EEG signal. Since ERP waveforms are calculated by averaging the raw EEG signal for trials of interest to increase the signal-to-noise ratio, ERPs only contain information that is time-locked and phase-locked to the stimulus presentation. Event-related electrophysiological signals are not always phase-locked to the stimulus however; thus valuable information may be missed through ERP analysis alone. Additionally, scalp ERPs are not utilized for examining brain networks. Often, methods with higher spatial resolution such as fMRI and PET are used to examine neurocognitive networks, but recently theories of neuronal oscillations have made clear the utility of using spectral analysis of EEG to examine networks. Thus using the N400 alone is not the optimal way to examine lexical-semantic processing especially within a network framework.

1.2 Theory of Networks and Oscillations

Electrical oscillations are ubiquitous phenomena in the brain and can be observed at multiple spatial scales. They reflect rhythmic fluctuations of local field potentials averaged over a few neurons (i.e., in vivo or in vitro microelectrode recordings) to hundreds of millions of neurons (scalp EEG and MEG). While the possible roles of these oscillations for brain function are still being debated, synchronization of neuronal oscillations has been postulated and largely supported as a mechanism for both local and long-distance communication within and between neural populations (for reviews, see Fries, 2005; Singer, 1999; Varela et al., 2001).
1.2.1 Mechanisms of oscillations

Oscillations often come about through a dynamic balance of opposing forces. In the case of the brain, excitation and inhibition provide these forces. As seen during certain pathological states such as a seizure, changes in the balance of excitation and inhibition modulate characteristics of oscillations lending intuitive evidence to their roles. While excitatory-only or inhibitory-only networks can create oscillatory activity too, all oscillations emerge from intrinsic cellular mechanisms. For example, properties of inhibitory GABA_A receptors are central in generating cortical gamma oscillations (30-90Hz) while GABA_B receptors, which have a slower time scale, would be more appropriate for generating the slower theta (4-7Hz) oscillations (Benchenane et al., 2011). The time constant of these receptors – tens of milliseconds for GABA_A and hundreds of milliseconds for GABA_B – determines the time between possible action potentials and thus influences the frequency of the oscillation. The relative strength of coupling between neurons can influence the amplitude of the oscillation (for reviews, see Buzsaki & Wang, 2012; Whittington et al., 2000). Oscillations may exist to help solve competing noise and energy issues in the brain (Buzsaki, 2006). As Buzsaki explains, the rhythmically fluctuating membrane potential of a neuron balances the neuron’s need to be robust to noisy inputs (so as not to cause extraneous firing) and energy efficient (oscillating requires a lower energy cost than just maintaining a lower spiking threshold to decrease sensitivity to noise). Ultimately, these and other mechanisms result in a wide range of frequencies (about 0.05 to 500 Hz) observed throughout the brain.

1.2.2 Possible roles for synchronous oscillations
In the last several decades, local and global oscillatory synchronization has been hypothesized to play specific roles for the brain. The main effect of oscillating potentials is the modulation of the excitability of a neuron affecting both the probability of firing and the sensitivity to synaptic input (Burchell et al., 1998; Volgushev et al., 1998). During the depolarizing phase of an oscillation, post-synaptic neurons are more excitable and sensitive to input from pre-synaptic neurons; during the hyperpolarizing phase, post-synaptic neurons are less excitable and less sensitive to input from pre-synaptic neurons. This rhythmicity effectively results in an opening and closing of a communication window for neurons or neuronal populations to interact with one another. This mechanism can work on a global scale too. If the communication windows of spatially distant neuronal populations are open at the same time, firing in one is more likely to cause firing in the other, and these populations can interact. Thus to efficiently synchronize their communication windows for information processing, the two groups can synchronize their oscillations. This mechanism allows neurons to form specific transient functional networks within the full network defined by anatomical connections alone.

Some of the initial evidence that neuronal populations can promote interactions by synchronizing their oscillations came when investigators were looking for a mechanism to bind information stored in different brain regions into a coherent percept. This so-called “Binding by Synchrony” hypothesis was tested in a number of studies in Wolf Singer’s lab examining gamma oscillations in the cat visual cortex. They found that the oscillations of spatially segregated neurons phase-locked when the cat viewed coherent motion of light stimuli but not incoherent motion (for a review, see Singer & Gray, 1995). This so-called “Binding by Synchrony” hypothesis was further tested and supported in different animals and sensory systems, and human
evidence that phase-synchrony was involved in the Gestalt perception of upright but not inverted ‘Mooney’ faces was soon to follow (Rodriguez et al., 1999).

A related and highly influential hypothesis regarding another role of synchronous oscillations is the “Communication through Coherence” (CTC) hypothesis put forward by Pascal Fries (Fries, 2005). Rather than binding elements of a percept together, coherent or phase-synchronous oscillations can be a mechanism to allow dynamic communication between distant brain areas to achieve a broader set of functions including attentional modulation of sensory processing (Fries et al., 2001). Still, the main idea is that the synchronizing of communication windows allows for information flow between brain regions. This method of dynamically linking networks on a functional level can be examined through spectral coherence between two electrodes (Varela et al., 2001). These dynamic networks still reflect the underlying anatomical connectivity between brain regions; however, coherence provides the flexibility to dynamically select more specific sub-networks of the larger anatomical network in a task-dependent manner.

1.2.3 Measuring Oscillatory Synchronization using EEG

In the following studies, we use Fourier analysis, namely power and coherence calculations, of EEG signals to study dynamic lexical-semantic networks. To transform the time series of our EEG signal into frequency and phase information while preserving time information, we use several advances on basic Fourier methods. First let us define our EEG time series as $V(t)$ as a sum of $n$ sinusoids each with amplitude $A_n$, frequency $f_n$, and phase $\theta_n$: 
After performing the Fourier transform, we detect the frequencies involved and represent them as a set of basis functions called the Fourier series \( F(f_n) \):

\[
F(f_n) = A_n e^{j \theta_n} \tag{Eq. 1.2}
\]

In Eq. 1.2, \( e \) is Euler’s constant and \( j \) is the imaginary unit \( \sqrt{-1} \). The power \( P(f_n) \) of each frequency component can thus be represented as

\[
P(f_n) = F(f_n)F^*(f_n) \tag{Eq. 1.3}
\]

where \( F^*(f_n) \) is the complex conjugate of the Fourier series for frequency \( f_n \). Typically only the amplitude of the power spectrum is plotted, so one can think of the power as the squared amplitude of the oscillation at the given frequency. Power is calculated on a single time series (single channel). In contrast, coherence \( \gamma \) is calculated between two time series (two channels) labeled \( u \) and \( v \) in Equation 1.4.

\[
\gamma_{uv}^2(f_n) = \frac{|F_u(f_n)F^*_v(f_n)|^2}{P_u(f_n)P_v(f_n)} \tag{Eq. 1.4}
\]
Coherence essentially estimates the constant relative phase difference between the two time series and ranges from a minimum of 0 to a maximum of 1. Regarding neurophysiological data, coherence or correlation values as low as 0.1 indicate prominent phase-locking (Harris and Thiele, 2011) although values of 0.3-0.4 are commonly observed in EEG data. Also interesting to note is that power and coherence are the spectral representations of auto- and cross-correlation calculations performed in the time domain.

One shortcoming of the power and coherence calculations is that their estimates are made over the whole time series (i.e., a whole EEG trial after segmentation). As we know from ERP studies, cognitive processes vary on the order of tens or hundreds of milliseconds, thus we often want finer estimates on this order. Advanced methods such as wavelet or multitaper methods have been developed and applied to neurophysiological data to preserve the time information by making spectral estimates over smaller time windows to create a time-frequency representation (TFR) (Mitra & Pesaran, 1999). The TFR temporal resolution depends upon the window size chosen and often is on the order of tens or hundreds of milliseconds. Thus the temporal resolution is inferior to ERP analysis which can be on the millisecond order. Another shortcoming is that coherence can be calculated between any two channels, and often coherence between two adjacent channels reflects the same neural source. In this case, high coherence between adjacent channels does not indicate synchronization between two sources; thus one must carefully interpret coherence results.

As our cognitive process of interest may both evoke new oscillatory activity and perturb ongoing activity, we want to preserve both types of activity named evoked and induced, respectively. While both types are time-locked to the stimulus, evoked is phase-locked while
induced is non-phase-locked. To preserve both, we calculate time-frequency representations of power and coherence over each trial (time-locked to stimulus presentation) and then average over all trials. If the time series of all trials are averaged first (essentially calculating the ERP), frequency components at different phases (i.e., not phase-locked to the stimulus) may be averaged out. For example, two trials containing an oscillation that is at the same frequency but out-of-phase by 180° will average to zero and will not measure that oscillatory component when doing the time-frequency analysis after ERP calculation. This is why ERP analysis averages out non-phase-locked information.

The interpretation of power and coherence is in line with discussions of oscillatory synchronization presented in section 1.2.2. While coherence between two EEG electrodes can reflect long-range synchronization between distant neuronal groups and enables communication between these distant brain areas, spectral power at a single electrode likely reflects local synchronization within a more local brain area. One must keep in mind though that a single EEG electrode can detect activity from multiple neural sources not necessarily directly under the sensor. Thus the local synchronization as measured by power analysis is thought to reflect perhaps several local networks, while the long-range synchronization measured by coherence analysis indicates the formation of functional long-range networks (Varela et al., 2001).

1.2.4 Cognitive correlates of oscillatory synchronization

The frequencies most robustly measured by EEG are delta (1-3Hz), theta (4-7Hz), alpha (8-12 Hz), beta (13-30Hz), and gamma (30-100Hz). These frequencies have been observed both
during spontaneous brain states (e.g., during sleep) and task-dependent states (during sensory or cognitive processing). Still a major question has lingered since the initial discovery of scalp EEG rhythms over 80 years ago by Hans Berger – how are these rhythms functionally related to specific cognitive operations?

This field has grown rapidly in the past two decades partly due to the increase in computing power which makes detailed spectral analysis more feasible. Recent reviews of the oscillatory correlates of object recognition (Tallon-Baudry & Bertrand, 1999), attention (Jensen et al., 2007), memory (Fell & Axmacher, 2011; Jensen et al., 2007; Klimesch, 1999), and language (Bastiaansen & Hagoort, 2006; Weiss & Mueller, 2003) (to name just a few) demonstrate the maturing of this field. So does frequency-band-specific synchronization correlate with specific cognitive processes? There is some evidence to support this notion but the dynamics are probably much more complex as there is no one-to-one correlation between frequency and a given cognitive process. For example, converging evidence suggests that alpha power is negatively correlated with cortical excitability and task performance as modulated by attention (for a recent review, see Palva & Palva, 2011). But attention also modulates gamma power though the correlation is in the opposite direction, i.e. gamma power increases over cortical areas corresponding to the attended modality (Jensen et al., 2007). Hippocampal theta oscillations have long been implicated in long-term memory and spatial navigation, but more recent work demonstrates that theta oscillations are also involved in working memory. For example, increases in anterior-posterior theta (4-7 Hz) coherence during working memory tasks may be a basis for functional coupling of frontal and posterior areas involved in working memory processing (Sarnthein et al., 1998; Sauseng et al., 2005; Summerfield & Mangels,
Accumulating evidence suggests that gamma is also involved in working and long-term memory (for reviews, see Fell & Axmacher, 2011; Jensen et al., 2007).

Since language processing utilizes both domain-general (e.g., attention, memory retrieval) and domain-specific (e.g., syntactic) processes, oscillatory correlates can be quite widespread. For example, Weiss & Mueller (2003) found that coherence changes that are common to both auditorily and visually presented words (thus, “language-specific”) are exclusively in the lower-frequency delta and theta bands (they analyzed but did not find coherence in alpha and beta bands). Converging evidence shows gamma synchronization to be involved in integrating semantic and syntactic information into a unified mental representation for comprehension (Bastiaansen and Hagoort 2006). As our main interest is in the correlates of semantic processing, we discuss this further in section 1.3 below. But first we want to further explore why it is that gamma correlates so often with a number of cognitive processes.

Gamma synchronization may be involved more generally in assembling local cortical networks and thus may not be restricted to a handful of cognitive operations. Gamma frequencies are thought to transiently bind together cell assemblies as the period of a single gamma cycle is about 10-25 ms, precise enough for synchronizing over the short distances of cortical columns (Buzsaki & Draguhn, 2004; Engel et al., 2001; Harris et al., 2003). Local neuronal assemblies are organized into temporal packets of 15-30 ms because pyramidal cells downstream from the assemblies can efficiently integrate excitatory inputs in this time window (Buzsaki, 2006). Indeed, gamma synchronization may be a fundamental cortical computation for such things as coincidence detection of synaptic input, rhythmic gain modulation, and synaptic plasticity that underlie many cognitive functions (Fries, 2009).
The other frequency often observed during cognitive processes, theta, has repeatedly been implicated in hippocampal function, but evidence is building for theta oscillations in the cortex. Several human intracranial EEG studies have specifically observed theta oscillations in the prefrontal and temporal cortices among other areas during working memory tasks (Jacobs et al., 2007; Meltzer et al., 2008; Raghavachari et al., 2001). Additionally, long-range theta synchronization has been reported across prefrontal-parietal MEG sensors (Cashdollar et al., 2009) during a working memory task and intracranially between prefrontal and hippocampal areas during an episodic memory task (Watrous et al., 2013; for a review of these interactions in rodents, see Colgin, 2011). These studies provide converging evidence that cortical theta is relevant during cognitive tasks and may be a coupling mechanism across distant brain areas. The cellular mechanisms for theta oscillations are not fully known, though GABA\textsubscript{B} receptors are prevalent throughout the cortex and have been proposed as a potential mechanism (Benchenane et al., 2011). Still, these studies suggest that it is plausible that theta oscillations are involved during semantic processing too.

One way in which these frequency bands may be organized is by scale. Transmission speed which is based on the length and myelination of axons of the neuronal groups involved in a functional network is one main determinant of the timing within and between neuronal groups. This constraint thus directly influences the width of temporal windows for information transfer and therefore the frequencies of the oscillations involved in synchronizing neuronal elements. Cognitive processes that involve more local integration may operate in the higher frequencies (beta and gamma) while global interactions across distant brain areas require longer transmission windows and therefore lower frequencies (theta and alpha) (Von Stein & Sarnthein, 2000). Some
evidence points to gamma also being involved in long-distance interactions between motor cortex and spinal cord neurons (Schoffelen et al., 2005) as the greater myelination of motor neurons makes faster interactions possible. Still, it is likely that many cognitive processes have correlates in both lower and higher frequencies since most require both local and long-distance interactions. Indeed, recent investigations into cross-frequency coupling often find that higher frequency oscillations are nested within lower frequencies suggesting that lower and higher frequencies can work together to support brain processes (for a review, see Canolty & Knight, 2010). Other mechanisms which might influence the frequency of synchronization include the specific receptors involved, the synaptic or extrasynaptic placement of those receptors, the activation time constant of calcium or potassium currents, the type and geometry of the neurons involved, and the resonance of those neurons (Wang, 2010). But these are more difficult to measure in humans; thus we primarily use the scale theory along with evidence from the pre-existing literature in formulating our hypotheses.

1.3 Semantic Correlates of Oscillatory Synchronization

Previous studies examining oscillatory synchronization during semantic paradigms have mainly examined spectral power rather than coherence and have demonstrated relationships between theta, alpha, and gamma power and lexical-semantic processing. Theta power changes have been seen during the comparison of open class words (having greater semantic content) and closed class words (less semantic content) in sentences (Bastiaansen et al., 2005) and the comparison of nouns with different semantic features (primarily visual v. auditory) over occipital and temporal cortices (Bastiaansen et al., 2008). Alpha power decreases have been observed
during semantic judgment between pairs of words (Klimesch et al. 1997a; Klimesch et al. 1997b). In addition, differences in gamma power for nouns v. verbs reflected differences in semantic associations (visual v. motor) (Pulvermüller et al., 1999). An intracerebral EEG study found increases in gamma power in the pars triangularis for a semantic v. phonological judgment task (Mainy et al., 2008). As a fast rhythm, the gamma oscillation is well suited to cognitive and language processing because of its ability to quickly form transient networks. As emphasized above, it has been proposed that faster rhythms like gamma are also well suited to the scale of local synchronization (mm-cm) while lower frequencies are better suited to long-range interactions since they typically synchronize more slowly (Von Stein & Sarnthein, 2000). Indeed, gamma power changes have been reported for other fast language processes such as word production (Crone et al., 2001), semantic violation in sentences (Hagoort 2004; Hald 2006; Penolazzi 2009), and word repetition priming (Matsumoto & Iidaka, 2008).

Evidence for long-range lexical-semantic networks using coherence analysis is more limited. Weiss and Mueller (2003) reported greater coherence at 30 Hz for semantically-congruent words in a sentence than for semantically-incongruent words but only for a single pair of channels, Pz-P4 in the 10-20 EEG electrode system. These channels are less than 10 cm apart, and therefore their coherence may be due to volume conduction and not two discrete neuronal populations participating in a large-scale semantic network (see Nunez & Srinivasan, 2006, for a discussion of volume conduction effects on coherence). A recent MEG study found coherence differences centered at 8 Hz and 333 ms for semantically primed words compared with unprimed words between left superior temporal cortex and right temporal cortex structures (Kujala et al., 2011). While these studies provide evidence for coherence as a viable method for investigating
long-range synchronization during semantic paradigms, neither study addresses the potential mechanism of interaction in the anterior-posterior semantic retrieval network. Based on scale, one might suggest that these distant brain areas synchronize through lower frequencies. Kujala et al. (2006) found a widespread network of areas synchronizing in the alpha band when subjects engaged in reading though this likely includes areas involved in many processing stages beyond just semantic processing. Evidence from other disciplines suggests that functional coupling between frontal and posterior areas during cognitive operations may be accomplished through anterior-posterior theta coherence (Sarnthein et al., 1998; Summerfield & Mangels, 2005). Thus, we are interested in examining lower frequencies in particular and their involvement in a long-range semantic network.

1.4 Overarching Goals and Hypotheses

We have two overarching questions regarding mechanisms of local and long-distance networks involved in lexical-semantic processing. First, if gamma synchronization is a possible mechanism for creating local cortical circuits, is it involved in the local circuits supporting the semantic representation? Second, fMRI results demonstrate that anterior and posterior regions of the brain are part of a larger semantic network and functionally connected – could oscillatory synchronization be the dynamic mechanism of interaction between these areas? We addressed these questions through two experiments using two semantic paradigms similar to those which have been shown to activate LIFG and posterior areas in fMRI experiments. The semantic priming paradigm is used to task semantic retrieval processing while the semantic ambiguity
paradigm is used to task semantic selection processing, although both retrieval and selection processing are likely involved in both paradigms. In Chapter 2, we present our first experiment using the semantic priming paradigm to investigate the oscillatory dynamics involved in retrieval of lexical-semantic representations. We provide evidence that posterior gamma oscillations are involved in the activation of lexical-semantic representations while left anterior-posterior theta coherence reflects retrieval processing likely between LIFG and posterior areas storing the semantic representation. The main basis of the interpretation of theta coherence reflecting this coupling lies in the carefully chosen paradigm known to activate these areas and the respective left frontal to posterior topography of coherence in our results. In Chapter 3, we present our second experiment where we used a semantic ambiguity paradigm to investigate if theta coherence is involved in another top-down semantic process, semantic selection and inhibition. When multiple semantic representations are activated as possible meanings of ambiguous words, fMRI results have shown that the LIFG and left pMTG help to select the contextually-correct meaning and inhibit incorrect meanings. Again, based on the specific paradigm chosen and the anterior-posterior distribution of coherence, we interpret the theta coherence as involved in coupling of these areas for semantic selection and inhibition. Finally, in Chapter 4, we summarize our novel contributions to the understanding of semantic networks, place them within the context of the broader literature, and address future directions to continue exploring local and long-range semantic networks.
Chapter 2

2.1 Introduction

In this study we used a semantic priming paradigm to investigate the anterior-posterior semantic retrieval network and, more generally, the roles of local and long-range synchronization during semantic processing. Through semantic priming, semantic retrieval demands of a target word are lessened when preceded by a semantically-related prime word (i.e., “elm” facilitates retrieval of “maple”) compared to an unrelated prime word. This prime word is thought to partially activate related words through automatic spreading activation hence lessening the retrieval demands of a related target word (Posner & Snyder, 1975). The decrease in semantic retrieval demands for related compared to unrelated targets is apparent through several measures including a decrease in reaction time and in the electrophysiological signal (as typically measured by the N400 ERP component) (see Kutas & Federmeier 2011, for a review). Thus we expected to see the decrease in semantic retrieval demands reflected in decreased gamma power and decreased low-frequency coherence for related compared to unrelated target words. Coherence is likely to occur in either the theta or alpha bands. Evidence for alpha comes from a recent MEG semantic priming study where a modulation in bilateral temporal lobe oscillatory synchronization was observed at 8 Hz (Kujala, et al., 2011). Coherence has been observed across left prefrontal and temporal regions in the theta range, although this was during working memory paradigms (Sarnthein et al., 1998; Sauseng et al., 2005; Summerfield & Mangels, 2005). As we are looking at a similar left prefrontal to posterior network, we may also observe coherence
modulations in the theta range. More specifically, we would expect that the larger anterior-posterior low-frequency coherence for unrelated target words would reflect the need for top-down processing when semantic retrieval demands are high. Thus, our study addressed the roles of both local and long-range synchronization in establishing local and long-range functional networks for lexical-semantic retrieval.

2.2 Materials and Methods

Subjects

Twenty-two healthy volunteers participated in the experiment and received monetary compensation for their participation. The data of one subject had to be excluded from group analysis due to excessive noise. Thus analysis was carried out for the remaining 21 subjects (age 18-30, 8 males). All were native English speakers without a history of neurological or psychiatric problems or learning disabilities. All were currently pursuing a university education or had completed an undergraduate degree. Three subjects reported being left-handed while the remaining reported being right-handed. All gave informed consent (approved by the Georgetown Medical Center IRB) before starting the experiment.

Stimuli

We used 200 semantically-related word pairs taken from published experiments (Anaki & Henik, 2003; Avons, Russo, Cinel, Verolini, Glynn, et al., 2009; Hutchinson, 2002; Rogers & Friedman, 2008; Slowiaczek, 1994; Stolz & Besner, 1998). In the pair, the prime word, e.g.
“elm”, was followed by a related target word, e.g. “maple.” These words were then scrambled to form an additional 200 unrelated word pairs which were examined to ensure no new related pairs were formed. This allowed matching across all lexical variables when comparing Related and Unrelated target words. Half of the Unrelated pairs were shown at a short ISI and half at a long ISI with the pairs corresponding to each ISI counterbalanced across subjects. The same method was used on the Related pairs. Short ISI pairs did not show a significant N400 effect, so we could not be certain about the level of semantic processing during those trials. Thus only long ISI pairs are examined here, and only nouns were used as stimuli.

**Design and procedure**

Subjects were asked to silently read the stimuli presented on the computer monitor in front of them while performing a delayed letter-search task (Kutas & Hillyard, 1989). In this task subjects made speeded responses identifying whether a certain letter, presented after the word pair, had been in either of the preceding words. On half of all trials, the letter was present (requiring a “yes” response); across those trials, 51% of the letters appeared in the prime and 49% appeared in the target. With this task the decision and response came well after the semantic priming occurred and did not interfere with the semantic neural response. Subjects were asked to minimize any movements and eyeblinking while words were on the screen. Stimuli were presented on the monitor in black Arial font against a gray background. Subjects viewed 200 trials which each consisted of a fixation cross (1800 ms), prime word (150 ms), blank screen (850 ms), target word (150 ms), blank screen (1150 ms), letter (250 ms), and fixation cross (until subject responded) (see Figure 2.1A). Reaction time (RT) was measured from the onset of the
letter until the button-pressing response. An additional 200 trials with a short ISI for the prime word (150 ms prime and 100 ms blank following prime) were also viewed but their data are not presented here. The order of Related and Unrelated targets was counterbalanced across subjects. Not including a short practice session of 12 trials at the beginning of the experiment, there were 4 blocks of stimuli less than 10 minutes each with subject-determined breaks in between. The total time for the session including setup was under 1.25 hours for each subject. After the recording session, subjects were debriefed. When asked if they noticed anything about the stimuli, all reported that some stimuli seemed to be related while others were not related. This helped us confirm that they were semantically processing the words.

**EEG recording and preprocessing**

EEG was continuously recorded using a 128-electrode EEG system (Electrical Geodesics Inc., Eugene, OR) sampling at 200Hz. Electrode locations are shown in Appendix A. During the recording, impedances were kept below 70kΩ, all channels were referenced to the vertex, and a bandpass hardware filter (0.1-100Hz) was applied. The following preprocessing steps were performed offline: data were bandpass (0.3-100Hz) and notch (60Hz) filtered to remove low frequency and line noise; data were segmented into trials from -1000ms to 2000 ms around target stimuli; ocular artifacts were corrected (Gratton, Coles, & Donchin, 1983); data from all channels were re-referenced to the average reference (Bertrand, Perrin, & Pernier, 1985); and the average baseline 200 ms before the target stimulus presentation was subtracted from trials. Trials with artifacts larger than ±100µV were removed before analysis. On average, the same
percentage of trials (13.8%) were removed from both Unrelated and Related conditions from each subject’s data.

**Time-frequency analysis**

Event-related changes in EEG power and coherence were examined by computing time-frequency representations (TFR) of the single word trial data using the multi-taper approach described by Mitra and Pesaran (1999). The open source Fieldtrip toolbox (Oostenveld et al., 2011) and in-house Matlab code were used for these calculations. Because we computed the TFRs of the single trials before averaging, our analysis reflects both evoked and induced EEG activity, i.e., oscillatory activity that is both phase-locked and non-phase-locked to the stimuli. We were motivated to examine both together since none of the previous lexical semantic studies examined differences between evoked and induced rhythms (Bastiaansen et al., 2005; Bastiaansen et al., 2008; Mainy et al., 2008; Pulvermüller et al., 1999), and indeed these types of rhythms reflect complementary underlying dynamics. In order to optimize the trade-off between time- and frequency resolution, TFRs were constructed in two different, partially overlapping, frequency ranges. In the low-frequency range (2–30 Hz), 400 ms Hanning windows were used to compute power and coherence changes in frequency steps of 1 Hz and time steps of 10 ms. Regarding temporal resolution, any given time-point in the resulting TFR is a weighted average of the time-points ranging from 200 ms before to 200 ms after this time point, and this gives a frequency resolution of $1/0.4 = 2.5$ Hz. In the high-frequency range (25-100 Hz), 400 ms discrete prolate spheroidal sequence windows (multitapers) were used to compute power and coherence changes in 2.5-Hz frequency steps and 10 ms time steps with 5-Hz frequency smoothing. These
calculations were performed starting 500 ms before the word appeared on the screen to 1500 ms after the word onset.

Coherence between electrodes has been used extensively as a measure of long-distance synchrony (e.g., Summerfield & Mangels, 2005; Weiss & Mueller, 2003). While power is calculated from the auto-spectrum of a single channel, coherence utilizes the normalized squared cross-spectrum between pairs of channels to quantify the stability of phase difference between the signals (see Equations 1.3 and 1.4). Coherence is high if the signals are synchronized, i.e., the relative phase difference is stable across trials. If the event-related coherence is greater than baseline, the TFR displays coherence increases. While there are some limitations in the interpretation of coherence between nearby electrodes, it is well-accepted to perform coherence between electrodes to investigate large-scale network dynamics (for a review, see Varela et al., 2001). Unlike measures that only take the phase into account, coherence computes the consistent synchronization based on both amplitude and phase and is thus more robust against noise and spurious phase-locking. Since coherence is then normalized by the power at each electrode, power in theory should not contribute to the level of coherence. We calculated TFRs of coherence using the same parameters as above. We tested a selection of 32 electrodes (see Figure 2.5E) spread across the scalp as seed channels with 12 of those channels clustered over left frontal areas. For each seed channel, 127 coherence TFRs were calculated (one for each pair of channels).

The TFRs of target word trials were averaged separately for Related and Unrelated conditions. The power and coherence changes were then expressed as percent increases or decreases relative to a baseline of -50 ms to 50 ms around the target stimulus.
Statistical analysis

For behavioral data, we performed a single t-test between grand-averaged RT for Unrelated v. Related conditions. Similarly, a t-test was used to assess the amplitude difference between the two conditions at the spatiotemporal peak of the N400 ERP component.

To evaluate statistical differences between conditions for TFRs, we used a nonparametric statistical method with False Discovery Rate (FDR) correction. This method is optimal when there is no a priori knowledge of the spatiotemporal locus of the effect. In undertaking the large number of comparisons to find a possible effect, we would run into a multiple-comparisons problem and would not be able to control the Type 1 error rate. The FDR correction with the nonparametric statistical method can control this error rate (Genovese et al., 2002), and we report results for which $q \leq 0.05$.

The nonparametric analysis is fully explained by Maris and Oostenveld (2007). Essentially, a simple dependent-samples t-test was performed on the observed data for each time-frequency-channel data point. Next, a null distribution which assumes no difference between conditions was created. This distribution is obtained by 1000 times randomly assigning the conditions in subjects and calculating the t-statistic for each randomization. Finally, we compared the t-statistics of the observed data to the nonparametric null distribution and calculated the proportion of t-statistics larger or smaller than the observed ones. These p-values were then thresholded using the FDR algorithm to ensure that the expected proportion of falsely rejected hypotheses was less than 5%. This allowed us to control the Type 1 error rate.
We examined the difference Unrelated-Related for both power and coherence data (please note that with EEG data, this subtraction allows us to examine both Unrelated > Related and Related > Unrelated contrasts which appear as positive and negative differences, respectively). We performed the nonparametric analysis with FDR thresholding on all pairs of time-frequency-electrode data points; this was done separately on lower frequencies (4-30 Hz) and higher frequencies (25-60 Hz). Thus the significant effects reported below span the theta, alpha, and beta bands (4-30 Hz) or the gamma band (30-60 Hz). Effects less than 165 ms long (the average minimum time to complete a full theta cycle) or spanning less than 3 adjacent channels were not considered as they were likely to be false positives and therefore not robust effects.

Regression Analysis

Regression was performed between the EEG effects and the RT effects across subjects. The peak EEG effects for each subject were selected by identifying each individual’s peak within the time-frequency-channel boundaries of the significant grand-averaged effects. Subsequently, these individual peaks were entered into the regression analysis. For coherence results, peaks were selected separately for each seed channel showing significant coherence, and regression between RT and coherence was performed separately for each seed channel.

2.3 Results

Behavioral Results
We found that behavioral responses were significantly faster for the Related compared to the Unrelated condition (Unrelated RT = 779 ms; Related RT = 760 ms; one-tailed, paired t-test: p=0.03) as measured from the onset of the letter. This effect has been shown repeatedly with the lexical decision task; to our knowledge, this is the first report of a RT difference using the delayed letter-search task. Average accuracy on the task was 93% with all subjects performing at greater than 80% accuracy. No difference in accuracy was seen between conditions (Unrelated correct = 93.7; Related correct = 92.7; two-tailed, paired t-test: p=0.22).

**ERP Results**

We first confirmed the neural effect of semantic priming by examining the N400 ERP component. Grand-averaged ERPs for Unrelated and Related conditions are presented in Figure 2.1B. The difference between the N400 amplitudes can be seen between approximately 275–500 ms. This N400 effect (greater negative deflection for the Unrelated than the Related condition) is significant as tested near its spatiotemporal peak at electrode 62 between 350-450 ms (one-tailed, paired t-test: p=0.02). Additionally, the topography of the difference between conditions has the typical broad negative distribution centered at parietal electrodes (Figure 2.1B). The positivity over the left frontal electrodes results from a greater positive waveform for the Unrelated than the Related condition and hence is likely the opposite end of the effective dipole causing the N400. This frontal effect is often too sparsely sampled by EEG systems with fewer electrodes on the forehead and cheek and therefore is not commonly observed or reported. Additionally, while the 1µV effect size may seem smaller than is normally reported, it is mainly a consequence of using the vertex as the reference and subsequently re-referencing to the average reference and
does not reflect a lack of semantic processing (for similar effects, see Hill et al., 2002; Hill et al., 2005). Thus the N400 priming effect helped us confirm that semantic processing took place.

**Figure 2.1. Semantic priming task and N400 ERP effect.** A) Subjects viewed prime-target pairs that were either semantically unrelated or related. They were then asked to identify if the given letter had appeared in either word. Please see the Methods section for a complete explanation of the paradigm. B) Grand-averaged ERP waveforms of Unrelated (dotted) and Related (solid) conditions at electrode 62 (electrode Pz in the 10-20 system). Note the N400 effect between 275 and 500 ms as delineated by the vertical gray lines. The topography of the difference wave shows the typical broad scalp distribution of the N400 effect centered over parietal electrodes between 350-450 ms. t=0 corresponds to the onset of the target words.
**EEG Power Results**

The contrast Unrelated-Related on power data revealed one significant effect in the gamma band in the hypothesized direction (Unrelated > Related), and two significant effects in the opposite direction (Related > Unrelated) which we call “reverse effects”. The gamma-band effect in the expected direction can be seen in Figure 2.2. Gamma power increased for the Unrelated compared to the Related condition in the window 45-50Hz, 150-450 ms. The significant difference as revealed by FDR thresholding (q ≤ 0.05) is outlined in black in the difference TFR (to show the extent in time and frequency of the significant difference) while the significant channels included in some portion of that significant time-frequency “cluster” are indicated with black stars in the topography plot. The main difference is centered over six right parietal electrodes near the peak of the N400 effect. There was also a significant difference at a single left frontal electrode (ch. 32), though isolated single channel effects are less robust.
Figure 2.2. Gamma power effect. TFRs showing significantly greater gamma power increases for the Unrelated than Related condition averaged over the six right parietal electrodes (78, 79, 84, 85, 86, 91) where the effect is maximal. The difference between conditions is plotted as well as the topography of that difference. The statistically significant (p<0.05, corrected) window is outlined in black in the difference TFR, and significant channels are highlighted with small black stars in the topography. The topography map also shows a significant difference at a single left frontal channel (32). Plots are shown as relative change compared to baseline. t=0 corresponds to the onset of the target words.

The two reverse effects were in the gamma and alpha bands. The reverse gamma effect (Figure 2.3) resulted from greater power for the Related than the Unrelated condition. This effect spanned a later time (300-800 ms) and lower frequency (35-40Hz) window and was centered more posteriorly than the positive gamma effect. The significant difference is shown in the masked graphs.
Figure 2.3. Late gamma power effect. TFRs showing reverse gamma-band effect averaged over 4 posterior electrodes (62, 72, 74, 75) where the effect is maximal. The displays follow the organization explained in Figure 2.

The reverse alpha effect is shown in Figure 2.4. As decreases in the alpha power are thought to reflect active processing (Klimesch et al., 2007), the greater power decreases for Related than Unrelated in our study reflect more task-related activity for Related than Unrelated (thus a “reverse” effect compared to the typical direction of the priming effect). This difference occurs between 600-1000 ms and 8-12Hz over left frontal electrodes. The significant difference can be seen in the masked graphs. No other robust significant differences in power were observed. Specifically, while theta power changes have been related to lexical-semantic processing (Roehm et al., 2007; Bastiaansen et al., 2005), we observed no robust difference in theta power here. The theta power increases observed for both Related and Unrelated conditions in Figure 2.4 did not differ between conditions. Also, we observed a short (<100ms) significant difference in theta power increases (Unrelated>Related) in right frontal electrodes (not pictured), but the brevity of this effect did not fit our reporting criteria to avoid false negatives.
**Figure 2.4. Late alpha power effect.** TFRs showing the lower-band activity averaged over the 8 left frontal electrodes (32, 38, 39, 43, 44, 49, 127, 128) where an alpha effect is maximal. The displays follow the organization explained in Figure 2.

**EEG Coherence Results**

Of the 32 seed channels tested, we only found five with robust significantly-different coherence changes. These differences were only in the theta band. We observed significantly greater theta coherence for Unrelated>Related in two time windows, 150-425 ms and 600-900 ms. These coherence differences resulted from increased theta coherence for the Unrelated condition but no coherence increases in the Related condition (see the effect in an example seed channel, Channel 34, in Figure 2.5A). The earlier theta effect appeared in three adjacent seed channels (of the 32 tested seed channels) over the left frontal cortex and displayed significant coherence with several adjacent posterior channels (Figure 2.5B showing topography of coherence changes for seed channels 32, 127, and 128). The later theta effect appeared in four
adjacent seed channels over the left frontal cortex. Each seed channel displayed significant coherence with a large number of adjacent posterior electrodes (Figure 2.5C showing topography of coherence changes for seed channels 32, 33, 34, 128). Each topographical map represents significant coherence changes from baseline across the scalp as calculated from the noted seed channel (indicated with the red star). Notably, we did not observe significant coherence differences for the channels which are right homologues to the left channels with significant coherence. We also did not observe significant coherence differences in other frequency bands that fit our criteria to eliminate false positives. Specifically, a beta effect may fit with another report of beta coherence differences during priming (Ghuman et al., 2008), but it was not robust enough (i.e., spanning at least 3 adjacent seed channels) for us to consider it a real effect (Figure 2.6).

We also confirmed that the observed theta coherence increases were independent of theta power increases. One might surmise that increases in both coherence and power are necessary to support formation of long-range networks. Physiologically, this would mean that formation of a long-range network (as reflected by increased coherence) is possible only when local synchrony within the same frequency band is strengthened in the participating local networks (as reflected by increased power). In this scenario, one would expect changes in coherence to always be accompanied by similar changes in power. If the two measures are independent, however, it would suggest that increased synchronization between distant brain areas may be sufficient to form a functional network without changes in local synchrony within local subparts of this network. Figure 2.5D shows the insignificant difference in power between the two conditions for the anterior seed electrodes (32, 33, 34, 127, 128) and for a selection of posterior electrodes (73,
74, 81, 82, 88) showing significant coherence with those seed channels. While there are some power increases in the theta band, the power changes do not follow the same pattern as coherence changes in either 150-425ms or 600-900ms in either of these TFRs. Thus the observed theta coherence changes cannot be tied to changes in theta power. This suggests that coherence alone is the mechanism for creation of this anterior-posterior network.

**Regression Results**

We examined the correlation between all four significant EEG effects and the RT effect across subjects. No correlations were observed for any power effects. Additionally, no correlation was observed between the level or timing of peak theta coherence and the RT effect.
A. Coherence TFRs, Seed Channel 34

B. Summary of Early Theta Coherence

C. Summary of Late Theta Coherence

D. Power Differences

E. Seed Electrode Locations
Figure 2.5. **Theta coherence effects.** A) Example of coherence at a single seed channel, Channel 34. TFRs showing theta-band coherence over three posterior electrodes (73, 81, 88) from seed channel 34 (red star in topographs). TFRs show a coherence increase for the Unrelated condition but not the Related condition. The displays follow the organization explained in Figure 2. B) Summary of coherence in the early time window. Topographies showing significantly greater coherence increases for Unrelated than Related between 150-425 ms for three adjacent left frontal seed channels. The red star indicates the placement of the seed channel for each topography plot. The unique time window chosen for each topography plot reflects the extent of the significant effect for that seed channel. The statistically significant (p<0.05, corrected) channels are highlighted with small black stars in the topography. Plots are shown as a relative change compared to baseline. C) Summary of coherence in the later time window. Topographies showing significantly greater coherence increases for Unrelated than Related between 600-900 ms for four adjacent left frontal seed channels. The displays follow the organization explained in part B. D) TFRs of raw power differences for the average of left frontal channels (32, 33, 34, 127, 128) and posterior channels (73, 74, 81, 82, 88). These posterior channels are a subset of those showing significant theta coherence with the left frontal seed channels. While there are some differences in power increases in the theta band, they were not significant differences, and the power changes do not follow the same pattern as coherence changes in either 150-425ms or 600-900ms in either of these TFRs. E) Locations of the seed electrodes used for coherence calculations. Note that there is a higher proportion over left frontal areas as we hypothesized that we would observe coherence from left frontal areas.
**Figure 2.6. Beta coherence effects.** Topographies of significantly smaller beta coherence for Unrelated than Related at two non-adjacent seed channels (left: Ch. 34; right: Ch. 43) demonstrating coherence with several posterior channels. This effect did not fit our reporting criteria for a robust result. These results, however, are in line with previous reports in the literature (Ghuman et al., 2008).

**2.4 Discussion**

In this study, we examined whether theta coherence might be the mechanism by which a dynamic anterior-posterior network retrieves semantic representations. Additionally, we investigated if gamma power was involved in forming local functional networks for the activation of lexical-semantic representations. Subjects engaged in a semantic priming paradigm, and their neural responses to the Unrelated and Related word pairs were compared. We first confirmed the effect of semantic priming on the neural response by examining the N400 ERP component. Then we analyzed the time-frequency responses. The results for power and coherence analyses are discussed below.

*Local Synchronization*

We hypothesized that decreases in gamma power would reflect facilitation of lexical-semantic processing for Related words compared with Unrelated words during single word reading. Our analysis of power changes did reveal this gamma effect (Unrelated > Related) between 45-50 Hz and 150-450 ms. Additionally there were two effects in the reverse direction
(Related > Unrelated) in the gamma and alpha bands; while their interpretation is less clear, they do not reflect facilitation of semantic retrieval.

The early gamma effect is in the same direction as the classic reaction time and N400 effects (Unrelated > Related). Thus, we believe that the gamma power increase between 45-50 Hz and 150-450 ms at the parietal electrodes in both conditions reflects the activation of local functional networks involved in the lexical-semantic representation. More specifically, the smaller gamma power increase in the Related condition may signify less gross activation or, in other words, more focused activation due to the priming of a related semantic representation and the automatic spreading activation which accompanies priming. We also cautiously interpret the gamma power difference at the single left frontal electrode as reflecting local networks in left frontal areas thought to be involved in top-down semantic processing. Gamma frequencies are thought to transiently bind together cell assemblies (Buzsaki & Draguhn, 2004; Engel et al., 2001; Harris et al., 2003) and work on a more local scale (Von Stein & Sarnthein, 2000); thus, they are a likely mechanism for dynamically forming local networks involved in semantic processing.

Gamma has been previously observed during studies with lexical-semantic processing demands. Studies of single word reading found differences in gamma power modulation based on the semantic features of the word or semantic demands of a task (Mainy et al., 2008; Pulvermüller et al., 1999). Pulvermüller et al. report significant gamma power decreases between 25-35 Hz and 500-800 ms at ROIs near motor and visual cortices when reading verbs and nouns. While we observed gamma power increases, our effect was in a different part of the gamma band (45-50 Hz) and in an earlier time window (150-450 ms). Thus, the difference between the two
results may be related to different networks being reflected in different parts of the gamma band (in fact, we see power decreases at 30 Hz though the difference was not significant). Using intracerebral EEG, Mainy et al. observed gamma power increases in the left pars triangularis during a semantic judgment task. Intracerebral EEG has several advantages over scalp EEG including reduced volume conduction and better localization ability, but the electrodes are necessarily confined to very local areas. EEG at the scalp usually reflects averaging over larger cortical areas and thus provides a more global measure of activity. So the gamma power increases that we observed likely reflect involvement of a lexical-semantic network even beyond the pars triangularis. Several studies have also found greater gamma power increases for semantically-congruent words in sentences than for semantically-incongruent words (Hagoort et al., 2004; Hald et al., 2006; Penolazzi et al., 2009). These gamma increases are interpreted as reflecting semantic unification, since there are no increases when an incongruent word cannot be integrated properly within the context of a sentence. On the whole, activity in networks relevant to semantic retrieval and unification seem to be reflected in the gamma band.

While our early gamma effect may reflect local networks involved in the activation of stored lexical-semantic representations, we also observed two later effects in the gamma- and alpha-bands (between 300-800 ms and 600-1000 ms, respectively) for which the interpretation is less clear. Since the direction of these effects was opposite to the early gamma effect, it is unlikely that they reflect facilitation of semantic retrieval processes. One possible interpretation is that they reflect attentional processing. Alpha power decreases are often correlated with increases in attention (see Klimesch, 1999, for a review) especially those in the lower alpha band (8-10 Hz). These decreases are also generally topographically widespread over the entire scalp.
Our data appear to be centered on the lower half of the alpha band and are also topographically widespread for both Related and Unrelated conditions (not pictured) though the significant difference between conditions is frontal. Gamma power increases have also been observed during increases in attention (see Jensen et al., 2007, for a review). It is possible that subjects increased their attention towards Related target words; they were unaware ahead of time that there would be semantically-related pairs, and the observed relationships may have peaked their interest and attention. As subjects noticed the relatedness of some pairs, they may also have been performing an implicit semantic relatedness judgment. The semantic judgment task has previously been correlated with topographically widespread alpha power decreases (Klimesch et al., 1997). It is possible that this judgment was made only for the related pairs as the unrelated pairs would not encourage a judgment without an explicit judgment task; this may explain the differential response in alpha power decreases. These interpretations are speculative though, and further research could help clarify our results.

**Long-range Synchronization**

It has been suggested that the LIFG is involved in providing top-down assistance to posterior storage areas when semantic retrieval demands are high (Badre et al., 2005; Gold et al., 2006; Wagner et al., 2001). Specifically, evidence from these studies shows that the LIFG is engaged for low relatedness or association (high retrieval demands) between pairs of words but not (or minimally) engaged for high relatedness (low retrieval demands); but until now, no mechanism has been proposed for dynamic communication between LIFG and posterior areas during top-down semantic retrieval. Our paradigm setup was similar: we modulated retrieval
demands through priming to test if and how a long-range network is dynamically created for semantic retrieval. Our analysis revealed anterior-posterior theta coherence for the Unrelated condition but not the Related condition; this resulted in coherence differences between 150-425 ms and 600-900 ms. Based on the timing and topography of coherence changes in our study, we suggest that the 150-425 ms theta coherence may be this dynamic mechanism for top-down retrieval. Synchronization is present in the anterior-posterior network when semantic retrieval demands are high and top-down communication is needed. While scalp EEG analysis is limited in localizing this coherence to specific brain areas, it seems reasonable to suggest that the coherence may reflect phase synchronization between LIFG and posterior semantic storage areas based on the topography of coherence, though this should be specifically tested in future studies.

On the contrary, we did not observe theta coherence for the Related condition which is in line with the lack of LIFG activation in the previous studies. Theta coherence would only need to serve as a coupling mechanism when both LIFG and posterior areas are involved in semantic retrieval. Since gamma power has been correlated with BOLD activity (e.g., Goense & Logothetis, 2008; Schölvinck et al., 2010), the gamma difference we observe at the single left frontal channel may reflect differences in LIFG activity observed in these previous neuroimaging studies. But since neither gamma power nor BOLD levels can speak to dynamic coupling between LIFG and posterior storage areas, the theta coherence analysis helps elucidate this mechanism.

Based on the later timing, the 600-900 ms theta coherence effect more likely reflects differences in post-retrieval semantic processing. The EEG correlates of post-retrieval processing are not as well studied especially for the semantic priming paradigm. Still, there may be some
parallels between the post-N400 positivity (PNP) ERP component and our theta coherence which can help us understand a possible function for this late theta coherence. The PNP is seen between 600-900 ms over left frontal cortex and is larger for incongruent or less preferred (low-cloze) final words of a sentence than high-cloze, congruent words completing a sentence (Van Petten & Luka, 2006; for a review, see Van Petten & Luka, 2012). The PNP is less commonly seen during the semantic priming paradigm. Holcomb (1988), however, observed a larger frontal positivity after 525 ms for unrelated v. related conditions under similar conditions as ours, and we have confirmed this effect in the current study (not pictured). Additionally, the PNP is absent in patients with LIFG lesions (Swick et al., 1998) suggesting that the LIFG may generate the PNP. The function of the PNP is still not fully clear, but Van Petten and Luka (2012) suggest that it may reflect disconfirmed predictions or inhibition of predicted words that were not presented (also see Kutas, 1993). Frith and colleagues (1991) have suggested that there may be an inhibitory interaction between frontal and temporal areas during word processing which Kutas (1993) suggested was related to the PNP. This inhibition may result from one of two controlled semantic processes – expectancy or semantic matching – in the case that extraneous representations must be inhibited (McNamara, 2005). Since the subjects noticed the semantic relationships, it is possible that they were expecting primes to be followed by some related targets (expectancy) or searching for a relationship from the target back to the prime (semantic matching), though it is not possible to confidently attribute the inhibition to a single controlled process based on our task demands. With anterior-posterior theta coherence, we may have an even clearer reflection of this inhibitory interaction than with the PNP. While the semantic priming paradigm does not provide as much contextual information for target word retrieval and
may not result in the same kind of prediction, a pre-activation of representations is likely still taking place. When this pre-activation is not confirmed for the unrelated/incongruent target words, the LIFG inhibits the mispredicted active semantic representations in posterior storage areas. As discussed above, anterior-posterior theta coherence may be a mechanism for communication between LIFG and posterior storage areas; thus the 600-900 ms anterior-posterior theta coherence may be reflecting this inhibitory, post-retrieval semantic processing.

This dual role for theta coherence during both retrieval and inhibitory semantic processing may at first seem to present a contradiction, but closer consideration helps to resolve it. As the frequency of synchronization is likely dictated by the distance and transmission speed between brain areas (Von Stein & Sarnthein, 2000), coupling in a lower frequency like the theta band is a good candidate for communication between LIFG and posterior storage areas. Evidence suggests that anterior and posterior areas of LIFG respectively support controlled retrieval and selection/inhibition of semantic representations (for a review, see Lau et al., 2008). In this study we might be observing theta coupling between anterior LIFG and posterior storage areas during the early window of retrieval and coupling between posterior LIFG and posterior storage areas during the later window of inhibition. Thus, as a mechanism for linking these brain areas, theta coherence could subserve both controlled retrieval and inhibition of semantic representations.

While a prevalent view of coherence is that it serves as a mechanism for large-scale integration and communication (Engel et al., 2001; Fries, 2005), the field still lacks a clear understanding of the effects of priming on coherence and how the effects relate to these large-scale functions. Two recent studies have found coherence increases and power or ERP decreases after priming. Ghuman et al. (2008) observed increased fronto-temporal beta coherence after
repetition priming between 200-300 ms, while Kujala et al. (2011) found bilateral temporal alpha coherence increases after semantic priming centered at 333 ms. It was suggested that increased coherence after priming may reflect more effective information transfer between areas while simultaneous decreases in power indicate less reliance on local processing; furthermore, this phenomenon could be a mechanism for facilitating behavioral responses (Ghuman et al., 2008). We also observed some increases in anterior-posterior beta coherence after priming although this effect was not very strong and thus is not considered as a main result. While these beta coherence increases are in line with the findings of Ghuman et al., the main result of our study was decreased theta coherence after priming. The differences in the frequency of these effects may suggest that there is more frequency specificity for the effective information transfer hypothesis than was initially thought. The effective information transfer hypothesis may function within the alpha and beta bands while another function is supported, in parallel, by theta coherence. We propose that this function is top-down retrieval and post-retrieval processing during demanding retrieval conditions. Theta coherence is the mechanism which supports this function because left frontal areas need to communicate with posterior storage areas to retrieve semantic information when target words are not primed and retrieval is more demanding and/or to inhibit incorrect predictions as explained above. Ghuman et al. and Kujala et al. did not report the theta coherence effects as their windows of analysis were more limited. Ghuman and colleagues did not examine theta frequencies while Kujala and colleagues did not examine theta responses after 650 ms nor from left frontal seed channels, and therefore those analyses may have missed the theta effects we observed. Nevertheless, our own and previous studies suggest that coherence, depending on the frequency band, can serve as a mechanism for both more efficient information transfer during
priming as well as dynamic communication for top-down retrieval and post-retrieval processing during demanding retrieval conditions.

Conclusions

Our results indicate that oscillatory synchronization serves as a mechanism to assemble both local and long-range networks for semantic retrieval. Initially, parietal gamma-band synchronization may reflect the activation of local functional networks of semantic representations while anterior-posterior theta coherence enables top-down retrieval of these representations when they are not related to the previous word and retrieval is more demanding. This is followed by later theta-band coherence which possibly reflects top-down post-retrieval processing to inhibit incorrect active semantic representations. Taken with previous neuroimaging results, we have a fuller picture of the mechanism of top-down retrieval processing – it likely involves not only recruitment of anterior and posterior brain areas but also theta phase synchronization between these areas. The semantic system is widespread and operates in diverse ways. Further work could help clarify how oscillatory synchronization might be the mechanism for local and long-range functional connectivity for other aspects of semantic processing, and moreover, for language networks in general.
Chapter 3

3.1 Introduction

Our first study suggested that theta coherence between 150-425ms may be involved in communication between LIFG and posterior areas housing semantic representations for controlled retrieval of these representations. We also interpreted the later theta coherence (600-900ms) as reflecting communication between these areas for controlled selection and inhibition of extraneous representations. This interpretation is more speculative, however, since the Unrelated condition of the semantic priming experiment seems to but does not unambiguously require more selection/inhibition than the Related condition. Thus, in our second experiment, we chose to more directly test the hypothesis that theta coherence is also involved in controlled selection/inhibition.

Functional neuroimaging studies have demonstrated that LIFG and often pMTG are involved when there is more than one response option and competing semantic information must be inhibited to select the appropriate response, for example in generating a single verb when prompted by a noun that has many associated verbs (Thompson-Schill et al., 1997; Badre et al., 2005; Snyder et al., 2011). Indeed, disruption of processing in healthy individuals using TMS or stroke damage in aphasia patients with semantic deficits result in impairments to controlled semantic processing. When repetitive TMS is applied to these areas, reaction time and accuracy suffer for experimental conditions requiring semantic control but not those that do not require semantic control or general cognitive (non-semantic) control (Whitney et al., 2011b). Aphasia
patients with semantic deficits (most of whom were suffering from transcortical sensory aphasia but also included a conduction aphasic, a mixed transcortical aphasic, and a global aphasic) sustained damage to the left prefrontal or temporo-parietal cortex and showed problems inhibiting irrelevant but prepotent semantic associations (Noonan et al., 2010). The hypothesis that these areas are involved in inhibition of irrelevant semantic knowledge was recently tested in a study of verb generation in anxious individuals (Snyder et al., 2010). Anxiety reduces GABAergic function, and Snyder and colleagues’ neuroimaging and modeling evidence suggest that this lack of inhibitory processing is behind deteriorating semantic selection ability in anxious individuals. Interestingly, administering the GABA agonist Midazolam subsequently improved semantic selection by increasing GABA and neural inhibition.

Another way to modulate semantic selection/inhibition demands is by using a task that requires retrieving different meanings of ambiguous words. Homonyms are ambiguous words that have unrelated meanings assigned to the same orthographic form. These meanings can be grouped as one dominant meaning (most frequently appearing meaning which is often the prepotent response when subjects are probed for a meaning) and one or more subordinate meanings (less frequent meaning). For example, the dominant meaning of ‘bark’ is related to a dog’s bark, while the subordinate meaning is related to the bark of a tree. Most studies suggest that automatic spreading activation within the semantic network activates both dominant and subordinate meanings (for a review, see Simpson, 1994), and this level of activation may be enough to select the dominant meaning without controlled selection. But if the subordinate meaning is to be selected based on the context or task demands, the prepotent/dominant response
must be inhibited. Thus the semantic selection and inhibition demands are higher for subordinate than dominant meaning selection.

Whitney and colleagues (2011a) recently exploited the differences in processing dominant and subordinate meanings to further explore the brain areas involved in the semantic selection and inhibition network. Subjects viewed a triplet of words presented consecutively with the last one being ambiguous and the first two potentially biasing the meaning of that ambiguous word. After seeing all three words, subjects had to judge if the words were related which forced the selection of a single meaning for the homonym. They used three conditions: 1) one of two primes biased the ambiguous target to its dominant meaning (Dominant condition), 2) one of the primes biased the target to its subordinate meaning (Subordinate condition), and 3) neither prime was related to the target (Unrelated condition). In contrasting these three conditions, they observed the fastest reaction times for Dominant followed by Subordinate and finally Unrelated conditions. Additionally, there was greater BOLD activation in LIFG, left orbital gyrus, left pMTG, and left AG for the Subordinate condition than the Dominant condition. Thus this study demonstrates that the ambiguity paradigm can elicit a similar semantic control network shown with other paradigms to be involved in semantic selection and inhibition. In our current experiment, we have chosen to use these conditions in a similar manner to modulate controlled semantic processing.

When might the selection and inhibition processing occur during the ambiguity paradigm? In our first experiment we interpreted the later theta coherence effects (600-900ms) as reflecting inhibitory processing; this is, then, a prime candidate for the current experiment. While the exact ambiguity paradigm we have chosen has not been examined using EEG, we may be
able to gain some insight into timing from an ERP study by Chwilla and Kolk (2003) who based their paradigm on one initially developed by Balota and Paul (1996). They utilized a semantic judgment task on a different ambiguity paradigm but one that also tested for inhibitory effects. They compared conditions where 1) two primes were related to the same meaning of the ambiguous target word (RR condition), 2) only the first of the two primes was related to the target word (RU condition), 3) only the second of the two primes was related to the target word (UR condition), and 4) neither prime was related to the target word (UU condition). Notably, they did not have separate dominant and subordinate conditions, although both dominant- and subordinate-biasing primes were included in the first three conditions, i.e., if the dominant appeared in the UR condition, the subordinate would appear in the RU condition or vice versa, and both appeared in the RR condition. Thus their RU and UR conditions mixed subordinate and dominant meaning selection. They define a priming effect as the difference between the UU and one of the other three conditions. The largest reaction time and ERP amplitude priming effects are seen for the RR condition, but smaller effects are seen for the RU and UR conditions. If there is no competition and subsequent inhibition of one meaning, Balota and Paul (1996) argue that the RU and UR priming effects should sum up to the larger priming effect seen for the RR condition. If there is inhibition, however, facilitation effects will be smaller (because inhibition slows and increases processing) for either the RU or UR, and the effects will be underadditive for the RR condition. Balota and Paul (1996) demonstrated this underadditivitly with reaction times, while Chwilla and Kolk (2003) extended the underadditive effects to the ERP effects, notably between 600-1000ms but not between 400-600ms suggesting that inhibitory processing happens after 600ms. This time window is similar to the theta coherence effects seen in our
semantic priming experiment. Thus we anticipate that any theta coherence reflecting inhibitory effects in our ambiguity paradigm will again appear in this later time window.

To summarize, we hypothesize that anterior-posterior theta coherence will be larger for the Subordinate than the Dominant condition reflecting the increased demand on the anterior-posterior semantic selection and inhibition network for the Subordinate condition. Additionally, we think this processing likely takes place in a time window after semantic retrieval processing, namely after 600ms.

3.2 Materials and Methods

Subjects

Twenty-three healthy volunteers participated in the experiment and received monetary compensation for their participation. The data of one subject had to be excluded from group analysis due to excessive noise possibly caused by skin potential artifacts. Thus analysis was carried out for the remaining 22 subjects (age 18-35, 10 males). All were right-handed, native English speakers without a history of neurological or psychiatric problems or learning disabilities. All were currently pursuing a university education or had completed an undergraduate degree. All gave informed consent (approved by the Georgetown Medical Center IRB) before starting the experiment.

Stimuli
We selected 126 homonyms from normed data gathered by Twilley et al. (1994) to use as target words. The normed data were created by presenting subjects with an ambiguous word and having them respond with the first word that came to mind. These responses were then classified as related to the dominant or subordinate meanings of the homonym based on the percentage of responses from the full cohort of subjects. We used only polarized homonyms from the normed data (defined here as >20% difference in the frequency of dominant v. subordinate responses). Other inclusion criteria included 1) the subordinate meaning had at least 5% of subjects responding and 2) homonyms could not change pronunciation based on meaning (e.g., “dove”). Each homonym was paired with two “context” words from the norms, namely the primary responses for the dominant and subordinate meanings. In this way we formed related pairs of words for the two conditions Dominant (DOM) and Subordinate (SUB). For example, pairing ‘dog’ with ‘bark’ formed the DOM condition, while ‘tree’ paired with ‘bark’ formed the SUB condition. To form the Unrelated (UNR) pairs, 126 of the context words were pseudo-randomized and re-paired with the homonyms. Thus the same homonym appeared in all three conditions to maintain matching across all lexical variables for each condition. Pairs were grouped such that the context word was in the prime position and the homonym was in the target position. We deemed using only one prime instead of two (as in Whitney et al., 2011a) as adequate for our experiment and confirmed that it still similarly taxed selection and inhibition processing with the reaction time effects (see below).

**Design and procedure**
Subjects were asked to silently read the stimuli presented on the computer monitor in front of them and perform a semantic relatedness judgment on the pair of words. In this task subjects were instructed to press one button with their left index finger if there was a relationship between the words and to press another button with their left middle finger if there was no relationship. They were asked to do this as quickly and accurately as possible and were not informed of the different conditions. Two-thirds of trials were related (DOM, SUB) while one-third of trials were not related (UNR). Subjects were asked to minimize any movements and eyeblinking while words were on the screen. Stimuli were presented on the monitor in black Arial font against a gray background. Subjects viewed 378 trials that each consisted of a fixation cross (1700-1900 ms, random), prime word (150 ms), blank screen (850 ms), target word (150 ms), and blank screen (2350 ms) (see Figure 3.1). Reaction time (RT) was measured from the onset of the target word until the button-pressing response. In order to counterbalance the three conditions, one third of target stimuli appeared in dominant trials before the other two conditions, one third appeared in subordinate trials before the other conditions, and one third appeared in unrelated trials before the other conditions. The one third of target stimuli selected in each case was counterbalanced across three versions of the experiment, and the presentation of these three versions was counterbalanced across subjects. The experiment started with a short practice session of 18 trials followed by six blocks of stimuli of about seven minutes each with subject-determined breaks in between. The total time for the session including setup was under 1.25 hours for each subject.
Figure 3.1. Semantic ambiguity paradigm. Subjects viewed prime-target pairs where the prime was related to the dominant or subordinate meaning of the ambiguous word (target) or was unrelated to the target. They were then asked to judge if the pair of words was related.

**EEG recording and preprocessing**

EEG was continuously recorded using a 128-electrode EEG system (Electrical Geodesics Inc., Eugene, OR) sampling at 250Hz. During the recording, impedances were kept below 30kΩ, all channels were referenced to the vertex, and a bandpass hardware filter (0.1-126Hz) was applied. The following preprocessing steps were performed offline: data were bandpass- (0.3-100Hz) and notch- (60Hz) filtered to remove low frequency and line noise; data were segmented into trials from -1500ms to 2500 ms around target stimuli; ocular artifacts were corrected (Gratton, Coles, & Donchin, 1983); data from all channels were re-referenced to the average reference (Bertrand, Perrin, & Pernier, 1985); and the average baseline 200 ms before the target stimulus presentation was subtracted from trials. Trials with artifacts larger than ±100µV were removed before analysis. Additionally, we removed any trials with incorrect responses. Two subjects had a noticeable heartbeat artifact throughout each of their sessions, and this was removed using independent component analysis (Jung et al., 2003) in EEGLAB following the above preprocessing steps. After artifact removal, there were on average 22% of DOM trials
removed and 37% of SUB trials removed from each subject’s data (paired t-test, p<0.05). An average of 21% of UNR trials were removed, but they are not examined here.

**ERP and Time-frequency analysis**

We calculated ERPs by averaging trials within each condition from -1500ms to 2500 ms around the target stimuli at each electrode. Subsequently, we found the grand-average by averaging the conditions across subjects.

Although we did not have any specific hypotheses for power changes, both event-related changes in EEG power and coherence were examined by computing time-frequency representations (TFR) of the single word trial data using the multi-taper approach described by Mitra and Pesaran (1999). The open source Fieldtrip toolbox (Oostenveld, Fries, Maris, & Schoffelen, 2011) and in-house Matlab code were used for these calculations. Because we computed the TFRs of the single trials before averaging, our analysis reflects both evoked and induced EEG activity, i.e., oscillatory activity that is both phase-locked and non-phase-locked to the stimuli. In order to optimize the trade-off between time- and frequency resolution, TFRs were constructed in two different, partially overlapping, frequency ranges. In the low-frequency range (2–30 Hz), 250 ms Hanning windows were used to compute power and coherence changes in frequency steps of 2 Hz and time steps of 36 ms. Regarding temporal resolution, any given time-point in the resulting TFR is a weighted average of the time-points ranging from 125 ms before to 125 ms after this time point, and this gives a frequency resolution of 1/0.25 = 4 Hz. In the high-frequency range (25-80 Hz), 250 ms discrete prolate spheroidal sequence windows (multitapers) were used to compute power (but not coherence) changes in 5 Hz frequency steps.
and 36 ms time steps with 10 Hz frequency smoothing. These calculations were performed starting 500 ms before the word appeared on the screen to 1500 ms after the word onset.

We calculated TFRs of coherence from several seed channels. Based on our hypothesis that the LIFG was involved in semantic selection and inhibition, we tested a selection of 13 electrodes positioned over the left frontal scalp as seed channels (see Figure 3.4E). For each seed channel, 127 coherence TFRs were calculated (one for each pair of channels).

The TFRs of target word trials were averaged separately for the three conditions. The power and coherence changes were then expressed as percent increases or decreases relative to a baseline of -50 ms to 50 ms around the target stimulus. Grand-averages were calculated by averaging TFRs of each condition across subjects.

Statistical analysis

For behavioral data, we performed a single paired t-test between grand-averaged RT biasing effects between conditions (calculation of biasing effect explained below). Note that this biasing effect is calculated in the same manner as the “priming effects” in the study by Chwilla & Kolk (2003). We, however, have decided to call them “biasing effects” as priming is a phenomenon of implicit (unconscious) memory, and the semantic judgment task requires a conscious decision about the relatedness. Thus this is not a true priming effect.

For ERPs and TFRs of power and coherence, we tested for significant differences between the grand-averaged SUB and DOM conditions as the comparison SUB-DOM reflects more predictable modulation of semantic selection demands. Since we cannot be certain which meaning is selected in the UNR condition (it likely depends not only on the frequency of the
meaning but also which meaning has been selected in prior trials), it is difficult to know the semantic selection demands relative to the other two conditions. Since this condition would not be as useful in answering our main question about selection processing, we did not include it in any statistical comparisons. Still, it was an essential component of the experiment to verify the behavioral results and to create a feasible semantic judgment task by providing negative trials.

For ERPs and TFRs of power and coherence, the significance of the difference between SUB and DOM conditions was evaluated by means of a cluster-based random permutation test (Maris & Oostenveld, 2007). This approach controls the Type-1 error rate in a situation involving multiple comparisons. The cluster-based random permutation test naturally takes care of interactions between time points, electrodes, and frequency bins by identifying clusters of significant differences between conditions in the time, space, and frequency dimensions. The procedure is briefly described below.

First, for every data point (electrode by time by frequency) of two conditions, a simple dependent-samples t-test is performed (giving uncorrected p-values). All adjacent data points exceeding a preset significance level (5%) are grouped into clusters. For each cluster the sum of the t-statistics is used in the cluster-level test statistic. Next, a null distribution that assumes no difference between conditions is created. This distribution is obtained by 1000 times randomly assigning the conditions in subjects and calculating the largest cluster-level statistic for each randomization. Finally, the actually observed cluster-level test statistics are compared against the null distribution, and clusters falling in the highest or lowest 2.5\textsuperscript{th} percentile are considered significant. As we did not have a priori hypotheses for power differences, we performed the cluster analysis separately on lower frequencies (2–30 Hz) and higher frequencies (25–80 Hz).
for power between 100-1000ms. But given our main hypothesis regarding theta coherence, we only performed cluster analysis on delta and theta (2-8 Hz) coherence between 100-1000ms. We included the neighboring delta band as visual analysis revealed that the peak of the effect was on the border of the two bands.

**Regression Analysis**

Regression was performed between the main coherence effects and the RT effect across subjects as well as between the alpha-beta power effect and the RT effect. The peak of each effect for each subject was selected by identifying each individual’s peak within the time-frequency-channel boundaries of the significant clusters from the grand-averaged effects. For coherence, peaks were selected by identifying the maximum theta difference from among all five seed channels with a significant cluster, and regression between RT and coherence was performed on these values. Also, the timings of those peak theta values were identified and also regressed with the RT differences. Outlier subjects were identified by examining residuals from the regression equation. If the residual for an individual subject was outside the 95% confidence interval for new observations, the subject was excluded from the regression.

### 3.3 Results

**Behavioral Results**

Similar to Chwilla and Kolk (2003) and Whitney et al. (2011a), biasing effects (BEs) for each subject were calculated by subtracting the reaction time (RT) of the related conditions from
the unrelated conditions, that is, $BE_{\text{DOM}} = RT_{\text{UNR}} - RT_{\text{DOM}}$ while $BE_{\text{SUB}} = RT_{\text{UNR}} - RT_{\text{SUB}}$. These BEs approximated normal distributions whereas RTs did not; thus statistical testing through paired t-tests is applicable to the BEs. The behavioral results are shown in Table 3.1. Only correct trials were used to calculate RT and BE as we cannot be sure which meaning was selected in incorrect trials. In line with results from Whitney et al. (2011a), comparisons between the BEs revealed a significant difference in the biasing effects for the DOM v. SUB conditions (paired t-test, $p<0.001$). Error rates were also comparable across studies.

<table>
<thead>
<tr>
<th>Conditions</th>
<th>$RT$</th>
<th>Error Rate</th>
<th>$BE$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dominant</td>
<td>817.4 (127.7)</td>
<td>8.0 (5.9)</td>
<td>217.2 (151.0)</td>
</tr>
<tr>
<td>Subordinate</td>
<td>907.6 (147.2)</td>
<td>25.4 (11.2)</td>
<td>127.0 (139.3)</td>
</tr>
<tr>
<td>Unrelated</td>
<td>1034.6 (177.2)</td>
<td>7.8 (8.4)</td>
<td>not applicable</td>
</tr>
</tbody>
</table>

Table 3.1. Behavioral effects. Means for reaction time (RT), error rate, and biasing effects (BE) with standard deviation shown in parentheses.

**ERP Results**

When comparing SUB and DOM conditions, cluster analysis across 100-1000ms revealed one significant positive cluster between 324-424ms ($p=0.048$) where SUB was more positive than DOM. This cluster may be related to differences in the N400 as the ERP is negative-going and peaking near 400ms over posterior channels. In addition to the topographical plots of the cluster over time, we have plotted the ERPs for all three conditions to show the N400
component of SUB and DOM relative to UNR (Figure 3.2; significant channels highlighted in black diamonds). Interestingly, the graded effect of DOM<SUB<UNR mirrors the graded RT effect. One might expect the N400 of the UNR condition to be the most negative of the conditions with the graded effect going in the other direction. The direction of our graded effect, however, is in line with the direction of the N400 effect demonstrated by Chwilla and Kolk (2003). When comparing their unrelated condition with the two single-prime-related conditions (which were mixed between biasing the subordinate v. dominant meanings of the ambiguous target and not separated as ours are here), their unrelated condition was less negative than their single-prime-related conditions and labeled an N400 effect. The significant effect may, however, just be the opposite end of the N400 effective dipole. The topography plots show a negative effect more centrally located, and channel 5 from that region shows the effect in the opposite direction: UNR is most negative followed by SUB and finally DOM. Thus the N400 may be located more anteriorly than in the semantic priming experiment but still centrally over the scalp.

We were also interested in differences in the time window of 600-1000ms based on differences in additivity found in the study by Chwilla & Kolk (2003), however cluster analysis did not find any significant clusters over this window. In looking closely at the left frontal channel 38 in Figure 3.2, one can see a larger negativity for the SUB than DOM conditions from 700-1000ms that also appeared in several surrounding left frontal channels. Based on this visual analysis and our a priori hypothesis for a possible effect in this window, we tested for a significant effect at the peak of this difference, averaging over adjacent left frontal channels 33, 38, and 39 between 700-900ms. We found a significant difference between SUB and DOM conditions (paired t-test, two-tailed, p=0.015).
A. Early ERP Cluster, Subordinate - Dominant

Time: 324 ms  348 ms  372 ms  396 ms  402 ms

B. Late ERP Effect, Subordinate - Dominant
**Figure 3.2. ERP effects.** A) The topography of a significant cluster spanning 324-424ms shows the N400 effect (SUB – DOM) in the grand-averaged data with significant channels highlighted in black diamonds. Representative ERPs from several of these significant channels are also plotted. Target word onset is at t=0 seconds. While the effect was tested only between SUB (red) and DOM (green) conditions, we plot the UNR (blue) condition also as a reference for visual comparison. Channel 5 was not included in the significant cluster but is shown to demonstrate what may be opposite end of the effective dipole causing the effect. B) A later effect (SUB – DOM) between 700-900ms was also significant as tested on an average of left frontal channels 33, 38, and 39 and 700-900ms.

**EEG Power Results**

We performed statistical testing separately on lower frequencies (2-30 Hz) and the gamma band (25-80 Hz). No significant clusters were found in the gamma range. There was a single significant cluster mainly in the beta band but also extending into the alpha band (10-22 Hz) after 600ms (p=0.003). Although from the same cluster, the beta and alpha effects peaked over different electrodes and have thus has been plotted separately in Figure 3.3A and 3.3B, respectively. As we had subjects make their decision through a button-press, it seemed possible that this movement influenced beta suppression from 600-1000ms since beta rhythms can be related to movement (beta power typically decreases before and during movement and increase following movement); thus, we extended our cluster analysis for power over the whole 100-1500ms time window which includes post-response processing. Looking at Figure 3.3A, the increase in beta power from 1000-1500ms occurs sooner for the DOM than the SUB condition mirroring the faster RTs for DOM than SUB (see behavioral results above) (significant channels within cluster highlighted with small black star). Thus the beta suppression and rebound effect is possibly related to response differences between conditions (elaborated upon below). This cluster
also extended into the alpha band as seen in Figure 3.3B. An initial alpha suppression was longer in the SUB than the DOM condition from 700-1000ms followed by an increase in alpha power after 1000ms that ramped up sooner for DOM than SUB.
**Figure 3.3. Alpha-Beta power effect.** A) The left column shows TFRs from the left frontal peak in the beta band within the significant cluster (averaged over Ch. 13, 20, 28, 29) for SUB, DOM, and SUB-DOM. Target word onset is at t=0 seconds. The extent of the cluster in time and frequency is outlined in black in the bottom graph. The middle column shows topographical plots of the conditions in the early part of the cluster (600-1000ms) where the effect is caused by longer beta power decreases for SUB than DOM. The right column shows topographical plots of the conditions in the later part of the cluster (1000-1500ms) where the effect is caused by earlier beta power increases for DOM than SUB. Channels included in the significant cluster are highlighted with small black stars. B) The left column shows TFRs from the left frontal peak in the alpha band within the significant cluster (averaged over Ch. 59, 60, 66) for SUB, DOM, and SUB-DOM. The extent of the cluster in time and frequency is outlined in black in the bottom graph. The middle column shows topographical plots of the conditions in the early part of the cluster (700-1000ms) where the effect is caused by longer alpha power decreases for SUB than DOM. The right column shows topographical plots of the conditions in the later part of the cluster (1000-1500ms) where the effect is caused by earlier alpha power increases for DOM than SUB. Channels included in the significant cluster are highlighted with small black stars.

**EEG Coherence Results**

Cluster analysis was performed in the delta-theta bands on coherence from each of the 13 seed channels, and significant or marginally significant clusters were identified for five of those seed channels (Ch. 25, p=0.025; Ch. 32, p=0.044; Ch. 43, p=0.043; Ch. 38, p=0.089; Ch. 44, p=0.081). Figure 3.4A demonstrates the TFRs for one representative electrode, Ch. 32, while Figure 3.4B&C summarize the coherence effects for each of the significant channels. The SUB>DOM effect spans the delta-theta bands and is mostly in the later time window of 500-1000ms between left frontal (indicated with the large red star) and left posterior channels (channels included in the cluster highlighted with small black stars) although three channels also
showed earlier coherence (100-500ms). Notably, cluster analysis did not identify any significant differences where DOM coherence > SUB coherence although the topographical plots show some such differences over the right hemisphere.

**Regression Results**

We examined the correlation between the significant delta-theta coherence effect and the RT effect as well as between the significant alpha-beta power effect and the RT effect across subjects. Figure 3.4D shows a significant correlation between the timing of the peak theta coherence effect ($r=0.54, p=0.01$) and the RT effect for each subject with one outlier subject removed. No correlation was observed between the level of peak theta coherence and the RT effect suggesting that timing, not strength, of theta coherence predicts the RT effect. More specifically, the RT cost that accompanies the additional selection burden in the SUB but not DOM condition is lessened if theta coherence occurs earlier. This correlation suggests that peak synchronization as early as 200-300ms may best decrease the selection cost. This result is similar to one observed by Ghuman et al. (2008) where the timing of peak beta synchronization predicted the level of repetition priming; this demonstrated that earlier synchronization benefited behavioral performance on repeated items. In contrast, our results suggest earlier theta synchronization quickens selection of subordinate meanings compared with selection of dominant meanings (thereby decreasing the RT effect). Taken together, both results suggest that it is the timing, and not necessarily the strength, of synchronization that influences behavioral advantages. There was no correlation with the RT effect of either peak level or time of the alpha-beta power effect.
A. Coherence TFRs, Channel 32

B. Summary of Seed Channels with Early Delta-Theta (2-8Hz) Coherence

Ch. 38, 200-500ms  Ch. 43, 100-500ms  Ch. 44, 200-500ms

C. Summary of Seed Channels with Late Delta-Theta Coherence

Ch. 25, 600-1000ms  Ch. 32, 550-1000ms  Ch. 38, 500-1000ms  Ch. 43, 500-1000ms  Ch. 44, 500-1000ms

D. Theta Timing Predicts RT Effect

E. Seed Electrode Locations
**Figure 3.4. Delta-Theta coherence effects.** A) Example of coherence at a single representative seed channel, Channel 32. TFRs showing delta- and theta-band coherence over four left posterior electrodes (51, 52, 59, 60) from seed channel 32 (large red star in topographs). Target word onset is at t=0 seconds. TFRs show a coherence increase for the SUB condition but not the DOM condition. The extent of the significant cluster in time and frequency is outlined in black in the difference plot. The channels showing significant coherence with seed channel 32 are highlighted with small black stars in the topographical plot. B) Summary of coherence over early time windows. Topography shows significantly greater coherence increases for SUB than DOM between 100-500 ms from seed channels 38, 43, and 44. C) Summary of coherence in the later time window. Topographies showing significantly greater coherence increases for SUB than DOM between 500-1000 ms for five adjacent left frontal seed channels. The displays follow the organization explained in part B. D) Correlation between the timing of peak theta coherence effect for each individual subject with their RT effect. Theta coherence values are the maximum values of all seed channels. E) Locations of the seed electrodes used for coherence calculations. We only chose seeds over left frontal areas as we strongly hypothesized that we would observe coherence from left frontal areas.

### 3.4 Discussion

In this study we examined whether theta coherence may be related to the long-range network involved in semantic selection and inhibition processing. We found evidence to support its involvement as a possible mechanism for communication between LIFG and posterior areas (pMTG and AG) when selecting the subordinate meaning of an ambiguous word and inhibiting the prepotent or dominant meaning of the homonym. Additionally, we examined and found differences between subordinate and dominant meaning retrieval in the reaction times, ERPs, and spectral power of the alpha and beta bands. Although ERP and power analysis were not the main focus of this experiment, we first briefly explore the possible interpretations of these effects.
Implications of the ERP

Differences in the amplitude of SUB and DOM conditions appeared in the window of the N400, an ERP component often reflecting the ease with which a semantic representation can be retrieved (Kutas & Federmeier, 2011). Thus our ERP effect may reflect easier access of the dominant meaning representation of the homonym compared with the subordinate meaning. One puzzling observation is the direction of the significant N400 effect. The N400 amplitude (in the negative-going direction) is largest for the DOM condition, smaller for the SUB condition, and smallest for the UNR condition which seems at first to be in the opposite direction from the typical N400 effect. While our results are in line with results from a similar paradigm (Chwilla & Kolk, 2003) which demonstrated a smaller N400 amplitude for UU than RU or UR conditions, it is possible that the significant effect actually reflects the opposite end of the effective N400 dipole. The typical N400 effect is seen in the negativity anterior to the significant effect in the topographies, and this notion is supported by the ERPs as shown in channel 5. Thus we believe that this effect is indeed related to the N400 but the opposite end of the effective N400 dipole.

A later effect (700-900ms) appeared over left frontal channels where the SUB condition was more negative than the DOM condition. Whitney and colleagues (2011a) found differences in LIFG activation levels for these conditions, and while the source of our ERP effect is unknown, we may be observing the neural correlate of their effect in this late ERP difference. This late difference is likely related to increased selection and inhibition processing for the subordinate condition. Whitney et al. (2011a) identified the LIFG as involved in this inhibition processing, and Chwilla and Kolk (2003) have also suggested that the underadditivity effects
found in this time window reflect the post-retrieval inhibition for ambiguous meaning selection. While our ERP results may reflect this inhibition processing, they are limited in suggesting how a dynamic network can be created between anterior and posterior regions involved in inhibition processing.

Local networks reflected by power

Based on our previous semantic priming study, one might expect to see facilitation effects in the gamma band; we did not, however, observe any significant effects there. In comparing SUB and DOM conditions with each other rather than each with the UNR condition, a facilitation effect may not be apparent between these two related conditions. The networks supporting semantic representations (which we suggested is reflected by gamma synchronization) are similarly primed by both DOM and SUB conditions as there is partial activation of both meanings of the ambiguous word in each of these conditions. Thus one could speculate that there should be no difference in gamma power between these two conditions. The differences in the N400s of these conditions may suggest otherwise. If biasing effects are apparent in the ERPs, why would they not be seen in the gamma-band response? As we are looking at differences between the two related conditions, any gamma power difference would likely be smaller than the difference between the UNR and either SUB or DOM conditions. Thus this supposed gamma power difference may be too small to confidently detect as significantly different.

The significant effects we observed in the alpha and beta bands are likely related to differences in processing time between SUB and DOM conditions. Both conditions displayed the
same pattern of alpha and beta power decreases followed by power increases following the left-handed button press. The time course of this initial decrease and subsequent increase appeared elongated for the subordinate compared with the dominant condition. As reaction times were also longer for subordinate meaning selection, we suggest that the longer alpha and beta time course are possibly due to the extra selection and inhibition processing for subordinate meanings. In fact, we are likely observing the typical beta power decrease that occurs before and during movement and beta increase after movement known as the post-movement beta rebound (PMBR). Pfurtscheller et al. (1996) have shown that while left-handed movements result in stronger PMBR over the right hemisphere, the beta power decreases and subsequent increases are bilateral, and others have found similar evidence for bilateral activation (Jurkiewicz et al., 2006; Salmelin et al. 1995; although see Parkes et al., 2006 for unilateral activation). Thus the bilateral distribution of beta in our data and resulting left-lateralized effect still likely reflect the typical movement-related beta modulations. The alpha power decreases and increases are also commonly seen during a variety of cognitive tasks; typically the duration of the decrease depends on the duration of the task and a power increase follows the completion of the task (Klimesch et al., 2007). Thus the elongated time course of alpha reactivity for subordinate meaning selection may reflect longer active cognitive processing rather than specifically more semantic processing. In our semantic priming experiment, we speculated that alpha power decreases were related to implicit semantic judgment processing. Unfortunately, it was not possible to test this hypothesis in this experiment as subjects performed a semantic judgment on all conditions, and no contrast would be able to capture modulation of semantic judgment demands.
The large-scale semantic control network

This experiment was designed specifically to test our hypothesis that theta coherence would be modulated based on the differing semantic selection and inhibition demands of subordinate v. dominant meaning selection. We did observe these expected modulations and suggest that they reflect and may be the mechanism for communication within an anterior-posterior semantic network involved in dynamic selection and inhibition of extraneous meaning representations. Additionally, a correlation between the timing of the peak theta synchronization effect and the RT effect suggests that earlier theta synchronization may be beneficial for subordinate meaning selection. The RT effect essentially reflects a cost for selection of the subordinate meaning, and interestingly this correlation shows the selection cost is lessened when theta coherence occurs earlier. In a previous fMRI study, activation in the LIFG, left pMTG, and left AG was greater when selecting the subordinate meaning of a homonym than when selecting the dominant meaning (Whitney et al., 2011a). Although functional connectivity evidence is lacking, presumably these areas interact within the framework of a large-scale semantic network; thus we suggest that our anterior-posterior delta-theta coherence reflects synchronization between LIFG and these posterior areas. Interestingly, Whitney and colleagues observed activation in both anterior and posterior LIFG (BA 47 and 45) and were not able to address the debate as to whether these regions separately perform semantic retrieval and selection/inhibition, respectively (as supported by Badre et al., 2005; Gold et al., 2006; Snyder et al., 2011). Thus we also cannot affirm that theta coherence related to selection is reflecting synchronization specifically from pLIFG as we suggested for our previous experiment. This coherence is
predominantly between 500-1000ms, but some significant coherence differences are also seen between 100-500ms. Indeed, these earlier theta coherence differences may be important to easing subordinate meaning selection as the regression analysis suggests. While previous ERP studies have suggested that selection and inhibition occurs during the later time window of 600-1000ms (Chwilla & Kolk, 2003; Van Petten & Kutas, 2012), our results highlight the importance of earlier effects in also influencing selection. Still, this correlation data cannot inform us of when selection processing occurs, i.e, during an earlier or later window (it likely does not happen so early otherwise RT would be much quicker). This study not only addressed this post-retrieval processing more directly than our previous experiment, but it also allowed us to examine coherence in the delta band more closely. In doing so, we found that the coherence effect did indeed reside partially in the delta band, although the spread between delta and theta may be partially due to an unavoidable smearing in the frequency dimension caused by time-frequency estimation.

As directly as this ambiguous word paradigm modulates semantic selection and inhibition processing, it unfortunately has some shortcomings. Dominant meanings by definition are more frequently occurring and therefore likely easier to retrieve than subordinate meanings. Contrasting subordinate and dominant meanings thus modulates not only selection processing but also pre-selection retrieval processing. Evidence for this was seen in the difference between the N400s of each condition, and it also may be reflected in the earlier (100-500ms) theta coherence seen in three left frontal seed channels. Our semantic priming experiment more directly modulated retrieval demands and found consistent theta coherence increases when semantic retrieval was more demanding (unrelated condition). Here, retrieval is more demanding
in the subordinate condition, and again we see evidence that LIFG and posterior areas may be communicating through theta coherence in the vicinity of 100-500ms.

Conclusions

In conclusion, we find evidence through reaction time, ERP, and coherence analysis for selection of the subordinate meaning and inhibition of the dominant meaning when context and task support this processing. ERP and coherence data suggest that this processing occurs most robustly after 500 ms but also may be engaged in an earlier time window. More importantly for theories of semantic selection and inhibition, we suggest that the delta-theta coherence between left frontal and left posterior channels may even be the mechanism for communication between LIFG and posterior areas during increased semantic selection and inhibition processing. To our knowledge, this is also the first study to examine the oscillatory dynamics during ambiguous word processing.
Chapter 4

4.1 Summary

With this work we have aimed to gain a better understanding of the local and long-range network dynamics involved in lexical-semantic processing. First, we wanted to examine if gamma synchronization, one mechanism for local cortical network formation, had a role in supporting local networks encoding the semantic representations. We performed a semantic priming study where we expected local network activity to decrease when primed by a semantically-related word. Indeed, we did observe a posterior decrease in gamma power between 150-450ms which suggests that gamma power reflects decreased network activity supporting the semantic representations. Second, we hoped to find a possible real-time mechanism for creating long-range semantic networks that are involved in top-down retrieval and selection of semantic representations. This network involves the LIFG and posterior storage areas, thus we expected synchronization between left anterior and posterior electrodes as measured with coherence analysis to reflect this long-range network. Based on results from our semantic priming study, anterior-posterior coherence in the theta frequency band is likely involved in this dynamic long-range communication. But it was unclear with the semantic priming paradigm (which primarily is thought to task top-down retrieval) if theta coherence reflected only retrieval or both retrieval and post-retrieval selection processing. Thus we performed a second experiment that more directly modulated this post-retrieval selection and inhibition processing by biasing the meaning of ambiguous words to their dominant or subordinate meanings. fMRI BOLD activity has

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indicated that subordinate biasing engages the broader anterior-posterior semantic network while dominant biasing does not (Whitney et al., 2011a). As expected, when this broader network is engaged for subordinate meaning selection, left anterior-posterior delta-theta coherence in a post-retrieval time window (500-1000ms) appeared larger than during dominant meaning selection. These results suggest that coherence near the delta-theta border is involved in top-down semantic retrieval from about 150-425ms and top-down selection and inhibition from about 500-1000ms.

While it is clear that this thesis work has provided a fuller picture of the oscillatory dynamics involved in lexical-semantic processing, what is the significance of these findings? While several studies had previous suggested structural (Friederici, 2009; Petrides & Pandya, 2009) and very slow (0.01-0.1 Hz) functional (Bokde et al., 2001; Xiang et al., 2010) connectivity between anterior and posterior lexical-semantic areas, our studies revealed that these networks are engaged in a different frequency band (around 4 Hz) for real-time processing in a task. Skeptics may still question why we should continue investigating the connectivity of these networks on a faster scale if we already know these networks exist structurally and functionally on a slower scale. Understanding that these networks engage on multiple time scales may better help us to understand the relative and/or shared functions of these individual oscillations. For example, it is possible that slow oscillations during a resting state serve to preserve strong network connections and maintain readiness for task-appropriate engagement with fast oscillations. Or perhaps information processing is happening at both slow and fast rates as implemented by slow and fast oscillations. Knowing the full extent of the network dynamics will ultimately give us a better understanding of brain network functions.
The specific frequency of coherence may also have implications for cognitive enhancement or therapeutic applications. If it is specifically known that anterior-posterior 4 Hz oscillations are involved in these semantic functions, boosting synchronization at this frequency through transcranial alternating current stimulation (tACS) or transcranial magnetic stimulation (TMS) may improve these functions in individuals. Based on our findings, we would hypothesize that phase-locked 4 Hz stimulation simultaneously applied to LIFG and posterior temporal lobe may be maximally effective. As indicated by the behavioral results from our semantic ambiguity experiment, performance of normal subjects can be quite variable for semantic selection. So potentially those subjects who performed relatively poorly could benefit from theta stimulation. Additionally, people with high anxiety have trouble selecting from multiple options. It was previously found that administering a GABA agonist improved their function by increasing inhibition (Snyder et al., 2010). Research on theta stimulation may also be helpful to those unable to tolerate this medication or even to compare the efficacy of pharmacological v. stimulation approaches. Stimulation techniques have previously been shown to be effective at boosting performance in normal populations (Klimesch et al., 2003; Marshall et al., 2006). In one study, normal subjects memorized pairs of words and then received 0.8 Hz stimulation during slow-wave sleep. They demonstrated improved post-sleep recall of words compared with sham stimulation conditions (Marshall et al., 2006). Stimulation in aphasia patients has also been shown to be effective at improving performance (e.g., Medina et al., 2012). Broca’s aphasia patients have subtle semantic deficits (Hagoort, 1993; Milberg et al., 1987), but those deficits may be improved with synchronized theta stimulation of perilesional frontal areas and posterior temporal gyrus. Using tACS and TMS stimulation can additionally
elucidate the causality of these oscillations. Several previous studies have taken this approach and demonstrated a causal relationship between specific oscillations and specific cognitive functions (Klimesch et al., 2003; Marshall et al., 2006). Most stimulation studies on humans modulate spectral power at a single location. Thus it would be quite novel and potentially informative to modulate coherence by stimulating in a synchronized manner at multiple locations as proposed here.

Closer consideration of theta coherence in relation to beta coherence in our semantic priming study is potentially revealing about a frequency-mediated dissociation of retrieval processing in the LIFG or the left prefrontal cortex (LPFC) more broadly. Neuroimaging studies demonstrate less activity in these areas and reduced reaction times during repetition priming (e.g., Buckner et al., 1998; Dobbins et al., 2004) and semantic priming (e.g., Badre et al., 2005). Many investigators have rightly focused on if and how these neural decreases can cause the behavior facilitation effect. One proposal by Ghuman et al. (2008) is that increased beta phase synchronization between left PFC and left temporal cortex (i.e. more efficient long-distance processing) can cause the shorter reaction times as earlier synchrony correlates with earlier reaction times. But less attention has been paid to a related question: why is there increased LIFG/LPFC activity in the first place for the repetition or semantically-unprimed items? This is a contextually-unsupported condition, and increased prefrontal activity seems to be involved in assisting retrieval of objects or words when context cannot facilitate retrieval. In this condition, we have shown increased theta coherence likely reflecting phase synchronization between LIFG and posterior temporal cortex. So phase synchronization measures in different frequency bands seem to dissociate between what we will term “contextual facilitation” for primed items and
“non-contextual assistance” for unprimed items. The juxtaposition of the LPFC’s role in both contextual facilitation and non-contextual assistance was not well contrasted before, but it highlights the ability of phase-synchronization to dissociate between retrieval processes and suggests some interesting questions. Why is the LPFC brought online when context is lacking? Exactly what information or computation is utilized in LPFC to provide assistance in an unsupportive context? One idea may come from a recent MEG study by Bar and colleagues (2006). They found that during object recognition low spatial frequency (LSF) but not high frequency (HSF) information is projected to orbitofrontal cortex (OFC) first and then followed in time by activation of representations in the temporal cortex. Thus the OFC may be using LSF information to provide a top-down “initial guess” to constrain the set of possible object representations activated. Perhaps a similar mechanism of using simplified visual information (such as the length of a word or first and last letters of a word) can be used to constrain lexical recognition. A possible mechanism for semantic recognition when reading words is more difficult to propose as it is not as evident that an initial guess at a semantic representation can come from simplified visual information of the word form. These matters would certainly benefit from further consideration.

4.2 Future Directions

Several directions exist for future studies that build upon the work presented here. As mentioned in the discussion of Chapter 3, semantic retrieval and selection demands are highly correlated in both of our paradigms making it difficult to modulate them separately. Following the thinking that selection and inhibition are post-retrieval processes and must occur after
retrieval of semantic representations (e.g., Badre et al., 2005), we attributed early theta coherence (150-450 ms) to retrieval and later theta coherence (500-1000ms) to selection processing. Nevertheless, to truly make this dissociation, we need a paradigm that separates the processes. A candidate is the verb generation paradigm used by Snyder et al. (2010) where subjects are presented with a noun and must generate a verb in response. Two factors, retrieval demand and selection demand, each have two levels, low and high, which results in the four conditions: 1) low retrieval and low selection, 2) low retrieval and high selection, 3) high retrieval and low selection, 4) high retrieval and high selection. They used latent semantic analysis (LSA) which assesses the similarity of words by analyzing text for co-occurrence information (Landauer et al., 1998) to assign words to each condition. Using a set of already normed data from a separate subject pool who also generated verb responses to nouns, they measured the strength of association between each noun and verb response by calculating LSA association values. Greater association between the words eases retrieval of the verb. Another measure, LSA entropy, measures the spread of possible verb responses for each noun. If there are many possible verb responses from the normed data, this increases competition and selection demands as reflected by high LSA entropy. Based on these measures, nouns are assigned to one of the four conditions. Unfortunately several obstacles prevented us from using this paradigm instead of the semantic ambiguity paradigm. First, no published normed noun-verb data exists, and this is an essential component for calculating the LSA measures. We also did not have the resources readily available to collect our own norms. Second, this paradigm requires a verbal response. EEG is very sensitive to any head movement, and overt responses introduce large artifacts into the data. While there is a recently developed method to remove these artifacts (De Vos et al., 2010), it is
not yet well-established and may have presented unanticipated problems. Utilizing covert responses was another possibility, but without verbal confirmation, it is not assured that the subject is correctly performing the task. If these barriers can be overcome, this experiment would provide an elegant way to test if theta coherence in early and later time windows reflects controlled retrieval and selection, respectively.

If theta coherence becomes a replicable index for controlled semantic processing, could it eventually be useful as an electrophysiological marker of semantic processing akin to the N400? Perhaps in some ways it could but this is unlikely in others. The N400 is widely used as a dependent variable to examine meaning of both linguistic and non-linguistic material. The N400 is most sensitive to meaning retrieval and not selection or inhibition. An ERP index for selection and inhibition has not become well-established, although our results along with Chwilla and Kolk’s (2003) suggest an ERP negativity after 600 ms may reflect post-retrieval processes. ERP calculations are computationally easier and quicker to perform than coherence calculations, thus ERPs most likely will stay the preferred index of semantic retrieval (and perhaps semantic selection if an ERP component becomes more established). Still, ERPs do not suggest which mechanisms may underlie transient functional networks while oscillatory synchronization can. Also, ERP analysis averages out non-phase-locked information that has been shown to be quite valuable in understanding how phase affects cognitive processing. For example, the phase of ongoing oscillations modulates visual perception on a trial-by-trial basis (Busch et al., 2009). Nevertheless, it is unlikely that theta coherence will become more commonly used as an index of semantic processing, though it should be recognized as valuable in examining dynamic networks.
Theta coherence may be more broadly involved in retrieval processing. Several studies (Evans et al., 2012; Prado et al., 2011) have found that retrieval of arithmetic information recruits the LIFG and posterior areas such as left pMTG and left SMG, both areas implicated in semantic processing. Autobiographical memory retrieval processing also recruits these areas (for a review, see Svoboda et al., 2006). To investigate whether theta coherence can stand as a more general retrieval mechanism between left anterior and posterior areas, arithmetic and autobiographical paradigms can be used.

We have summarized our findings, highlighted their significance for the field, and discussed some potential directions for future research based on the above findings. But this work and the possible future avenues are but a few ripples in the vast fields of oscillatory synchronization and semantics. We hope that these contributions will nevertheless encourage others to push forward in pursuing how semantics, and more generally cognition, is implemented in the brain.
Appendix A

Electrode layout for the EGI 128-electrode net
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