FUNCTIONAL ROLE OF NEURAL OSCILLATIONS IN ATTENTION AND MEMORY IN HUMANS

By

RAJASIMHAN RAJAGOVINDAN

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To my Mom and Dad, for their love and support
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FUNCTIONAL ROLE OF NEURAL OSCILLATIONS IN ATTENTION AND MEMORY IN HUMANS

By

Rajasimhan Rajagovindan

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Synchronized oscillatory neural activity involving widespread neural ensemble is common in the central nervous system, and is hypothesized to enable the integration of various attributes of the sensory input, resulting in a unified percept. While activity evoked to external sensory input has been instantly recognized to reflect stimulus processing, ongoing neural activity preceding stimulus onset is often considered as background noise and irrelevant to subsequent stimulus processing. Our study seeks to advance the idea that ongoing neural oscillations are critical indices of the brain state and, as such, play an important role in stimulus-evoked cognitive processing. Applying advanced multivariate spectral analysis to invasive and non-invasive electrophysiological recordings from animals and humans, we address the mechanisms and the functional roles of synchronized prestimulus oscillatory activity in processes such as anticipatory attention, visual processing and encoding of memory.

First, applying computational techniques to invasive local field potential recordings from primates we expound the mechanisms leading to zero-lag synchrony across widely separated cortical areas, a phenomenon critically implicated in effective neuronal communication and thus higher-order perceptual processes. Second, we assessed the functional role of prestimulus theta band oscillation in memory related stimulus encoding in the human cortex using invasive
electrocorticogram. Third, a physiological model linking prestimulus oscillations and stimulus-evoked response is proposed and is tested on noninvasive studies of human visual processing. Finally, the neural control of anticipatory attention and stimulus selection using electroencephalogram is investigated. The objective here is to expound the signals and the neural mechanisms that mediate these top-down processes that enable selective sensory integration during attentive behavior in humans.

In conclusion, our findings suggest that effective sensory-perceptual processing and thus cognitive and behavioral performance to an impending stimulus, depends on the excitability state of the brain defined by these neural oscillations at its onset. Further, it is shown that the prestimulus activity is not merely a random fluctuation in excitability but one that is actively controlled in a goal-directed manner through neural synchronization across widespread functionally relevant cortical networks. Thus, this study bolsters the functional role of prestimulus ongoing activity in subsequent sensory-perceptual and higher-order cognitive processing.
CHAPTER 1
INTRODUCTION

The ubiquitous nature of oscillatory neural activity in the human and animal brain is well established. In 1989, Gray, Singer and colleagues (1989), showed that neurons with distinct receptive fields in the primary visual cortex when jointly stimulated with one ‘perceptual’ object, produced synchronized oscillatory responses. On the other hand, when stimulated by two distinct perceptual objects in their respective receptive fields, the firing rates remained unaltered, and the synchrony was abolished. Ever since this early study, it has been shown consistently that all cognitive processes involve transient integration of several widely distributed cortical areas (Singer and Gray, 1995; Malsburg, 1995; Roskies, 1999; von Stein et al., 2000). These synchronous oscillations, resulting from dynamic interaction between distant yet functionally relevant cortical regions, have been suggested as a putative mechanism for the large-scale integration of sensory inputs, known as the ‘binding’ problem (Eckhorn et al., 1988; Sarnthein et al., 1998; Weiss and Rappelsberger, 2000; Engel et al., 2001; Varela et al., 2001; Fries, 2005; Jones and Wilson, 2005). Numerous studies have recently reported synchrony with zero time lag across widely separated cortical regions, and have interpreted the observation as precise timing of neural activation within sub-millisecond range across functionally relevant cortical regions facilitating binding and functional integration (Roelfsema et al., 1997; Chawla et al., 2001). However the mechanisms leading to such zero-lag synchrony across spatially distant areas are yet unclear.

The field potential of neuronal ensembles as measured by invasive macro-electrodes or by non-invasive EEG / MEG, exhibits a broad range of oscillatory activity, usually described in terms of frequency bands, delta (1-3 Hz), theta (4-9 Hz), alpha (8-12 Hz), beta (13-25 Hz) and gamma (25-90 Hz). The oscillatory neural activity both in humans and animals exhibit task
related modulation in their strength and synchrony. Theta and alpha range oscillations have been long shown to reflect memory processes (Kahana et al., 1999; Klimesch, 1999; Weiss and Rappelsberger, 2000; Raghavachari et al., 2001; Jensen and Tesche, 2002; Sederberg et al., 2003; Summerfield and Mangels, 2005; Vertes, 2005). Alpha oscillations have been associated with alertness, arousal and attentional demands (Ray and Cole, 1985; LaBerge, 1997; Foxe et al., 1998; Bastiaansen and Brunia, 2001; Babiloni et al., 2006; Keil et al., 2006; Kelly et al., 2006; Thut et al., 2006; Fan et al., 2007; Klimesch et al., 2007). The beta rhythm has been shown to reduce in strength preceding movement and subsequently increase in strength after the movement is complete (Pfurtscheller and da Silva, 1999). The gamma range oscillations are often found in early sensory areas and have been suggested to be involved in the binding of sensory information (Miltner et al., 1999; Muller et al., 2000; von Stein and Sarnthein, 2000; Fell et al., 2003; Herrmann et al., 2004; Palva et al., 2005; Womelsdorf et al., 2006; Hermer-Vazquez et al., 2007; Landau et al., 2007; Doesburg et al., 2008).

Increasing number of studies suggest that neural oscillations play significant roles in cognitive functions such as attention (Worden et al., 2000; Fries et al., 2001; Womelsdorf and Fries, 2007; Doesburg et al., 2008), anticipation (Foxe et al., 1998; Worden et al., 2000; Bastiaansen and Brunia, 2001; Liang et al., 2002), associative learning (Miltner et al., 1999), memory (Burgess and Gruzelier, 1997; Gevins et al., 1997; Klimesch, 1999; Jensen and Tesche, 2002; Herrmann et al., 2004; Jones and Wilson, 2005), motor functions (Roelfsema et al., 1997; Farmer, 1998; Brovelli et al., 2004; Hermer-Vazquez et al., 2007) and perception (Eckhorn et al., 1988; Rodriguez et al., 1999; Babiloni et al., 2006; Melloni et al., 2007). In particular, the neuronal oscillatory activity is considered the substrate for communication between functionally relevant cortical areas (Roelfsema et al., 1997; Miltner et al., 1999; Fries, 2005).
Although neural oscillations have been studied extensively, emphasis has traditionally been on stimulus-evoked responses and stimulus-related changes in oscillatory activity while the ubiquitous spontaneous oscillations were regarded as ‘noise’ and irrelevant for subsequent stimulus related processing. A landmark study by Arieli et al., (1996) using optical recordings showed for the first time that the state of the brain at the onset of an external stimulus predicts the effectiveness of the ensuing stimulus processing, providing the early impetus for a systematic investigation of the role of spontaneous brain activity in stimulus processing. Recent work has begun to explore this issue. Computational modeling as well as in-vitro and in-vivo single unit recordings in animal preparations have explored mechanisms by which background synaptic activity can influence the responsiveness of cortical neurons to afferent input (Ho and Destexhe, 2000; Chance et al., 2002; McCormick et al., 2003; Wolfart et al., 2005; Haider et al., 2007). How these mechanisms manifest in humans is not yet clearly established.

This dissertation explores the role of prestimulus ongoing oscillations as well as their relationship to subsequent stimulus processing and higher-order cognitive processes along four specific aims.

**Aim 1:** To identify factors contributing to near zero time lags in synchronous oscillatory cortical networks. Given that the conduction delay between two brain areas is only a small fraction of the oscillation cycle, a near-zero phase-lag relation could stem either from reciprocal communication between the two areas (bidirectional interaction) or from the two areas being readied to communicate by a third set of areas (common input). The testing of these possibilities has not been carried out empirically. The main reason is that the commonly used methods such as cross correlation and coherence lack the ability to decompose neural interactions into their constituent components. We expound the mechanisms leading to zero-lag synchrony across
widely separated cortical areas by introducing Geweke’s time series decomposition theorem into
the analysis of multivariate neural data. Employing Geweke’s decomposition theorem, we
decompose the neural synchrony between two areas (A and B) into its constituent terms (A→B),
(B→A) describing the direction of neural interaction and a term representing the instantaneous
correlation (instantaneous common input). We then characterized the influence of each of the
constituent interaction terms on the phase-lag to address the factors contributing to near-zero lags
across widely separated cortical areas using simulation examples and local field potential data
recorded from behaving monkeys performing a visuomotor pattern discrimination task.

**Aim 2:** To investigate the functional role of prestimulus theta band oscillation in memory-
related sensory encoding. It is well known that when instructed to memorize a set of items, we
typically are capable of recollecting only a fraction of the items previously presented. Toward
addressing the question of why some words are remembered better while others are not, it was
shown that the level of physiological responses evoked by the visual word presentation in the
prefrontal cortex (PFC) and the medial temporal lobe (MTL) is predictive of successful
subsequent recall and can thus can be considered an indicator of encoding efficacy. However, the
question that still remains to be addressed is that, why are some words encoded better while
others are not? We hypothesize that the efficacy of memory encoding in humans depends on the
level of excitability over the frontal-medial temporal memory network and that the strength of
frontal-medial temporal interaction immediately prior to stimulus presentation, possibly
reflecting the strength of top-down attentional control originating in the frontal cortex (Furey et
al., 2000; Kimura, 2000; Hasselmo and McGaughy, 2004), is positively correlated with the
efficacy of stimulus encoding and the likelihood of its subsequent recall. Considering that
noninvasive electroencephalogram (EEG) lacks the spatial resolution and the ability to sample
areas proximal to the medial temporal lobe, the hypotheses were instead tested by recording
electrocorticogram (ECoG) from multiple implanted grids in five patients undergoing presurgical
evaluation for intractable epilepsy who performed a subsequent memory task. In this study we
characterize how ongoing oscillatory brain activities in the fronto-temporal network immediately
preceding stimulus presentation affect memory encoding and thus later recall.

**Aim 3:** To investigate the functional role of ongoing oscillations during anticipatory
attention and their relation to evoked responses in a spatial visual attention task. While numerous
EEG/MEG studies have considered the role of prestimulus oscillations in the genesis of sensory
evoked potentials, no consensus has emerged, and disparate reports remain unreconciled (Brandt
and Jansen, 1991; Foxe et al., 1998; Marrufo et al., 2001; Makeig et al., 2002; Ergenoglu et al.,
2004; Linkenkaer-Hansen et al., 2004; Sauseng et al., 2005; Babiloni et al., 2006; Mazaheri and
Jensen, 2006; Thut et al., 2006; Hanslmayr et al., 2007a; Hanslmayr et al., 2007b; Paul et al.,
2007; Romei et al., 2008b; Romei et al., 2008a; Van Dijk et al., 2008; Zhang and Ding, in press).

Further, sensory information processing depends to a great extent on to what and where an
individual deploys attention. It is well known from early studies that responses to stimuli at
attended locations and attended sensory modalities are enhanced relative to unattended stimuli. It
has also been shown in recent years that attention modulates baseline ongoing brain activity in
advance of sensory input (Kastner et al., 1999; Dehaene and Changeux, 2005; Bestmann et al.,
2007). However, the mechanisms linking the pre and poststimulus attentional effects remain not
well understood.

Our approach to investigating the relation between prestimulus activity and stimulus
evoked response starts by considering a theoretical model in which synaptic input to a sensory
neuronal ensemble comes in two forms: external stimulus (exogenous) or other brain structures
(endogenous). Supposing that, in the absence of sensory input, the firing rate of the neuronal ensemble is related to the magnitude of endogenous synaptic fluctuations through a sigmoidal function, and sensory input has an additive synaptic effect, it follows that the stimulus-evoked response corresponds to the derivative of the sigmoidal function, referred to as the gain, which is an inverted-U function of the prestimulus level of background activity. Reformulated in terms of EEG variables where field oscillations and the early component of event-related potential are treated as indices of background synaptic activity and stimulus-evoked response, the model makes a number of predictions, which were then tested by recording EEG data from human volunteers performing a trial-by-trial cued covert spatial visual attention task. The systematic model based characterization of the pattern of relationship between the early visual-evoked responses and the prestimulus oscillatory activity also offers an added benefit in that it may yield insights into the fundamental question of how cognitive operations such as attention modulate baseline ongoing neural activity to achieve enhanced stimulus information processing.

Based on the proposed model linking prestimulus oscillatory activity and subsequent stimulus-evoked response, a mechanism on how changes in the global state of the brain, such as selective attention, influenced the aforementioned sigmoidal curve was proposed. Through experimental data and computational modeling we present a mechanism of how attention modulates baseline ongoing activity over early sensory areas to enable enhanced sensory-perceptual processing.

**Aim 4:** To investigate the functional role of ongoing oscillations in top-down control of human visual cortex during anticipatory spatial visual attention. The theoretical framework adopted thus far emphasizes the role of ongoing EEG oscillations over early sensory areas, in this case the visual cortex, and addresses the mechanisms linking the attention induced
prestimulus modulations to stimulus-evoked attentional enhancements. However, such
goal-directed prestimulus modulation of sensory cortical activity is not an inherent property of
the early sensory areas. Instead, it is believed that the higher-order areas such as the
frontal-parietal network facilitates an enhancement of the excitability of the task-relevant and
feature-specific visual areas and perhaps a suppression of activity in task-irrelevant visual areas
in advance of visual stimulation by modulating its baseline activity (Chelazzi et al., 1993; Luck
et al., 1997; Hillyard et al., 1998; Kastner et al., 1999; Hopfinger et al., 2000; Kastner and
Ungerleider, 2001; Corbetta and Shulman, 2002; Gazzaley et al., 2005; Giesbrecht et al., 2006;
Grent-'T-Jong and Woldorff, 2007; Klimesch et al., 2007). In line with this notion, it has been
identified that deployment of covert spatial visual attention is associated with increased
activation in a network involving dorsal frontal and parietal cortices with concomitant increases
in activation over retinotopic early visual areas (Desimone, 1996; Gitelman et al., 1999; Kastner
et al., 1999; Hopfinger et al., 2000; Corbetta and Shulman, 2002; Giesbrecht et al., 2003).

While prior neuroimaging and lesion studies of the top-down control of visual attention
have offered insights into the areas in the brain that exert control over stimulus processing, the
neural mechanisms of how this increased excitability over the visual sensory areas is brought
about has not been clearly established. What is the neural signal that mediates the top-down
biasing influence? Is the increased excitability achieved by increasing the excitatory drive on
local pyramidal neurons (excitation) or by decreasing excitatory drive on local inhibitory
interneurons (disinhibition)? Is the top-down influence transient or sustained? These questions
are addressed by applying time-frequency analysis of power, coherence and Granger causality to
scalp EEG recordings from healthy volunteers performing a spatial visual attention task.
CHAPTER 2
GENERAL METHODS

The primary goals of this dissertation involve the investigation of prestimulus ongoing activity and its relation to stimulus evoked responses and hence cognitive performance. Neural ensemble activity exhibit a wide range of oscillations and the role of these oscillations in cognitive information processing have been increasingly studied in recent years. Physiologically, cortical field oscillations recorded by scalp EEG/MEG reflect the rhythmic fluctuations in the correlated background synaptic activity and provide an index of the excitability of the underlying neural population (Dasilva, 1991). EEG/MEG signals consist of several simultaneous oscillations, which have traditionally been subdivided into frequency bands such as delta (1-3 Hz), theta (4-9 Hz), alpha (8-12 Hz), beta (about 13-25 Hz) and gamma (25-90 Hz) each of which are distinctly related to cognitive information processing and hence behavior. The oscillatory nature of the signal necessitates the need for a spectral domain approach to study this problem. Further, it is well agreed upon that complex cognitive processes involve complex interaction between disparate regions of the brain. Synchrony (functional connectivity) and Granger causality (effective connectivity) analysis have emerged as principled approach of identifying and quantifying inter-areal interaction and infer causal influence among distributed networks (Eckhorn et al., 1988; Schack et al., 2000; von Stein and Sarnthein, 2000; Baccala and Sameshima, 2001; Kaminski et al., 2001; Varela et al., 2001; Liang et al., 2002; Brovelli et al., 2004; Tallon-Baudry et al., 2004; Palva et al., 2005; Seth, 2005; Ding et al., 2006; Wang et al., 2007b; Bollimunta et al., 2008; Cadotte et al., 2008; Hermer-Vazquez, 2008; Rajagovindan and Ding, 2008b; Zhang et al., 2008a; Zhang et al., 2008b; Cadotte et al., 2009). Granger causality is a statistical approach that decomposes neural synchrony into causal directional interactions, which provides a non-invasive alternative to identify the direction of neural interaction. Below,
some of the spectral estimation techniques employed in this study to quantify neural activity and also the mathematical framework of Granger causality with special emphasis on its spectral decomposition is reviewed. Practical issues concerning how to estimate such measures from time series data are then discussed. The description in the following sections follow that of (Granger, 1969; Geweke, 1982; Ding et al., 2000; Chen et al., 2006; Ding et al., 2006; Wang et al., 2007b; Rajagovindan and Ding, 2008b)

2.1 Parametric Multivariate Spectral Estimation

Multivariate autoregressive (MVAR) modeling is a parametric spectral analysis method in which time series models are estimated from datasets having either one long realization or a number of realizations. In the latter case, the fundamental assumption of this algorithm is that the short-window time series can be treated as realizations of an underlying stationary stochastic process. As cognitive information processing involves transient changes in neural activity, MVAR can be used to investigate time series in short window size (<100 ms). The following is the procedure of MVAR (Ding et al., 2000).

Let \( X(t) = [X(1,t), X(2,t), \ldots, X(m,t)]^T \) be a \( m \)-dimensional jointly stationary random process. \( T \) denotes matrix transposition. In the case of neural recordings, \( m \) refers to the total number of recording channels to be analyzed. Assuming \( X(t) \) is a zero mean stationary process, \( X(t) \) can be modeled by the following \( p \)-th order autoregressive equations:

\[
X(t) + A(1)X(t-1) + A(2)X(t-2) + \cdots + A(p)X(t-p) = E(t)
\]

where \( p \) is the model order, and \( A(i) \) are the unknown \( m \times m \) coefficient matrices and \( E(t) \) is the uncorrelated noise term with covariance matrix \( \Sigma \). Multiplying \( X^T(t-k) \) to Eq. 2-1 and taking expectation on both sides we arrive at the Yule-Walker equations.

\[
R(\tau) + A(1)R(\tau+1) + \cdots + A(p)R(\tau+p) = 0
\]
where $R(j)$ is covariance matrices of $X(t)X^T(t+j)$ with lag $j$. Also note that $<E(t)\cdot X^T(t-k) >= 0$, since $E(t)$ is an uncorrelated noise process. The unbiased estimator of the covariance matrix in Eq. 2-2 for a single realization of the $X$ process is given by

$$
\hat{R}(n) = \frac{1}{N-n} \sum_{i=1}^{N-n} x(i)x^T(i+n)
$$

In the case of multiple realizations of the process as is usually the case, the covariance matrix is computed for each individual realization and then averaged across all the realizations to obtain the most robust estimate. In the case of short window of data, i.e. short sample length where $N$ is small, it is apparent that the estimation from a single realization is poor. However, with increasing number of realizations this problem can be offset for short sample length time series. In the limiting case with number of realizations approaching infinity, the sample length of each realization may be as short as the model order plus one ($N = p+1$).

Coefficient matrices $A(i)$ and covariance matrix $\Sigma$ of noise term $E(t)$ is obtained by solving Eq. 2-2 through the Levinson, Wiggins and Robinson (LWR) algorithm. The noise covariance matrix $\Sigma$ is obtained as part of the LWR algorithm. One may also obtain $\Sigma$ as

$$
\Sigma = R(0) + \sum_{i=1}^{p} A(i)R(i)
$$

It is instructive to note that the Eq. 2-2 contain a total of $pm^2$ unknown model coefficients to be estimated from the same number of simultaneous linear equations.

Although the primary objective is to fit the best model to the data, which is to minimize the residual noise variance, this constraint alone may result in over-parameterization. The reason for this is because the variance of the residual term decreases monotonically with incorporating more and more past values of the process. Over-parameterization leads to inaccuracies in the estimation of the model coefficient besides the obvious increase in the computational
complexity. Thus a penalization scheme to avoid over-parameterization is employed. Criteria that incorporate both minimization of the variance of the residual term and penalize excessive coefficients are the Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) among several other similar criterions. The AIC is defined as
\[
AIC(p) = -2 \log[\det(\Sigma)] + \frac{2m^2 p}{N_{total}}
\]
where \(N_{total}\) is the total number of data points from all the trials. The first term on the right hand side accounts for the variance minimization and the second term correspond to the cost associated with increasing parameters. Plotted as a function of \(p\), the optimum model order corresponds to the minimum of this function. For typical neurobiological data \(N_{total}\) is very large and hence for practical ranges of \(p\), the AIC function does not achieve a minimum due to inadequate penalization as the second term vanishes with large values of \(N_{total}\). An alternative criterion is the Bayesian Information Criterion (BIC), which is defined as
\[
BIC(p) = -2 \log[\det(\Sigma)] + \frac{2m^2 p \log N_{total}}{N_{total}}
\]
This criterion can compensate for the large number of data points and may perform better in neuroscientific applications. A final step and critical step necessary for determining whether the autoregressive time series model is suited for a given data set, is to check whether the residual term is white. Here the residual term is obtained by computing the difference between the model’s predicted values and the actually measured values.

Once an autoregressive model is adequately estimated, it becomes the basis for both time domain and spectral domain causality analysis. Spectral features are derived from MVAR models after acquiring \(A(i)\) and \(\Sigma\) estimates. Taking the Fourier transform, Eq. 2-1 can be rewritten in the spectral domain as
\[ A(f)X(f) = E(f), \]

Defining \( H(f) = \left( \sum_{i=0}^{m} A(i)e^{-j2\pi f} \right)^{-1} \), then \( X(f) = H(f)E(f) \)

where \( H(f) \) is the transfer function. The spectral matrix can be readily derived from

\[ S(f) = \lim_{N \to \infty} \frac{1}{N} E[X(f)X^*(f)] = H(f)\Sigma H^*(f) \]

where * means both transpose and complex conjugate.

Spectral power is contained in the diagonal terms of the spectral matrix and the off-diagonal terms represent the cross spectra. Coherence spectra between two random process \( X(i,t) \) and \( X(j,t) \) is defined as:

\[ C_{ij}(f) = \frac{|S_{ij}(f)|^2}{S_{ii}(f)S_{jj}(f)} \]

If the coherence value is equal to 1 or 0, the two processes are maximally interdependent or independent, respectively. Once the transfer function, the noise covariance and the spectral matrix are estimated, Granger causality may be derived according to the procedures outlined in the following sections.

### 2.2 Granger Causality Analysis

#### 2.2.1 Time Domain Formulation

Consider two jointly stationary stochastic processes \( X_t \) and \( Y_t \), each having an autoregressive representation given by

\[
X_t = \sum_{j=1}^{\infty} a_{ij} X_{t-j} + e_{it}, \quad \text{var}(e_{it}) = \Sigma_x \\
Y_t = \sum_{j=1}^{\infty} d_{ij} Y_{t-j} + \eta_{it}, \quad \text{var}(\eta_{it}) = \Sigma_y
\]

(2-3)
Jointly, they can be represented by the following bivariate autoregressive model

\[ X_t = \sum_{j=1}^{\infty} a_{2j} X_{t-j} + \sum_{j=1}^{\infty} b_{2j} Y_{t-j} + \epsilon_{2t} \]
\[ Y_t = \sum_{j=1}^{\infty} c_{2j} X_{t-j} + \sum_{j=1}^{\infty} d_{2j} Y_{t-j} + \eta_{2t} \]

(2-4)

where, \( \epsilon_{2t} \) and \( \eta_{2t} \) are uncorrelated over time, and their contemporaneous covariance matrix is

\[ \Sigma = \begin{pmatrix} \Sigma_{xx} & \Sigma_{xy} \\ \Sigma_{yx} & \Sigma_{yy} \end{pmatrix} \]

If \( b_j \) is not uniformly zero for \( j = 1, 2, \ldots, \infty \), then \( Y_t \) is said to have a causal influence on \( X_t \). Likewise, \( X_t \) is said to have a causal influence on \( Y_t \) if \( c_j \) is not uniformly zero for \( j = 1, 2, \ldots, \infty \). The total interdependence between \( X_t \) and \( Y_t \) is defined as (Gelfand and Yaglom, 1959)

\[ F_{X,Y} = \ln \frac{\Sigma_{xx}}{|\Sigma|} \]

where \(|\cdot|\) denotes the determinant of the enclosed matrix. It can be easily verified that according to this definition \( F_{X,Y} = 0 \) when the two time series are independent, and \( F_{X,Y} > 0 \) when they are not. Considering Eq. 2-3, 2-4, \( \Sigma_x \) represents the prediction error of \( X_t \) based on its past values and \( \Sigma_{xx} \) represents the prediction error, when predicting the present value of \( X_t \) based on past values of \( X_t \) and \( Y_t \). If \( \Sigma_{xx} \) is less than \( \Sigma_x \), then \( Y_t \) is said to have causal influence on \( X_t \) quantified by (Granger, 1969; Geweke, 1982)

\[ F_{Y \rightarrow X} = \ln \frac{\Sigma_x}{\Sigma_{xx}} \]
It may be noticed that when there is no causal influence from \( Y \) to \( X \), \( F_{Y \rightarrow X} = 0 \) and \( F_{Y \rightarrow X} > 0 \) otherwise. Similarly the causal drive from \( X \) to \( Y \) may be defined as (Granger, 1969; Geweke, 1982)

\[
F_{X \rightarrow Y} = \ln \frac{\Sigma_{xy}}{\Sigma_{yx}}
\]

If \( \Sigma_{xy} = \Sigma_{yx} \neq 0 \), indicating that the noise terms \( \varepsilon_{zt} \) and \( \eta_{zt} \) are correlated at time \( t \), then the interdependence between \( X \) and \( Y \) has another contributor that is not explained by the interaction between \( X \) and \( Y \). This component possibly representing common input from a third system, will be referred to as the instantaneous causality, defined by (Geweke, 1982)

\[
F_{X \rightarrow Y} = \ln \frac{\Sigma_{sx} \Sigma_{sy}}{\Sigma_{y}}
\]

Notice that when \( \Sigma_{xy} = \Sigma_{yx} = 0 \) the instantaneous causality is zero and greater than zero otherwise.

It follows from definition that the total interdependence is the sum of mutual interaction between \( X \) and \( Y \), and a component exogenous to the system given by (Geweke, 1982)

\[
F_{X,Y} = F_{X \rightarrow Y} + F_{Y \rightarrow X} + F_{X,Y}
\]

**2.2.2 Frequency Domain Formulation**

To derive Geweke’s formulation of Granger causality in the frequency domain it is convenient to repose the autoregressive equations in terms of lag operator. The lag operator \( L \) is defined as \( LX_t = X_{t-1} \). Rewriting Eq. 2-1 in terms of lag operator

\[
\begin{pmatrix}
a_z(L) & b_z(L) \\
c_z(L) & d_z(L)
\end{pmatrix}
\begin{pmatrix}
X_t \\
Y_t
\end{pmatrix}
= 
\begin{pmatrix}
\varepsilon_{zt} \\
\eta_{zt}
\end{pmatrix}
\]

(2-5)

where, \( a_z(0) = 1, b_z(0) = 0, c_z(0) = 0, d_z(0) = 1 \) Fourier transforming both sides of Eq. 2-5
\[
\begin{pmatrix}
a_x(\omega) & b_x(\omega) \\
c_x(\omega) & d_x(\omega)
\end{pmatrix}
\begin{pmatrix}
X(\omega) \\
Y(\omega)
\end{pmatrix} = A(\omega)
\begin{pmatrix}
X(\omega) \\
Y(\omega)
\end{pmatrix} = 
\begin{pmatrix}
E_x(\omega) \\
E_y(\omega)
\end{pmatrix}
\]

where,

\[
a_x(\omega) = 1 - \sum_{j=1}^{\infty} a_j e^{-i\omega_j}, \quad b_x(\omega) = 1 - \sum_{j=1}^{\infty} b_j e^{-i\omega_j}, \quad c_x(\omega) = 1 - \sum_{j=1}^{\infty} c_j e^{-i\omega_j}, \quad d_x(\omega) = 1 - \sum_{j=1}^{\infty} d_j e^{-i\omega_j}
\]

Further simplifying

\[
\begin{pmatrix}
X(\omega) \\
Y(\omega)
\end{pmatrix} = 
\begin{pmatrix}
H_{xx}(\omega) & H_{xy}(\omega) \\
H_{yx}(\omega) & H_{yy}(\omega)
\end{pmatrix} \begin{pmatrix}
E_x(\omega) \\
E_y(\omega)
\end{pmatrix}
\]

where, the transfer function \(H(\omega) = A^{-1}(\omega)\) and

\[
H_{xx}(\omega) = \frac{1}{|A|} d_x(\omega), \quad H_{xy}(\omega) = -\frac{1}{|A|} b_x(\omega)
\]
\[
H_{yx}(\omega) = -\frac{1}{|A|} c_x(\omega), \quad H_{yy}(\omega) = \frac{1}{|A|} a_x(\omega)
\]

Performing proper ensemble averaging, the spectral matrix can be derived as

\[
S(\omega) = \begin{pmatrix}
S_{xx}(\omega) & S_{xy}(\omega) \\
S_{yx}(\omega) & S_{yy}(\omega)
\end{pmatrix} = H(\omega) \Sigma H^*(\omega),
\]

where * denotes complex conjugate and matrix transpose.

The diagonal terms of the spectral matrix denote the auto spectra (power spectrum) and the off-diagonal terms denote the cross spectra. If \(X\) and \(Y\) are independent, the off-diagonal elements are zero. The spectral domain representation of the total interdependence between \(X\), and \(Y\), at frequency \(\omega (=2\pi f)\) is given by (Geweke, 1982)

\[
f_{X,Y}(\omega) = \ln \frac{S_{xx}(\omega)S_{yy}(\omega)}{|S(\omega)|} = -\ln(1 - C(\omega))
\]
where \( C(\omega) = \frac{|S_{xy}(\omega)|^2}{S_{xx}(\omega)S_{yy}(\omega)} \) is the coherence function. The phase-lag between \( X \) and \( Y \) at a given frequency is given by 

\[
\tan^{-1}\left(\frac{\text{Im}\{S_{xy}(\omega)\}}{\text{Re}\{S_{xy}(\omega)\}}\right).
\]

Further, \( |S(\omega)| = S_{xx}(\omega)S_{yy}(\omega) - S_{xy}(\omega)S_{yx}(\omega) \) and \( S_{xy}(\omega) = S_{yx}^*(\omega) \). Notice that when \( X \) and \( Y \) are independent, \( |S(\omega)| \) reduces to the product of the auto spectra, hence it can be verified that the total interdependence is zero. Expanding the entries of the spectral matrix,

\[
S_{xx}(\omega) = H_{xx}(\omega)\Sigma_{xx}H_{xx}^*(\omega) + 2\Sigma_{xy} \text{Re}(H_{xx}(\omega)H_{xy}^*(\omega)) + H_{xy}\Sigma_{yx}H_{xy}^*(\omega)
\]

(2-6)

consider the case when \( \Sigma_{xy} = 0 \) that is when there is no instantaneous causality. Then, \( S_{xx}(\omega) \) reduces to the sum of the first and the third term in the right hand side of Eq. 2-6. Intuitively, this can be understood as decomposing the auto spectrum into an intrinsic part and a component representing the causal drive from the other time series. However if \( \Sigma_{xy} \neq 0 \) this form of interpretation may not be obvious. Consider a transformation introduced by Geweke (Geweke, 1982) referred to as normalization, that removes the effects of the cross terms and enables the identification of a similar intrinsic power terms and a causal power term possible. Left multiplying on both sides of Eq. 2-5 by the transformation matrix \( P \) given by (Geweke, 1982)

\[
P = \begin{pmatrix}
1 & 0 \\
\Sigma_{xy} & 1 - \Sigma_{xx}
\end{pmatrix}
\]

we obtain

\[
\begin{pmatrix}
a_x(\omega) & b_x(\omega) & X(\omega) \\
c_x(\omega) & d_x(\omega) & Y(\omega)
\end{pmatrix} = \tilde{A}(\omega) \begin{pmatrix} X(\omega) \\ Y(\omega) \end{pmatrix} = \begin{pmatrix} E_x(\omega) \\ \tilde{E}_x(\omega) \end{pmatrix}
\]

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\[ c_1(\omega) = c_2(\omega) - \frac{\Sigma_{xx}}{\Sigma_{xx}} a_2(\omega), \quad d_1(\omega) = d_2(\omega) - \frac{\Sigma_{xx}}{\Sigma_{xx}} b_2(\omega), \quad \tilde{E}_x(\omega) = E_x(\omega) - \frac{\Sigma_{xx}}{\Sigma_{xx}} E_x(\omega) \]

The new transfer function \( \tilde{H}(\omega) \) is the inverse of the \( \tilde{A}(\omega) \)

\[
\tilde{H}(\omega) = \begin{pmatrix} \tilde{H}_{xx}(\omega) & \tilde{H}_{xy}(\omega) \\ \tilde{H}_{yx}(\omega) & \tilde{H}_{yy}(\omega) \end{pmatrix} = \frac{1}{|A|} \begin{pmatrix} d_1(\omega) & -b_1(\omega) \\ -c_1(\omega) & a_1(\omega) \end{pmatrix}
\]

Also, \(|\tilde{A}| = |A|\), thus we have

\[
\tilde{H}_{xx}(\omega) = H_{xx}(\omega) + \frac{\Sigma_{xx}}{\Sigma_{xx}} H_{xy}(\omega), \quad \tilde{H}_{xy}(\omega) = H_{xy}(\omega)
\]

\[
\tilde{H}_{yx}(\omega) = H_{yx}(\omega) + \frac{\Sigma_{yy}}{\Sigma_{yy}} H_{xx}(\omega), \quad \tilde{H}_{yy}(\omega) = H_{yy}(\omega)
\]

Note that \( E_x \) and \( \tilde{E}_y \) are uncorrelated. The variance of the residual term for the normalized equation for \( Y_i \) is \( \tilde{\Sigma}_{yy} = \tilde{\Sigma}_{yy} - \frac{\Sigma_{xy}^2}{\Sigma_{xx}} \). Thus after normalization the auto spectrum of \( X_i \) can be written as

\[
S_{xx}(\omega) = \tilde{H}_{xx}(\omega) \tilde{\Sigma}_{xx} \tilde{H}_{xx}^*(\omega) + H_{xy} \tilde{\Sigma}_{yy} H_{yy}^*(\omega)
\]

As earlier, the auto spectra can now be interpreted as the sum of intrinsic power and causal power component of \( X_i \) due to \( Y_i \). Based on this formulation we now define the frequency domain causal influence from \( Y_i \) to \( X_i \) at frequency \( \omega \) as (Geweke, 1982; Ding et al., 2006)

\[
f_{X \rightarrow Y}(\omega) = \ln \frac{S_{xx}(\omega)}{\tilde{H}_{xx}(\omega) \tilde{\Sigma}_{xx} \tilde{H}_{xx}^*(\omega)} \tag{2-7}
\]

Notice that this definition of causal influence is expressed in terms of the intrinsic power rather than the causal power. It is expressed in this way so that the causal influence is zero when the causal power is zero (i.e., the intrinsic power equals the total power), and
increases as the causal power increases (i.e., the intrinsic power decreases).

Now by taking the transformation matrix as

\[
\begin{pmatrix}
1 & \frac{\Sigma_{xy}}{\Sigma_{yy}} \\
0 & 1
\end{pmatrix}
\]

and performing the same operations as earlier, we get the influence of \( X_t \) to \( Y_t \) given by

\[
f_{Y \rightarrow X}(\omega) = \ln \frac{S_{yy}(\omega)}{\tilde{H}_{yy}(\omega)\Sigma_{yy}\tilde{H}_{yy}^*(\omega)}
\]

(2-8)

where, \( \tilde{H}_{yy}(\omega) = H_{yy}(\omega) + \frac{\Sigma_{xy}}{\Sigma_{yy}} H_{yx}(\omega) \)

Having identified the total interdependence and both the directional influences, the spectral decomposition of the instantaneous causality can now be readily determined as

\[
f_{X \rightarrow Y}(\omega) = \ln \frac{(\tilde{H}_{xx}(\omega)\Sigma_{xx}\tilde{H}_{xx}^*(\omega))(\tilde{H}_{yy}(\omega)\Sigma_{yy}\tilde{H}_{yy}^*(\omega))}{|S(\omega)|}
\]

(2-9)

The above set of variables are related through (Geweke, 1982; Ding et al., 2006)

\[
f_{X,Y}(\omega) = f_{X \rightarrow Y}(\omega) + f_{Y \rightarrow X}(\omega) + f_{X \rightarrow Y}(\omega)
\]

Under general conditions, the spectral measures derived above are related to the time domain measures as

\[
F_{X,Y} = \frac{1}{2\pi} \int_{-\pi}^{\pi} f_{X,Y}(\omega) \, d\omega,
\]

\[
F_{X \rightarrow Y} = \frac{1}{2\pi} \int_{-\pi}^{\pi} f_{X \rightarrow Y}(\omega) \, d\omega,
\]

\[
F_{Y \rightarrow X} = \frac{1}{2\pi} \int_{-\pi}^{\pi} f_{Y \rightarrow X}(\omega) \, d\omega,
\]
The invertible nature of Geweke’s formulation between the time domain and frequency
domain representation is a desirable characteristic that is not possessed by other current causality
measures. For practical purposes, the same quantities listed above (Eq. 2-7, 2-8, 2-9) with simple
algebraic modification may be expressed as (Brovelli et al., 2004)

\[ F_{X \rightarrow Y} = \frac{1}{2\pi} \int_{-\pi}^{\pi} f_{X \rightarrow Y}(\omega) d\omega, \]

\[ f_{X \rightarrow Y}(\omega) = -\ln(1 - \left( \frac{\Sigma_{xx} - \Sigma_{yx}^2}{\Sigma_{yy}} \right) |H_{yx}(\omega)|^2 S_{xx}(\omega)) \]

\[ f_{Y \rightarrow X}(\omega) = -\ln(1 - \left( \frac{\Sigma_{yy} - \Sigma_{xy}^2}{\Sigma_{xx}} \right) |H_{xy}(\omega)|^2 S_{yy}(\omega)) \]

2.2.3 Mathematical Formulation of Block Granger Causality

Application of Granger causality to the investigation of causal influences between different
brain structures have so far mainly utilized pairwise analysis (Brovelli et al., 2004) in which two
time series are analyzed at a time. However, pairwise analysis may be considered inadequate
given large sets of multivariate neural time series data. A more pragmatic approach for many
purposes is to combine the time series recorded from different brain regions of interest into
blocks, and then to analyze the relations between the blocks. Although it is possible to achieve
blockwise analysis by combining the results of repeated pairwise analyses, a more effective, and
theoretically more elegant, approach is to address the relation between two blocks of time series
directly (Wang et al., 2007b). This blockwise approach is contained in the general methodological framework developed by Geweke (1982).

Let the block of signals from two recording sites be denoted by $\mathbf{X}_t$ and $\mathbf{Y}_t$ with dimensions $k$ and $l$. In the case of pairwise Granger causality, $\mathbf{X}_t$ and $\mathbf{Y}_t$ are two one-dimension time series ($k=1, l=1$); while in the case of block Granger causality, $\mathbf{X}_t$ and $\mathbf{Y}_t$ are two sets of time series of dimensions $k$ and $l$ typically not equal to 1 and have no overlap. Jointly, they can be represented by the following multivariate autoregressive model

$$
\begin{align*}
\mathbf{X}_t &= \sum_{j=1}^{p} a_j \mathbf{X}_{t-j} + \sum_{j=1}^{p} b_j \mathbf{Y}_{t-j} + \mathbf{\tilde{e}}_t \\
\mathbf{Y}_t &= \sum_{j=1}^{p} c_j \mathbf{X}_{t-j} + \sum_{j=1}^{p} d_j \mathbf{Y}_{t-j} + \mathbf{\tilde{\eta}}_t
\end{align*}
$$

(2-10)

where $\mathbf{\tilde{e}}_t$ and $\mathbf{\tilde{\eta}}_t$ are uncorrelated over time, and their contemporaneous covariance matrix is

$$
\Sigma = \begin{pmatrix}
\Sigma_{xx} & \Sigma_{xy} \\
\Sigma_{yx} & \Sigma_{yy}
\end{pmatrix}
$$

If $b_j$ is not uniformly zero for $j = 1,2,\ldots, p$, then $\mathbf{Y}_t$ is said to have a causal influence on $\mathbf{X}_t$. Likewise, $\mathbf{X}_t$ is said to have a causal influence on $\mathbf{Y}_t$ if $c_j$ is not uniformly zero for $j = 1,2,\ldots, p$.

The model order $p$ is determined using either the Akaike Information Criterion (AIC) or the Bayesian Information Criterion (BIC) which reflects a tradeoff between sufficient spectral resolution and over-parameterization. Fourier transforming Eq. 2-10 and performing proper ensemble average, we obtain the spectral matrix

$$
S(\omega) = \begin{pmatrix}
S_{xx}(\omega) & S_{xy}(\omega) \\
S_{yx}(\omega) & S_{yy}(\omega)
\end{pmatrix} = H(\omega)\Sigma H^*(\omega),
$$
where \(*\) denotes complex conjugate and matrix transpose, and \(H(\omega)\) is the transfer function matrix.

Similar to the procedure described in the previous section, the Granger causality spectrum of the two blocks of time series, for \(X_i\) driving \(Y_i\), is given by,

\[
f_{X \rightarrow Y}(\omega) = -\ln\left(1 - \frac{\left(\Sigma_{xx} - \Sigma_{yx}^2 / \Sigma_{yy}\right)|H_{yx}(\omega)|^2}{S_{xx}(\omega)}\right)
\]

which can be interpreted as the proportion of \(X_i\)’s causal contribution to the power of the \(Y_i\) series at frequency \(\omega\). The logarithm is taken to preserve certain favorable statistical properties. Similarly, the causality spectrum for \(Y_i\) driving \(X_i\) is given by

\[
f_{Y \rightarrow X}(\omega) = -\ln\left(1 - \frac{\left(\Sigma_{yy} - \Sigma_{xy}^2 / \Sigma_{xx}\right)|H_{xy}(\omega)|^2}{S_{yy}(\omega)}\right)
\]

To obtain the magnitude of causality for a particular frequency band, the above spectrum may be averaged over the desired frequency band.

2.2.4 Interpretation

Statistically, for two simultaneously measured time series, one series can be called causal to the other if we can better predict the second series by incorporating past knowledge of the first one (Wiener, 1956). This concept was formalized by (Granger, 1969) in the context of linear regression models of stochastic processes. Specifically, if the variance of the prediction error for the second time series at the present time is reduced by including past measurements from the first time series in the linear regression model, then the first time series can be said to have a causal (directional or driving) influence on the second time series. Reversing the roles of the two time series, one repeats the process to address the question of causal influence in the opposite
direction. From this definition it is clear that the flow of time plays an essential role in allowing inferences to be made about directional causal influences from time series data. Alternatively, improvement in prediction can also be viewed from the perspective of comparing relative estimates of conditional probability. Recent work has modeled the relation between multiple point processes along this view (Okatan et al., 2005; Truccolo et al., 2005). In our analysis, the EEG data constitute the time series, and Granger causal influence is equated with the direction of synaptic transmission between neuronal ensembles.

2.2.5 Assessment of Statistical Significance

For coherence and Granger causality spectra, we have adopted a random permutation approach (Brovelli et al., 2004) to build a baseline null-hypothesis distribution from which statistical significance can be derived. Consider two channels of recordings with many repeated trials. We can reasonably assume that the data from different trials are approximately independent of one another. Randomly pairing data for channel 1 with data for channel 2 from a different trial leads to the creation of a synthetic ensemble of trials for which there is no interdependence between the two channels based on construction, while preserving the temporal structure within a channel. Performing such random pairing with many different permutations will result in a distribution of coherence or causality spectra corresponding to the null hypothesis of no statistical interdependence. The calculated value for a given statistic from the actual data is compared with this baseline null hypothesis distribution for the assessment of significance levels. Bootstrap resampling techniques (Efron and Gong, 1983; Efron, 1985, 2000) were used to estimate confidence intervals.

2.3 Multitaper Spectral Estimation

Multitaper spectral estimation (Thomson, 1982) refers to a set of non parametric methods for estimating power spectra, coherences and related spectral quantities using an orthogonal set
of data tapers, in specific, the discrete prolate spheroidal a.k.a Slepian sequences and their approximate minimum bias sine tapers.

Before proceeding to the mathematical formulation of the Multitaper spectra estimation techniques it is worth noting the several favorable properties that motivated the use of this approach from among several other available estimation techniques. The problem of optimum spectral estimation is confronted with several key issues including that of minimizing the (a) bias of the estimators (b) variance of the estimators and (c) the spectral leakage among several other considerations. For further details on each of these considerations the readers may refer to (Lfeachor and Jarvis; Thomson, 1982; Mitra and Pesaran, 1999; Mitra and Bokil, 2007). For example consider one of the conventional nonparametric spectral analysis techniques, the Welch’s method. In order to reduce the variance in the estimation, the approach involves splitting the data into overlapping segments followed by the estimation of the power or the cross spectrum for each segment and then averaging over all the segments. For data of short length, such approaches suffer from severe bias in the estimation. In comparison, multitaper approach does not suffer from these limitations. Both reduction in bias and variance of the estimation is achieved since averaging the spectral estimates over different tapers enable reduction in the variance and since each taper is applied to the entire data instead of short segments of the data as in Welch’s method the resulting bias in the estimation is smaller in comparison. Further the choice of the orthonormal Slepian tapers enables maximum sidelobe suppression hence offering the least spectral leakage in comparison to all other spectral estimation techniques. Thus multitaper approach offers the optimum spectral estimation in the face of short sample length data or short sample length and limited realizations of data as often encountered in neuroscientific applications as is the case in this study. It is apparent from the aims set out to be
addressed that it is crucial to be able to achieve single-trial estimation of the spectra. In light of this crucial requirement, this study utilizes the full advantage of this technique to enable single-trial estimation of spectral features during short prestimulus time periods which otherwise would not have been possible to estimate with sufficient accuracy using either the parametric framework based on autoregressive models presented earlier or through other common non parametric approaches.

A brief exposition of the mathematical formulation of the multitaper spectral estimation technique for univariate case is as follows. The extension to multivariate case is straightforward. Consider time series $x(t)$ ($t = 1, 2\ldots N$) a zero mean second order stationary random process and let $w_k(t)$ denote the $k^{th}$ Slepian taper (window sequence) and $k = 1, 2\ldots K$.

Step 1: Let us define the time-bandwidth product given by $C = NW$, where $N$ is the sample length and $W$ the desired spectral bandwidth. If $C$ is too small, the estimate will be unstable and may not have sufficient dynamic range and if $C$ is too large, the estimate may not have adequate frequency resolution. For a given choice of $C$ there are $K = 2C$ data taper sequences. Since the energy concentration of higher order tapers is poorer than the low order tapers, in practice it is common to choose $K = 2C-1$ or $K = 2C-2$.

Step 2: The Slepian tapers having the maximum energy concentration in the bandwidth $W$ is determined by solving the following eigenvalue problem

$$\lambda_k w_k(t) = \sum_{j=0}^{N-1} \frac{\sin[2\pi W(t - j)]}{\pi(t - j)} w_k(j), \quad \text{for } t = 1, 2\ldots N.$$  

Step 3: The eigen coefficients of this problem reduces to the Fourier transform of the data sequence multiplied by the tapers (similar to periodogram). The windowed Fourier transform of the data $x(t)$ is given by
\[ \hat{\lambda}_k = X_k(\omega) = \sum_{t=0}^{N-1} x(t)w_k(t)e^{-j\omega t} \]

**Step 4:** The spectrum then estimated as the average of the spectra obtained through each taper is given by

\[ S(\omega) = \frac{1}{K} \sum_{k=0}^{K-1} X_k(\omega)X_k^*(\omega) \]

In the case of multiple realizations, the above estimate is further averaged across all realizations. For further treatment of this topic refer (Thomson, 1982; Thomson, 2007).
CHAPTER 3
DECOMPOSING NEURAL SYNCHRONY: TOWARD AN EXPLANATION FOR NEAR-ZERO PHASE-LAG IN CORTICAL OSCILLATORY NETWORKS

3.1 Introduction

Cortical information processing involves the coordinated activity among many distinct regions of the brain. Statistically, this coordinated activity manifests as correlated or synchronized co-variations in the recorded multivariate data. Early studies in animals have shown that stimulus-evoked short-range synchrony between neurons in the primary visual area subserves perceptual binding of sensory information (Singer and Gray, 1995; Tallon-Baudry et al., 2004). Simultaneous action potentials fired by lower order neurons (Malsburg, 1995; Roskies, 1999) provide an effective drive on higher order neurons, the activations of which enable pattern discrimination and conscious awareness. In humans, similar observations have been made (Slotnick et al., 2002) where highly synchronized EEG activity occurs in response to stimulus input. In all these cases, a near-zero phase-lag relation between different data series is observed, reflecting the millisecond or even sub-millisecond precision required for feature integration (Singer and Gray, 1995; Munk et al., 1996; Roelfsema et al., 1997; Witham et al., 2007).

Increasingly, long-range synchronization of oscillatory field activity with near-zero phase-lag, often in the absence of stimulus input, has been reported (Bressler et al., 1993; Roelfsema et al., 1997; von Stein et al., 2000; von Stein and Sarnthein, 2000; Brovelli et al., 2004). Depending on the task, the strength of the synchronization can influence the efficiency of both sensory and motor processing (von Stein et al., 2000; Engel et al., 2001; Liang et al., 2002; Womelsdorf et al., 2006), suggesting that it has a functional role. To date, however, an explanation of the observed near-zero phase-lag relation in these large-scale networks has not been forthcoming. Recent work have considered this issue from the perspective of neuronal communication.
Physiologically, field oscillations provide an index of the excitability level of a neuronal ensemble (Lakatos et al., 2007; Lakatos et al., 2008). During the excitable phase of the oscillation cycle, presynaptic neurons are more likely to fire action potentials, whereas for the postsynaptic neuron, action potentials received during the excitable phase are more effective at integrating the synaptic input and triggering a response (Volgushev et al., 1998; Fries, 2005; Lakatos et al., 2007). This suggests that long-range synchrony could serve as a gating mechanism of information flow in cortical circuits (Salinas and Sejnowski, 2001; Averbeck and Lee, 2004; Fries, 2005; Siapas et al., 2005). Given that the conduction delay between two brain areas is only a small fraction of the oscillation cycle, a near-zero phase-lag relation could stem either from reciprocal communication between the two areas (bidirectional interaction) or from the two areas being readied to communicate by a third set of areas (common input).

Mathematically, it is intuitively clear that a positively correlated common input, if strong enough, can drive the two areas into near-zero phase-lag synchrony. Alternatively, a recent computational model based on the anatomical connectivity pattern in the visual system proposes that the emergence of near-zero phase-lag synchrony can also result from two or more cortical areas experiencing bidirectional interaction (Chawla et al., 2001). The testing of these possibilities has not been carried out. The main reason is that the commonly used methods such as cross correlation and coherence lack the ability to decompose neural interactions into their constituent components.

In this paper we attempt to address this problem by introducing Geweke’s time series decomposition theorem into the analysis of multivariate neural data. Let the two brain areas be denoted by A and B. The interaction between these two areas may be mediated by A influencing B (A→B), B influencing A (B→A), and/or A and B both receiving a common input. Geweke’s
The theorem states that the total interdependence (synchrony) between two stochastic processes from A and B can be expressed as the sum of the three components: \((A \rightarrow B) + (B \rightarrow A) + \text{(common input)}\). Here the arrow is understood in the sense of Granger causality and the common input is represented by the instantaneous causality (Geweke, 1982; Chen et al., 2006; Ding et al., 2006).

In this framework it is hypothesized that bidirectional interaction or common input or a combination of both contributes to the establishment of near-zero phase-lag synchrony. In particular, when the interaction is clearly unidirectional (e.g. \(A \rightarrow B\) equals zero but \(B \rightarrow A\) does not), the phenomenon of near-zero phase-lag can only occur as a result of strong positively correlated common input, arising exogenously to A and B. We tested these ideas by analyzing local field potential data recorded from behaving monkeys performing a visuomotor pattern discrimination task.

### 3.2 Materials and Methods

#### 3.2.1 Simulation

**3.2.1.1 Setup**

Auto-regressive model of the form in Eq. 3-1 was used to generate all the simulated time series. Two representative types of interaction pattern, namely (a) unidirectional interaction with positively correlated instantaneous common input and (b) bidirectional interaction, were considered. The phase-lag as a function of appropriate model parameters for both cases was studied.

**3.2.1.2 Positively correlated common input**

A bivariate AR(3) process \([p = 3 \text{ in Eq. 3-1}]\) in which X drives Y was used. The coefficients of the model were \(a_1 = 0.4428, a_2 = -0.5134, a_3 = 0, d_1 = 0.506, d_2 = -0.6703, d_3 = 0, b_1 = b_2 = b_3 = 0, c_1 = c_2 = 0, c_3 = 0.1, \) and \(\sum_{xx} = \sum_{yy} = 1\). The cross terms in the noise covariance matrix, \(\sum_{yx} = \sum_{xy} \), reflecting the strength of positively correlated common input, was
systematically varied. The parameter choice above enabled the model to oscillate at 40 Hz for which the phase-lag was computed. The dataset consisted of 100 epochs of 200 sample points each. The sampling rate was assumed to be 200 Hz.

3.2.1.3 Bidirectional interaction

A bivariate AR(4) process \([p = 4\) in Eq. 3-1\] was used. The coefficients of the model were 
\[a_1 = 0.9, \ a_2 = -0.5, \ a_3 = 0, \ a_4 = 0, \ d_1 = 0.8, \ d_2 = -0.5, \ d_3 = d_4=0, \ \sum_{xx} = \sum_{yy} = 1, \text{ and } \sum_{xy} = \sum_{yx} = 0.\]
The coefficients of the interaction terms \(b_{1,2,3,4}\) and \(c_{1,2,3,4}\) were varied in tandem to achieve simultaneous increase in the strength of both feed-forward and feed-back interaction. The model exhibited narrow frequency band oscillations with a frequency peak at 32 Hz for which the phase-lag was computed. The dataset consisted of 100 epochs of 200 sample points each. The sampling rate was assumed to be 200 Hz.

3.2.2 Experiment

3.2.2.1 Behavioral paradigm

Two monkeys (GE and LU) were trained to perform a GO/NO-GO visual pattern discrimination task in the Laboratory of Neuropsychology at the National Institute of Mental Health (Bressler et al., 1993; Ledberg et al., 2007). Animal care was in accordance with institutional guidelines at the time. The monkey initiated each trial by depressing a hand lever and maintained its depression while anticipating the onset of a visual stimulus. Four squares arranged in either a line (left-slanting and right-slanting) or a diamond (left-slanting and right-slanting) shaped formation appeared on a visual display after a random time interval triggered by the lever depression. The monkey made either a GO (lever release) or a NO-GO (maintaining lever depression) response upon discriminating the input pattern. For the GO trials, the time between stimulus onset and the lever release is defined as the response time (RT). The experiment was conducted in sessions of approximately 1000 trials.
3.2.2.2 Data acquisition

Local field potentials (LFPs) were recorded with bipolar teflon-coated platinum microelectrodes (51-µm diameter and 2.5-mm tip separation) from up to 15 distributed sites located in the hemisphere contralateral to the dominant hand (right hemisphere in monkey GE and left hemisphere in monkey LU). The data collection period started 90 ms before the stimulus onset and ended approximately 500 ms after (Bressler et al., 1993). LFPs were amplified by Grass P511J amplifiers (-6 dB at 1 and 100 Hz, 6 dB/octave falloff) and digitized at 200 Hz. As this study is concerned with the phase between two signals, the bipolar derivation carries certain arbitrariness. Reversing the order of the two subtracting recording leads can change the phase from 0 to π or vice versa. This can affect the formulation of the hypothesis to be tested. See Results and Discussion sections for more details.

3.2.2.3 Data set selection

Previous analysis of the same experiment (Brovelli et al., 2004) has identified a coherent beta (14 to 30 Hz) oscillatory network in the sensorimotor cortex involving both pre- and post-central sites during the prestimulus time period. For this work the three recording sites that are common to both monkeys were selected for further analysis: primary somatosensory area (S1), primary motor area (M1) area, and posterior parietal area 7b. Trials contaminated with artifacts or associated with incorrect behavioral responses were rejected. To achieve a sufficient number of trials, different sessions having similar RT distributions were combined to yield a data set of approximately 2400 and 1400 trials for monkeys GE and LU, respectively. The prestimulus time interval from -90 ms to 20 ms was considered.

3.2.2.4 Time series decomposition

Let the LFP data from two recording sites be denoted by \( X_t \) and \( Y_t \). Jointly, they can be represented by the following bivariate autoregressive model
\[ X_t = \sum_{j=1}^{p} a_j X_{t-j} + \sum_{j=1}^{p} b_j Y_{t-j} + \epsilon_t \]

\[ Y_t = \sum_{j=1}^{p} c_j X_{t-j} + \sum_{j=1}^{p} d_j Y_{t-j} + \eta_t \]

(3-1)

where \( \epsilon_t \) and \( \eta_t \) are uncorrelated over time, and their contemporaneous covariance matrix is

\[ \Sigma = \begin{pmatrix} \Sigma_{xx} & \Sigma_{xy} \\ \Sigma_{yx} & \Sigma_{yy} \end{pmatrix} \]

If \( b_j \) is not uniformly zero for \( j=1,2,...,p \), then \( Y_t \) is said to have a causal influence on \( X_t \). Likewise, \( X_t \) is said to have a causal influence on \( Y_t \) if \( c_j \) is not uniformly zero for \( j=1,2,...,p \). If \( \Sigma_{yx} = \Sigma_{xx} \neq 0 \), indicating that the noise terms \( \epsilon_t \) and \( \eta_t \) are correlated at time \( t \), then the interdependence between \( X_t \) and \( Y_t \) has another contributor that is not explained by the interaction between \( X_t \) and \( Y_t \). This contributor, possibly representing influences exogenous to the \( (X,Y) \) system such as a common input from a third system, will be referred to as the instantaneous causality (Geweke, 1982; Ding et al., 2006). It can be shown that the above set of variables are related through (see section 2.2.2)

\[ f_{x,y}(\omega) = f_{x\rightarrow y}(\omega) + f_{y\rightarrow x}(\omega) + f_{x,y}(\omega) \]

(3-2)

Intuitively, the decomposition in Eq. 3-2 means that the total amount of statistical synchrony between two LFP signals is the sum of their causal drives on one another and a common input component. The expression in Eq. 3-2 can be integrated over the entire frequency domain to yield the time-domain counterpart. While the frequency-domain formulation is convenient for estimation, the above decomposition is more readily interpretable in the time-domain.
3.2.2.5 Data analysis protocol

For each monkey there are 3 distinct pairs of recording sites: (M1, S1), (M1, 7b) and (S1, 7b). For each pair, previous work (Brovelli et al., 2004) has identified a prominent coherence peak in the beta frequency range (14 to 30 Hz). Except for (M1, S1) in monkey LU the coherence in other five channel pairs is concentrated in the beta frequency range. These five channel pairs are further analyzed as the time-domain quantities are equivalent to that in the beta range. The relative phase, referred to as the phase-lag in this study, is well-defined for the peak frequency. The dependence of this phase-lag on the factors in Eq. 3-2 was investigated by carrying out the following analysis. (1) The phase-lag in the beta frequency range was estimated for each single trial by Fast Fourier Transform (FFT) and sorted according to its value. The sorted trials were grouped into subensembles with 30% overlap, resulting in 33 and 19 groups in monkeys GE and LU, respectively. Each subensemble contained 100 trials. (2) For each subensemble the ensemble mean was estimated and removed from the individual trials within the subensemble. This is to ensure that the data may be treated as coming from a zero-mean stochastic process. An AR model of order $p=9$ was fit to the mean-removed data. (3) For each subensemble, power, coherence, causality spectra as well as phase-lag at the peak frequency were derived from the AR model (Chen et al., 2006; Ding et al., 2006). (4) Spearman rank correlation (SRCC) and Spearman rank partial correlation (Macklin, 1982) (SRPCC) were computed between the instantaneous causality measure and the estimated phase-lag to assess the prediction that the two variables are negatively correlated. To remove the effect of directional influences a partial correlation analysis was performed. Significance was determined through one tail t-test with $p<.05$. (5) For channel pairs determined to have bidirectional interactions, Spearman rank correlation (SRCC) and Spearman rank partial correlation (Macklin, 1982)
Pairwise Granger analysis has been adopted since phase-lag is a bivariate phenomenon. However, evaluating causal interaction patterns in a bivariate framework may ignore potential influences from other areas that may or may not be sampled. In order to assess more reliable causal interaction patterns, a multivariate approach applied to all the relevant simultaneously sampled data may be resorted to and one such approach is the conditional Granger causality (Chen et al., 2006; Ding et al., 2006). In the broader context of conditional Granger causality analysis applied to multivariate data, it is only reliable to submit channel pairs that exhibit significant nonzero conditional Granger causality to the data analysis protocol described above.

### 3.2.3 Logic of Analysis Protocol

The goal of this work is to test that (a) positively correlated common input and (b) bidirectional interaction contributes to near-zero phase-lag. In the simulation examples, this is accomplished by changing the strength of input correlation and bidirectional interaction and observing the corresponding change in the phase-lag. For actual data, while Geweke’s theorem allows the extraction of various causal influences through the decomposition of synchrony, the strength of input correlation and bidirectional interaction is not easily manipulated. The sorting of trials according to their phase-lag is the strategy to deal with this problem. Each subensemble of trials gives rise to a different phase-lag value. Performing Geweke’s decomposition for each subensemble provides the avenue to observe the correlation between phase-lag and common input/bidirectional interaction. It is important to note that, for a given pair of recording sites, both instantaneous causality and the two directional influences may change as functions of the sorted phase-lag. A simple pairwise correlation analysis may thus become confounded. Partial
correlation is used here to make possible the examination of one factor’s contribution to near-zero phase-lag while the contribution of other factors is statistically removed.

3.3 Results

3.3.1 Simulation

The impact of (a) positively correlated common input and (b) directional interaction on phase-lag is examined using simulated time series and summarized in Table 3-1 and Table 3-2. In the case of unidirectional interaction, increased common input to the network, measured by instantaneous causality, reduces the magnitude of phase-lag from 2.19 radians to a near-zero value of 0.16 radians (Table 3-1). Similar effect of instantaneous common input was observed in networks with bidirectional interaction as well (not shown). In the case of the system with bidirectional interaction and no instantaneous common input, the parametric increase in the model coefficients $b_{1,2,3,4}$ and $c_{1,2,3,4}$ (Eq.3-1) resulted in corresponding increase in the estimated feed-forward and feed-back interaction patterns and a decrease in the magnitude of phase-lag to near-zero values (Table 3-2). However, not all reciprocally interacting systems exhibit near-zero phase-lag synchrony. The actual phase-lag in a network depends on many factors including delays involved in the feed-forward and feed-back pathways and the strength/type of coupling. The approach outlined in this study enables one to empirically test the influences of each of the factors on phase-lag in any given data.

3.3.2 Experiment

3.3.2.1 Network identification

Granger causality spectra are shown in Figure 3-1 for a pair of sites experiencing unidirectional interaction (A) and another pair of sites undergoing bidirectional interaction. Figure 3-2 shows the interaction patterns for all five sites pairs in both monkeys in the beta frequency range where the same significance threshold criterion described in (Brovelli et al.,
2004) were used. Except for S1 and 7b in monkey GE and M1 and S1 in monkey LU, the remaining site pairs in both monkeys exhibited unidirectional interaction. An earlier study examining the causal patterns on the same dataset in a multivariate context using conditional Granger causality has shown that the network analyzed here is robust and free of any significant mediated influences from other simultaneously recorded areas that were not included in the pairwise analysis pursued in this study. Unlike the other five site pairs where the interaction is concentrated in the beta range (see Figure 3-2), the (M1,S1) pair in monkey LU also exhibited significant interaction in the gamma frequency range, in addition to that in the beta range. For this pair, the causal influences in the time-domain where instantaneous causality is most readily interpreted, are confounded and is thus excluded from further analysis. Functionally, the observation that S1 and 7b play a pivotal role in the organization of the network has led to the hypothesis that the beta network supports the maintenance of lever depression by facilitating sensorimotor integration (Brovelli et al., 2004; Ding et al., 2006).

3.3.2.2 Phase-lag distribution

For a given site pair, the phase-lag at the peak beta frequency was estimated for each trial. Figure 3-3 shows the phase-lag distribution for two different pairs of sites in monkey LU and GE. Both distributions are unimodal. In particular, despite a unidirectional interaction pattern between M1 and 7b (Figure 3-2B), the phase-lag is approximately centered around zero with a mean of 0.04 radians. This suggests that for such pairs the instantaneous causality may contribute significantly to the overall degree of synchrony. Table 3-3 summarizes the mean phase lag in the beta band for all five pairs of recording sites.

3.3.2.3 Synchrony decomposition and near-zero phase-lag

For recording sites A and B, according to Eq. 3-2, the total synchrony, which is derived from the coherence function can be written as the sum of two directional influences (A → B) and
(B→A) and instantaneous causality (A.B) (Table 3-4). Intuitively, positively correlated common input measured by the instantaneous causality has the effect of bringing phase-lag close to zero. This is particularly so for pairs experiencing unidirectional causal influence. In monkey LU, the phase-lag between M1 and 7b is near zero (Figure 3-2B and Figure 3-3B), and not surprisingly, the instantaneous causality in this case makes up 72% percent of total interdependence, a substantial percentage (Table 3-4). Below we tested the idea by carrying out an analysis for the site pairs characterized by unidirectional interaction with the analysis protocol outlined in section 3.2.2.5.

3.3.2.4 Instantaneous causality and phase-lag

For each site pair the phase lag was estimated for each trial and the estimated value was used to sort all trials into subensembles. The phase-lag and the instantaneous causality measure for each subensemble constituted a point on a scatter plot. Figure 3-4 shows the result for (S1,7b) in monkey GE and LU. Clearly, the two quantities are negatively correlated, indicating that as the instantaneous causality increases, the phase-lag decreases and, in fact, approaches zero. Spearman’s rank correlation and Spearman’s rank partial correlation coefficients were computed for all the site pairs and listed in Table 3-5 and 3-6. All correlation coefficients were negative. Except for (M1,7b) in monkey GE, they were statistically significant at p=0.05 level (one tail t-test) (Table 3-5). By partialing out the effects of the directional influences, the correlation for (M1,7b) also became significant (Table 3-6).

3.3.2.5 Bidirectional interaction and phase-lag

Inspection of the causality spectrum between the site pair (S1,7b) in monkey GE revealed the presence of bidirectional interaction in the beta band (Figure. 3-1B and Figure 3-2B and Table 3-4). The coherence function and the associated phase spectrum are shown in Figure 3-5. This channel pair was further analyzed to identify the effect of reciprocal interaction on the
phase-lag. The strength of directional interaction is expressed as the sum of feedforward and feedback influences. After partialing out the influence of the common input the phase-lag was negatively correlated with the mutual interaction ($r = -0.455$, $p = 0.0045$). This result supports our early assertion that in addition to instantaneous causality, bidirectional interaction may also lead to near-zero phase-lag.

### 3.4 Discussion

The relative phase between two neural signals A and B, referred to as phase-lag here, can be calculated from the cross-spectrum. For decades, the sign and magnitude of phase-lag have been used to infer direction of information transmission and delay (Cassidy and Brown, 2003). Increasingly, phase-lag is found to be near zero in synchronous cortical networks, sometimes involving distant sites. Such phenomenon renders the use of phase-lag as a measure to identify directional influences ambiguous. The phenomenon of zero phase-lag has been examined from the point of view of neuronal communication and is considered a manifestation of the brain integrating information from diverse sources (Singer and Gray, 1995; Roelfsema et al., 1997; Engel et al., 2001; Brovelli et al., 2004). Two factors can be identified that contribute to near-zero phase-lag: (a) positively correlated common input and (b) bidirectional interaction. Recent reports of near-zero phase-lag arising in networks with a predominantly unidirectional interaction pattern further highlights the importance of the first factor.

The influence of the two factors on phase-lag was tested on simulated datasets generated by bivariate autoregressive models. First, it was observed that, for a linear system with unidirectional interaction, a near-zero phase-lag was unlikely in the absence of an instantaneously positively correlated input. As such an input is introduced and increased, phase-lag is seen to decrease and approach zero. A similar influence on phase-lag was also observed in bidirectionally interacting networks. Second, for the case of a bidirectionally
interacting system with no common input, increase in the strength of both feed-forward and feed-back interaction leads to the reduction in the magnitude of phase-lag.

The empirical testing of the above ideas faces considerable challenge as a standard correlation or coherence analysis do not offer sufficient information on the relation between the two signals A and B. Recently, advanced connectivity tools have been proposed (Baccala and Sameshima, 2001; Kaminski et al., 2001; Seth, 2005; Chen et al., 2006; Lungarella and Sporns, 2006; Wang et al., 2007b; Guo et al., 2008; Wu et al., 2008) which aim at parsing the synchrony into directional interaction. Mathematically, a theorem proven by Geweke promises deeper insights. It states that the total interdependence between A and B can be written as the sum of three contributing factors: (A → B), (B → A) and (A.B). The arrow is understood in the sense of Granger causality and (A.B) signifies instantaneous causality interpreted as reflecting a common input. In the present study Geweke’s theorem was applied to study the contribution of the two factors identified above to near-zero phase-lag.

Local field potentials from primary somatosensory (S1), primary motor (M1), and posterior parietal (7b) areas were recorded in two monkeys performing a sensorimotor integration task. A beta oscillatory network involving all three sites was identified by coherence. The total interdependence was then decomposed into its directional components. Out of five distinct pairs of recording sites studied, four exhibited predominantly unidirectional interaction in the beta band. The phase-lag was nearly zero for one of the five pairs and relatively small for another three. Unlike simulated models, neither the strength of input correlation nor the strength of feed-forward / feed-back interaction can be manipulated to infer their influences on phase-lag. The sorting of trials according to their phase-lag is a strategy to deal with this problem. By sorting the trials according to single trial estimated phase-lag, a negative correlation was found
between the phase-lag and instantaneous causality for all pairs, implying that the stronger is the
common input the closer to zero is the phase-lag. Despite this tendency, the actual value of the
phase-lag for a given pair depends on the relative contribution of the each of the factors in
Eq. 3-2, and may vary broadly [from 0.04 (near-zero) to -1.34 (far-from-zero), see Table 3-6].

If the common input is negatively correlated, then the stronger is this input the close to ±π
is the phase-lag (Figure 3-6). A careful inspection of the five pairs of recording sites revealed
that the noise terms in their respective autoregressive models (see Eq. 3-1) were all positively
correlated with the exception of the channel pair (S1,7b) in GE where the noise terms was
negatively correlated. Since the order of the recording leads used for the bipolar derivation was
arbitrary, the signal from S1 was reversed in polarity, which is equivalent to a depth-to-surface
recording. This correction enables the data from all five pairs to be considered under the same
hypothesis. Channel pair (S1, 7b) in monkey GE also has another differing characteristic: the
interaction is bidirectional in the beta range. In light of the earlier discussion, the reciprocal
interaction in addition to common input could also contribute to the observed near-zero
phase-lag. This prediction was confirmed by a partial correlation analysis between the phase-lag
and the strength of feedforward and feedback interaction after removing the influence of the
instantaneous common input.

In sum, based on our simulated as well as experimental data, for two cortical regions
engaged in unidirectional interaction, instantaneous causality/common input is likely a main
contributor for the near-zero phase-lag between the sites. On the other hand, for two cortical
areas engaged in bidirectional interaction, near-zero phase-lag synchrony can emerge as a result
of reciprocal interaction or instantaneously correlated influence or a combination of both.
Geweke’s decomposition theorem, combined with the analysis protocol outlined in the Methods
section can help to ascertain the exact network mechanism for a given problem. Each measure obtained through this decomposition technique has the desirable feature that they all have clear physiological correspondence. For example, bidirectional interaction is highly interpretable in terms of the anatomical connectivity principle of reciprocity in the cortex (Felleman and Van Essen, 1991). Instantaneous causality/common input may be taken to collectively reflect activation of a distinct cortical or subcortical region that project to the sampled sites. Volume conduction, while a possible contributor to instantaneous causality, is an unlikely factor in the present study as bipolar derivation localizes neural activity to its generator. However, for scalp EEG, the influence of volume conduction is likely to be significant and must be carefully considered.

Table 3-1. Influence of increased instantaneous causality on phase-lag

<table>
<thead>
<tr>
<th>Instantaneous causality</th>
<th>Phase-lag (radians)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>2.19</td>
</tr>
<tr>
<td>0.04</td>
<td>1.16</td>
</tr>
<tr>
<td>0.29</td>
<td>0.44</td>
</tr>
<tr>
<td>1.02</td>
<td>0.16</td>
</tr>
</tbody>
</table>

Simulated data were generated by a bivariate model with unidirectional interaction. Here instantaneous causality characterizes the strength of common input. Magnitude of phase-lag is seen to decrease with increase in instantaneous causality.

Table 3-2. Influence of increased bidirectional interaction on phase-lag

<table>
<thead>
<tr>
<th>$F_{X\rightarrow Y}$ / $F_{Y\rightarrow X}$</th>
<th>$F_{X\rightarrow Y} + F_{Y\rightarrow X}$</th>
<th>Phase-lag (radians)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.038 / 0.081</td>
<td>0.119</td>
<td>1.31</td>
</tr>
<tr>
<td>0.085 / 0.117</td>
<td>0.202</td>
<td>0.94</td>
</tr>
<tr>
<td>0.267 / 0.131</td>
<td>0.398</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Simulated data were generated by a bivariate model with bidirectional interaction. $F_{X\rightarrow Y}$ and $F_{Y\rightarrow X}$ quantify the feed-forward and feed-back components estimated by Granger causality analysis. Magnitude of phase-lag is seen to decrease with increase in strength of bidirectional interaction measured by feed-forward and feed-back Granger causality.
Table 3-3. Mean beta band phase-lag (in radians) for monkeys GE and LU

<table>
<thead>
<tr>
<th>Site pairs</th>
<th>GE</th>
<th>LU</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1,S1</td>
<td>-1.34</td>
<td>-</td>
</tr>
<tr>
<td>M1,7b</td>
<td>0.9</td>
<td>0.04</td>
</tr>
<tr>
<td>S1,7b</td>
<td>-0.42</td>
<td>-0.4</td>
</tr>
</tbody>
</table>

Table 3-4. Contribution of intrinsic and exogenous components to total interdependence

<table>
<thead>
<tr>
<th>Causality</th>
<th>GE (%)</th>
<th>LU (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1→S1</td>
<td>13</td>
<td>29</td>
</tr>
<tr>
<td>S1→M1</td>
<td>75</td>
<td>27</td>
</tr>
<tr>
<td>M1→S1</td>
<td>12</td>
<td>44</td>
</tr>
<tr>
<td>M1→7b</td>
<td>1</td>
<td>72</td>
</tr>
<tr>
<td>7b→M1</td>
<td>86</td>
<td>25</td>
</tr>
<tr>
<td>M1→7b</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>S1→7b</td>
<td>17</td>
<td>48</td>
</tr>
<tr>
<td>7b→S1</td>
<td>17</td>
<td>9</td>
</tr>
<tr>
<td>S1→7b</td>
<td>66</td>
<td>43</td>
</tr>
</tbody>
</table>

‘—’ indicates instantaneous causality, the exogenous component
‘→’ indicates directed interaction, the intrinsic components.

Table 3-5. Correlation between instantaneous causality and phase-lag

<table>
<thead>
<tr>
<th>Site pairs</th>
<th>GE</th>
<th>LU</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1,S1</td>
<td>-0.79</td>
<td>-</td>
</tr>
<tr>
<td>M1,7b</td>
<td>-0.33</td>
<td>-0.70</td>
</tr>
<tr>
<td>S1,7b</td>
<td>-0.68*</td>
<td>-0.73</td>
</tr>
</tbody>
</table>

Strength of Spearman’s rank correlation coefficient between instantaneous causality and magnitude of phase-lag in the beta band between site pairs specified in column 1 for monkeys GE and LU. The results that did not satisfy significance at p<0.05, are included with their corresponding p-value. * denotes the channel pair that exhibits bidirectional interaction in the beta frequency band.

Table 3-6. Partial correlation between instantaneous causality and phase-lag

<table>
<thead>
<tr>
<th>Site pairs</th>
<th>GE</th>
<th>LU</th>
</tr>
</thead>
<tbody>
<tr>
<td>M1,S1</td>
<td>-0.79</td>
<td>-</td>
</tr>
<tr>
<td>M1,7b</td>
<td>-0.31</td>
<td>-0.44</td>
</tr>
<tr>
<td>S1,7b</td>
<td>-0.41*</td>
<td>-0.81</td>
</tr>
</tbody>
</table>

Strength of Spearman’s partial rank correlation coefficient between instantaneous causality and magnitude of phase-lag in the beta band between site pairs specified in column 1. The partialing is against the directional influences for monkeys GE and LU. The results that did not satisfy significance at p<0.05, are included with their corresponding p-value. * denotes the channel pair that exhibits bidirectional interaction in the beta frequency band.
Figure 3-1. Granger causality spectra. (A) a pair of sites experiencing unidirectional interaction and (B) a site pair experiencing bidirectional interaction in the beta frequency band. The threshold level for significance at $p = 0.005$ is overlaid as a flat line.

Figure 3-2. Schematic Granger causality graph. (A) monkey GE and (B) monkey LU. Solid arrows indicate directions of causal influence in the beta frequency band that were significant at $p = 0.005$. 
Figure 3-3. Phase distribution. Histogram of single trial phase-lag values at peak beta frequency for site pairs (A) (S1, 7b) in monkey GE and (B) (M1,7b) in monkey LU.

Figure 3-4. Influence of common input on phase-lag. Scatter plot showing strong negative correlation between instantaneous causality (IC) and magnitude of phase-lag between site pairs (S1,7b) in monkeys (A) GE and (B) LU.
Figure 3-5. Coherence and phase spectra for site pair (S1,7b) in monkey GE. (A) Coherence spectra for site pair (S1,7b) in monkey GE indicating strong beta band synchrony. (B) The relative phase spectra for the same site pair. The near-zero phase-lag in the beta band is the result of both positively correlated common input and reciprocal interaction.

Figure 3-6. Phase locking modes. Schematic illustration of different modes of phase locking for a network with unidirectional interaction pattern and instantaneously correlated inputs. $\phi_{AB}$ denotes the phase-lag between sites A and B.
CHAPTER 4
PRESTIMULUS THETA OSCILLATIONS IN FRONTO-TEMPORAL NETWORK PREDICT SUBSEQUENT MEMORY RECALL IN HUMANS

4.1 Introduction

Items presented under identical environmental conditions are sometimes remembered and sometimes not. Research into the origin of this variability has linked the efficacy of memory encoding in the prefrontal cortex (PFC) and the medial temporal lobe (MTL) with memory performance. In particular, it has been shown that the level of physiological responses in PFC and MTL to presented items reliably predicts the likelihood of these items subsequently being remembered (Fernandez et al., 1999; Friedman and Johnson, 2000; Tendolkar et al., 2000; Weiss and Rappelsberger, 2000; Sederberg et al., 2003; Takashima et al., 2006; Sederberg et al., 2007). While most studies emphasized the stimulus-evoked activity and its variability as a neural correlate of memory performance, research has gradually expanded to include the characterization of the state of the brain prior to stimulus input and its impact on memory encoding (Seager et al., 2002; Guderian et al., 2009). Ongoing brain activity is replete with oscillations of various frequencies (Niedermeyer et al., 1999; Buzsaki, 2006). Summarizing the extensive literature on the theta rhythm (4-9 Hz) in the rodent hippocampus, Vertes (2005) proposed that theta oscillations represent a depolarizing drive on NMDA containing cells, and a stimulus presented during strong theta activity leads to enhanced response and facilitated long-term potentiation (LTP) (Buzsaki, 1989; Huerta and Lisman, 1993; Staubli and Xu, 1995; Buzsaki, 1996; Kocsis et al., 1999; Berry and Seager, 2001; Buzsaki, 2002; Seager et al., 2002; Vertes et al., 2004; Hasselmo, 2005; Kocsis and Kaminski, 2006). How this hypothesis manifests in human memory is not well understood. The first goal of the present investigation is to test the hypothesis that the efficacy of memory encoding in humans depends on the level of excitability.
indexed by the strength of theta activity in PFC and MTL immediately preceding the stimulus onset, with stronger theta predicting better subsequent recall.

Memory is a network phenomenon. Formation of memory traces depends on the coordinated activity in many brain areas. In particular, the importance of PFC-MTL interaction in memory encoding has been supported by evidence from a variety of studies using lesion (Petrides and Milner, 1982; Gershberg and Shimamura, 1995; Shimamura, 1995; Shimamura et al., 1995; Bechara et al., 1998), neuroimaging (Kapur et al., 1996; Wagner et al., 1998; Cohen et al., 1999; Grady et al., 2003; Gazzaley et al., 2004), and electrophysiological techniques (Sarnthein et al., 1998; Weiss and Rappelsberger, 2000; Anderson et al., in press). Similar to the earlier hypothesis where theta oscillations serve to index the level of tissue excitability in single brain areas, it is expected that the level of neuronal interaction and synchrony prior to stimulus onset acts as a gating mechanism and provides an index of increased processing capacity at a network level (Ohara et al., 2006; Ohara et al., 2008). The second goal of this investigation is to test the hypothesis that the strength of PFC-MTL interaction immediately prior to stimulus presentation, possibly reflecting the strength of top-down attentional control originating in the PFC (Furey et al., 2000; Kimura, 2000; Hasselmo and McGaughy, 2004), is positively correlated with the efficacy of stimulus encoding and the likelihood of its subsequent recall.

The above goals are accomplished by recording electrocorticogram (ECoG) also known as intracranial electroencephalogram (iEEG), from multiple implanted electrode grids in five patients undergoing presurgical evaluation for intractable epilepsy who performed a subsequent memory task. The subjects were given a series of words to remember. Then, following a distraction period, the subjects were asked to recall the words from memory. Data from the period of initial presentation of words (encoding period) was analyzed where the level of
regional prestimulus oscillatory activity and interregional interaction immediately prior to the presentation of the words was compared between those that were subsequently recalled and those that were not.

4.2 Materials and Methods

4.2.1 Subjects and Electrode Placement

Five patients (4 female and 1 male, mean age 38 years) with medically intractable epilepsy, undergoing invasive video-EEG monitoring for localization of the epileptic focus and subsequent epilepsy surgery, participated in the study. All participants gave informed consent. The experimental and recording protocol was approved by the institutional review board of the University of Florida. Figure 4-1 illustrates the approximate positions of the implanted electrode grids in each of the five subjects. Subjects 1, 2 and 3 had subdural grids covering the lateral prefrontal cortex (PFC), Subjects 1, 2 and 4 had subdural grids covering the lateral temporal lobe (LTL), Subjects 1, 2 and 4 had subdural subtemporal strips on the ventral surface of the temporal lobe, and Subject 5 had bilateral depth electrodes inserted through the occipital lobes into the hippocampi. Data from the electrodes of the subtemporal strips and hippocampal depth electrodes in Subjects 1, 2, 4 and 5 were treated as proxies of medial temporal lobe (MTL) activity. For Subjects 1 and 2 the frontal and the temporal regions were simultaneously sampled.

4.2.2 Paradigm

The subjects were asked to perform a subsequent memory task. An LCD monitor placed approximately 90 cms in front of the subjects was used to present the stimuli. A fixation cross remained in the center of the screen throughout the experiment. The entire experiment was divided into blocks. Each block, as illustrated in Figure 4-2, consisted of a presentation (encoding) period, followed by a distraction period, then a free-recall period, and finally a recognition period. The encoding period consisted of the sequential presentation of 20 words
chosen from the Kucera and Francis word pool (Kucera and Francis 1967). Each word was displayed on the screen for 2 seconds with a random delay between words of either 1 or 2 seconds (mean 1.5 seconds). Subjects were instructed to memorize as many of the words as possible. The distraction period lasted 30 seconds and consisted of counting aloud backwards by threes, starting at a random number. This distraction period served to attenuate both the recency effect and further encoding by rehearsing. During the free-recall period, subjects were given 50 seconds to recall aloud as many of the previously studied words as they could. This was followed by a second presentation period of a different set of 20 words, followed by another distraction period, and a free recall period. Finally, a longer distraction period which lasted 60 seconds was given followed by the recognition period that consisted of the presentation of 80 words sequentially on the screen, including the 40 previously studied words along with 40 foil words not seen previously. The subjects were asked to respond by button presses to indicate whether or not they recognized the word as being a previously presented word or a new word. The word stayed on the screen until the subject responded. Each response was followed by a random delay of either 1 or 2 seconds (mean 1.5 seconds) before the appearance of the next word. Subjects performed either two or three blocks depending on their tolerance. The focus of this investigation is how brain activity preceding each word to be memorized (shaded interval in the expanded encoding period in Figure 4-2) influences subsequent encoding and later recall.

4.2.3 Data Preprocessing

Data were sampled at 400 Hz by a Nicolet amplifier system, band pass filtered from 0.1 to 100 Hz, which was subsequently subject to an offline lowpass filter with a cutoff at 30 Hz and then downsampl ed to 250 Hz. Only channels (electrodes) free of pathological abnormalities and epileptic spikes were included for analysis. Table 4-1 summarizes the number of the studied electrodes in each cortical area for each of the five subjects. After rejecting data segments
contaminated by movement and other artifacts, the remaining artifact-free data recorded during the encoding period was epoched from -500 ms to 0 ms (length of the shaded interval in the expanded encoding period in Figure 4-2), with 0 ms denoting the onset of word presentation. Epochs where the words were subsequently free-recalled were combined into an ensemble of trials, referred to as recall ensemble, and epochs where the words were not recalled were combined into another ensemble of trials, referred to unrecall ensemble. Power and synchrony estimates (see below) were obtained for each ensemble for the prestimulus time period -500 ms to 0 ms (see Figure 4-2). The statistical differences in these variables between the recalled and unrecalled conditions were assessed.

4.2.4 Spectral Analysis

4.2.4.1 Power estimation

A multitaper approach was used to estimate power spectra for each of the two ensembles of trials (recalled versus unrecalled) from frontal, lateral temporal and medial temporal channels in each of the five subjects (Thomson, 1982; Mitra and Pesaran, 1999; Mitra and Bokil, 2007). Three tapers were found to give the optimal balance between spectral smoothness and frequency resolution.

4.2.4.2 Significance test for difference in power between conditions

For a given electrode, the difference between spectral power for the recalled ensemble and that for the unrecalled ensemble was tested with a nonparametric Jackknife procedure (Bokil et al., 2007; Thomson, 2007). Figure 4-3A illustrates the behavior of the test statistic for the difference in power across all frequencies between the recalled and unrecalled ensembles (dark line) for a single electrode from the frontal grid of Subject 3. The horizontal gray line denotes the 90% confidence interval based on Gaussian assumption of the log spectra. If the test statistic lies within the 90% confidence band, then the null hypothesis that no difference in power between
the two conditions is not rejected. On the other hand, if the test statistic lies outside the confidence band, then the null hypothesis of equal power is rejected at the significance level of $\alpha=0.1$. To reduce false positives as a result of multiple comparisons, the rejection of the null hypothesis for any particular frequency ($f$) was carried out only if the test statistic lay outside the confidence band for a contiguous frequency range between ($f-2$) and ($f+2$) Hz (Figure 4-3A). For the channel illustrated in Figure 4-3A significant differences in power were observed in the theta band (4-9 Hz). The aforementioned procedure was carried out for the frequency range between 3 and 28 Hz. Figure 4-3B summarizes the total number of electrodes over all five subjects that exhibited significant difference in power between the recalled and unrecalled ensembles for each frequency in the 3-28 Hz range.

**4.2.4.3 Group power analysis**

The channels having significant differences in power between the recalled and unrecorded conditions were subjected to group analyses. Band averaged power for each condition was normalized by dividing by the sum of band averaged power from both conditions and averaged across electrodes within each of the three brain regions (PFC, LTL, MTL) which was further averaged across subjects. The group average was compared between the two conditions and all statistical comparisons were performed using Student’s t test.

**4.2.4.4 Inter-areal synchrony analysis**

The raw data from each implanted electrode were recorded against a common reference which is typically not free of neural activity. Volume conduction presented a further complicating factor for connectivity analysis. To overcome these problems, bipolar derivations or signals, which were computed as the differences between horizontally, vertically, and diagonally neighboring electrodes, were used for synchrony analysis. Table 4-2 summarizes the number of bipolar derivations for the two subjects (Subject 1 and 2) who had simultaneous PFC
and temporal lobe recordings. For each pair of inter-grid bipolar signals, a frequency domain interdependence measure called the phase locking value (PLV) (Jean-Philippe et al., 1999) was used to evaluate the degree of phase synchrony between the two brain regions in a given frequency band, with larger PLV values indicating higher levels of phase synchrony, which is taken to imply greater functional connectivity.

To calculate PLVs, the data were bandpass-filtered between 4 and 9 Hz for theta band, 10 and 14 Hz for the alpha/low beta band and 21 and 25 Hz for the high beta/low gamma band. The instantaneous phase of the signal was extracted using the Hilbert transform on a trial-by-trial basis and the difference in phase between the bipolar pairs of interest was computed. Following an ensemble averaging of the estimate, the instantaneous phase locking measure was derived according to

$$PLV(t) = \frac{1}{N} \sum_{n=1}^{N} \exp(j(\phi_1(t, n) - \phi_2(t, n)))$$

where $\phi_i(t, n)$ is the phase of the i-th signal at time t and trial n (i=1 or 2). This PLV measure was calculated for the recalled ensemble and unrecalled ensemble separately for each subject and averaged over the 500 ms period immediately prior to word presentation (i.e. -500 ms to 0 ms). The values of PLV range from 0 to 1, where 1 indicates perfect synchrony across trials, and 0 indicates that the phase relationship is completely random from trial to trial.

4.2.4.5 Random permutation test for statistical significance

To test the significance of inter-grid PLV, the following procedure was followed (Jean-Philippe et al., 1999; Brovelli et al., 2004), the aim of which is to create a null hypothesis distribution for the PLV measure in the frequency band of interest. (1) For each subject, the 500 ms prestimulus epochs were numbered from 1 to N where N is the total number of epochs across both recalled and unrecalled ensembles. (2) For a specific inter-grid comparison, the
4.3 Results

Preliminary analysis of this experiment has appeared previously in an abstract form (Rajagovindan et al., 2007). The subjects were attentive throughout the experiment and completed the task according to instructions. On average, 31% of the words were free-recalled, and 88% of the words were correctly identified during the recognition period. These behavioral results are in line with published reports (Sederberg et al., 2003).

4.3.1 Power

Spectral power over the interval (-500 ms to 0 ms) preceding word presentation in the encoding period (shaded interval in the expanded encoding period in Figure 4-2) was estimated for the recalled ensemble of trials and for the unrecalled ensemble of trials. The number of recording channels exhibiting significant differences between the two conditions across all three brain areas and subjects is summarized in Figure 4-3B. Strongest modulation is seen in the theta band (4-9 Hz) with smaller effects also observed in the alpha/low beta band (10-14 Hz) and the
high beta/low gamma band (21-25 Hz). Figure 4-4 shows the group-averaged theta band power from the significantly modulated channels in Figure 4-3B for each of the three brain regions. Over the PFC region, theta band power was significantly higher prior to the words that were subsequently free recalled relative to words that were not (p=0.026). Results in the MTL and LTL regions are mixed. While the theta band power is generally higher for the recalled ensemble compared to the unrecalled ensemble, the difference failed to reach the statistical significance level of p=0.05. However, by pooling LTL and MTL channels together, the overall temporal lobe theta band power was found to be significantly higher for the recalled words relative to unrecalled words (p=0.046). Similar analysis for the alpha/low beta band power (10-14 Hz) and high beta/low gamma band power (21-25 Hz) revealed no statistically significant difference in any of the three brain regions (p>0.1).

4.3.2 Inter-Areal Phase Synchrony

For the two subjects (Subjects 1 and 2 in Figure 4-1) with simultaneous coverage of PFC, MTL and LTL, the pattern of interaction between these areas over the prestimulus interval (-500 ms to 0 ms) was evaluated by computing the PLV measure in theta, alpha/low beta, and high beta/low gamma bands between all possible pairwise combinations of (a) PFC-LTL bipolar derivations, (b) PFC-MTL bipolar derivations, and (c) MTL-LTL bipolar derivations. Each black dot in Figure 4-5A (Subject 1) and Figure 4-5B (Subject 2), represents the PLV value for a distinct pair of bipolar signals, and the height of the rectangular bars is the mean of all black dots for a given condition. Significantly higher prestimulus theta band synchrony is present for the recalled ensemble relative to the unrecalled ensemble in all three pairwise combinations of brain areas (PFC-MTL, PFC-LTL, MTL-LTL) (p<7e-6). Another way of quantifying the task-related modulation of inter-areal theta synchrony is the number of pairwise combinations whose theta band PLV values exceed the threshold corresponding to the significance of p=0.001 (horizontal
lines in Figure 4-5A and 4-5B; see Methods). Since the number of bipolar signals in each grid varied between subjects, the percentages of pairwise bipolar combinations above threshold were calculated and averaged across subjects. As seen in Figure 4-6A, the percentage of pairs showing significant theta synchrony is significantly higher for the recalled ensemble than for the unrecalled ensemble (p=0.0028) in all pairwise combinations of the three brain areas: PFC-MTL, PFC-LTL and LTL-MTL. The same synchrony analysis in the alpha/low beta band (Figure 4-6B) and high beta/low gamma band (Figure 4-6C) revealed a similar pattern of higher prestimulus synchrony between frontal and temporal lobe structures for words that were subsequently recalled than words that were not (p=5e-5 and p=0.0002, respectively). A schematic illustrating the relation between the level of prestimulus interregional synchrony and subsequent memory performance is given in Figure 4-6D.

4.4 Discussion

In this study, we investigated how neuronal activity preceding the events to be memorized affects their subsequent encoding and recall. ECoG signals from the lateral prefrontal cortex (PFC), medial temporal lobe (MTL), and lateral temporal lobe (LTL) were recorded from implanted subdural electrodes in five epilepsy patients who performed a subsequent memory task. Applying nonparametric spectral methods to the data we obtained two results. First, free-recalled words were associated with higher theta oscillation prior to their presentation over the frontal and temporal lobe structures compared to unrecalled words. Second, inter-areal synchrony in theta as well in alpha/low beta and high beta/low gamma bands preceding the presentation of free-recalled words was higher than that preceding the presentation of unrecalled words.
4.4.1 Prestimulus Ongoing Activity, Theta Oscillations and Memory Encoding

Studies on the neuronal mechanisms of memory encoding have placed emphasis on stimulus-evoked responses and their ability to predict memory performance (Klimesch et al., 1996; Fernandez et al., 1999; Friedman and Johnson, 2000; Tendolkar et al., 2000; Weiss and Rappelsberger, 2000; Jensen and Tesche, 2002; Sederberg et al., 2003; Takashima et al., 2006; Sederberg et al., 2007). In many areas of cognitive neuroscience recent work has begun to elucidate the importance of ongoing brain activity immediately before stimulus onset in defining a state of the brain and the effect of such a state on subsequent stimulus processing (Engel et al., 2001; Liang et al., 2002; Dehaene and Changeux, 2005; Ohara et al., 2006; Ohara et al., 2008; Zhang et al., 2008b).

Ongoing brain activity is replete with oscillatory phenomena. In particular, the role of hippocampal and limbic theta-band (4-9 Hz) EEG activity in learning and memory has been extensively studied (Buzsaki, 1989; Huerta and Lisman, 1993; Staubli and Xu, 1995; Buzsaki, 1996, 2002; Vertes et al., 2004; Hasselmo, 2005; Vertes, 2005). Pharmacological blocking of acetylcholine and medial septum lesions decrease theta activity and lead to memory impairments (Winson, 1978; Givens and Olton, 1990; Berry and Seager, 2001; Siok et al., 2006) while pharmacological blocking of serotonin enhances theta rhythms and leads to improved performance in spatial memory tasks (Staubli and Xu, 1995; Berry and Seager, 2001; Seager et al., 2002). At the cellular level, episodes of theta oscillations represent a strong depolarizing influence on NMDA receptor-containing cells. Glutamate release triggered by the stimulus input, when temporally coupled with the theta-induced depolarization, activates the theta-facilitated NMDA channels and leads to stronger Ca2+ influx, which in turn facilitates LTP and memory trace formation (Grunwald et al., 1999; Seager et al., 2002; Vertes et al., 2004; Honey et al., 2005; Vertes, 2005; Gallinat et al., 2006; Lisman et al., 2007; Meador, 2007). This suggests that
the level of theta activity prior to the presentation of stimulus is an index of tissue excitability and should be positively correlated with the efficacy of subsequent memory encoding and recall (Otten et al., 2006; Guderian et al., 2009). Our first finding is consistent with this hypothesis. In addition, our data demonstrates that the theta-facilitation principle can be extended beyond animal preparations and the temporal lobe to manifest strongly in human neocortical structures important for memory encoding such as the prefrontal cortex.

4.4.2 Inter-Areal Synchrony and Network Excitability

PFC, MTL and LTL are part of a network of brain areas involved in memory encoding, consolidation and retrieval (Scoville and Milner, 1957; Janowsky et al., 1989; Tulving et al., 1994; Kapur et al., 1996; Wagner et al., 1998; Kirchhoff et al., 2000; Otten et al., 2002; Strange et al., 2002; Simons and Spiers, 2003). While stimulus-triggered inter-areal synchronization and its influence on memory performance has been examined in the past (Sarnthein et al., 1998; Weiss and Rappelsberger, 2000; Summerfield and Mangels, 2005), little is known about how inter-areal synchrony prior to stimulus onset serves as a gating mechanism to facilitate subsequent stimulus-driven network operations. Our second finding can be seen as offering the first evidence in humans demonstrating that increased inter-areal synchrony in the fronto-temporal network prior to word presentation is associated with higher likelihood of the word being recalled in the subsequent test (see Ohara et al., 2008 for report of a similar analysis in pain perception). The changes in inter-areal synchrony, taken as an indicator of changes in network excitability, may be a result of spontaneous fluctuations in the level of anticipatory attention. Recent studies have shown that anticipatory attention can modulate phase synchrony in a diverse set of cortical networks (Engel et al., 2001; Fries et al., 2001; Ohara et al., 2006; Rajagovindan and Ding, 2008b) and differences in prestimulus inter-areal synchrony are correlated with conscious perception of stimuli in different sensory modalities (Hanslmayr et al.,
2007a; Ohara et al., 2008; Zhang and Ding, in press). It is worth noting that, unlike the theta-facilitating hypothesis where activity in a single frequency band is implicated in the indexing of tissue excitability, the prestimulus facilitation at the network level is across a broad range of frequencies, including theta, alpha, beta and low gamma.

Table 4-1. ECoG electrode information. Number of recording channels within each grid overlying the prefrontal cortex (PFC), lateral temporal lobe (LTL) and medial temporal lobe (MTL) in each of the five subjects.

<table>
<thead>
<tr>
<th>Subject #</th>
<th>PFC</th>
<th>LTL</th>
<th>MTL</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>14</td>
<td>15</td>
<td>4</td>
</tr>
<tr>
<td>2</td>
<td>20</td>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>43</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>-</td>
<td>25</td>
<td>7</td>
</tr>
<tr>
<td>5</td>
<td>-</td>
<td>-</td>
<td>9</td>
</tr>
</tbody>
</table>

Table 4-2. ECoG bipolar electrode derivation summary. Total number of bipolar derivations in each area and total number of inter-grid pairwise combinations of bipolar signals.

<table>
<thead>
<tr>
<th>Subject #</th>
<th># bipolar derivations</th>
<th># inter-grid combinations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PFC</td>
<td>LTL</td>
</tr>
<tr>
<td>1</td>
<td>26</td>
<td>29</td>
</tr>
<tr>
<td>2</td>
<td>55</td>
<td>20</td>
</tr>
</tbody>
</table>
Figure 4-1. Approximate placement of electrode grids for each of the five subjects.

Figure 4-2. Schematic of the experimental paradigm. The sequence of events within a single block of the subsequent memory paradigm is given and the encoding phase (shaded in gray) is expanded to highlight the prestimulus interval (-500 to 0 ms) which is the focus of this work.
Figure 4-3. Prestimulus differences in spectral power between the recalled and unrecalled ensembles of words. (A) The test statistic for the difference in prestimulus power between the recalled and unrecalled ensembles across frequencies from 0-30 Hz obtained from a representative frontal electrode. Notice that for this channel the power in the theta band was significantly higher preceding the subsequently free-recalled words relative to the unrecalled words (shaded in gray). The horizontal gray line marks the p=0.1 level of significance. (B) The number of electrodes exhibiting significant differences in prestimulus power between the two ensembles of words across frequencies from 3-28 Hz.
Figure 4-4. Comparison of theta band power. Group-averaged prestimulus theta band power for the recalled and the unrecalled ensembles of words over the three brain regions. Here PFC = prefrontal cortex, LTL = lateral temporal lobe, and MTL = medial temporal lobe.

Figure 4-5. Comparison of inter-areal synchrony. Inter-grid phase locking value (PLV) results for Subject 1, (A) and Subject 2, (B). (A) and (B) Theta band PLV values for every pairwise combination of bipolar signals for each inter-grid pair is plotted as black dots. From left to right are PFC-MTL, PFC-LTL, and LTL-MTL. Height of gray bars and white bars is the mean PLV for the recalled and the unrecalled conditions respectively. The gray horizontal lines indicate the p=0.001 level of statistical significance for different grid pairs.
Figure 4-6. Comparison of percentage of bipolar signal pairs with significant PLVs. Average percent of inter-grid bipolar signal pairs whose theta (A), alpha/low beta (B) and beta/low gamma (C) PLV exceeds the significance threshold for the recalled (gray bars) and the unrecalled (white bars) conditions. (D) Schematic of the relation between levels of prestimulus inter-areal synchrony, represented by the thickness of the curves connecting different brain regions, and subsequent memory performance.
CHAPTER 5
FROM PRESTIMULUS ALPHA OSCILLATION TO VISUAL EVOKED RESPONSE: AN INVERTED-U FUNCTION AND ITS ATTENTIONAL MODULATION

5.1 Introduction

Research into the neuronal mechanisms of cognition has mainly relied on stimulus evoked responses and their modulation by higher mental functions such as attention and memory. Recent work has begun to explore how ongoing neural activity prior to stimulus onset influences stimulus processing and behavior. In the human visual cortex the relation between prestimulus alpha activity (8-12 Hz) and the subsequent event-related potential (ERP) has been the subject of extensive investigation. The phase-reset model supposes that the ERP is generated as a result of stimulus-triggered alpha phase realignment and predicts a positive correlation between the prestimulus alpha power and the magnitude of early visual evoked response (Makeig et al., 2002; Hanslmayr et al., 2007b) also see (Mazaheri and Jensen, 2006) . Two lines of empirical evidence appears to be at variance with this prediction: (1) a state of low alpha is found to improve detection and discriminability of threshold-level stimuli (Ergenoglu et al., 2004; Hanslmayr et al., 2007a; Romei et al., 2008a; Van Dijk et al., 2008) and (2) covert attention reduces prestimulus alpha amplitude and at the same time increase stimulus-evoked response (Mangun and Hillyard, 1991; Foxe et al., 1998; Hillyard et al., 1998; Mangun et al., 1998; Marrufo et al., 2001; Sauseng et al., 2005; Thut et al., 2006). The hypothesis that prestimulus alpha power should be inversely proportional to stimulus evoked response proves to be also contradicted by studies where (1) alpha episodes over the parieto-occipital areas immediately preceding the stimulus onset enhanced the ability to detect a threshold-level visual stimuli (Babiloni et al., 2006) and (2) higher alpha power led to stronger evoked response (Brandt and Jansen, 1991; Brandt et al., 1991; Paul et al., 2007). These divergent reports, in conjunction with recent findings in the somatosensory domain where the mu rhythm (7-13 Hz) is found to exhibit an
inverted-U relationship with the event-related potential and behavior (Ho and Destexhe, 2000; Linkenkaer-Hansen et al., 2004; Zhang and Ding, in press), suggest that a new assessment of the relation between alpha and visual information processing is needed. An added benefit of such a reexamination is that it may yield insights into the fundamental question of how cognitive operations such as attention modulate baseline ongoing neural activity to achieve enhanced stimulus information processing.

Noninvasively recorded EEG and invasively recorded local field potentials are a measure of dendritic activity in populations of neurons. Computational as well as in vitro and in vivo studies in animal preparations have shown that synaptic background activity can exert a significant influence on the responsiveness of sensory neurons to stimulus input (Ho and Destexhe, 2000; Chance et al., 2002; McCormick et al., 2003; Wolfart et al., 2005; Haider et al., 2007). Our approach to investigating the relation between prestimulus activity and stimulus evoked response starts by considering a theoretical model in which synaptic input to a sensory neuronal ensemble comes in two forms: external stimulus (exogenous) or other brain structures (endogenous). On a moment by moment basis, the endogenous brain activity fluctuates randomly, and the effective processing of a stimulus depends on the state of the brain defined by these fluctuations at its onset. Supposing that, in the absence of sensory input, the firing rate of the neuronal ensemble is related to the magnitude of endogenous synaptic fluctuations through a sigmoidal function, and sensory input has an additive synaptic effect, it follows that the stimulus evoked response corresponds to the derivative of the sigmoidal function, referred to as the gain, which is an inverted-U function of the prestimulus level of background activity. Reformulated in terms of EEG variables where alpha oscillations and the P1 component in the event-related potential are treated as indices of background synaptic activity and stimulus-evoked response,
the model makes a number of predictions, which were then tested by recording EEG data from human volunteers performing a trial-by-trial cued covert spatial visual attention task. Finally, a mechanism on how changes in the global state of the brain, such as selective attention, influenced the aforementioned sigmoidal curve was proposed. Through experimental data and computational modeling, the reduced magnitude and trial-to-trial variability of alpha activity is linked to an increase in cortical excitability brought about by attention, which enables an increase in the overall slope of the sigmoidal curve and hence higher gain to sensory input.

### 5.2 Materials and Methods

#### 5.2.1 Subjects

The experimental protocol was approved by the University of Florida Institutional Review Board. Nineteen subjects, free from movement and neurological disorders and with normal or corrected-to-normal vision, gave written informed consent and participated in the study. Data from twelve subjects (20-31 years of age, 25.16 ±3.5 years, 5 females and 7 males, all right handed) were included in the analyses reported here. The remaining 7 participants were excluded for a combination of three reasons: (1) poor behavioral performance (target detection rates less than 75%; 3 subjects), (2) excessive eye blinking, eye movement, and muscle activity or electrolyte bridging (3 subjects), and (3) inability to complete the experiment (1 subject).

#### 5.2.2 Paradigm

Seated in a dimly lit, acoustically and electrically shielded room, the subject was instructed to fixate a central cross on a VGA monitor placed approximately 85 cm from the eye. Two square boxes, each delineated by white dots placed at the four corners in the upper left visual field and in the upper right visual field, were displayed permanently on the monitor (Figure 5-1). Each box, centered 4.7° above the horizontal meridian and 7.2° lateral to the central fixation, subtended a visual angle of 3.35°. A trial began with the onset of a cue, which consisted of either
a left or right pointing arrow of 200 ms in duration at the location of the central fixation cross, instructing the subject to deploy covert attention to the square box on the side indicated by the arrow. After a random time delay between 1800 ms and 2200 ms, a standard or a target stimulus of 100 ms in duration appeared either inside the attended square box (valid trial) or inside the square box on the opposite side (invalid trial). The standard stimulus was a circular checkerboard subtending a 3.3° visual angle, and the target stimulus was also a circular checkerboard, but of a slightly smaller diameter. The subject was required to press a button with their right index finger in response to the valid target stimulus and withhold response to any other stimuli. The standards appeared 80% of the time with 50% validity and the targets appeared 20% of the time with 66% validity. The interval between the cue offset of the previous trial and the cue onset of the successive trial was randomly varied between 4700 to 5700 ms. The entire experiment was comprised of 15 to 16 blocks of approximately 6 min each (60 trials). Breaks were given between blocks. Subjects received practice sessions of 150 trials to familiarize themselves with the task and to minimize the effect of learning.

Four of the twelve subjects also took part in an additional behavioral experiment in which they responded to targets for both valid and invalid trials. The purpose was to establish the validity effect on the reaction time. In this task, the standards appeared 80% of the time and the targets appeared 20% of the time, both with 50% validity. This additional experiment consisted of 10 blocks of 64 trials each.

5.2.3 Data Acquisition

The electroencephalogram (EEG) data was recorded with a 128-channel BioSemi ActiveTwo System at a sampling rate of 1024 Hz. Four additional electrooculogram (EOG) electrodes were placed around the eyes to monitor eye blinks and horizontal and vertical eye movements. EEG and EOG data was amplified and lowpass-filtered with a cutoff set at 205 Hz.
The stimulus and the response was delivered and registered by a BeriSoft Experimental Run Time System (ERTS) and by a Berisoft EXKEY microprocessor logic pad respectively. In addition to the attention experiment, five minutes of EEG activity during relaxed fixation was also recorded for baseline purposes.

5.2.4 Data Preprocessing

Analysis was performed using a combination of BESA 5.1 (MEGIS software GmbH, Munich, Germany) and custom scripts written in MATLAB 7.4 (MathWorks Inc., Massachusetts). The EEG data was filtered off-line between 1 and 83 Hz and downsampled to 250 Hz. The channels were re-referenced off-line against the average reference (Nunez et al., 1997). Trials contaminated by any of the following factors were excluded from further analysis: (1) incorrect behavioral response, (2) excessive muscle or movement artifact, (3) eye blinks during a 150 ms period around the onset of the cue and the standard stimulus, and (4) horizontal eye movement following the cue onset and during the period -1000 ms to 300 ms with 0 ms denoting the presentation of the standard stimuli. The average trial rejection rate was 24%. The remaining eye blinks were removed using the adaptive artifact correction procedure in BESA 5.1. The high rejection rate is necessary because the single-trial based analysis protocol here places stringent requirements on the quality of the EEG signal (see below). The data from the fixation only condition was segmented into 300ms long non-overlapping artifact free epochs. For the spatial attention task, the continuous EEG data was epoched from -1000 ms to 800 ms. For event-related potential (ERP) analysis, the data epochs were baseline corrected by subtracting the mean voltage over the interval -150 ms to 0 ms.

There are four conditions for comparison: a) Attend Left (cued left and standard stimulus appearing on the left; valid cue), b) Attend Right (cued right and standard stimulus appearing on the right; valid cue), c) Ignore Left (cued right and standard stimulus appearing on the left;
invalid cue), and d) Ignore Right (cued left and standard stimulus appearing on the right).

Stimulus evoked neural activity measured by ERP as well as ongoing neural activity from the prestimulus time period during which preparatory attention is engaged were studied. Between two to four neighboring channels overlying the occipital and parieto-occipital areas with comparable magnitudes of P1 evoked component (peak, 90-160 ms) and prestimulus alpha band power (8-12 Hz) exhibiting attentional modulation were chosen for analysis.

5.2.5 Behavior and Event-related Potential Analysis

Behavior was quantified by three measures: (1) target detection rate defined as the number of correctly identified valid targets divided by the total number of valid targets presented, (2) false alarm rates for the conditions where the participants had to withhold their responses was defined as the number of responses to (a) invalid targets, (b) valid standards and (c) invalid standards, each divided by total number of trials in each of these conditions, and (3) mean reaction time for correctly detected valid targets. The visual event-related potential (ERP) was computed by averaging the EEG response elicited by the left and right field standard stimuli for the attended and ignored conditions. The amplitude of the ERP components were estimated using the baseline-to-peak method where the baseline period was defined to be (-150 to 0 ms) (Luck, 2005). Wilcoxon’s signed-rank test was used to evaluate the statistical significance for the attentional enhancement of the ERP components over the occipital and parieto-occipital areas.

5.2.6 Correlation Between Prestimulus Alpha Power and P1 Amplitude

A key objective of this study is to investigate how the state of the brain immediately preceding the onset of stimulus affects stimulus processing. The former is characterized by the power of alpha oscillation (8-12 Hz) during the time period from -300 ms to 0 ms and the latter by the amplitude of the visually evoked P1 component (90-160 ms). The method for accomplishing the objective is correlation analysis and it has the following steps. (1) Prestimulus
power for each of the pre-selected channels overlying the parieto-occipital area contra-lateral to the visual field of stimulation was computed on a trial by trial basis using the multitaper spectral estimation technique (Thomson, 1982; Mitra and Pesaran, 1999). This power was then averaged over the alpha frequency band and across the set of pre-selected channels. (2) The trials from each subject were then sorted, according to the magnitude of the prestimulus alpha power, from the smallest to the largest, into 5 groups of equal size (Liang et al., 2002; Zhang et al., 2008b) with 50% overlap. Each group, containing 30% of the total trials, will be henceforth referred to as a power group. (3) For every power group, the group-mean prestimulus alpha power and the baseline-to-peak group visually evoked P1 component were estimated for each subject. (4) To minimize the effect of inter-subject variability on population averaging, the normalized P1 amplitude was obtained by dividing the evoked P1 for each power group by the largest evoked P1 component across all power groups under the attend condition for every individual subjects. (5) The normalized evoked P1 component was averaged across subjects and plotted against the power group index. The relation between the two variables, reflecting prestimulus and poststimulus activities respectively, was assessed from the scatter plot.

5.2.7 Characterization of Ongoing Alpha Activity

Ongoing brain activity in the visual cortex is dominated by oscillations in the alpha band. On a trial by trial basis, the amplitude of alpha activity varies markedly; collectively, these amplitudes form an alpha power distribution. Past work has focused on the mean of this distribution (mean alpha power) and its modulation by attention. Here, in addition to the mean, the variance of the distribution is also given physiological importance and compared across conditions. Three conditions are considered: attend, ignore, and relaxed fixation. For the first two conditions, the 300 ms interval prior to the onset of the standard stimulus constitutes a trial. For the relaxed fixation, continuous recordings were divided into 300 ms nonoverlapping epochs,
and each epoch is considered a trial. The same method as that described above was used to estimate the single-trial alpha power for each hemisphere of every subject. To test the difference in alpha variance between conditions, single-trial alpha power was log transformed to ensure an approximate normal distribution. Population differences across subjects in the magnitude of the estimates between a pair of conditions were tested for statistical significance using Wilcoxon’s signed-rank test.

5.2.8 Computational Modeling

A computational model was employed to further test the validity of the proposed framework at a single neuron level. To assess the influence of change in excitability on the slope of synaptic input–output curve, the point-conductance model of background activity introduced by Destexhe et al., (Destexhe et al., 2001) was employed here. The model comprises of a single compartment Hodgkin-Huxley type neuron with excitatory and inhibitory conductance representing the collective effect of a large number of synaptic inputs and the membrane potential is described by the following equation:

\[
C \frac{dV}{dt} = -I_{\text{Leak}} - I_{\text{Na}} - I_{\text{Kd}} - I_{\text{M}} - \frac{1}{a} I_{\text{syn}}
\]  

(5-1)

where \(C = 1 \mu F/cm^2\) is the specific membrane capacitance, \(V\) is the membrane potential and \(a=34636 \text{ mm}^2\) is the total membrane area of a representative cortical pyramidal cell (Destexhe et al., 2001). \(I_{\text{Na}}\) is the voltage-dependent Na\(^+\) current, \(I_{\text{Kd}}\) is the delayed rectifier K\(^+\) current, \(I_{\text{M}}\) the noninactivating K\(^+\) current, and \(I_{\text{Leak}}\) the leak current. The parameters of the passive and voltage-dependent currents were taken from (Destexhe et al., 2001). The total synaptic current in Eq. 5-1, \(I_{\text{syn}}\), is decomposed into a sum of two independent currents:

\[
I_{\text{syn}} = g_e(t)(V - E_e) + g_i(t)(V - E_i)
\]  

(5-2)
where \( g_e(t) \) and \( g_i(t) \) in Eq. 5-2 are time-dependent global excitatory and inhibitory conductance, respectively, with reversal potentials of \( E_e = 0 \) mV and \( E_i = -75 \) mV. The synaptic conductance are described by Ornstein–Uhlenbeck stochastic processes (Destexhe et al., 2001):

\[
\begin{align*}
\frac{dg_e}{dt} &= -\frac{1}{\tau_e}(g_e - g_{e0}) + \frac{2\sigma_e^2}{\tau_e}x_e(t) \\
\frac{dg_i}{dt} &= -\frac{1}{\tau_i}(g_i - g_{i0}) + \frac{2\sigma_i^2}{\tau_i}x_i(t)
\end{align*}
\]

(5-3)

where, \( g_{e0} \) and \( g_{i0} \), \( \sigma_e \) and \( \sigma_i \), \( \tau_e \) and \( \tau_i \), are the average conductance, standard deviations, and time constants, for the excitatory and inhibitory inputs, respectively. \( x_e(t) \) and \( x_i(t) \) are zero mean Gaussian white noise processes of unit standard deviation. The parameter values of Eq. 5-3 were taken as \( \tau_e = 2.73 \) ms and \( \tau_i = 10.49 \) ms, \( g_{i0} = 0.06 \) \( \mu \)S, \( g_{e0} \) was varied between 0.01\( \mu \)S and 0.0364 in steps of 0.0033 resulting in 8 levels of increasing excitability state. 25 levels of background synaptic activity were simulated by changing the standard deviation of inhibitory conductance \( \sigma_i \) between 0 and 0.0375\( \mu \)S in steps of 0.0015\( \mu \)S. The parameter \( \sigma_e \), the standard deviation for excitatory conductance, was kept constant at 0.006\( \mu \)S. Qualitatively, similar results were obtained when \( \sigma_e \) was varied with \( \sigma_i \) kept constant or when both \( \sigma_i \) and \( \sigma_e \) were varied in tandem. Note that varying \( \sigma_i \) or \( \sigma_e \) also shares a correspondence with varying input correlation between individual synapses (Destexhe et al., 2001). The firing rates were collected for 40 simulation trials of 200 ms duration each, for 25 values of \( \sigma_i \) for 8 excitability levels.

5.3 Results

The relation between prestimulus alpha oscillation and stimulus evoked response and its attentional modulation were investigated by combining a theoretical model with human visual attention experiment. Below, basic experimental findings are reported first, which is followed by model analysis and test of model predictions.
5.3.1 Behavior

The average target detection rate across subjects was 87.27% (± 3.2% SEM) for attended targets appearing in the left visual field and 87.44% (± 3.68% SEM) for attended targets appearing in the right visual field. These results suggest that the level of task difficulty was equated between the attend-left and the attend-right conditions (p=0.8, two-tailed Wilcoxon’s signed-rank test). The average false alarm rate stemming from responses to the target appearing in the ignored location, to the attended standard stimulus, and to the ignored standard stimulus was 1.58%, 4% and 0.15%, respectively. The mean reaction time (RT) was 540.8 ms (±36ms SEM) to attended targets appearing in the left visual field and 501.5 ms (±27.8ms SEM) to attended targets appearing in the right visual field. The difference between the two mean RTs is not statistically significant. For the 4 subjects who performed the additional task of responding to targets appearing in either the left or right visual field after the cueing period, the mean RT to validly cued targets was significantly faster than to invalidly cued targets: 358.825 (±56.67 ms SEM) versus 550.422 (±104.21 ms SEM), (p=0.0078, Wilcoxon’s signed-rank test), demonstrating the behavioral benefit of cued preparatory attention.

5.3.2 ERP Analysis

Event-related potential (ERP) profiles elicited by the standard stimuli under the attend and ignore conditions were compared. Waveforms from a single channel of a representative subject are shown in Figure 5-2A. Consistent with previous reports, the P1 component (90-160 ms), reflecting early response of the extrastriate cortex to stimulus input, is significantly higher for attend versus ignore condition over the posterior electrodes (p = 0.0005, right hemisphere for attend left versus ignore left and p = 0.0002, left hemisphere for attend right versus ignore right); see Figure 5-2. The scalp distribution of the P1 attention effect has an amplitude maximum over the lateral occipital sites contralateral to the visual field of stimulation for the
attend-left condition (Figure 5-3A). For the attend-right condition the pattern is more bilateral (Figure 5-3B). Attentional enhancement of the N1 component (160-210 ms) over the parieto-occipital areas was also observed but will not be pursued here. Further our emphasis below is on the attentional modulation of prestimulus baseline activity and its relation to the early stimulus-evoked P1 component.

5.3.3 Prestimulus Alpha Oscillations

Grand-average power spectra from the left and right occipital areas are shown in Figures 5-4A and 5-4B, respectively, for three conditions: attend, ignore and fixation only. Data used for the attend and ignore conditions were taken from the prestimulus time period, -300 to 0 ms, with 0 ms denoting the onset of the standard stimulus. For the fixation only condition, continuous recording was divided into non-overlapping epochs of 300 ms in duration. The mean spectral peak frequency averaged across subjects is $9.5 \pm 0.39$ Hz and no frequency difference is seen between conditions. The power of alpha activity for both attend and ignore conditions is significantly lower than that for the fixation condition. Alpha power is further reduced with attention when the attend condition is compared to the ignore condition ($p<0.002$). These effects were established shortly after the cue onset and persisted until the onset of the stimulus. The scalp distribution of alpha power difference between the conditions is shown in Figure 5-4. A hemisphere-specific modulation is seen in Figure 5-4 where alpha activity was maximally suppressed over the parieto-occipital areas contralateral to the attended visual field. Specifically, for the right occipital areas, the alpha power was significantly lower when attention was directed to the left visual field compared to when attention was directed to the right visual field, ignoring the left visual field ($p=0.0034$ Wilcoxon’s signed-rank test). For the left occipital areas, the alpha band power was significantly lower when attention was directed to the right visual field compared to when attention was directed to the left visual field, ignoring the right visual field.
(p=0.0024 Wilcoxon’s signed-rank test). Figures 5-4D and 5-4E show the comparison with the fixation condition where hemispheric-specific lateralization patterns are also seen.

5.3.4 From Ongoing Activity to Evoked Response: A Model

Attention enhanced the stimulus-evoked P1 component and reduced alpha power prior to stimulus onset. Presumably, the prestimulus alpha power reduction contributed to the subsequently improved stimulus processing. The physiological mechanism that mediates such improvement remains to be understood. The first step in our attempt to address this issue consisted of putting forth a plausible model linking ongoing prestimulus activity with stimulus evoked response and validating the model by testing its prediction. The model was then used to delineate different mechanisms of prestimulus attention modulation.

5.3.4.1 The sigmoidal input-output function

Consider a neuronal ensemble in the sensory cortex. It is well-accepted that the level of synaptic input $S$ it receives is related to its output $O$ measured in firing rate through a sigmoidal function $O(S)$ in Figure 5-5A (Freeman, 1979; Destexhe et al., 2001). The synaptic input $S$ can come in two forms: external stimulus (exogenous) or other brain structures (endogenous). Let $S_N$ denote the amount of endogenous prestimulus background activity at the time of stimulus onset and $S_X$ the amount of synaptic activity induced by the sensory input. From the schematic in Figure 5-5A, the stimulus-evoked response is the difference: $O(S_N+S_X)-O(S_N)$. For a constant sensory stimulus, as is the case here, $S_X$ is approximately the same from trial to trial over the physiological range of $S$. The stimulus-evoked response is then proportional to the first derivative of the sigmoidal input-output function $O(S)$, $[O(S_N+S_X)-O(S_N)]/S_X$, referred to as the gain function. As shown in Figure 5-5B, the gain function has an inverted-U shape, suggesting that $S_N$ has an effective operational range, denoted by $W$, beyond which stimulus input evokes a negligible response. Also based on this model, it is worth noting that for a very strong input
the response to the stimulus may saturate for all levels of endogenous prestimulus background activity hence giving rise to a purely decreasing gain with increasing $S_N$. An estimate of $W$ is provided by the distribution of $S_N$ on a trial by trial basis. Knowledge of this distribution, combined with the magnitude of the stimulus-evoked response which reflects the slope of the sigmoidal input-output function, forms the basis for evaluating how attention modulates the sensory cortex to achieve enhanced input processing.

5.3.4.2 Model reformulation in terms of electroencephalogram variables

The abscissa and ordinate of the model in Figure 5-5 are synaptic input and firing rate. While these variables can be precisely controlled and measured in computational models and in slice preparations, they are not readily available in noninvasive human experiments. Thus, the model in Figure 5-5 requires reformulation to be applicable to our EEG data. First, consider the abscissa. Physiologically, EEG reflects the fluctuating extracellular field due to spatially summated dendritic currents which are in turn caused by synaptic input (Niedermeyer and Lopes Da Silva, 2005). There is evidence suggesting that the amplitude of EEG fluctuation is proportional to the level of correlated synaptic input (Ho and Destexhe, 2000; Niedermeyer and Lopes Da Silva, 2005). In this sense, the abscissa of the model in Figure 5-5A may be equivalently expressed by the amplitude of EEG fluctuation, which is further replaced here by the power of the alpha oscillations. Next, consider the ordinate. Firing rates are not accessible. This means that the sigmoidal input-output curve during the ongoing brain state cannot be directly established with EEG. But the consequence of this curve on stimulus processing can be assessed via the early ERP component P1 (90-160 ms). Dipole modeling and imaging studies have identified the ventral-lateral extrastriate cortex as the putative source for P1 (Heinze et al., 1994; Clark and Hillyard, 1996; Mangun et al., 1997). Invasive recordings in animals revealed that, upon receiving afferent input from the thalamus or lower visual areas, layer 4 stellate cells
fire action potentials which excite the supragranular pyramidal cells at their basal dendrites spanning layer 3 or portion of layer 4 (Gilbert and Wiesel, 1983; Mitzdorf, 1985; Callaway, 1998; Thomson and Lamy, 2007). This activation causes an extracellular sink in layer 3/4 and an extracellular source near the apical dendrite in layer 1/2, with the latter manifesting as a positive going potential at nearby surface electrodes. See Figure 5-6A for an illustration. This dendritic response in the superficial layers is the summated EPSPs to the impinging action potentials arriving from layer 4 and the magnitude of dendritic response is proportional to the intensity of the action potential input (Jagadeesh et al., 1993; Cash and Yuste, 1999; Araya et al., 2006). The reformulated model in Figure 5-6B establishes the relation between prestimulus EEG power and stimulus-evoked P1 amplitude, where an effective operational range \( W \) for baseline activity can again be defined.

5.3.4.3 Experimental test of model predictions

In our experiment, although the stimulus is kept constant, the background synaptic activity prior to stimulus onset, assessed by the amplitude of alpha oscillations, varies from trial to trial, leading to significant trial-to-trial variability in stimulus-evoked responses. Given the model in Figure 5-5, and its reformulation in terms of EEG variables in Figure 5-6, it is expected that the amplitude of the P1 component follows an inverted-U function of the prestimulus alpha power. This prediction is tested in Figure 5-7 for the attend condition. For each trial the amplitude of the prestimulus (-300 to 0 ms) EEG activity in the frequency range of 8 to 12 Hz was estimated, rank-ordered from the smallest to the largest, and sorted into equal-sized groups. The average normalized P1 amplitude in each prestimulus power group was plotted against group index. Consistent with the model prediction, an inverted-U relation is clearly seen. This relationship was robust across all 12 subjects, with the exception of subject 2 and subject 10, where a non-systematic and a negatively correlated relationship, respectively, were observed over the
right parieto-occipital regions. Quantitatively, for the left occipital areas, when the subject was validly cued to the right visual field, the P1 amplitude for power group 3 (intermediate alpha power) is 63% and 104% higher than that for power group 1 (lowest alpha power) and power group 5 (highest alpha power) (p=0.0005 and p =0.00025 respectively, one-tail Wilcoxon’s signed-rank test). For the right occipital areas, when the subject is validly cued to the left visual field, the normalized P1 amplitude for power group 3 is 57% and 165% higher than that for power group 1 and power group 5 (p=0.02 and p = 0.0025 respectively, one-tail Wilcoxon’s signed-rank test). Quadratic fits appear as solid smooth curves in Figure 5-7 to guide the eye.

5.3.5 Attentional Modulation of Baseline Ongoing Activity: Possible Mechanisms

Based on the model in Figures 5-6 and results in Figure 5-7, it is plausible that deployment of effortful covert attention through top-down compensatory mechanisms modulates the prestimulus ongoing neural activity, hence optimizing the cortical excitability (Bressler et al., 2008; Fischer et al., 2008; Lakatos et al., 2008) to increase the overall slope of the sigmoidal function O(S) in Figures 5-5 and 5-6, as illustrated in Figure 5-8A. This global change in the sigmoidal function, corresponding to an increase in global gain, can account for both reduced alpha power and enhanced P1 by attention (Figure 5-8A). Two predictions can be made according to Figure 5-8A. First, the attention-induced increase in local gain is not uniformly distributed over the level of the prestimulus EEG power. Specifically, the ratio between the two gain functions (attend versus ignore) has again an inverted-U shape, as shown in Figure 5-8B. Second, the overall increased steepness in the slope (gain) is accompanied by a reduced effective operational range W, from W1 to W2, implying a reduction in the trial-to-trial variability of prestimulus alpha activity by attention to maximize stimulus-evoked response.

Test of prediction 1: The data in Figures 5-7A and 5-7B, together with the data obtained in the same way from the ignore condition, are plotted in Figures 5-9A and 5-9B. It is evident
that the gain reflecting the slope of the sigmoidal function is enhanced for the attend condition relative to the ignore condition. The ratios of P1 amplitude between the two conditions for different prestimulus alpha power groups are shown in Figures 5-9C and 5-9D. As expected, the gain ratio is maximal for the intermediate power group, in agreement with the model prediction in Figure 5-8B. Quantitatively, for the left occipital areas, the P1 amplitude ratio for power group 3 (intermediate alpha power) is 52% and 68% higher than that for power group 1 (lowest alpha power) and power group 5 (highest alpha power). For the right occipital areas, the P1 amplitude ratio for power group 3 is 16% and 60% higher than that for power group 1 and power group 5.

It is worth noting that the P1 component is relatively small for the ignore condition. Its subensemble estimation is further complicated by the fact that each power group in a given subject has only about 30 trials. These factors may explain the weak and sometimes even the lack of inverted-U appearance in Figures 5-9A and 5-9B, respectively, for the ignore condition.

**Test of prediction 2:** Alpha band power in the interval -300 to 0 ms was estimated on a single-trial basis for each of the three conditions over the parieto-occipital sites and log-transformed. Figure 5-10A shows the Gaussian fits to the empirical distributions from a representative subject. The left-ward shift of the distributions under task conditions corresponds to the reduced mean alpha power reported in Figures 5-4 and 5-5. In addition, both the attend and ignore conditions have narrower alpha power distributions relative to that of the fixation condition, with the distribution for the attend condition further narrowed from that for the ignore condition. Figures 5-10B, 5-10C and 5-10D summarizes the variance of the empirical alpha distribution across all subjects for the attend and ignore conditions. The variance reduction when attention is deployed to the contralateral visual field (attend) relative to the ipsilateral visual field (ignore) was significant at $p = 0.003$ over both hemispheres, and the reduction relative to the
fixation condition was significant at $p = 0.0005$. The variance over the left hemisphere for the attend-right condition was significantly lower than that for the attend-left condition and for the fixation condition at $p = 0.00075$ and $0.0005$ respectively. The variance over the right hemisphere for the attend-left condition was lower than that for the attend-right condition and for the fixation condition at $p = 0.088$ and $0.021$ respectively. In addition, the variance for the ignore condition collapsed over both hemispheres is lower than that for the fixation condition at $p = 0.01$.

5.3.6 Role of Excitability: Validation in a Single Neuron Model

A computational model was constructed as described in section 5.2.8. The firing rates were collected and averaged over 40 simulation trials of 200 ms duration each, for 25 increasing values of $\sigma_i$ (variance of inhibitory synaptic input) in the range of 0–0.0375µS, for 8 levels of increasing excitability (mean membrane depolarization. Firing rate over the 200 ms interval was averaged across trials and plotted as a function of the variance of background synaptic activity in Figure 5-11A for three levels of excitability: low excitability (less depolarized, red curve); intermediate excitability (more depolarized, black curve) and high excitability (excessively depolarized, blue curve). The derivatives of all three sigmoidal functions are given in Figure 5-11B. Notice from Figure 5-11A and 5-11B that a moderate increase in depolarization increases gain, but too much excitability causes a decrease in gain. This nonlinear relation is further demonstrated by plotting the firing rate as a function of all 8 levels of excitability and the 25 levels of variance of background synaptic activity in Figure 5-11C. The average gain, defined as the weighted mean of the inverted-U function in Figure 5-11B, is plotted for each level of excitability in Figure 5-11D, which suggests the existence of an optimal range of excitability for enhanced stimulus processing. The results of this modeling study confirm the influence of excitability (mean membrane depolarization) on the gain curve, where within optimal ranges, an
increase in excitability effects an increase in gain. The results obtain through this modeling study is in complete agreement with the observations of attentional modulation at the scalp EEG level hence providing further validation of the proposed model.

5.4 Discussion

We considered the relation between visually evoked response and prestimulus alpha activity. Three results were found: (1) the P1 amplitude is shown to be an inverted-U function of the prestimulus alpha power (Figure 5-7), providing key evidence for the validity of the sigmoidal function model in Figures 5-5 and 5-6; (2) attentional enhancement of the P1 amplitude is interpreted as reflecting an increase in the overall slope of the sigmoidal function; and (3) in addition to amplitude reduction, the trial-to-trial variability of alpha is also reduced by attention, corresponding to a reduced working range as a consequence of the attentional modulation of the sigmoidal function (Figure 5-8). In light of these results some of the seemingly conflicting observations in relation to alpha oscillations and stimulus processing may be reconsidered. First, in a given behavioral state (e.g. attend, ignore, or fixation), the inverted-U relation in Figures 5-6 and 5-7 indicates that intermediate levels of prestimulus alpha activity lead to strongest stimulus-evoked response. This may explain why both high and low levels of prestimulus alpha activity are not conducive to the detection of a threshold level stimulus (Ergenoglu et al., 2004; Babiloni et al., 2006; Romei et al., 2008b; Romei et al., 2008a). This explanation, together with reports in the somatosensory domain where the rate of detecting a weak stimulus is highest for intermediate levels of mu activity (Linkenkaer-Hansen et al., 2004; Zhang and Ding, in press), appears to suggest a mechanism of sensory processing that is modality independent. Second, attentional reduction of alpha power, possibly mediated by top-down compensatory mechanisms, is taken to indicate the increased overall slope of the sigmoidal
function and hence the higher global gain to input, and should not be extrapolated to imply that prestimulus alpha should be inversely proportional to stimulus evoked response.

### 5.4.1 Theoretical Model

The state of the brain fluctuates in a seemingly random manner. The fate of a sensory stimulus depends on the waxing and waning of the physiological variables characterizing these fluctuations (Lakatos et al., 2005; Lakatos et al., 2008). While behavior such as attention modulates the global dynamics of these variables (Foxe et al., 1998; Sauseng et al., 2005; Thut et al., 2006; Fischer et al., 2008), on a given trial, the processing of a stimulus is affected by the magnitude of these variables immediately preceding its onset. In this work, the global state of a neuronal ensemble is assumed to be defined by a sigmoidal function, where the horizontal axis is the level of background synaptic activity over a suitably defined time interval and the vertical axis is the output firing rate over the same interval. On a trial by trial basis, the stimulus-evoked response is proportional to the derivative of the sigmoidal curve referred to as local gain, which is an inverted-U function of background synaptic activity level preceding the stimulus (Figure 5-5). Attention is hypothesized to enhance the global gain to sensory input by increasing the overall slope of the sigmoidal function. This model, while inspired by recent computational studies on the impact of mean and variance of membrane potential fluctuations on a neuron’s responsiveness to input (Ho and Destexhe, 2000; Chance et al., 2002; McCormick et al., 2003; Wolfart et al., 2005; Haider et al., 2007), differs from these models in two important ways. First, the horizontal axis in Figure 5-5, rather than being the external input of varying intensity, is the level of moment by moment synaptic background activity assessable by dendritic field potentials. Second, an explicit mechanism is given, which stipulates that the stimulus-evoked response is an inverted-U function of the level of background synaptic activity immediately preceding stimulus onset.
5.4.2 Model Testing and Validation

In Figure 5-6, the model in Figure 5-5 is reformulated in which the amplitude of the P1 component is equated with the intensity of stimulus-evoked firing and the prestimulus alpha power with the level of background synaptic activity. A single-trial based analysis was carried out, and as predicted, an inverted-U relationship between the P1 amplitude and the prestimulus alpha power was found for both hemispheres (Figure 5-7). Considered a validation of the model, this finding suggests that the observed increase in P1 amplitude to the attended stimulus reflects increased global gain, which is defined by an increase in the overall slope of the sigmoidal function (Figures 5-8 and 5-9). The change in the sigmoidal function further predicted a possible leftward shift of the sigmoidal function and a reduced effective operational range, both of which were confirmed by computing and comparing across experimental conditions the mean prestimulus alpha power (Figure 5-4) and the variance of the alpha power distribution estimated on a trial by trial basis (Figure 5-10). It is worth noting that qualitatively similar results were observed when alpha power was replaced by total signal variance to index background activity. The alpha activity was chosen as a proxy for the strength of background synaptic activity because (1) all subjects exhibited prominent spectral power in this band accounting for most of the total signal variance and (2) robust attentional modulation was observed in this band. In our data attentional modulation in the other frequency bands including theta, beta and gamma was either completely absent or were not statistically significant across subjects. In addition, power in higher frequency bands such as beta and gamma are too small to serve as a representative of total synaptic background activity.

5.4.3 P1 Genesis and Attentional Modulation

The visually evoked P1 component reflects the early response of the extrastriate cortex and is enhanced by spatial attention. See Figures 5-2 and 5-3. Concerning the generating mechanisms
of P1, Mitzdorf (Mitzdorf, 1985) showed in cats that a surface positive potential may arise due to excitatory synaptic activation of the supragranular pyramidal cells at their basal dendrites spanning layer 3 or portion of layer 4, which causes an extracellular sink at layer 4 and a superficial source sensed by the surface electrode. In behaving macaques, Schroeder et al. (Schroeder et al., 1991) localized the P60 component, the monkey equivalent of the P1 component in humans, to pattern evoked and pattern reversal VEP to layer 2/3. Associated with the P60 was an increase in MUA activity signifying that it is predominantly a depolarization of the supragranular pyramidal cells in the superficial layers. The excitatory input to the superficial layers is considered to be from the layer 4 stellate cells which receive afferent input from either thalamocortical projections or inputs from earlier sensory areas (Figure 5-6A). According to these results, the increased P1 amplitude by attention reflects the increased firing of neuronal populations in layer 4, which is the basis for the choice of P1 for our analysis. The origins of the N1 and other later evoked components (Clark and Hillyard, 1996; Di Russo et al., 2002; Di Russo et al., 2003) are more complex. Their generation, involving reentrant processing and the interaction among multiple brain areas (Garrido et al., 2007), depends to a limited degree on visual alpha. These components are not pursued further.

5.4.4 Alpha Oscillation: Neuronal Mechanisms and Attentional Modulation

The genesis of alpha oscillations in visual cortex is debated. While early investigators focused on the pacemaking role of the thalamus, more recent work stresses the cortical origin of the alpha oscillations. Bollimunta et al.(2008), analyzing laminar field potentials and multiunit activity from extrastriate cortical areas V2 and V4 of behaving macaques, found local generators of alpha in superficial layers, layer 4 and deep layers, and showed that the activities of these generators are highly synchronized. According to this view, the widely observed decrease of EEG alpha power in areas contralateral to the attended visual field (Figures 5-4), likely reflects
similar decreases in the entire cortical column, allowing us to establish a link between scalp measured alpha power and layer 4 neuronal firing, the latter being proportional to the magnitude of the P1 component.

Physiologically, the suppression of alpha is taken to imply increased cortical excitability (Foxe et al., 1998; Bastiaansen and Brunia, 2001; Marrufo et al., 2001; Sauseng et al., 2005; Thut et al., 2006; Klimesch et al., 2007) (Jones et al., 2000; Worden et al., 2000; Goldman et al., 2002; Kelly et al., 2006; Rihs et al., 2007; Jones et al., 2008; Romei et al., 2008a). Cortical excitability is often understood in terms of mean depolarization levels of cellular membrane potentials and it is known to have a complex relation with stimulus-evoked response. For example, the absence or very low levels of spontaneous oscillatory activity may fail to bring local neuron populations closer to firing threshold and excessive depolarization due to high levels of spontaneous activity may cause short-term synaptic depression, both of which can lead to diminished response to sensory input (Abbott et al., 1997; Chung et al., 2002; Petersen et al., 2003; Dehaene and Changeux, 2005). While enhanced stimulus processing by attention in our experiment is thought to be mediated by increase in the slope of the sigmoidal function or gain, as defined in Figure 5-8, excitability and gain in the current framework are not mutually exclusive concepts, and their relationship was explored in a computational study (Figure 5-11). The results show that (1) there is an optimal range in the mean membrane depolarization which gives rise to highest overall slope of the sigmoidal function, and (2) both insufficient and excessive depolarization reduce the slope of the sigmoidal function, thereby hindering the gain to sensory input. This computational study, together with the experimental data, suggests that (1) stimulus processing benefits directly from increased global gain and (2) attention optimally modulates excitability to enable such gain increase.
Figure 5-1. Experimental task. At the beginning of each trial, the cue (left/right pointing arrow) presented at the fixation instructs the subjects to attend to one of two demarcated locations. After 1800 to 2200 ms a unilateral imperative stimulus (target/standard) is presented on one of the locations. The subjects had to indicate by a speeded response to the occurrence of the target stimulus at the attended location.
Figure 5-2. ERP attention effect. (A) Typical waveform of visual ERP over the parieto-occipital region contralateral to the visual field of stimulation. Note that attending to the stimulus location produces an enhanced P1 and N1 component. (B) Grand average peak P1 amplitudes averaged over channels overlying the occipital / parieto-occipital areas contralateral to visual field of stimulation, indicating attentional enhancement when the stimulus location was attended relative to ignored. ATL – attend left, IGL – ignore left; ATR – attend right, IGR – ignore right. Panels (C) and (D) summarize the normalized visual evoked P1 component over 12 subjects over the left parieto-occipital areas (C) and right parieto-occipital areas (D) when attention was paid to the contralateral visual field (filled black-Attend), contralateral visual field was ignored (filled white-Ignore). Normalization was performed only for display purposes and was obtained by dividing the respective conditions by the sum of estimates of both conditions.
Figure 5-3. Scalp distribution of attentional enhancement. Difference ERPs of grand average over 12 subjects at 120 ms after presentation of the standard stimulus. Note the posterior P1 (shaded red) and fronto-central N1 (shaded blue) attention effect. (A) Attend minus ignore difference ERP for left visual field input and (B) Attend minus ignore difference ERP for right visual field input.
Figure 5-4. Attentional modulation of alpha band activity. Grand average power spectrum over 12 subjects over left parieto-occipital (A) and right parieto-occipital areas (B) when attention was paid to the contralateral visual field (black), contralateral visual field was ignored (red) and for relaxed fixation condition (blue). (C)-(E) highlights the scalp topography of difference in alpha band power (-300 to 0 ms prior to standard stimulus) averaged across subjects. (C) Attend left minus attend right, blue shading over the right parieto-occipital areas indicate lower alpha band power to attend left (contralateral visual field) relative to attend right (ipsilateral visual field) and red shading over the left parieto-occipital areas indicate lower alpha band power to attend right relative (contralateral visual field) to attend left (ipsilateral visual field). (D) Attend left (ATL) minus relaxed fixation condition (FIX), blue shading over the right parieto-occipital areas indicate a reduction in the alpha band with attention as against relaxed fixation. (E) Attend right (ATR) minus relaxed fixation condition, both left and right parietal-occipital regions show reduction in alpha band power (blue shading) when attention is directed to the right visual field as compared to relaxed fixation condition.
Figure 5-5. Schematic illustration of theoretical model. (A) For a neuronal ensemble the spontaneous output firing rate $O$ measured over a suitably defined time interval is a sigmoidal function of endogenous background synaptic activity level $SN$ measured over the same interval. Letting $SX$ denote stimulus-induced synaptic activity, the stimulus-evoked firing rate, $O(SN+SX) - O(SN)$, is proportional to the derivative (local gain) of the sigmoidal curve, $[O(SN+SX) - O(SN)] / SX$, shown as the red curve in (B). In this model, when the stimulus is kept constant, the stimulus-evoked response is an inverted-U function of the prestimulus level of background synaptic activity. The variable $W$ in (B) defines an effective range of prestimulus level of synaptic activity beyond which stimulus evokes a negligible response.
Figure 5-6. Model reformulation in terms of EEG variables. (A) Neural genesis of visually evoked P1. Feedforward activation of layer 4 stellate cells excites the basal dendrites of the superficial layer pyramidal cells, leading to an extracellular source comprised mainly of passive return current near the cortical surface, which is sensed by the scalp electrode as a positive-going ERP component. (B) Reformulated model in which prestimulus EEG power in alpha band is equated with level of background synaptic activity and magnitude of P1 with intensity of stimulus-evoked response. This model predicts that the P1 amplitude is an inverted-U function of prestimulus alpha power with the variable W defining a range of effective operation.
Figure 5-7. Relationship between prestimulus alpha power and stimulus processing. Trials with attended standard stimuli were considered (valid trials). Single trials were rank ordered by the magnitude of prestimulus alpha power (-300 ms to 0 ms) and sorted into 5 groups of equal size. The P1 component was determined for each group, normalized and averaged across subjects, and plotted as function of group index in (A) for left parieto-occipital areas and (B) for right parieto-occipital areas. An inverted-U relationship is clearly seen where the solid lines represent quadratic fits. Error bars are the standard error of the mean.

Figure 5-8. Schematic illustration of attentional modulation mechanisms of ongoing activity. (A) Attention shifts the sigmoidal curve in Figures 4 and 5 left-ward and increases its overall slope (global gain). (B) The ratio of the gain curves in (A) for attend and ignore conditions is again an inverted-U function.
Figure 5-9. Gain ratio as a function of prestimulus alpha. P1 amplitude as a function of prestimulus alpha power is plotted for both attend and ignore conditions in (A) and (B). The ratios between the two curves are shown in (C) and (D). Maximum gain is achieved for intermediate levels of prestimulus alpha activity.
Figure 5-10. Distribution of alpha power. (A) Distributions of log-transformed single trial alpha power for attend, ignore and fixation conditions over left parieto-occipital areas from a representative subject. Variance of the single trial alpha power distribution is compared over subjects between attend and ignore conditions in (B) where a reduction in variance is evidence of decreased trial-to-trial alpha power variability.
Figure 5-11. Computational study of relation between excitability and gain. (A) Firing rate over a 200 ms interval as function of background synaptic level for three levels of mean membrane depolarization (blue: high excitability, black: intermediate excitability, and red: lower excitability). (B) Derivative of the sigmoidal curves in (A) showing nonlinear relationship between gain and excitability. (C) Firing rate as a function of mean membrane depolarization levels and variance of background synaptic activity. (D) Average gain for increasing levels of membrane depolarization.
CHAPTER 6
TOP-DOWN CONTROL OF HUMAN VISUAL CORTEX IN ANTICIPATORY SPATIAL VISUAL ATTENTION

6.1 Introduction

Early studies into the neuronal mechanisms of attention focus on attention’s role in the selective processing of stimuli. How attention modulates endogenous anticipatory/preparatory processes that precede the appearance of stimuli is less known. Emerging reports indicate that preceding changes in stimulus-evoked response properties, deployment of attention modulates the excitability of the sensory areas that facilitate subsequent stimulus processing (Liang et al., 2002; Dehaene and Changeux, 2005; Padilla et al., 2006; Weissman et al., 2006; Bestmann et al., 2007; Eichele et al., 2008; Zhang et al., 2008b; Gregoriou et al., 2009; Zhang and Ding, in press). However, such goal-directed prestimulus modulation of sensory cortical activity is not an inherent property of the early sensory areas. Instead, it is believed that the frontal–parietal network facilitates an enhancement of the excitability of the task-relevant and feature-specific visual areas and perhaps a suppression of activity in task-irrelevant visual areas in advance of visual stimulation by modulating its baseline activity (Chelazzi et al., 1993; Luck et al., 1997; Hillyard et al., 1998; Kastner et al., 1999; Hopfinger et al., 2000; Kastner and Ungerleider, 2001; Corbetta and Shulman, 2002; Gazzaley et al., 2005; Giesbrecht et al., 2006; Grent-'T-Jong and Woldorff, 2007; Klimesch et al., 2007). In line with this notion, it has been identified that deployment of covert spatial visual attention is associated with increased activation in a network involving dorsal frontal and parietal cortices with concomitant increases in activation over retinotopic early visual areas (Desimone, 1996; Gitelman et al., 1999; Kastner et al., 1999; Hopfinger et al., 2000; Corbetta and Shulman, 2002; Giesbrecht et al., 2003).

While prior neuroimaging and electrophysiological studies of the top-down control of spatial visual attention have offered insights into the areas in the brain that exert control over
stimulus processing, the neural mechanisms by which this is implemented are still unclear. Apart from prestimulus modulation of activity over visual areas that facilitate stimulus processing, putatively induced by top-down signals from the frontal–parietal network, empirical evidence of such inter-areal interaction is lacking with the exception of (Fuster et al., 1985; Siegel et al., 2008; Gregoriou et al., 2009). However, recent microstimulation and rTMS studies in monkeys and humans respectively on frontal eye fields (FEF) and intraparietal sulcus (IPS) have provided casual evidence of top-down influences of these areas on activity in the visual cortices (Armstrong et al., 2006; Taylor et al., 2007; Capotosto et al., 2009) during anticipatory attention. Additional evidence of frontal dependent tonic top-down modulatory influence on visual processing in humans comes from lesion studies (Knight, 1997; Knight et al., 1999; Barcelo et al., 2000; Yago et al., 2004) which is also supported by anatomical evidences of neural substrates that enable such long-distant communication coming from axonal tract-tracing and diffusion tensor imaging in animals and humans (Ungerleider et al., 1989; Felleman and Van Essen, 1991; Petrides and Pandya, 1999; Barbas, 2000; Rempel-Clower and Barbas, 2000; Petrides and Pandya, 2002).

To identify the neural signals that mediate the interaction between the fronto-parietal and early visual areas during anticipatory attention, we studied the activity during the delay period between an attention directing cue and the subsequent imperative stimulus from human volunteers performing a trial-by-trial cued spatial visual attention task. Physiologically, EEG field potential oscillations reflect the rhythmic shifting in excitability due to fluctuating extracellular dendritic currents which are in turn caused by synaptic input (Niedermeyer and Lopes Da Silva, 2005). Recent studies on animals and humans have shown that the alpha rhythm (8-12 Hz) over the visual areas is attenuated in a topographically-specific fashion dependent on
the hemifield of attentional cueing and this state of reduced alpha activity is considered to reflect increased cortical excitability (Foxe et al., 1998; Worden et al., 2000; Bastiaansen and Brunia, 2001; Marrufo et al., 2001; Sauseng et al., 2005; Kelly et al., 2006; Thut et al., 2006; Jokisch and Jensen, 2007; Klimesch et al., 2007; Rihs et al., 2007; Romei et al., 2008b; Romei et al., 2008a; Van Dijk et al., 2008). While synchronization of neuronal oscillations within and across cortical areas has long been suggested as a potent mechanism of attentional selection and sensory gating (Salinas and Sejnowski, 2000; von Stein et al., 2000; Engel et al., 2001; Fries et al., 2001; Salinas and Sejnowski, 2001; Fries, 2005; Buschman and Miller, 2007; Lakatos et al., 2007; Melloni et al., 2007; Lakatos et al., 2008; Rajagovindan and Ding, 2008b; Rajagovindan and Ding, 2008a; Siegel et al., 2008; Gregoriou et al., 2009), evidence as to whether and how selective attention modulates the rhythmic synchronization between frontal, parietal, and early visual regions in the human brain remains sparse (Doesburg et al., 2008; Siegel et al., 2008). Further the exact neural mechanism of how this increased excitability over the visual sensory areas is brought about has not been clearly established. The goal of this study is to examine the neural mechanism by which the visual cortical excitability is controlled by the frontal-parietal network. In light of prior anatomical and lesion evidence (Gonchar and Burkhalter, 2003; Knight et al., 1999), two competing hypotheses may be put forth: increased visual excitability and reduced alpha rhythm is mediated through (1) increased excitatory top-down input to local pyramidal neurons or (2) decreased excitatory top-down input to local inhibitory interneurons. In particular, three questions are considered: (1) what is the signal that implements the frontal-parietal control in visual cortex, (2) how functional connectivity between executive and sensory areas is modulated by attention, and (3) whether top-down control of visual activity is transient or sustained. These questions were addressed by recording scalp EEG from healthy volunteers.
performing a trial-by-trial cued spatial visual attention task and by performing multivariate
spectral analysis to assess the regional and the inter-areal oscillatory synchronization and causal
interaction between the fronto-parietal and the visual areas during a period of sustained covert
attention.

6.2 Materials and Methods

6.2.1 Subjects

The experimental protocol was approved by the University of Florida Institutional Review
Board. Nineteen subjects, free from movement and neurological disorders and with normal or
corrected-to-normal vision, gave written informed consent and participated in the study. Data
from twelve subjects (20-31 years of age, 25.16 ±3.5 years, 5 females and 7 males, all right
handed) were included in the analyses. The remaining 7 participants were excluded due to poor
performance or excessive artifacts.

6.2.2 Paradigm

Seated in a dimly lit, acoustically and electrically shielded room, the subject was instructed
to fixate on a central cross on a VGA monitor placed approximately 85 cm from the eye. Two
square boxes, each delineated by white dots placed at the four corners in the upper left visual
field and in the upper right visual field, were displayed permanently on the monitor (Figure 6-1).
Each box, centered 4.7° above the horizontal meridian and 7.2° lateral to the central fixation,
subtended a visual angle of 3.35°. A trial began with the onset of a cue, which consisted of either
a left or right pointing arrow of 200 ms in duration at the location of the central fixation cross,
instructing the subject to deploy covert attention to the square box on the side indicated by the
arrow. After a random time delay between 1800 ms and 2200 ms, a standard or a target stimulus
of 100 ms in duration appeared either inside the attended square box (valid trial) or inside the
square box on the opposite side (invalid trial). The standard stimulus was a circular checkerboard
subtending a 3.3° visual angle, and the target stimulus was also a circular checkerboard, but of a slightly smaller diameter. The subject was required to press a button with their right index finger in response to the valid target stimulus and withhold response to any other stimuli. The standards appeared 80% of the time with 50% validity and the targets appeared 20% of the time with 66% validity. The interval between the cue offset of the previous trial and the cue onset of the successive trial was randomly varied between 4700 to 5700 ms. The entire experiment was comprised of 15 to 16 blocks of approximately 6 min each (60 trials). Breaks were given between blocks. Subjects received practice sessions of 150 trials to familiarize themselves with the task and to minimize the effect of learning.

6.2.3 Data Acquisition

The electroencephalogram (EEG) data was recorded with a fully DC-coupled 128-channel BioSemi ActiveTwo System at a sampling rate of 1024 Hz. Four additional electrooculogram (EOG) electrodes were placed around the eyes to monitor eye blinks and horizontal and vertical eye movements. EEG and EOG data was amplified and lowpass-filtered with a cutoff set at 205 Hz. The stimulus and the response was delivered and registered by a Berisoft Experimental Run Time System (ERTS) and by a Berisoft EXKEY microprocessor logic pad respectively.

6.2.4 Data Preprocessing

Analysis was performed using BESA 5.2 and custom scripts written in MATLAB 7.4. The EEG data was low-pass filtered off-line with a cutoff set at 83 Hz and downsampled to 250 Hz. The channels were re-referenced off-line against the average reference (Nunez et al., 1997; Ferree, 2006). Trials contaminated by muscle artifacts, movement artifacts, or excessive eye blinks were excluded from further analysis. Trials with correct and incorrect behavioral responses to validly cued target stimulus were analyzed separately. The voltage time series was transformed into continuous current source density (CSD) estimates (Perrin et al., 1989; Nunez
et al., 1997; Scherg et al., 2002) to mitigate the adverse impact of volume conduction and common reference on functional connectivity measures. The continuous CSD data was epoched to yield two datasets (a) from -300 ms to 1500 ms around the cue onset with 0 ms indicating the presentation of the left-pointing or right-pointing arrow and (b) from -300 ms to 0 ms with 0 ms indicating the onset of the imperative stimuli (standards and targets).

6.2.5 Data Analysis

**Spectral measures:** Three analyses were performed on the EEG data. The multivariate autoregressive (MVAR) modeling method was used in all three analysis (Ding et al., 2006). For an ensemble of trials at each recording site the ensemble mean was removed from each trial. This allowed the residuals to be treated as coming from a zero mean stochastic process required by MVAR data modeling. Model order between 23 and 25 were found to be optimal across subjects, determined both by the Akaike information criterion and comparing the spectral estimates obtained by Fourier based methods (Thomson, 1982; Mitra and Pesaran, 1999). Hence a fixed model order of 24 was chosen for all subjects. Three spectral quantities were derived from the model: power, coherence, and Granger causality. The regional oscillatory activity quantified by the power was averaged across the preselected channels overlying the regions of interest and further averaged within the frequency bands of interest. The inter-areal coherence was obtained by averaging the coherence across all pairs of sites representing the different regions of interest and further averaged within a given frequency band. Granger causality was calculated in which the set of channels representing a given area (frontal, parietal, or visual) was treated as a block (Wang et al., 2007b). From the model, Granger causality spectra for Frontal→Occipital, Parietal→Occipital, Occipital→Frontal, Occipital→Parietal, Frontal→Parietal and Parietal→Frontal were derived and averaged over the frequency band of interest. As with any other physiological variables, power, coherence and Granger causality values varied markedly
from subject to subject. To remove the possible adverse effect of this variability on population averaging, the spectral measures for each condition were first normalized by dividing by the corresponding measures from the ignore condition, and then averaged across subjects. The Wilcoxon’s rank-sum test was then applied to assess the statistical significance of the differences between conditions.

**Analysis 1:** Attentional modulation of power, coherence and Granger causality in the time period -300 ms to 0 ms prior to the onset of the imperative stimulus was analyzed for trials with correct behavioral responses. Five regions of interest were identified: anterior medial frontal, medial frontal, parietal and lateral occipital areas where each area is represented by six neighboring channels (Figure 6-2D).

**Analysis 2:** The behavioral consequences of anticipatory oscillatory activity were examined. Trials with validly cued targets were rank-ordered according to the reaction time (RT) and divided into two non-overlapping groups of equal size: fast RT group and slow RT group. Error trials were given a reaction time of infinity. Spectral measures over a period of -300 to 0 ms prior to stimulus onset were estimated and the Wilcoxon’s rank-sum test was then applied to assess the statistical significance of the differences in the ongoing oscillatory activity preceding the two classes of trials.

**Analysis 3:** Temporal functions of power, coherence and Granger causality were estimated using a sliding window approach. Each window was 140 ms (35 sample points) in length and stepped forward in 4 ms increment. A total of 416 windows resulted for the time period -300 ms to 1500 ms around the onset of the attention directing cue. The time designation of each window corresponded to the middle of the covered interval.
**Significance testing:** For interdependence measures the following random permutation procedure was adopted for statistical significance assessment (Nichols and Holmes, 2002; Brovelli et al., 2004). (1) Consider the data from two recording sites (A and B). Randomly pairing data for site A with data for site B from a different trial leads to the formation of a synthetic ensemble of trials for which there is no interdependence. Performing such random pairing with many different permutations (500 permutations used for this study) will result in the null-hypothesis distribution for the interdependence quantity of interest from which a threshold can be derived that corresponds to a given significance level ($\alpha = 0.01$ chosen for this study). The value from the actual data is compared with the threshold for the assessment of statistical significance. This procedure was implemented for the coherence measures over each subject during the prestimulus time period for Analysis 3. Eleven out of the twelve subjects exhibited significant alpha band coherence between the frontal, parietal and occipital areas, revealing a coherently oscillating network. Granger causality was then estimated between the regions of interest over the eleven subjects who exhibited coherent oscillations in the alpha band between areas implicated in the visual attention network. (2) Between the attend and ignore conditions there are two temporal functions of averaged alpha band spectral estimates for Analysis 3. The statistical significance of their difference was assessed by employing the Wilcoxon’s sign-rank test over each sliding window. The differences were deemed statistically significant only if the differences were significant over at least 34 consecutive sliding windows to minimize potential false positives due to multiple comparisons. Time periods of significant difference were indicated on the plots for comparison.

**6.3 Results**

Twelve subjects performed the task according to instructions. The average target detection rate was 87% and the mean reaction time (RT) was 521 ms. The average false alarm rate
stemming from (1) response to the target appearing in the ignored location, (2) response to the attended standard stimulus, and (3) response to the ignored standard stimulus was 1.6%, 4.0% and 0.2%, respectively.

**Analysis 1:** For the time period -300 to 0 ms prior to the onset of the standard stimulus all subjects exhibited prominent power spectral peaks in the alpha band (8-12 Hz) accounting for most of the total signal variance. No consistent power spectral peaks were seen in theta (4-8 Hz), beta (13-25 Hz), and gamma (25 to 40 Hz) frequency bands. In agreement with previous work, alpha activity for the attend condition is significantly lower than for the ignore condition (p=1.2e-7), and maximum alpha suppression was seen over the parieto-occipital areas contralateral to the attended visual field. While theta and beta power were reduced by attention (p=0.04 and p=1.6e-3 respectively), given the lack of consistent spectral peaks in theta and beta frequencies across participants, it is highly probable that their attentional modulation stems from power leakage associated with the spectral estimation procedure from the alpha band. Gamma band power was not different between the attend and the ignore conditions (p=0.59). Frontal-Occipital and Parietal-Occipital coherence in each frequency band was evaluated using the channels overlying the anterior medial frontal, medial frontal, parietal, and lateral occipital areas in Figure 6-2D and the difference between the two conditions were not statistically significant (p>0.13). However, Granger causality spectra in Figures 6-2A and 6-2B between the same set of channels for a typical subject shows a reduction in the alpha band when the attend is compared with the ignore condition. This reduction of Frontal→Occipital and Parietal→Occipital causal influences in the alpha band was consistent across subjects as shown in Figure 6-2C. Statistically, collapsed across left and right occipital areas, alpha range Frontal→Occipital and Parietal→Occipital for attend condition is significantly lower than for ignore condition (p=0.035...
and \( p=0.06 \) respectively). The difference in causal influences in the opposite direction, Occipital→Frontal and Occipital→Parietal, between attend and ignore condition for the same time period failed to reach statistical significance \((p>0.79)\). In addition, as summarized in Table 1, Granger causality values in theta, beta and gamma bands are not modulated by attention, suggesting that the alpha oscillatory activity is likely the signal that mediates top-down attentional influences.

**Analysis 2:** To identify if the alpha oscillatory activity during the anticipatory attention period preceding the presentation of the targets is correlated with behavioral performance, power, coherence and Granger causality in alpha band were derived for the period -300 to 0 ms before validly cued target stimulus for the fast and slow reaction time groups (Figure 6-3). In line with the result of Analysis 1, we found that for the trials in the fast reaction time group where the subjects correctly identified the targets and made a quicker response, the alpha band power over the occipital areas contralateral to the attended location, and the alpha band coherence between the fronto-parietal areas and the occipital areas contralateral to the attended location, were significantly reduced relative to the slow reaction time group \((p=2.4e-5\) and \(2.2e-4\) respectively). Similarly, the causal influence from the anterior medial frontal region into occipital areas contralateral to the attended location was significantly reduced for the fast reaction time group compared to the slow reaction time group \((p=0.035)\). However, no statistically significant difference in causal influence from the medial frontal areas sampled around the electrode Fz and from the medial parietal areas into the occipital areas were observed \((p>0.12)\). Statistically significant difference in causal influence from occipital regions into the frontal and parietal regions, possibly reflecting bottom-up influence, were observed \((p=0.035)\) with the faster reaction time group trials exhibiting reduced
**Analysis 3:** Figure 6-4A compares the time course of alpha band power over the occipital areas when attention was allocated to the contralateral visual field (attend, solid line) with when the contralateral visual field was ignored (ignore, dotted line). Periods of significant differences between the two conditions ($p < 0.05$) are indicated in Figure 6-4. Post-cue alpha power decreased markedly shortly after the presentation of the cue over the occipital regions with the attend condition having greater alpha power reduction compared to the ignore condition and this difference was sustained throughout the anticipatory attention period.

The time courses of coherence and causality between the combined fronto-parietal areas (anterior medial frontal, medial frontal and parietal) and the occipital visual areas are shown in Figures 6-4B-6-4D. These functional connectivity measures exhibited marked decrease post-cue for both attend and ignore conditions, suggesting a substantial weakening of the oscillatory network in the alpha band. Although a similar post-cue decrease in coherence and causal influences between the frontal and parietal regions were observed, there were no significant differences between the attend and ignore conditions, consistent with the notion that both attend and ignore conditions involve effortful attention deployment and the frontal-parietal areas are equally engaged in both conditions (Hopfinger et al., 2000; Corbetta and Shulman, 2002; Bressler et al., 2008).

### 6.4 Discussion

Anticipatory attention is a cognitive process critical for top-down control. The maintenance of anticipatory attention following an attention directing cue has been shown to entail sustained delay period activity in the fronto-parietal network hypothesized to enable preparatory biasing of the task-relevant sensory areas (Luck et al., 1997; Kastner et al., 1999; Kastner and Ungerleider, 2001; Corbetta and Shulman, 2002). Further support for the tonic frontal top-down regulation comes from selective cooling in animals (Fuster, 1990) and human lesion studies where the loss
of frontal control impaired both inhibitory and excitatory influences on early sensory and sensory association areas (Knight et al., 1995; Knight et al., 1999; Barcelo et al., 2000; Yago et al., 2004). With accumulating evidence for the hypothesis, we predicted that with anticipatory visual attention, the frontal areas facilitated the excitability of the posterior visual areas contralateral to the attended location in preparation for the to-be-detected visual target stimulus. In this study, we evaluated whether visual cortex receives top-down modulation from frontal-parietal areas during anticipatory attention using scalp EEG recordings from healthy volunteers performing a trial-by-trial cued spatial visual attention task.

6.4.1 Alpha Band Oscillation: A Neural Correlate of Top-Down Attentional Control

It has been amply demonstrated that attention modulates ongoing brain activity prior to stimulus onset. In the human visual system, depending on the hemifield of attention deployment, alpha band power is shown to be reduced in a topographically selective manner over the extrastriate areas. In this study we consider whether visual alpha modulation is subjected to the control of higher-order executive structures. Four results were found. First, alpha band inter-areal synchrony and Granger causality between frontal-parietal areas and occipital visual areas were decreased by attention following an attention-directing cue. Second, the decrease was sustained throughout the anticipatory attention period. Third, the degree of fronto-parietal-occipital alpha band interaction is correlated with behavioral performance. Fourth, regional visual cortical activity and inter-areal interaction in other frequency bands (theta (4-8 Hz), beta (13-25 Hz), and gamma (25 to 40 Hz)) did not show consistent differences between attend and ignore conditions and were not systematically correlated with behavior across participants. Taken together, it is suggestive that the alpha oscillatory activity is likely a signal that mediates top-down attentional influences over the visual areas. Recent evidence of the causal role of the frontal-parietal network in the attentional modulation of the visual alpha oscillation (Capotosto et al., 2009) and
visual ERP (Taylor et al., 2007) using rTMS in humans further supports this notion, where the application of rTMS on FEF and IPS during the anticipatory attention period aimed at disrupting their top-down influence over early visual areas was characterized by the lack of the customary alpha power reduction and was associated with deteriorated attentional performance and target detection (Capotosto et al., 2009).

6.4.2 Top-Down Control of Visual Alpha: Excitation or Disinhibition?

Attention-induced alpha power reduction occurred approximately 200 ms after the cue and this state of suppressed alpha activity was sustained throughout the anticipatory period between cue and imperative stimulus. Reduced alpha power led to enhanced visual evoked response (not shown) and better behavioral performance (Figure 6-3). This is consistent with the notion that reduced alpha activity indexes increased excitability of the task-relevant visual sensory areas (Foxe et al., 1998; Bastiaansen and Brunia, 2001; Marrufo et al., 2001; Goldman et al., 2002; Laufs et al., 2003; Sauseng et al., 2005; Thut et al., 2006; Klimesch et al., 2007; Romei et al., 2008b; Romei et al., 2008a) and that a state of increased alpha activity potentially reflects functional inhibition (Worden et al., 2000; Kelly et al., 2006; Klimesch et al., 2007; Rihs et al., 2007).

In addition to regional modulation in oscillatory activity, interareal synchronization between the regions involved in attentional orienting, maintenance and processing is modulated in a topographic-specific manner. Specifically, we observed a strong reduction in interareal synchronization in the alpha frequency band between the higher-order areas represented by frontal and parietal areas and early visual extrastriate regions contralateral to the attended visual field relative to both the pre-cue baseline level and when the contralateral visual field was ignored for the same network. This reduction suggests a counterintuitive dissolution of the frontal-parietal-occipital network with deployment of attention. However given the evidence of
alpha band oscillation reflecting inhibitory control (Klimesch et al., 2007) and evidence from neuroimaging and lesion studies (Knight et al., 1995; Knight et al., 1999; Barcelo et al., 2000; Pliszka et al., 2000; Sieroff et al., 2004; Yago et al., 2004; Gazzaley et al., 2005; Murias et al., 2007) of tonic frontal inhibitory influence over early sensory areas either through cortico-cortical projections (Jones et al., 2000; Gonchar and Burkhalter, 2003) or through cortico-thalamo-cortical projections (Yingling and Skinner, 1975; Skinner and Yingling, 1976; Yingling and Skinner, 1976; LaBerge, 1997, 2005), it is likely that the observed synchronized network in the alpha band prior to attention deployment reflects tonic frontal-parietal inhibition of extrastriate areas. The subsequent attention related reduction may reflect a release from tonic inhibition, to facilitate an optimal excitability state over the sensory cortex, favoring a disinhibition mechanism.

Coherence being a symmetric measure does not offer distinct information on the contributions of the different directions of neural interaction between the regions. To dissociate top-down from bottom-up interaction and to characterize the attentional modulation and its time course, the data was subjected to Granger causality analysis. Granger causality in the alpha band between the frontal-parietal areas and occipital areas in both directions were found to be reduced as early as 200 ms following the presentation of the attention directing cue. Comparison of magnitude of Granger causality in the alpha band for frontal and parietal driving extrastriate regions revealed a further reduction when the attend condition is compared to the ignore condition reflecting differences in attentional deployment and attentional load. Given the evidence of long distance projections, e.g. from higher-order areas to occipital lobe, tend to arise from pyramidal neurons and terminate on interneurons (Jones et al., 2000; Gonchar and Burkhalter, 2003), this reduced Granger causality with deployment of attention likely reflects
reduced excitatory drive on local interneurons, suggesting a disinhibitory role of attention in which its goal-oriented deployment leads to the release of the visual cortex from tonic top-down inhibitory influence (Knight et al., 1999). EEG predominantly measures the activity due to pyramidal cells. Prior to the attention directing cue, frontal/parietal mediated tonic excitatory drive to the visual cortical interneurons would result in inhibitory postsynaptic potential (IPSP) in the pyramidal cells over the visual areas sensed by scalp EEG. The temporal precedence of activity between the fronto-parietal areas and the visual areas would manifest as strong pre-cue frontal driving posterior Granger causality characterizing the tonic inhibitory influence. The putative reduction in excitatory drive to the visual interneurons with deployment of goal directed attention would result in the release of tonic inhibition over the visual pyramidal cells and thus increase in excitability. This reduction in the tonic drive upon deployment of attention would account for the decreased fronto-parietal driving posterior Granger causality post-cue.

Further insights on the role of alpha band synchronization comes from low frequency rTMS (~1 Hz) studies known to induce inhibitory effects (Hilgetag et al., 2001; Brignani et al., 2008) where it has been shown to induce long-lasting increases in alpha band power and cortico-cortical alpha band coherence with associated decreases in evoked potential (Strens et al., 2002; Brignani et al., 2008). Gathering from evidences across modalities it emerges that a state of reduced excitability or functional inhibition is accompanied by increased alpha band activity and enhanced interareal coherence in the alpha frequency band. The reduction in the alpha band power, frontal-parietal-occipital coherence and reduced frontal-parietal driving extrastriate with deployment of attention strongly suggests an attentional control through a disinhibition mechanism, which likely subserves prestimulus biasing and maintenance of attentional state. It is however worth noting that long-range alpha band desynchronization has also been explained in
terms of an enhanced direct or indirect excitatory facilitation of local neural population, which
due to reciprocal interaction between local pyramidal cells and interneurons and complex
interplay of h and T ionic currents resulted in varying levels of jitter in the firing time of cells
leading to asynchrony and hence a reduction in local and interareal synchronization in the alpha
band (Jones et al., 2000). Unlike recent animal (Gregoriou et al., 2009) and human attention
studies (Siegel et al., 2008), the differences in higher frequencies between conditions were not
statistically significant across subjects. The inability of scalp EEG to clearly resolve gamma band
activity (25-90 Hz) may be a contributing factor. It should also be pointed out that, while
supporting a role of frontal-parietal areas in exerting top-down modulatory influence on the
excitability of visual cortex, our data do not have the requisite spatial resolution to resolve
whether this influence is anatomically mediated by the cortico-cortical or cortico-thalamo-
cortical forms of signal transmission (Watson et al., 1981; LaBerge, 1997; Heilman et al., 2000;

Additionally, bottom-up influence of the early visual areas on parietal and frontal areas
showed a drastic reduction following attention directing cue and further showed a significant
reduction with attention to contralateral visual field relative to when it was ignored specifically
in the alpha band (Figures 6-3 and 6-4D). Given that feedforward projections from lower-order
areas to higher-order areas are predominantly excitatory and that they terminate on excitatory
cells, it is surmised that this dissolution of causal influence from the early visual areas reflect a
weakening of the bottom-up excitatory drive supporting a reduction in the information transfer in
the bottom-up direction during anticipatory attention (Bressler et al., 2008) serving to reduce
interference due to distracters. Alternatively if the alpha band synchrony emerges from feed-
forward inhibition, this reduction in alpha band coupling similar to the top-down drive, may
reflect a opening up of a more efficient bottom-up communication channel enabling a more
effective sensory-perceptual and higher-order processing of the subsequent stimuli in the
attended domain.

6.4.3 Top-Down Control of Visual Alpha: Transient or Sustained?

Several areas including prefrontal cortex (PFC), frontal eye field (FEF), intraparietal sulcus
(IPS) and superior parietal sulcus (SPL) have been implicated in the top-down control of early
visual areas in covert spatial visual attention (Gitelman et al., 1999; Hopfinger et al., 2000;
Corbetta and Shulman, 2002). However, the question of whether the top-down biasing
originating from these higher-order areas to extrastriate regions during sustained attention is
transient or sustained remains unclear. It has been hypothesized that areas such as FEF and SPL
which are involved in shifting of attentional focus, may invoke a transient top-down control
(Luks et al., 2008) but see (Gregoriou et al., 2009) where as regions such the anterior PFC,
dorsolateral PFC and IPS implicated in maintaining anticipatory attention to spatial locations
may be continuously engaged throughout the anticipatory attention period (Kastner et al., 1999;
Hopfinger et al., 2000; Corbetta and Shulman, 2002; Luks et al., 2008). Although, our data do
not have the requisite spatial resolution to resolve the anatomical structure mediating the top-
down influence, it is likely that the frontal scalp electrodes sample activity from the anterior
PFC, FEF and the anterior cingulate regions and the parietal scalp electrodes sample activity
from the SPL and IPS among other neighboring structures. Our data suggests that upon initiation
of attention orienting activity, both the frontal, parietal and the posterior visual regions appear to
maintain sustained levels of activity throughout the cue-imperative interval indexing a continued
engagement of the frontal-parietal-occipital regions in the maintenance of the attentional state
and a tonic preparatory biasing of the relevant visual sensory areas. Further, any momentary
lapse within this frontal-parietal-occipital anticipatory attention network characterized by
increased magnitude of visual alpha power and interareal interaction resulted in deteriorated behavioral performance evidenced by response errors and slowed response. This weakening of top-down biasing may either be actively controlled in a goal-directed manner as is the case during the ignored condition or may be due to a momentary lapse in attention resulting in deficient visual processing of the subsequent stimulus and hence in errors.

Table 6-1. Attention modulation of oscillatory activity. p values of Wilcoxon rank-sum test result (two-tailed) for difference in magnitude of Granger causality between attend and ignore conditions over theta, alpha, beta and gamma frequency bands during the time period 300 to 0 ms immediately preceding the onset of the standard stimulus (Analysis 1).

<table>
<thead>
<tr>
<th>Granger Causality</th>
<th>Region of interest</th>
<th>Theta (4-8 Hz)</th>
<th>Alpha (8-12 Hz)</th>
<th>Beta (13-25 Hz)</th>
<th>Gamma (25-40 Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Top-down Granger</td>
<td>Frontal→Occipital</td>
<td>0.71</td>
<td>0.036*</td>
<td>0.71</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>Parietal→Occipital</td>
<td>0.29</td>
<td>0.06</td>
<td>0.12</td>
<td>0.29</td>
</tr>
<tr>
<td>Bottom-up Granger</td>
<td>Occipital→Frontal</td>
<td>0.13</td>
<td>0.79</td>
<td>0.45</td>
<td>0.45</td>
</tr>
<tr>
<td></td>
<td>Occipital→Parietal</td>
<td>0.49</td>
<td>1.00</td>
<td>0.30</td>
<td>0.49</td>
</tr>
</tbody>
</table>
Figure 6-1. Experimental task. At the beginning of each trial, a cue (left/right pointing arrow) was presented at the fixation point instructing the subjects to covertly attend one of two predefined locations in the upper left and upper right visual fields. After 1800 to 2200 ms of delay, a unilateral imperative stimulus of either target or standard type appeared at one of the two locations, and the subjects indicated the occurrence of the target stimulus at the attended location by a speeded keypress response.
Figure 6-2. Top-down attentional control of visual areas. Granger causality spectra for (A) (Frontal → Occipital) and (B) (Parietal → Occipital) from a representative subject are shown for the attend (black) and the ignore (gray) conditions. (C) Normalized Granger causality in the alpha frequency band for (Frontal → Occipital) and (Parietal → Occipital) are averaged across subjects and compared between attend (black) and ignore (white) conditions. The error bars are the standard error of the mean. (D) Regions of interest marked by shaded colors correspond to frontal (Fpz, Fz), parietal (Pz) and occipital cortices. * - denotes statistically significant difference (p<0.05).
Figure 6-3. Pre-target alpha band activity predicts performance. The figure summarizes the regional alpha band oscillatory synchrony over the Occipital electrodes, averaged coherence between (Frontal-Occipital) and (Parietal-Occipital) areas, Granger causality measurements of (Frontal → Occipital) indexing top-down influence and average of (Occipital → Frontal) and (Occipital → Parietal) indexing the bottom-up interaction during the 300 ms period immediately prior to the presentation of the validly cued targets for two classes of trials: correct and quicker responded trials (black) and incorrect and slower responded trials (white). The figure highlights the notion that a state of increased regional and network-wide alpha band oscillatory synchrony and interaction reflects a weakening or disruption of top-down biasing and hence impaired performance. * - denotes statistically significant difference (p<0.05).
Figure 6-4. Temporal evolution of regional and network-level alpha band activity. (A) Normalized spectral power in the alpha frequency band over lateral Occipital areas are averaged across subjects and compared between attend (solid black) and ignore (dotted lines) conditions. Normalized coherence (B), and Granger causality indexing top-down (C) and bottom-up (D) influences in the alpha frequency band collapsed across (Frontal-Occipital) and (Parietal-Occipital) are averaged across subjects and compared between attend (solid black) and ignore (dotted lines) conditions. The shaded time periods denote periods that exhibit statistically significant differences between conditions.
The dissertation investigated the functional role of ongoing oscillations in stimulus processing and higher-order cognitive processes such as anticipatory attention and encoding of memory along four cogent studies. The evidences garnered from these studies debunk the long held notion that ongoing neural activity preceding stimulus onset is noise and irrelevant to subsequent stimulus processing. It is also amply shown that the prestimulus activity is not merely a random fluctuation in excitability but one that is actively controlled in a goal-directed manner through neural synchronization across widespread functionally relevant cortical networks. In addition, a biophysically inspired framework to assess and characterize the dependence of sensory processing on the excitability state of the brain indexed by the prestimulus ongoing brain activity was proposed and tested.

In the first study, we sought to identify the factors that lead to near zero-lags in synchronous networks and resolve the ambiguity of such observations in unidirectional networks. We decomposed neural synchrony into components quantifying directed interaction and instantaneous correlation between the regions and further, quantified their influence on phase-lag between the areas. From our findings, we confirmed our hypothesis that two factors: (a) instantaneous causality, which may be due to common input, such as cortical or subcortical sources which may or may not be sampled in the recordings, and / or (b) reciprocal interaction pattern between the regions, account for the coherent activity with zero-lag across long distances. In cases where the interaction is clearly unidirectional determined by Granger causality analysis, the phenomenon of zero-lag was completely explained by instantaneous causality. For cases wherein the interaction is bidirectional, the reciprocal nature of the network in addition to instantaneous causality may cause near zero time lags. Hence we show that zero-lag synchrony is
an emergent phenomenon dependent on the topology of the interacting network of neural ensembles and is not representative of the conduction delay between the interacting areas as often misconstrued.

In a following study examining the role of prestimulus ongoing oscillatory brain activity in encoding of memory we provided the first evidence in humans demonstrating that increased inter-areal synchrony in the fronto-temporal network prior to item presentation is associated with higher likelihood of the item being recalled in the subsequent test. The changes in inter-areal synchrony, taken as an indicator of changes in network excitability, may be a result of spontaneous fluctuations in the level of anticipatory attention and hence waxing and waning of top-down influence. Possibly as a consequence of top-down influence the level of regional theta activity indexing depolarizing influence on NMDA receptor-containing cells and hence tissue excitability over the fronto-temporal structures prior to the presentation of the item was positively correlated with the efficacy of subsequent memory encoding and later recall. Based on rodent studies on theta oscillations and memory, we propose that the temporal coupling of the sensory input triggered glutamate release and theta-induced depolarization activates the theta facilitated NMDA channels leading to stronger calcium influx, which in turn facilitates LTP and thus leads to more effective encoding-related processes.

As part of the third study, we provided a thorough characterization of the relationship between the prestimulus ongoing oscillatory activity specifically the alpha band activity (8-12 Hz) and the subsequent early visual-evoked response. A mechanism linking the dynamics of prestimulus ongoing oscillatory activity and the generation of early evoked response was proposed by invoking the sigmoidal relationship between the endogenous synaptic fluctuations and the firing rate of the neural ensemble, and that external sensory input has an additive
synaptic effect. It follows that the stimulus-evoked response corresponds to the derivative of the sigmoidal function, which is an inverted-U function of the prestimulus level of background activity. Reformulated in terms of EEG variables where field oscillations and the early component of event-related potential are treated as indices of background synaptic activity and stimulus-evoked response, an inverted-U relationship between early evoked response and prestimulus field oscillations was predicted and confirmed empirically through noninvasive EEG studies of human visual processing. Attention has been thought to selectively enhance the perceptual salience of attended stimuli through competing mechanisms of sensory gain control. Based on the mechanism linking pre and poststimulus activity and using computational modeling and empirical evidence from EEG studies of visual attention we show that attention through active control of (a) mean membrane depolarization (excitability) and (b) the variance of background synaptic level (membrane potential fluctuation) over the early sensory areas enable preferential facilitation of processing in the attended domain over the unattended domain.

Although the previous aim addressed the attention modulation of excitability of the early visual areas and hence the subsequent visual processing, such goal-directed prestimulus modulation is not an inherent property of the early sensory areas. Further, the neural mechanisms by which this is implemented are still unclear. As part of the fourth and final study, we assessed how attention modulates endogenous anticipatory processes employing time-frequency spectral analysis. Applying coherence analysis to the anticipatory attention period we identified a synchronous frontal parietal-occipital network in the low frequency range (alpha band), where Granger causality analysis further defined the direction of causal interaction. The degree of inter-areal synchrony and the magnitude of Granger causality were found to be decreased by attention. In light of prior lesion and EEG/MEG studies and anatomical evidences this reduced
fronto-parietal driving occipital Granger causality is seen to lend support to the ‘disinhibition mechanism’, where attention serves to increase excitability through reduced excitatory drive on local interneurons, suggesting a disinhibition function of attention in which its goal-oriented deployment leads to the release of the visual cortex from tonic top-down inhibitory influence.

It is evident from our studies and from other previous studies that all cognitive function depends on the coordinated interaction among neural assemblies distributed across the brain. Although we have exclusively focused on neural oscillations and synchrony to address the mechanisms of executive processes and other cognitive processes in healthy human volunteers, it is equally relevant to address pathological brain states in diseases including Schizophrenia, Alzheimer’s disease, Parkinson’s disease and other developmental diseases causing neurocognitive impairments such as autism and ADHD among others. A common thread among all these diseases is the deficits in coordinated processing across distributed cortical networks leading to specific cognitive deficits especially in executive functioning, attention and memory. Measures of inter-areal connectivity such as coherence and Granger causality in addition to anatomical metrics quantifying white matter and thus neuroanatomical substrates of inter-areal connectivity may enable objective measures of functional integrity of pathways between different areas of the brain and thus may serve as biomarkers offering diagnostic potential. Further the findings from our studies regarding the critical role of spontaneous brain state on subsequent stimulus processing and behavioral performance have implications in neurodiagnostic and neurofeedback based intervention capability to detect and treat cognitive decline and dementia caused by aging and possibly ameliorate psychiatric conditions afflicting the emotion circuits by employing brain-state contingent training which may effect a facilitatory pattern of brain activity and hence behavioral improvement. Thus, synchronous oscillations
quantifying regional and large-scale integration of neural activity as assessed from noninvasive and invasive electrophysiological recordings may be of critical value not only in elucidating mechanism related to normal cognitive functioning but also to address cognitive impairments brought about by multitude of debilitating neurological and psychiatric disorders.
REFERENCES


BIOGRAPHICAL SKETCH

Rajasimhan Rajagovindan was born in 1983, in Chennai, India. He grew up in Chennai, graduating from Padma Seshadri Bala Bhavan Senior Secondary School in 2000. He earned the Bachelor of Engineering degree in electronics and communication engineering from the University of Madras, Chennai in 2004 following which Raj enrolled in the graduate program at the University of Florida where he earned the Master of Science degree in biomedical engineering in 2008. He continued at the University of Florida to earn his Doctor of Philosophy in the fall of 2009 in biomedical engineering specializing in cognitive neurosciences under the mentorship of Dr. Mingzhou Ding. Raj intends to pursue his research interests in functional biomarker discovery to develop diagnostic tools to identify and assess the progression of neurological and psychiatric illnesses and the effectiveness of therapeutic interventions to enable therapy augmentation.