

THE FRONTO-PARIETAL NETWORK AND BEYOND:
A STUDY OF THE SPATIOTEMPORAL PATTERNS
UNDERLYING VISUAL WORKING MEMORY

by

Nicholas Monroe Dotson

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ABSTRACT

Working memory, an integral component of higher cognitive functions, involves the short-term retention and utilization of behaviorally relevant information when that information is no longer available in the environment. Tragically, individuals suffering from traumatic brain injuries, psychiatric disorders, and other neurological disorders often exhibit working memory deficits. The study of working memory may thus provide insight into the mechanisms underlying cognitive functions and the potential to alleviate major health problems. In order to understand cognitive processes, like working memory, several pieces of information must be considered: the cortical and sub-cortical areas involved, the manner in which these areas integrate, or share information, and the underlying dynamics of these integrative processes. These pieces form a hierarchical structure of investigation, from the individual areas to global principles of coordination. The objective of this study is to elucidate the relevant spatiotemporal patterns of oscillatory synchronization underlying visual working memory in the fronto-parietal network and across the brain. Relevant patterns for consideration are those that encode stimulus information, are modulated by the task, and those with distinct anatomical variations. The results of the studies presented in Chapters 2-4 provide extensive evidence that oscillatory synchronization is a mechanism for distributed integration. We show that the patterns of coherent activity 1) encode working memory items, 2) are indicative of the task period, 3) provide the potential for multiple functional networks, defined by the relative phase and, 4) are highly dynamic, with large fluctuations in magnitude and relative phase. Future studies will be necessary to further investigate the role of oscillatory synchronization. Efforts to perturb oscillatory activity in order to illustrate its utility, rather than simply correlating its activity with stimulus and task components, will be crucial. Finally, understanding the spatiotemporal activity patterns underlying working memory may ultimately allow for the identification of aberrant patterns, such as those brought on by disease, and allow for these patterns to be meaningfully interacted with - via neuroprosthetic devices.

CHAPTER ONE

GENERAL INTRODUCTION

Introduction

Working memory involves the short-term retention and utilization of behaviorally relevant information when that information is no longer available in the environment (Baddeley, 1983), and it is considered an integral component of higher cognitive functions - such as language comprehension, learning, reasoning (Baddeley, 1992), general fluid intelligence (Engle et. al., 1999), and reading comprehension (Daneman & Carpenter, 1980). Unfortunately, individuals suffering from traumatic brain injuries, psychiatric disorders, and other neurological disorders often exhibit working memory deficits (Bradley et. al., 1989; Baddeley et. al., 1991; Park & Holzman, 1992; Goldman-Rakic, 1994; Owen et. al., 1997; Manoach, 2003; Müller, 2006). The study of working memory may thus provide insight into the mechanisms underlying cognitive functions and the potential to alleviate major health problems.

In order to understand cognitive processes, like working memory, several pieces of information must be considered: the cortical and sub-cortical areas involved, the manner in which these areas integrate, or share information, and the underlying dynamics of these integrative processes. These pieces form a hierarchical structure of investigation, from the individual areas to global principles of coordination. Evidence from neuroimaging studies in humans and neurophysiological studies in non-human primates suggest that cognitive processes, like working memory, involve coordinated interactions

over large parts of the brain – including, prefrontal, posterior parietal, visual, and sub-cortical areas (Mountcastle, 1978, 1995; Mesulam, 1990; Jonides et. al., 1993; Bressler, 1995; Fuster, 1997, 2002; Engel et. al., 2001; Salinas & Sejnowski, 2001; Pessoa, 2002; Varela et al., 2001; Brovelli et. al., 2004; Bressler & Menon, 2010; Fell & Axmacher, 2011; Siegel et. al., 2012). Even primary visual cortex in humans has been shown to encode working memory items (Harrison & Tong, 2009). While there is clear evidence for a host of areas involved in working memory, the way in which distributed areas integrate information remains largely unknown. In an attempt to answer this question, neurophysiological studies in non-human primates have provided evidence for a role of synchronous neuronal oscillations (Brovelli et. al., 2004; Buschman et. al., 2007, 2012; Pesaran et. al., 2008; Gregoriou et. al., 2009; Hipp et. al., 2011; Liebe et. al., 2012). Similarly, the way in which synchronous activity is coordinated across the brain is also very much unknown. Concepts from coordination dynamics, such as metastability and self-organization, provide a framework for the role of synchronous neuronal oscillations in the balance of segregation and integration across the brain (Kelso, 1995; Friston, 1997; Bressler & Kelso, 2001; Fingelkurts & Fingelkurts, 2004; Freeman & Holmes, 2005; Werner, 2007). Collectively, these studies provide the groundwork for understanding cognitive functions. In order to further these ideas, large-scale, microelectrode recordings may be used to better quantify the contribution of individual areas, to identify spatiotemporal patterns of synchronous activity, and then attempt to quantify the underlying dynamics of these spatiotemporal patterns.

The objective of this study is to elucidate the relevant spatiotemporal patterns of oscillatory synchronization underlying visual working memory in the fronto-parietal network and across the brain. Relevant patterns for consideration are those that encode stimulus information, are modulated by the task, and those with distinct anatomical variations. The primary components of synchronous oscillations under consideration are the magnitude and relative phase of coherence, between local field potentials (LFP). Spike-field coherence and Wiener-Granger causality are also employed to further investigate the directionality of these interactions. Understanding the spatiotemporal activity underlying working memory may ultimately allow for the identification of aberrant patterns, such as those brought on by disease, and allow for these patterns to be meaningfully interacted with - via neuroprosthetic devices. Furthermore, these concepts may be generalized toward efforts to understand attention, planning, and other cognitive operations, and potentially other complex systems.

The remainder of the General Introduction will provide the necessary theoretical and experimental background to sufficiently motivate the studies presented in Chapters 2-4. Chapter 2 will describe the content specific nature of fronto-parietal interactions. Chapter 3 will further describe the dynamic patterns of correlation during visual working memory - showing how in-phase and out-of-phase LFP beta-band correlations co-exist during working memory, and are capable of 180° flips. Chapter 4 will demonstrate the widespread nature of working memory, and extend the findings from the previous Chapter to show that the distribution of relative phases across the brain - in the beta-band - is bimodal, and highly dynamic. Chapter 5, General Discussion, will begin to

incorporate the concepts of coordination dynamics into this body of work and provide some future directions for research.

Working Memory Theories

The first notable formalization of working memory, termed the “standard model”, was devised to describe a limited capacity system that is capable of storing and retrieving the information necessary to complete complex tasks (Baddeley & Hitch, 1974). Several, more neurophysiologically relevant theories, which largely focus on visual working memory, have followed. These theories generally agree that visual working memory maintenance is an active process achieved by top-down control from prefrontal and posterior parietal cortical areas on sensory representations in extra-striate visual areas (Desimone & Duncan 1995; Fuster, 2000; Miller & Cohen, 2001; Corbetta & Shulman, 2002; Ruchkin et. al., 2003; Lebedev et al., 2004; Postle, 2006; Ranganath, 2006; Jonides et al., 2008; Wolters & Raffone, 2008; Fuster & Bressler, 2012). One prominent model for visual attention and working memory is the “biased competition model”. This model proposes that both bottom-up and top-down mechanisms are capable of biasing the neural responses in visual areas to facilitate the selection of behaviorally relevant stimuli (Desimone & Duncan 1995; Miller et. al., 1996). The model is based on the assumption that incoming sensory information competes for representation throughout the visual hierarchy. These competitive interactions may then be biased by bottom-up signals, as in visual “pop-out”, or top-down signals via attention. In the case of working memory, the sample stimulus is thought to provide a template that is then maintained by top-down

feedback from prefrontal cortex. Support for bottom-up, or automatic, biasing signals comes from the neural responses in V1, MT, and IT cortex, to visual “pop-out” and temporal novelty (Allman et. al., 1985; Moran & Desimone, 1985; Tanaka et. al., 1986; Miller & Desimone 1994). Evidence that visual areas receive top-down biasing signals is supported largely by the neural activity in V2, V4, and IT cortex, during tasks requiring active attention and working memory (Moran & Desimone, 1985, Richmond et. al., 1983; Luck et. al., 1993, Reynolds et. al., 1999), wherein the neural responses to multiple stimuli in a single receptive field reflect only the stimulus that is being attended.

In a similar vein, but from neuroimaging work, Postle (2006) proposes that working memory functions arise from directing attention to cortical areas representing perception and action information. In this view, working memory is an emergent property of a system with the ability to both direct attention and represent information. Subsequently, any type of information that can be represented may then be the content of working memory. Importantly, the application of this model negates the necessity of specialized buffer systems instantiated in specific cortical areas, such as areas of prefrontal cortex (Goldman & Rosvold, 1970; Goldman-Rakic et. al., 1996; Ungerleider et. al., 1998), for working memory processes. While much work is needed to better ground this theory in neurophysiological terms, it does provide a more global perspective of visual working memory.

Another set of ideas from Fuster (2000) and, Fuster and Bressler (2012), place the prefrontal cortex at the center of the perception-action cycle. In this view, sustained activity during a memory delay provides “cross-temporal mediation”, which is thought to

bridge the gap between sensory perception and motor actions. In the case of a delayed matching task, cross-temporal mediation would occur during the delay, bridging the temporal gap between the sensory information - provided by the sample image or spatial cue - with the motor response. In a study supporting this hypothesis, dorsolateral prefrontal neurons were demonstrated to both encode working memory items and intentional plans (Quintana & Fuster, 1999). Moreover, the sustained activity patterns – the neural correlates of cross-temporal mediation - observed during the delay are thought to arise from reentrant circuits (Hebb, 1949; Sporns et al., 1989; Zipser et al., 1993) within and between prefrontal and perception/action areas. Importantly, this component provides a mechanism for memory maintenance outside of specific cortical areas; instead, memory maintenance is a product of multiple interacting areas.

These biologically based models all provide an account of working from several different perspectives. The “biased competition model” describes the process of selecting relevant information from the environment at the level of single cells. The work by Postle is less neurophysiologically specific, but it promotes the large-scale nature of working memory and attempts to account for the fact that anything may be the subject of working memory. The work by Fuster and colleagues further promotes the concepts of cooperation between multiple areas and importantly they don’t place the locus of working memory on any one anatomical area, but on the interactions between areas. Overall, as mentioned above, they agree that working memory processes are distributed and involve some manner of top down attentional control on perception/action areas.

The Neural Correlates of Visual Working Memory

In this section, the experimental evidence supporting the general themes of the aforementioned theories will be provided. As suggested above, the prefrontal and posterior parietal cortex is thought to be primarily involved in top-down attentional control, or working memory maintenance, while extra-striate areas are presumed to be largely involved in the representation of working memory items. Importantly, this separation of functions is not absolute: a substantial amount of commonalities are seen across areas and the co-activation patterns that have been observed suggest that working memory, and the individual components of working memory, are a highly distributed processes. Separate functions are imposed on this dynamic process in order to describe the differences in the observed task and stimulus related activity patterns, and in an effort to maintain the concepts of top-down attentional control. The first sub-section will focus specifically on prefrontal cortex, due to the substantial body of literature on the role of prefrontal cortex in visual working memory. The remaining sub-sections will support a special role for the activity within and between prefrontal and posterior parietal cortical areas as a “fronto-parietal network”, and briefly discuss the observed activity patterns of extra-striate areas. Due to the volume of literature, an in depth discussion of the oscillatory and synchronous activity throughout the cortex will be discussed in the next major section.

The Role of Prefrontal Cortex in Visual Working Memory

In a study by Jacobsen (1936), monkeys with bilateral prefrontal lesions were shown to exhibit working memory deficits in a delayed response task. This provided the first experimental evidence that prefrontal cortex played a role in working memory. Several other lesion (Mishkin, 1957; Goldman & Rosvold, 1970; Goldman et. al., 1971; Passingham, 1975; Mishkin & Manning, 1978) and reversible deactivation (Bauer & Fuster, 1976) studies have provided further evidence of a role for PFC in working memory. A seminal microelectrode study by Fuster and Alexander (1971) corroborated the findings from lesion and reversible deactivation studies, by demonstrating that the firing rates of single neurons in the prefrontal cortex and the mediodorsal nucleus of the thalamus remained elevated during a memory delay period – a property that is often considered the neural correlate of working memory. Since these initial findings, a large body of work using microelectrode recordings and neuroimaging has demonstrated that the prefrontal cortex displays a variety stimulus and task related information. Much of this work - from the very beginning - has been in an attempt to localize different functions to distinct areas of PFC (Goldman & Rosvold, 1970; Pigarev et. al., 1979; Wilson et. al., 1993; Goldman-Rakic et. al., 1996; Scailidhe et. al., 1997). These notions are not unfounded; in fact, anatomical evidence provides grounds for parcellating PFC based on its connections with other cortical and sub-cortical areas (Pandya & Kuypers, 1969; Jones & Powell, 1970; Selemon & Goldman-Rakic, 1985; Cavada & Goldman-Rakic, 1989). Goldman-Rakic (1988) describes these distinct patterns of connectivity between large numbers of cortical areas as “parallel distributed networks”. The concepts

of parallel networks are further supported by common functions within anatomically defined networks, such as those for eye and hand movements (Marconi et. al., 2001). Importantly, this description of cortical function moves forward from a directed flow of cortical processing, in which successive stages simply add information (Pandya & Seltzer, 1982), to a more unitary view of cortical function, in which distributed areas are integrating information simultaneously. However, there may not be a clear distinction between these parallel networks, due to extensive evidence that specific functions are not entirely localizable within PFC, and across the brain; in fact, they might be better described as “orthogonal distributed networks”. Even the localization of basic object and spatial information is debatable. A study by Wilson and colleagues (1993) claims to find a distinct parcellation for object and spatial working memory in ventral and dorsal PFC, respectively. In contrast, a study by Rainer and colleagues (1998) indicates that object, spatial, and a combination of object and spatial, information is encoded in both ventral and dorsal PFC during visual working memory (similar to a previous study by Fuster and colleagues (1982b)).

Several neurophysiology studies in behaving monkeys, such as the one by Rainer and colleagues (1998) described above, have lead to the view that the prefrontal cortex is multi-functional. For instance, memory fields that encode visual information, such as the location of a sample stimulus, have been demonstrated in many PFC areas, including FEF (Funahashi et. al., 1989; Rainer et. al., 1998; Funahashi et. al., 2004). Largely overlapping these cortical areas, there is also support for object-based memory maintenance (Fuster et. al., 1982; Miller et. al., 1996; Rainer et. al., 1998). Context, or

rule, information is also encoded throughout PFC (Asaad et. al., 2000; Stoet & Snyder, 2004), along with category tuning (Freedman et. al., 2001, 2002). Multi-functionality is further exemplified by a recent study demonstrating that FEF – an area known primarily for spatial attention and intention - is shape selective (Peng et. al., 2008). Finally, to complicate the picture even more, there is evidence that FEF encodes both relevant and non-relevant information during visual working memory (Clark et. al., 2012). Similarly, neuroimaging studies in humans have indicated overlapping areas in spatial and object working memory to further support the idea that prefrontal cortex is multi-functional (Owen, 1997; Owen et. al., 1998; Postle et. al., 2000; see Courtney et. al., 1996 for an opposing view).

These studies, and many others, have provided much insight into the role of the prefrontal cortex in working memory processes. However, along with demonstrating that working memory components are widely distributed across PFC, they have also illuminated the adaptive nature of prefrontal cortex. This is blatantly captured by Duncan (2001): “A first remarkable fact is that, whatever arbitrary task a monkey has been trained to carry out, a substantial proportion of lateral prefrontal neurons will be found to show selective responses to some aspect of that task’s events”. An explicit example of this adaptive nature comes from Rao and colleagues (1997), which demonstrated that prefrontal neurons often mirror the task demands. In this study animals were required to remember the identity and then the location of a sample object. A subset of prefrontal neurons demonstrated tuning to both the identity and the location in a sequential manner - a response they describe as switching modes. In light of all these findings, it would seem

that wide spread areas of PFC are going to be involved in any mentally demanding activity, and given enough time and money a very nice table could be made of its neural correlates. However, this is obviously no longer a productive way to study PFC and cortical activity in general, so then what is? The approach taken in this thesis - and several studies mentioned throughout this Chapter - is to observe how the activity in PFC, PPC, and many other cortical areas, co-vary during visual working memory in an attempt to identify general mechanisms, rather than adding to the list of cognitive functions individual areas are involved in.

The Role of the Fronto-parietal Network in Visual Working Memory

The previous section provided clear evidence for an integral role of the PFC in visual working memory. However, there is substantial evidence that similar functions are also carried out in areas of the PPC, including visuomotor integration, motor planning, representation of categories, and the encoding of spatial and non-spatial information (Andersen et al., 1987; Gnadt and Andersen 1988; Constantinidis & Steinmetz, 1996; Chafee & Goldman- Rakic, 1998; Marconi et. al., 2001; Pesaran et. al., 2002; Freedman & Assad, 2006, 2009). Even eye movements can be elicited by microstimulation in area LIP (Shibutani et. al., 1984), a quality that is used to define FEF (Bruce et. al., 1985). Furthermore, lesion and reversible inactivation studies in monkeys (Petrides, 1995, 1999; Chafee & Goldman-Rakic, 2000) demonstrate specific disruptions of performance on working memory tasks when prefrontal or posterior parietal areas are affected. Neuroimaging studies in humans also support a distinct role of prefrontal and posterior

parietal cortex in top-down control of attention and high-level aspects of working memory, such as maintenance, monitoring, and manipulation of working memory information (Rowe et al., 2000, 2001; de Fockert et. al., 2001; Sakai et al., 2002; Munk et al. 2002; Gazzaley et. al., 2004; Yoon et. al., 2006; Bressler et al., 2008; Courtney et al. 1997; Champod & Petrides, 2007). Anatomically, prefrontal and posterior parietal cortical areas are heavily interconnected and mutually connected with other cortical and subcortical areas, including the ACC, thalamic nuclei, and areas of temporal cortex (Petrides & Pandya, 1984, 2006; Yeterian & Pandya, 1985; Selemon & Goldman-Rakic, 1988; Ungerleider et. al., 1989; Cavada & Goldman-Rakic, 1989; Baizer et. al., 1991; Schall et. al., 1995; Rempel-Clower & Barbas, 2000; Cavada, 2001; Germuska et. al. 2006; Zikopoulos & Barbas, 2006, 2007). These overlapping response properties and dense anatomical connectivity promote a distinct role for the combined activity of the prefrontal and posterior parietal cortex, leading to the concept of the fronto-parietal network.

Further support for distributed processing in the fronto-parietal network comes from electrophysiological studies performing simultaneous recordings in areas of both PFC and PPC. Several studies have demonstrated inter-areal synchronization, and other correlated interactions, between PFC and PPC areas during attention, decision-making (Buschman & Miller, 2007; Pesaran et. al., 2008), and working memory (Crowe et. al., 2013). In other related studies of working memory and attention, inter-areal synchronization has been shown between PFC areas and V4 (Gregoriou et. al., 2009,

2012; Liebe et. al., 2012), indicating that similar functional networks might exist between PFC and visual areas.

Collectively, there is substantial evidence that PFC and PPC cooperate to form a fronto-parietal network. However, there are only a few neurophysiological studies that demonstrate coordination within the fronto-parietal network, and even fewer that address coordination during working memory. This leaves a large gap in our knowledge of the fronto-parietal network and visual working memory. This gap in our current knowledge was a primary motivation for the studies presented in Chapters 2 and 3 of this thesis.

Activity Patterns in Visual Areas During Visual Working Memory

A core tenant of most current working memory theories is the representation of working memory items in the same areas involved in perception. Here we will define representation as simply providing information about working memory items during a memory delay period. Support for this comes from microelectrode studies in monkeys which have demonstrated sustained activity during memory delays in IT, PPC V4, MT and V3A (Fuster & Jervey, 1981; Fuster et. al., 1982a; Miyashita & Chang, 1988; Fuster, 1990; Miller et. al., 1993; Naya et. al., 2003; Takeda et al., 2005; Gnadt & Andersen, 1988; Constantinidis & Steinmetz, 1996; Chafee & Goldman-Rakic, 1998; Motter, 1994; Nakamura & Colby, 2000; Bisley et al., 2004; Lee et al., 2005). Furthermore, human neuroimaging studies extensively document the occurrence of task- and stimulus specific sustained activity throughout widespread areas of visual association, extrastriate, and even primary visual cortex during the delay-period of working memory tasks (Smith &

Jonides, 1998; Ungerleider et al., 1998; Rowe et al., 2000; Courtney et al., 1997; Wager & Smith, 2003; Postle, 2006; Ranganath, 2006; Jonides et al., 2008; Harrison & Tong, 2009). While there is much support for the representation of working memory items in the areas described above, there is, however, no real consensus on the utility of these sustained activity patterns. For instance, an important distinction between PFC activity and the rest of the cortex is resistance to interference, and this will be elaborated on below.

In order to further elucidate the role of IT and PPC in visual working memory, experiments have been performed that incorporate distracting stimuli. In these studies, the activity patterns in IT and PPC are disrupted in the presence of visual distractors, and in some cases they encode the distractors, during visual working memory tasks (Miller et. al., 1993; Constantinidis & Steinmetz, 1996; Powell & Goldberg, 2000). Prefrontal neurons on the other hand have been shown to be resistant to interference (Miller et. al., 1996; Sakai et. al., 2002; Suzuki & Gottlieb, 2013). Importantly, in these studies the presence of visual distractors and the induced changes in the neural activity patterns does not prevent the animals from correctly completing the tasks. However, cooling areas such as IT does affect working memory performance (Fuster et. al., 1981). Further work is necessary to elucidate the role of these visual and association areas in working memory, potentially by using more delicate methods – such as optogenetics – to selectively perturb their activity patterns.

Collectively, these studies demonstrate the truly distributed nature of working memory. While many of the details have been left out, the picture that this section wishes

to convey is that no single area is likely to work alone. However, studies demonstrating different degrees of resistance to interference between areas and fine grain differences in the activity patterns throughout different working memory tasks indicate that the orchestration of working memory involves a diverse set of components. It should be noted though - as previously discussed - that attempts at localizing and dissecting these components might in the end be futile, when one considers that the activity from any area is always being influenced by a large number of other cortical areas. In fact, it was recently demonstrated that the cortex is more densely connected than previous research indicated, with 66% of the possible inter-areal connections existing (Markov et. al., 2012).

Summary of the Neural Correlates of Working Memory

Largely the roles of individual cortical areas in visual working memory are still an active debate. The general framework assumes a basic distinction between top-down maintenance and memory representations. In a very broad sense, a better description is simply that the complexity of working memory processes progress the farther one gets from primary sensory and primary motor areas (Courtney et. al., 1997), and these functions are adaptive, providing results for any "arbitrary" task one might choose (Duncan, 2001). The previous sections and the studies cited within should provide some insight into this web of ideas and support the need for a better understanding of how distributed areas interact. A lofty goal would be to not only determine the way in which these areas integrate information, but also to identify the mechanisms that bring about

their integration. Ultimately, with the goal of providing a general framework, or set of laws, that can enable the prediction of novel situations. The next two sections will discuss the role of synchronous oscillations as a mechanism for integration and memory maintenance, and begin a discussion about using coordination dynamics to quantify the underlying dynamics of working memory.

Synchronous Neuronal Oscillations and Visual Working Memory

The previous section provided an account of the cortical areas currently understood to be active, or modulated, during visual working memory. These areas, including PFC and PPC, are spread across the brain. An obvious question that can be posed, based on these findings, is what is the mechanism used to integrate these distributed neuronal populations and how do these distributed interactions contribute to working memory processes? As mentioned in the introductory paragraphs, recent experimental and theoretical evidence suggests working memory and other cognitive processes may be mediated by synchronized interactions across the brain. However, in order to appreciate these studies, a discussion of oscillatory synchronization must first be provided. Oscillatory synchronization, in general, refers to the transient synchronization of spikes, LFPs, or spikes with LFPs, and is commonly measured using time lagged cross-correlations, phase locking measures, or coherence (König, 1994; Tass, 1998; Lachaux et. al., 1999, 2000; Le Van Quyen et. al., 2001; Bokil et. al., 2010). A highly influential study in this field was performed by Gray and colleagues (1989), in which they demonstrate stimulus specific synchronization of spikes in the visual cortex of

anesthetized cats. Sites, with similar receptive fields, separated by up to 7 mm engaged in synchronous oscillations when optimally stimulated by light bars moving in the same direction. This effect was enhanced when a single light bar was used and drastically diminished when light bars moved in opposite directions. These observations, when incorporated with long standing ideas of cell assemblies (Hebb, 1949; Milner, 1974; Braitenberg, 1978; Edelman & Mountcastle, 1978; von der Malsburg & Willshaw, 1981; von der Malsburg, 1985), provided the basis for the “temporal correlation hypothesis” (Singer & Gray, 1995; Gray, 1999). Briefly, this hypothesis proposes that perceptual grouping and segmentation of visual scenes may be carried out by the transient synchronization of distributed neural populations. Furthermore, these cell assemblies then have a higher efficacy on their downstream targets due to their synchronized output (Abeles, 1982; König et. al., 1996). Synchronization and spike timing have also been combined to emphasize the routing of information (Fries, 2005; Sejnowski & Paulsen, 2006; Womelsdorf et. al., 2007). In this scheme, communication only occurs when pre-synaptic spikes arrive during the receptive phase, or period of enhanced excitability, of post-synaptic neurons (Haider & McCormick, 2009).

To go back to the original question - which is, how many distant areas integrate information during working memory - oscillatory synchronization may provide this mechanism. Importantly, this concept of integration is not necessarily distinct from binding or routing; it is simply a more general concept of sharing information between areas. Indeed, neurophysiological studies in monkeys have demonstrated oscillatory activity and synchronization in widespread areas of the cortex, including theta-band (4-8

Hz) oscillations in the temporal pole and area V4 (Nakamura et al., 1992; Lee et al., 2005). Synchronous beta- (15-30 Hz) and gamma-band (30-80 Hz) oscillations have been observed in area V4 and posterior TE (Tallon-Baudry et al., 2004), and in areas LIP (Pesaran et al., 2002) and PRR (Scherberger et al., 2005) of the posterior parietal cortex. Also, in dorsolateral PFC, synchronized firing among adjacent groups of neurons has been demonstrated (Funahashi & Inoue, 2000; Sakurai & Takahashi, 2006). Furthermore, several studies have demonstrated inter-areal synchronization during working memory, including between areas LIP and MT (Saalmann et al., 2007), between areas in PPC and dorsolateral PFC (Buschman & Miller, 2007), and between lateral PFC and V4 (Liebe et al., 2012). Inter-areal synchronization has also been observed between several combinations of PFC, somatomotor, association, and visual areas during a variety of tasks in behaving animals (Murthy & Fetz, 1992, 1996; Bressler et al., 1993; Roelfsema et al., 1997; Pesaran et al., 2008; Gregoriou et al., 2009; Verhoef, 2011; Bosman et al., 2012). The study by Liebe and colleagues (2012) is of particular interest to this work because it demonstrates long-range synchronization during working memory. In this study simultaneous recordings were made in lateral PFC and V4 while the animals performed a delayed match-to-sample task. Increased theta-band (3-9 Hz) phase synchrony was observed above baseline during the memory delay. Moreover, the consistency of inter-area spike-field relationships was diminished during incorrect trials. They conclude that this increased synchronization mediates the timed cooperation across these areas and is a general mechanism for integration. Collectively, this study and the ones mentioned above, establish that the same areas that have been identified as the

neural substrate of working memory by firing rate analyses are often seen to be involved in synchronous, task specific, interactions.

Oscillatory synchronization has also been observed in human EEG and MEG recordings during working memory tasks in the theta (4-8 Hz), alpha (8-15 Hz), beta (15-30 Hz), and gamma (30-80 Hz) frequency bands (Sarnthein et al., 1998; Jensen & Tesche, 2002; Gonzalez-Hernandez et al., 2002; von Stein et al., 1999; Tallon-Baudry et al., 1998, 1999; Deiber et al., 2007; Jensen et al., 2002, 2007; Jokisch & Jensen, 2007). Intracranial electrophysiological studies in neurosurgical patients have also provided evidence of large scale coupling at several different frequencies (Tallon-Baudry et al., 2001, 2005; Howard et al., 2003; Raghavachari et al., 2001, 2006; Halgren et al., 2002; Sarnthein et al., 2005; Axmacher et al., 2007; Mainy et al., 2007).

In summary, oscillatory synchronization is observed throughout the brain, is posited as the mechanism in which distributed areas integrate information, and it is likely integral to all aspects of cognition (Gray, 1994; Singer & Gray, 1995; Bressler, 1995; Gray, 1999; Singer, 1999; Bressler & Kelso, 2001; Engel et al., 2001; Varela et al., 2001; Buzsaki & Draguhn, 2004; Fries, 2005; Siegel, 2012). It is, however, still unknown how these patterns of synchronous activity emerge and their specific function. Thus, a critical gap in our knowledge of the neural basis of working memory can be filled by investigating the detailed structure and task dependence of synchronous neuronal activity within and between prefrontal and posterior parietal cortical areas and throughout the brain.

Coordination Dynamics

What is the origin of coordinated states? That is, the observable activity patterns underlying all aspects of brain function and dysfunction. In the last section, synchronous neuronal oscillations were proposed as a mechanism to integrate distributed cortical areas - these are the observable activity patterns. Now the question becomes, how are these spatiotemporal patterns of synchronous neuronal oscillations manifested? Attention, for example, is often defined by the coordinated activity between prefrontal and extra-striate visual areas. How does “attentional control” arise? Is it directional, as the terms “top-down” and “bottom-up” imply, or is it an emergent phenomena (Chialvo, 2010), from the interactions of many, if not all, areas of the brain? The principles considered in coordination dynamics, including metastability and self-organization, provide a framework for the investigation of these questions (Schoner & Kelso, 1988; Kelso, 1995, 2012; Kelso & Tognoli, 2009; Bressler & Kelso, 2001). Along with the work by Kelso and colleagues, there are several other programs of study focused on quantifying the underlying dynamics of large-scale brain function (Kelso 1995, 2012; Friston, 1997; Bressler & Kelso, 2001; Fingelkurts & Fingelkurts, 2004; Freeman & Holmes, 2005). This topic will be re-visited in Chapter 5 (General Discussion), and discussed in light of the work contained within this thesis.

Specific Aims

Several paradigm shifts are in progress in the study of the neural substrates and mechanisms of working memory. Including a shift from the localization of functions to the role of distributed processes, the mechanisms of cortico-cortical integration, and the origins of brain-wide organization. Large-scale microelectrode recordings are now providing the requisite time and spatial resolution to address these essential questions. The specific aims of this study are to elucidate relevant spatiotemporal activity patterns in the fronto-parietal network and to further investigate the distributed nature of working memory processes using a large-scale microelectrode recording system.

Specific Aim 1: Content Specificity

To test the hypothesis that specific spatiotemporal patterns of neuronal activity, distributed over the fronto-parietal network, encode the content of visual working memory. Sub-aims: 1) Describe the task related changes in coherence during working memory, and 2) Identify directional influences in fronto-parietal interactions during working memory.

Specific Aim 2: Spatiotemporal Activity Patterns

To test the hypothesis that multiple functional networks, defined by the relative phase angle, exist within and between PFC and PPC and to identify periods of re-organization. Sub-aims: 1) Describe the task dependence of correlated interactions within and between PFC and PPC, and 2) Describe the relationship between distance and correlation magnitude

Specific Aim 3: Large-scale
Spatiotemporal Dynamics

To test the hypothesis that the functional networks, defined by the relative phase, identified within and between PFC and PPC are prevalent throughout large areas of the cortex, and to identify if these functional networks are able to re-organize. Sub-aims: 1) Determine the extent of task and stimulus related spiking activity, 2) Investigate the spatial and task related patterns of beta-band coherence, and 3) Determine if the task dependence of correlated interactions on a large-scale are similar to those seen within and between PFC and PPC.

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CHAPTER TWO

CONTENT SPECIFIC FRONTO-PARIETAL SYNCHRONIZATION
DURING VISUAL WORKING MEMORY

Contribution of Authors and Co-Authors

Manuscript in Chapter 2

Author: Rodrigo F. Salazar

Contributions: study design, data collection, data analysis, and preparing manuscript.

Co-Author: Nicholas M. Dotson

Contributions: data collection, data analysis, and editing manuscript.

Co-Author: Steven L. Bressler

Contributions: study design, and editing manuscript.

Co-Author: Charles M. Gray

Contributions: study design, and preparing manuscript.

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Rodrigo F. Salazar, Nicholas M. Dotson, Steven L. Bressler, Charles M. Gray
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Abstract

Lateral prefrontal and posterior parietal cortical areas exhibit task-dependent activation during working memory tasks in humans and monkeys. Neurons in these regions become synchronized during attention demanding tasks, but the contribution of these interactions to working memory is largely unknown. Using simultaneous recordings of neural activity from multiple areas in both regions, we find widespread, task-dependent and content specific synchronization of activity across the fronto-parietal network during visual working memory. The patterns of synchronization are prevalent among stimulus selective neurons and are governed by influences arising in parietal cortex. These results indicate that short-term memories are represented by large-scale patterns of synchronized activity across the fronto-parietal network.

Results

Working memory enables the short-term representation and utilization of behaviorally relevant information when that information is no longer available from the environment. How are such representations maintained in the brain? Extensive evidence demonstrates sustained activation in frontal and parietal areas during memory delay periods (1-4). Although the specific role of these activity patterns is not fully understood, theoretical, anatomical and electrophysiological studies suggest that synchronous interactions among these cortical regions support working memory processes (5-11). While task-specific synchronization has been observed between prefrontal and parietal areas (12, 13), its contribution to working memory is largely unknown. We tested the

hypothesis that neuronal synchronization across the fronto-parietal network carries content-specific information that contributes directly to visual working memory. The pattern of fronto-parietal synchronization should thus vary as a function of the object held in memory.

We performed multi-electrode recordings of broadband neuronal activity (separated into unit activity and local field potentials (LFPs)) in prefrontal (PFC) and posterior parietal (PPC) cortices in two macaque monkeys (A and B) while they performed an oculomotor, delayed match-to-sample task (Fig. 1A,B) (14). This task required the monkeys to match the identity of the sample object. Figure S1 shows the recording locations and sample sizes relative to the cortical sulci in both monkeys. We simultaneously sampled activity from up to 6 PPC and 6 PFC areas (see Fig. S2 for an example), yielding a total of 30 fronto-parietal, inter-areal comparisons. The resulting data set, consisting of LFPs and unit activity recorded over 27 and 47 days, in monkeys A and B, respectively, is given in table S1.

We first determined the time course of fronto-parietal synchronization by computing the time-frequency coherence spectrum on correct trials for fronto-parietal LFP pairs from all sessions (14). These calculations revealed a common temporal pattern of synchronization that correlated with the events of the task (Fig. 1C). In this example, coherence in the 15-25 Hz band peaked during the pre-sample period, transiently declined following the sample stimulus onset, and increased again during the delay (15) reaching a maximum prior to the match. The relative phase between the signals in this frequency range also varied over the course of the trial (Fig. 1D). During the pre-sample

and sample periods, PFC showed a phase lead near 25 degrees that increased during the delay period to ~40 degrees.

To determine how synchronization varies with the sample stimulus held in memory, we first identified pairs having significant coherence (Table 1) and then applied mutual information analysis to the LFP coherence spectra from those pairs at all time-frequency bins (14). (Since the analysis of mutual information is applied to coherence spectra, rather than individual trials, we refer to the resulting metric as the coherence selectivity index (CSI).) Because the sample stimuli differed in their location and identity, we assessed the identity selectivity at each stimulus location and the location selectivity for each identity (16). Figure 2A shows a fronto-parietal pair displaying identity specific coherence during the delay period. A band of elevated coherence (centered at ~20 Hz) during the delay period differs in magnitude and time-course with the object held in memory. Figure 2B quantifies this effect, revealing a significant increase in CSI during the late delay period.

To assess the stimulus selectivity across the entire sample, we first identified pairs with significant CSI (Table 1) and then pooled the data separately for identity and location for those pairs having significant CSI during the delay. If a pair showed selectivity for multiple locations and/or objects, the stimulus condition with the highest coherence was chosen. The median CSI value, as a function of time and frequency ($CSI(t,f)$), from the selected pairs is shown in Fig. 2C. (The $CSI(t,f)$ distributions for identity are shown separately for each monkey in Fig. S3A). Several effects are notable. First, location specificity, and to a lesser extent identity specificity, appear during the

sample period at frequencies less than 15 Hz. This likely reflects the spatial and identity selectivity of neuronal populations in fronto-parietal networks (17-20). Second, on average, an increase in CSI occurs throughout the delay period with a peak frequency at ~15 Hz. Third, we found no significant differences in the CSI values between the pairs tuned for location and identity, in the frequency range of 12-22 Hz, at any time bin throughout the trial (minimum $p = 0.6$; KS-test, Bonferroni correction). Consistent with delay-period selectivity observed at the cellular level (16, 19-21), these findings demonstrate both identity and location specificity of fronto-parietal synchronization during the memory period.

The content specificity of delay-period coherence observed in the CSI raised the question of how coherence magnitude and phase vary as a function of time and stimuli. Since a major objective of this study was to characterize identity specific activity, using the identity matching-rule, we focused all subsequent analysis on identity specificity. For each identity-selective pair, we rank ordered the mean delay-period coherence in the 12-22 Hz range for the three identities (maximum, intermediate and minimum). Figure 2D shows the time-course of the ranked mean coherence ($\pm$ SEM) for each category. The coherence values for the three objects maintain a clear difference throughout the delay. (Distributions of the maximum coherence for each monkey are shown in Fig. S3B). The mean relative phase ranged from 15 to 40 degrees throughout the trial (at the center frequency of 17 Hz, these relative phase values correspond to time lags of 2.45 ms and 6.53 ms, respectively), showing a consistent prefrontal phase lead that gradually increased over time, but showed no apparent difference with respect to the stimuli (Fig.

S4). (Interestingly, a small percentage of phase values ranged between 140-180 degrees indicating a near anti-phase relationship). To further identify the source of the coherence differences, we analyzed the mean and variance of the relative phase and power across the distributions in the 12-22 Hz range. The phase variance showed a significant difference across the population in the interval between 1.15 and 1.70 s. ($p < .05$, Kruskal-Wallis (KW) test, Bonferroni corrected), indicating an inverse relation between coherence magnitude and phase variance in the identity selective pairs (Fig. 2E). We found no difference in the power in the same frequency range for any of the three stimuli in either PPC or PFC (KW test; $p > .05$, Bonferroni corrected) (Fig. S5), suggesting that the differences in coherence were due primarily to differences in phase consistency.

To determine which cortical areas engage in the synchronous memory-related activity, we sorted the fronto-parietal pairs showing significant delay-period CSI according to their respective cortical areas. The results reveal several notable findings (Fig. S6). First, although our sample distribution was non-uniform, we found content-specific, fronto-parietal coherence among all sampled cortical areas. Second, the incidence of significant coherence selectivity varied widely (ranging from 4% to 50%) and occurred more often than expected from a uniform distribution ($p < .05$; randomization test) for both identity and location only among pairs involving the lateral bank of the intra-parietal sulcus (i.e. areas PG and LIP). Thus, memory-related, fronto-parietal synchronization is a widespread process distributed across multiple cortical regions (15, 22, 23).

Having demonstrated content specific synchronization during the delay period, we sought evidence for which cortical areas exert influences that might control or modulate this activity. Using Wiener-Granger Causality (WGC) in the time-frequency domain, we estimated the two directions of predictive influence within each fronto-parietal pair for the object yielding the maximum delay-period coherence (14). Figure 3A shows the time course of the mean ($\pm$ SEM) WGC for the two directions in the 12-22 Hz band. On average the influence is greater from PPC to PFC and both directions of influence increase during the delay period ($p < 0.001$ for time and causation; two-way ANOVA). Because taking the average obscures the heterogeneity of causal influences across the population, we implemented a method to detect significant differences between the two directions of influence for each pair ((14), Fig. S7). We applied this method to the 400 ms of data preceding match onset to avoid potential nonstationarities due to the sample stimulus offset. For each pair with significant directional difference in WGC, the source of the larger value (PFC or PPC) was considered the sender and that of the smaller value the receiver. We then parsed the data according to cortical area in PFC and PPC regions, and plotted the incidence of senders and receivers of each area in the 12-22 Hz band with respect to all areas in the other cortical region (Fig. 3, B and C; areas PGM and 9L were excluded due to small sample sizes). All cortical areas displayed directional influences as senders and receivers, but the incidence of senders was greater in PPC (13.6%) than PFC (7.5%), and some PPC areas did not receive causal influence at all from some PFC areas. The area with the highest incidence of senders was LIP (25.7%) and that with the highest incidence of receivers was dPFC (17.5%).

Our WGC analysis suggests that fronto-parietal synchronization is governed by synaptic influences in PFC that arise in PPC. We used inter-areal spike-field coherence (SFC) measurements to evaluate this prediction (14), reasoning that this measure is indicative of directed synaptic influences (13). For each fronto-parietal pair, we calculated the SFC between spikes in one region and the LFP in the other during the delay period (1.0-1.8 sec) and detected significant SFC as a function of frequency ($p < 0.01$). This revealed significant spectral peaks at frequencies between 10-30 Hz (see Fig. 3D for an example). We then calculated the mean incidence of significant SFC in the 12-22 Hz range for each cortical area in which the unit activity was recorded (see Table S2 for sample distribution). The results support the WGC finding of a dominant PPC to PFC influence by demonstrating that significant SFC occurred more often in PPC_{unit}–PFC_{lfp} pairs than PFC_{unit}–PPC_{lfp} pairs (Fig. 3E, $p < 0.05$, KS test). The agreement between the WGC and SFC results, supporting a dominant PPC to PFC influence, as opposed to the relative phase results showing a PFC phase lead, supports previous findings that relative phase is not a reliable index of neural influence (24).

To further evaluate the contribution of unit response selectivity, we calculated the mutual information for firing rate as a function of time (Fig. S8) and, consistent with previous reports (19, 20, 25), found widespread selectivity during the sample and/or delay across both PFC and PPC areas (Table S3). We then subdivided the SFCs according to the identity selectivity of the cellular responses. The results for the PPC_{unit}–PFC_{lfp} pairs show that significant SFC with PFC involves both selective and non-selective parietal neurons (Fig. 3F). (PFC_{unit}–PPC_{lfp} pairs were not included due to small

sample sizes.) However, the majority of spike-field interactions involving identity selective units come from cells recorded in areas LIP, PG and to a lesser extent MIP.

Our findings demonstrate that fronto-parietal synchronization during visual working memory is widespread, task-dependent and content specific during the delay period. The patterns of synchronization are governed by influences arising in PPC (26) and are prevalent among parietal neurons that display identity selectivity (19). These findings are consistent with other reports on the relationship between synchronization and performance in working memory tasks (15, 22, 27), the presence of fronto-parietal synchronization during memory-related search (12), and the spatial attention modulation of inter-areal coherence (28). Thus, while other cognitive processes, such as attention, anticipation and motor planning, are likely to contribute to these effects, our findings demonstrate that short term memories are represented as stimulus specific patterns of synchronized activity that are widely distributed throughout the fronto-parietal network (29). This raises the question of how these patterns, their directional influences, spectral dynamics and spatial distribution are modified by other working memory processes, such as retrieval, resistance to distraction, load, manipulation and object-based attention. Other frequency bands have been associated with working memory (22, 30-32) and abundant evidence indicates that other cortical areas contribute to these representations. A major challenge will be to elucidate the neuronal mechanisms underlying memory-related, fronto-parietal interactions, and their relationship to different frequency bands and other cortical areas.

Tables

Table 1. Number of fronto-parietal pairs with significant coherence and CSI between 10 to 42 Hz.

N=2191		PRE (0.1-0.4 s)	SA (0.6-0.9 s)	DE1 (1.1-1.4 s)	DE2 (1.4-1.7 s)	DE (DE1 and/or DE2)
Identity	Sig. Coh	1349	1216	1369	1599	1662
	Sig. CSI	51	199	244	290	438
		3.8%	16.4%	17.8%	18.1%	26.4 %
Location	Sig. Coh	1286	1160	1274	1488	1550
	Sig. CSI	41	194	223	263	409
		3.2%	16.7%	17.5%	17.7%	26.4%

Abbreviations:

PRE: presample period

SA: sample period

DE1: early delay period

DE2: late delay period

DE: the whole delay consisting of either DE1 and/or DE2

The timing of these periods is shown in parentheses.

Table S1. Sampling distribution of LFP and unit activity in both monkeys.

Cortical areas	Multi units	Single units	LFP sites
6DR	7	3	7
8AD	27	9	27
8B	66	33	64

Table S1 Continued

dPFC	121	67	113
vPFC	17	3	17
9L	11	8	11
PFC	249	123	239
PEC	104	51	100
PGM	3	0	3
PE	58	17	58
PG	60	35	58
MIP	34	8	34
LIP	46	19	45
PPC	305	130	298

The sample sizes for LFP and multi-unit activity differ because of artifact rejection applied to the LFP signals. Areal abbreviations follow the nomenclature of (Paxinos et al., 1999) with the exception of dPFC and vPFC.

PFC – prefrontal cortex
 PPC – posterior parietal cortex
 6DR – dorsorostral area 6
 8AD – anterodorsal area 8
 8B –area 8B
 dPFC – dorsal prefrontal cortex
 vPFC – ventral prefrontal cortex
 9L – lateral area 9
 PEC – caudal area PE
 PGM – medial area PG
 PE – area PE

PG – area PG

MIP – medial intraparietal area

LIP – lateral intraparietal area

Table S2. Sample distribution of spike-field coherence pairs in both monkeys.

Cortical areas	Number of SFC pairs
6DR	130
8AD	399
8B	851
dPFC	972
vPFC	177
9L	34
PFC	2563
PEC	806
PGM	34
PE	600
PG	317
MIP	378
LIP	427
PPC	2562

The cortical area indicates the location of the recorded unit activity and the numbers indicate all possible pairings with the LFP recorded in the other cortical region. The abbreviations are the same as Table S1.

Table S3. Distribution of stimulus selective unit activity with respect to cortical area in both monkeys.

	Identity selective	Location selective	Total cells
6DR	2	1	10
8AD	12	13	36
8B	24	27	99
dPFC	41	63	188
vPFC	8	12	20
9L	3	6	19
PFC	90	122	372
PEC	27	31	155
PGM	2	2	3
PE	12	23	75
PG	25	64	95
MIP	11	19	42
LIP	32	53	65
PPC	109	192	435

The abbreviations are the same as Table S1.

Figures

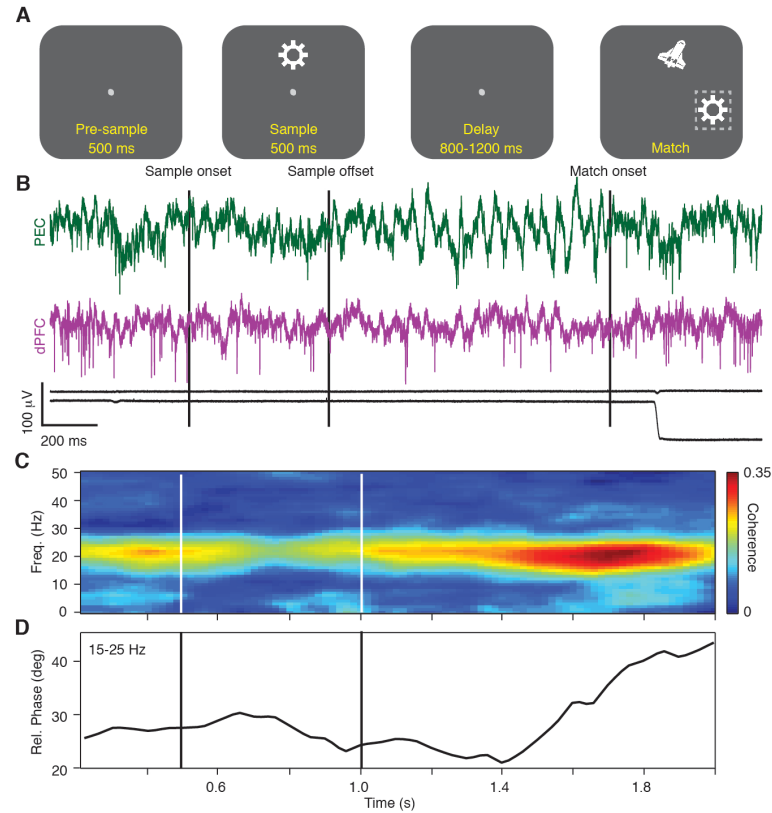


Fig. 1

Fig. 1. Task dependence of fronto-parietal coherence. (A) Timeline of the identity-matching task. During visual fixation, a sample stimulus, consisting of 1 of 3 possible objects positioned at 1 of 3 possible locations, was presented for 500 ms, followed by a random delay of 800-1200 ms. At the end of the delay a match stimulus was presented, consisting of the previous sample object (target) and a distracter object positioned at 2 out of 3 possible locations. A saccadic eye movement to the target was rewarded with juice (14). (B) Example of the signals recorded on a single trial in monkey A. Top two traces: broadband signals from area PEC of the parietal cortex (PEC, green) and dorsolateral prefrontal cortex (dPFC, purple). Bottom two traces: horizontal and vertical eye position. (C,D) Time-frequency coherence spectrum (C) and average relative phase between 15 and 25 Hz (D) locked to the sample presentation (all stimuli, correct trials, 400 ms window, 50 ms step). In B-D, and in all subsequent figures, the vertical lines show the onset and offset of the sample. Time-frequency distributions in this and subsequent figures are interpolated at 1 Hz and 2 ms resolution.

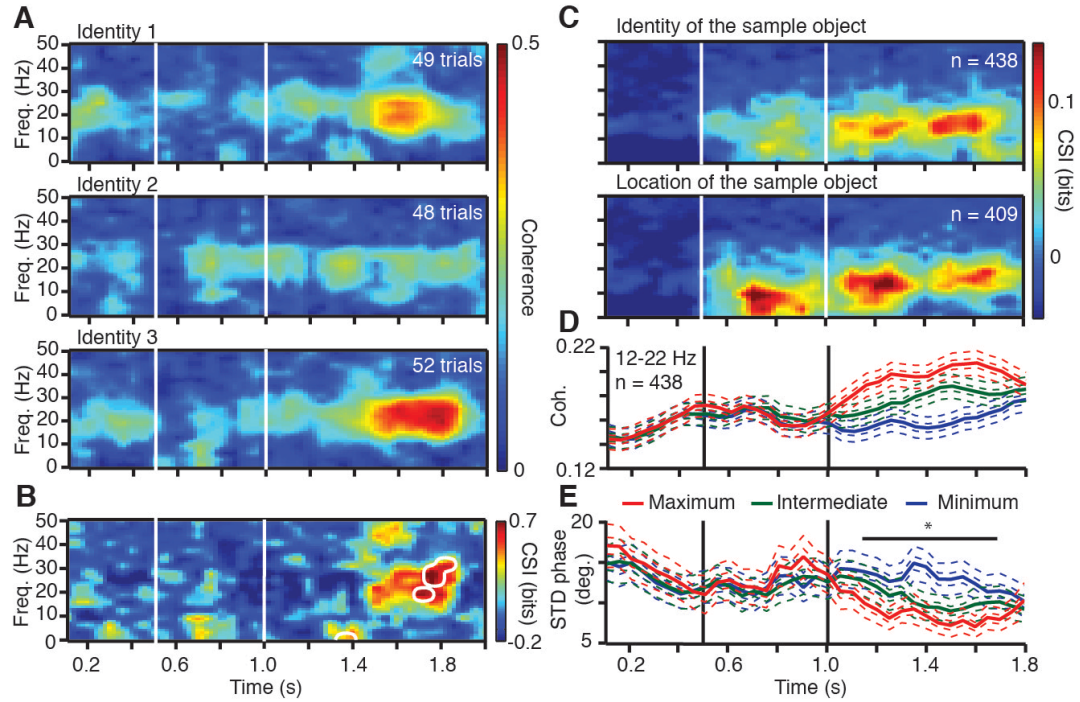


Fig. 2 (2 columns width)

Fig. 2. Content specific fronto-parietal synchronization during working memory. (A) Time-frequency coherence spectra for an LFP pair for the three sample objects presented at one location. (B) Coherence selectivity index as a function of time and frequency ($CSI(t,f)$) for the same pair showing significant selectivity (significance threshold at $p < .02$ indicated by white contours) during the delay period. (C) Median value of $CSI(t,f)$ for LFP pairs showing selectivity for the sample identity (upper) and location (lower) during the delay. (D) Mean rank-ordered coherence ($\pm$ SEM) in the 12-22 Hz band for the same identity selective pairs as in the upper plot of C. (E) Mean standard deviation of the relative phase ($\pm$ SEM) in the 12-22 Hz band for the same identity selective pairs as in the upper plot of C. In plots D, E and Figure 3A, the two SEMs were calculated with the number of pairs or sessions as the degree of freedom.

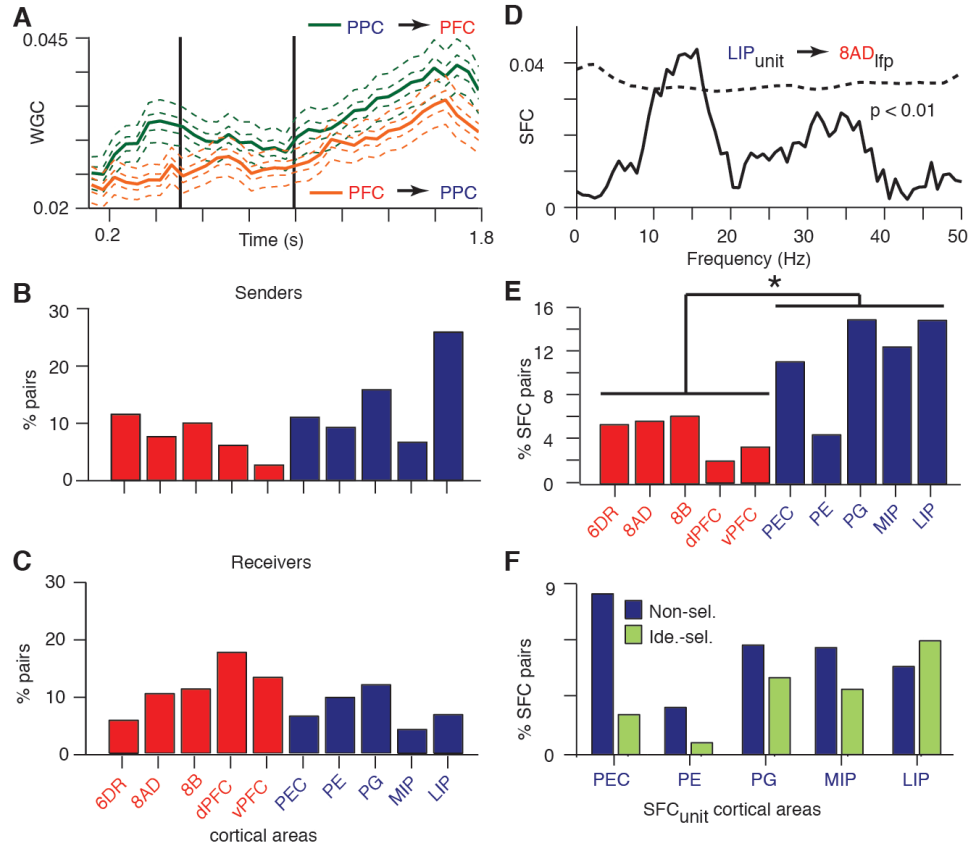


Fig. 3

Fig. 3. Fronto-parietal interactions are dominated by parietal-to-frontal influences. (A) Time course of WGC in the 12-22 Hz frequency range for all identity selective pairs (mean $\pm$ SEM; $n = 438$). (B, C) Bar charts of the incidence of significant WGC directional differences with respect to cortical area for all the signal pairs in A. (D) Example of the SFC for a LIP unit and the field recorded in area 8AD. Dashed line indicates confidence limit ($p < .01$, randomized surrogate). (E) Percentage of fronto-parietal pairs with significant SFC between 12 and 22 Hz. The unit activity was recorded in the labeled areas. See Tables S1 and S3 for abbreviations and sample sizes. (F) Percentage of significant PPC_{unit}–PFC_{lfp} pairs with respect to the parietal area in which the unit activity was recorded and split according to the stimulus selectivity of the cellular responses.

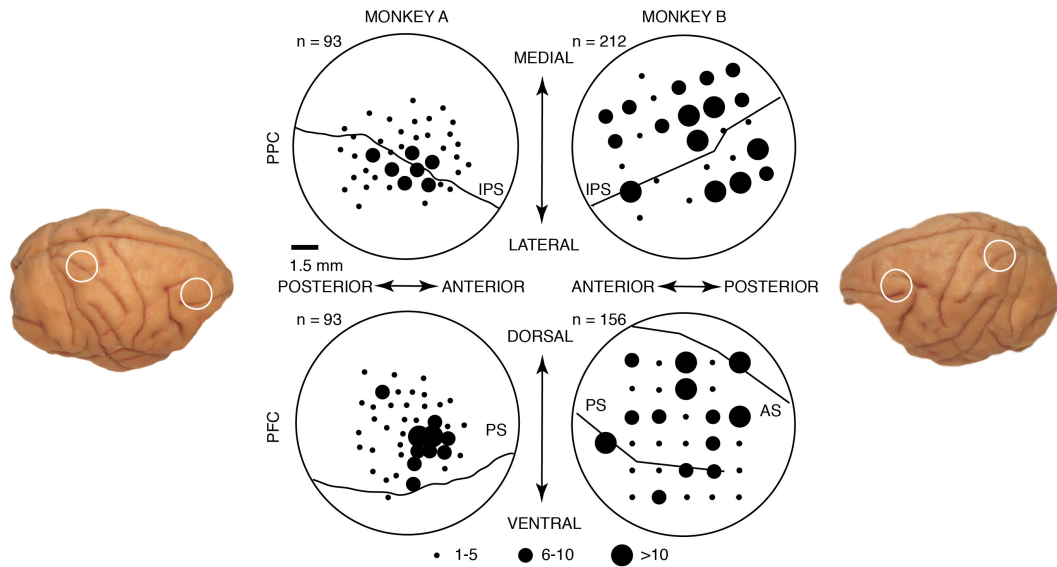


Fig. S1

Fig. S1. Anatomical locations of recording sites relative to the posterior parietal (PPC; upper panels) and prefrontal (PFC; lower panels) chambers in both monkeys. Photographs of the left and right hemispheres of a separate macaque brain, along with approximate locations of the recording chambers, are shown to the left and right. The sample size within each chamber is represented by the size of the dots. IPS: intra-parietal sulcus, PS: principal sulcus, AS: arcuate sulcus.

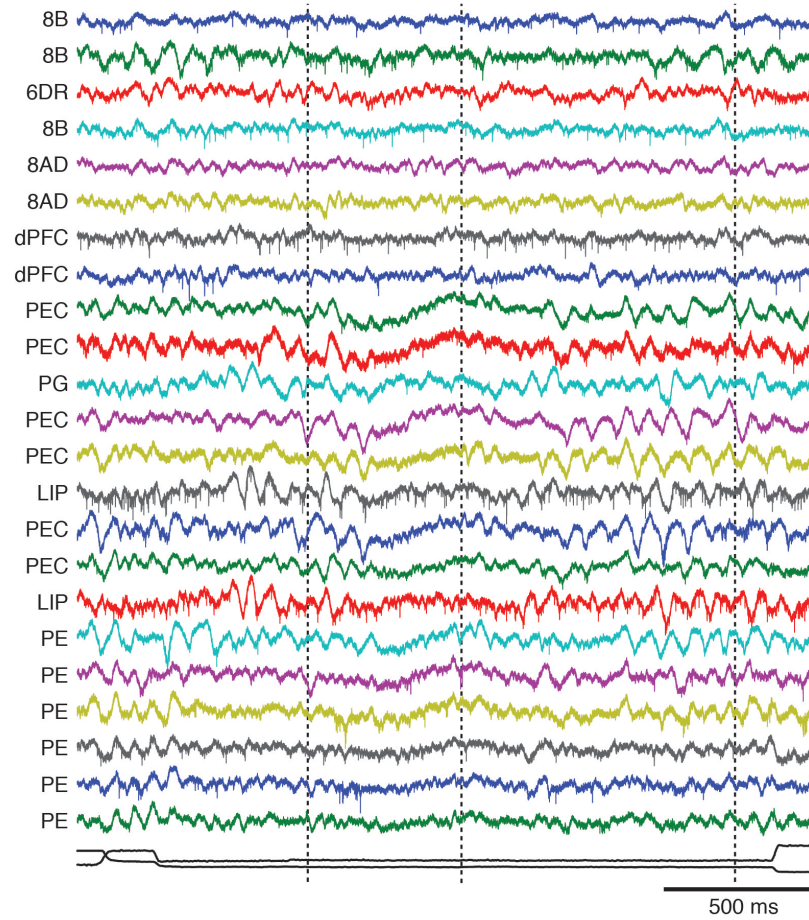


Fig. S2

Fig. S2. Example of raw traces for a single trial for all channels displaying unit activity during a single recording session in monkey B. The timing of the sample onset, offset and the match stimulus onset are represented by the vertical dashed lines from left to right, respectively. The vertical and horizontal eye position signals are shown in the two lower traces. The abbreviations on the left of each trace correspond to the cortical area recorded. See Table S1 for the abbreviations.

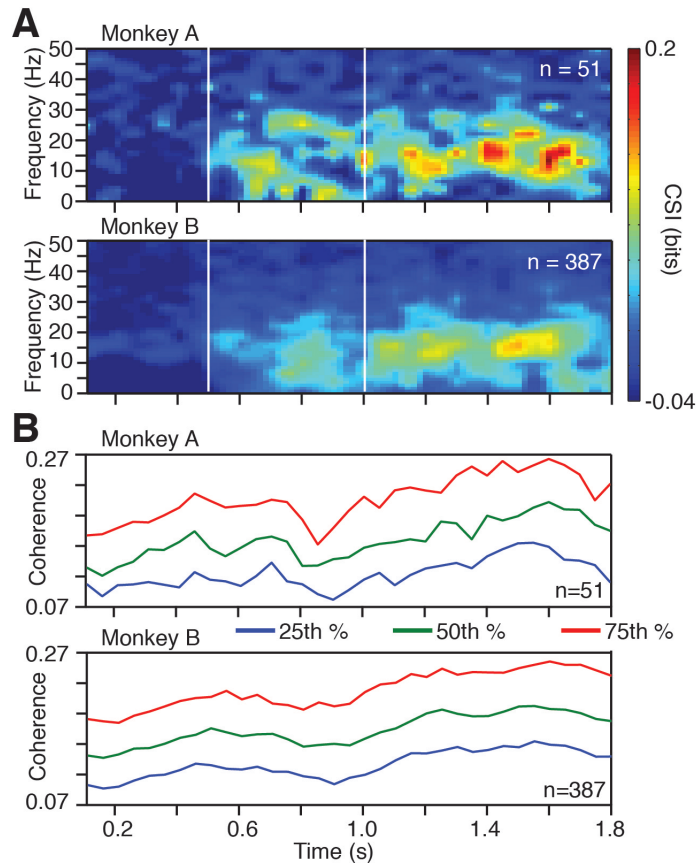


Fig. S3

Fig. S3. Content specific fronto-parietal synchronization during the working memory task plotted for each monkey separately. (A) Median value of the CSI as a function of time and frequency for LFP pairs selective to the sample identity during the delay for monkeys A and B, respectively. (B) Median value (and interquartiles) of the coherence as a function of time for the two monkeys in the 12-22 Hz frequency range for the stimulus identity that yielded the maximum coherence.

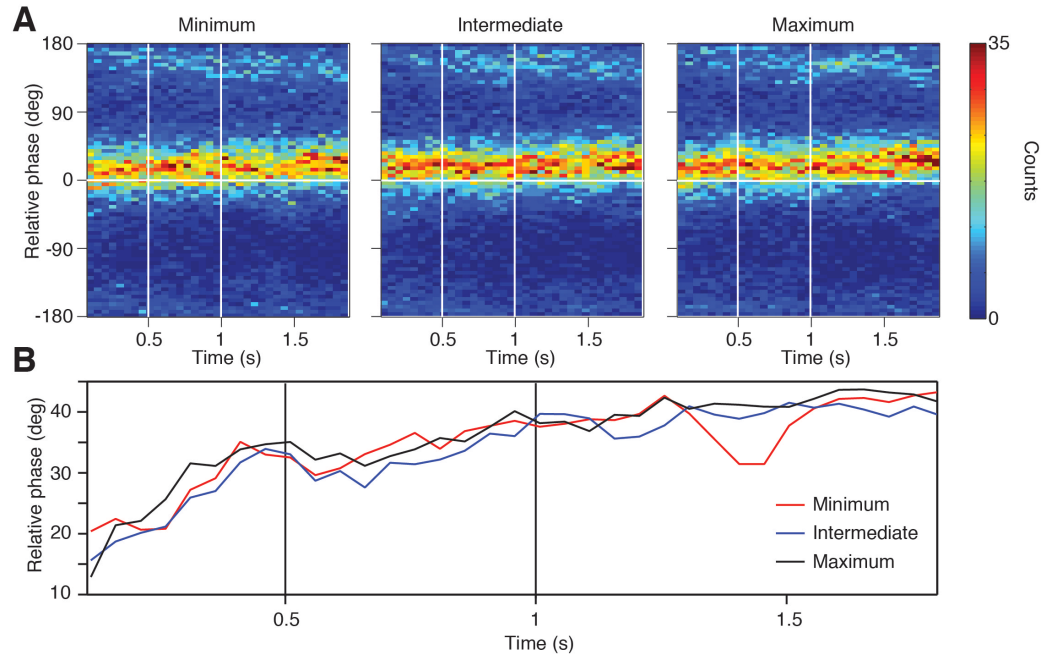


Fig. S4

Fig. S4. Time-dependence of relative phase in the 12-22 Hz range for all fronto-parietal LFP pairs showing identity selectivity during the delay. For each pair, the phase distributions correspond to the coherence values that were rank ordered with respect to sample identity during the delay (1.1 to 1.7 s) and are referred to as minimum, intermediate and maximum to match the legend of Figure 2D and E in the main text. (A) Histogram of relative phase as a function of time for the three rank ordered stimulus identities. (B) Mean relative phase for each of the three stimuli. Vertical lines mark the onset and offset of the sample stimulus. Horizontal white line marks the zero relative phase value.

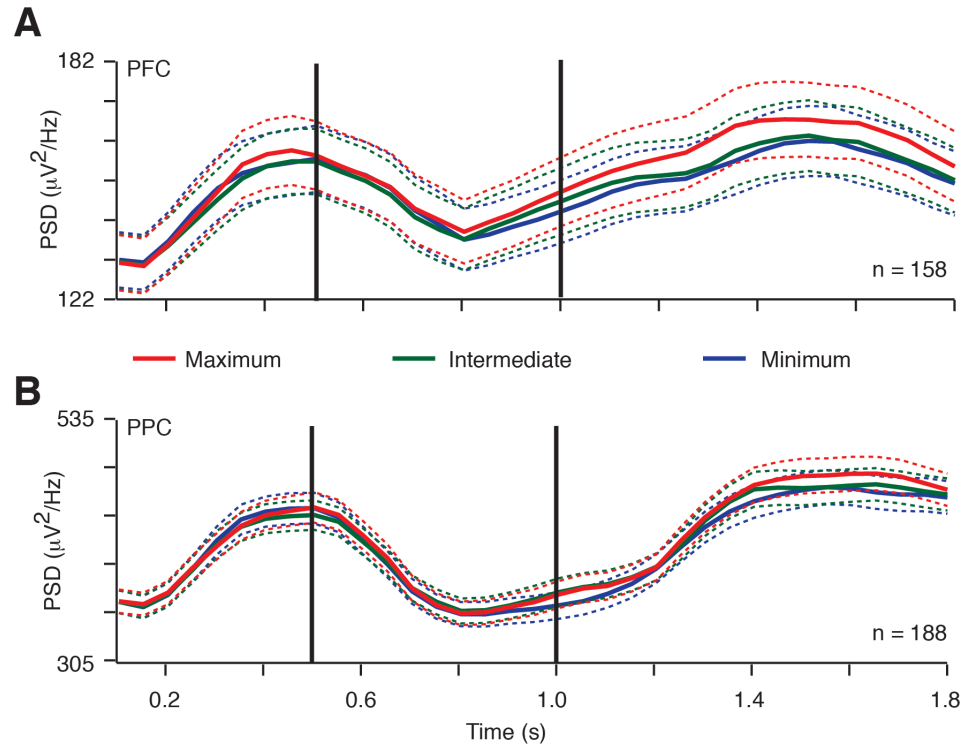


Fig. S5

Fig. S5. Time-dependence of power in the 12-22 Hz range (Mean $\pm$ SEM) for all frontal (A) and parietal (B) LFP signals obtained from pairs showing identity selective coherence during the delay. For each signal, the power spectra were rank ordered according to the corresponding coherence values as in Fig. 2D and E of the main text and Fig. S4. Vertical lines mark the onset and offset of the sample stimulus.

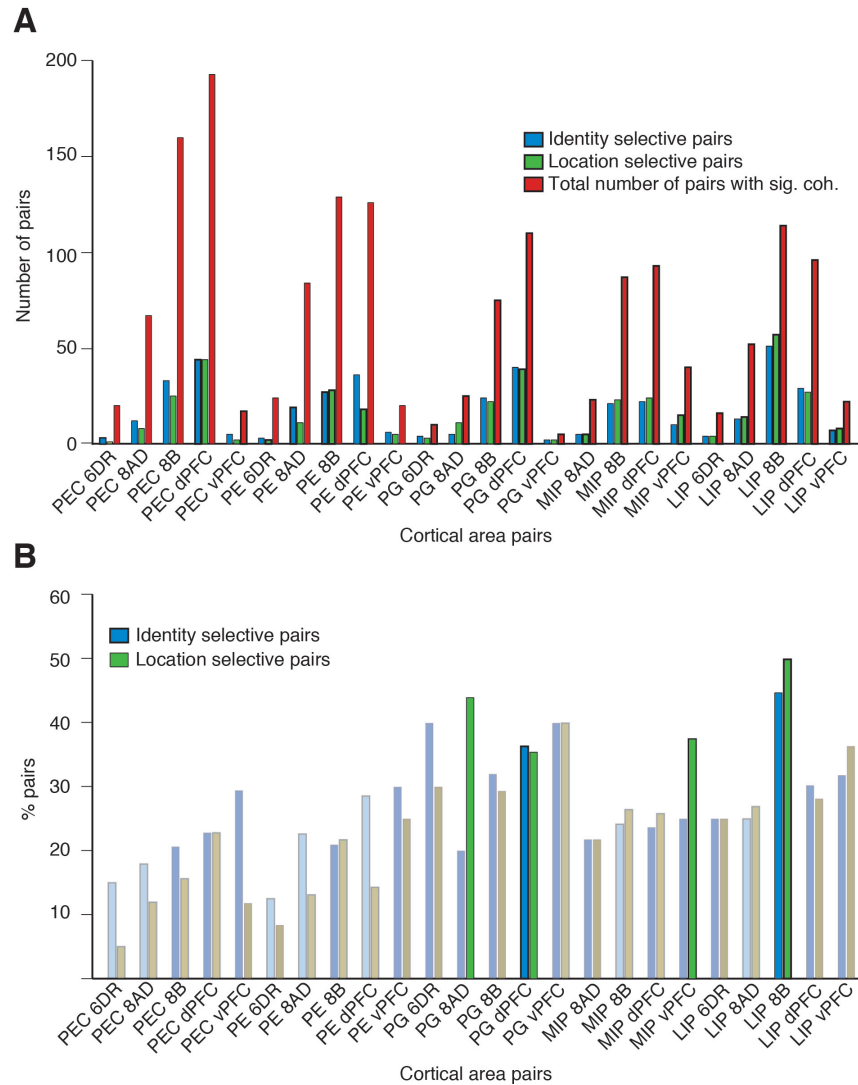


Fig. S6

Fig. S6. Sample distribution of fronto-parietal LFP coherence for both monkeys with respect to inter-areal combinations. (A) Bar chart showing the total number of pairs with significant coherence (red), and those with identity (blue) and location (green) selective coherence. (B) Bar chart of the corresponding percentages for identity and location selectivity shown in blue and green, respectively. The highlighted values were statistically significant ($p < .05$) with respect to a random shuffling of the sampled locations ($n = 1000$). Areal names are taken from (Paxinos et al., 1999) with the exception of dPFC and vPFC. Data from areas PGM and 9L were excluded due to small sample size.

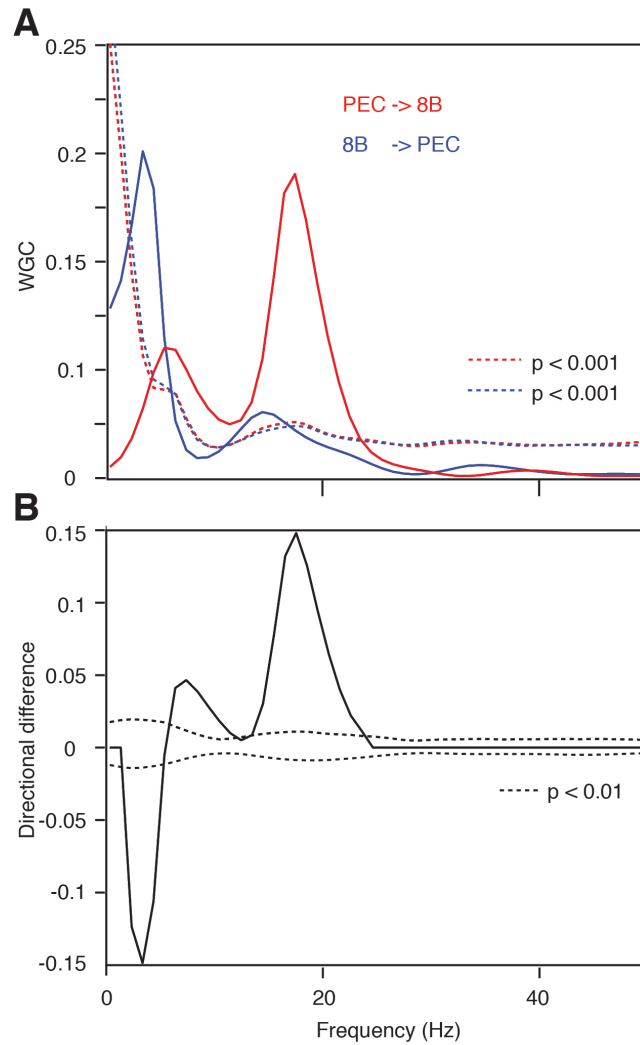


Fig. S7

Fig. S7. Illustration of the method used to detect significant differences in the directions of WGC influence. (A) Example of the WGC spectra, computed from all correct trials, for a single fronto-parietal LFP pair during the late phase of the delay period. The two directions (solid red and blue lines) are presented along with their respective significance levels ($p < .001$) (dashed red and blue lines). (B) The difference between the two WGC directions (solid line) and the significance level ($p < .01$, dashed line) based on a surrogate distribution of differences.

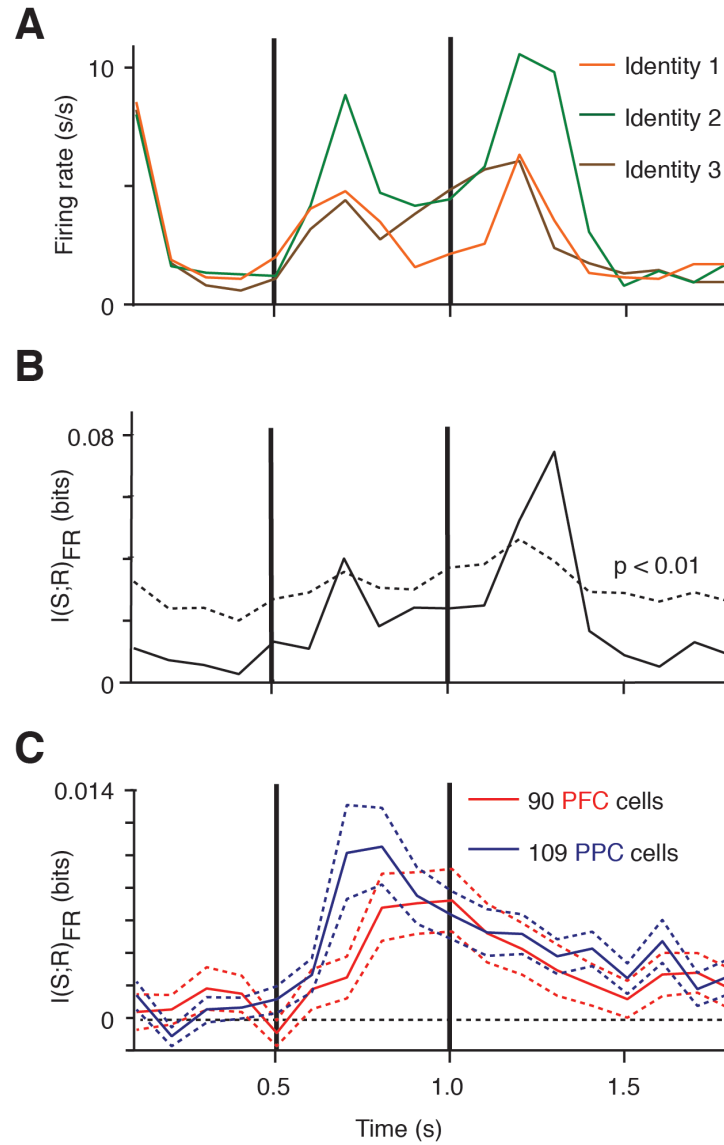


Fig. S8

Fig. S8. Cellular response selectivity for the identity of the sample stimuli. (A) Mean firing rate of a LIP single unit in response to the three sample objects. (B) Time course of $I(S;R)_{FR}$ for the cell shown in A. Dashed line is the 99% confidence limit based on a surrogate distribution. (C) Time course of $I(S;R)_{FR}$ (mean $\pm$ SEM) for all frontal and parietal identity selective units.

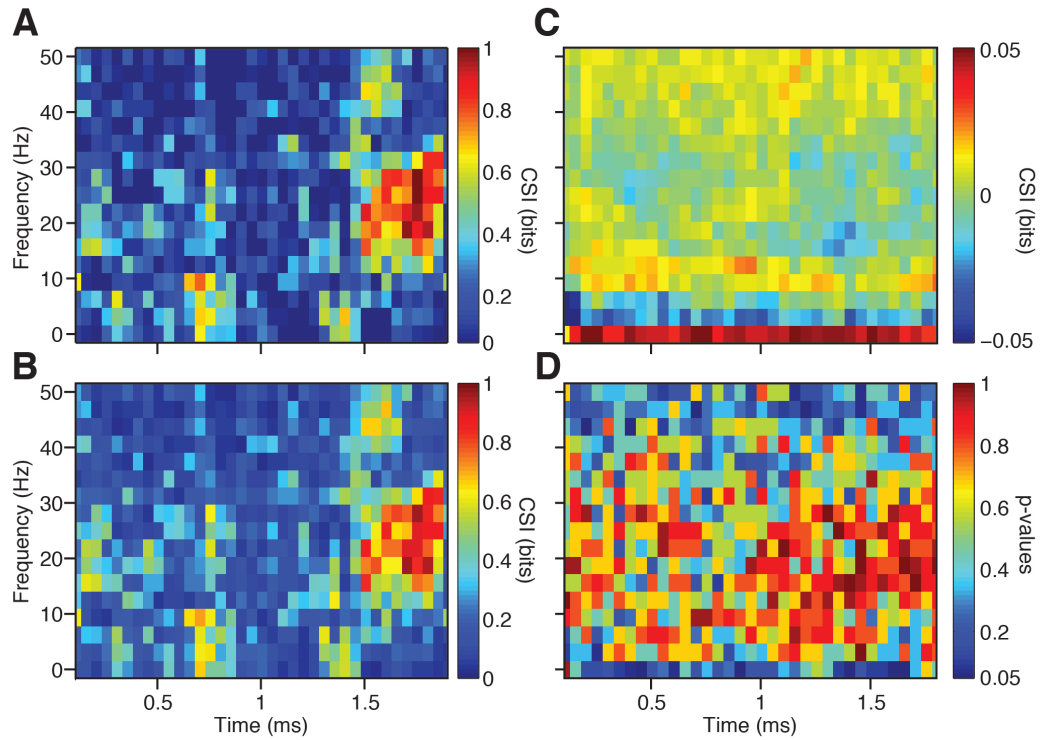


Fig. S9

Fig. S9. Comparison between two different ways to measure CSI . (A) $CSI(t,f)$ for the example pair shown in Fig. 2A in the main text, computed using the Jackknife estimate of the standard deviation of the coherence. (B) $CSI(t,f)$ for the same pair computed using the bootstrap estimate of the probability distribution of the coherence. (C) Mean difference of $CSI(t,f)$ between the two methods for 100 randomly selected pairs having significant CSI (based on the Jackknife method) during the delay period. (D) P-values obtained from the Kolmogorov-Smirnov test comparing the CSI values from the two methods at each time-frequency bin.

Supporting Material

Materials and Methods

Subjects. Using established techniques, two female rhesus monkeys (Monkey A and B, *Macacca mulatta*) were implanted with a scleral search coil to track eye position (Judge et al., 1980), a cranial post for head restraint and two recording chambers (Gray et al., 2007) located above the prefrontal (PFC) and posterior parietal (PPC) cortical regions of the same hemisphere. A craniotomy was made within each chamber, one spanning the middle-to-posterior portion of the principal sulcus and the other spanning the dorsal portion of the intra-parietal sulcus. A structural MRI scan provided guidance for the chamber placement in Monkey B. The chambers were placed in the right and left hemispheres of Monkeys A and B, respectively. All hardware was fixed in place using Titanium bone screws and acrylic cement. All surgical procedures were performed using sterile technique and Isoflourane anesthesia, and all procedures involving the animals were performed in accordance with NIH guidelines and the Institutional Animal Care and Use Committee of Montana State University.

Behavioral Task. The monkeys were trained to perform an oculomotor, delayed match-to-sample task involving a non-instructed rule switch. In this task, each trial is initiated with the appearance of a central fixation spot presented on a grey background. The monkey, seated in a primate chair in front of a 19-inch monitor (85 Hz refresh rate, 57 cm distance), is required to maintain visual fixation within a three degree window throughout the trial until an appropriate oculomotor response is made. At a latency of 500

ms, one of three possible sample objects (size: 3x3 deg., eccentricity: 5 deg.) is presented for 500 ms at one of three possible locations lying at the vertices of an invisible triangle. This design resulted in 9 unique sample stimuli on each session. The sample stimulus is followed by a randomized delay, ranging from 800-1200 ms in one set of experiments and 1 to 3 sec in a second set of experiments, in which no stimulus is present. At the end of the delay period, the fixation target is extinguished and a match stimulus is presented that consists of a target and a distracter object positioned at two of the three possible locations. While the match stimulus is visible, the monkey must make a saccadic eye movement to the target object and maintain gaze on the object for 300 msec. The target object is defined by the matching rule in effect, either location or identity. After the monkey had reached criterion performance ($> 80\%$ correct responses for at least 300 consecutive trials using a sliding-window of 100 trials), the rule was switched without cueing the animal. Several rule switches could occur each day, but in general only one to two switches were achieved. Correct trials were rewarded with a drop of juice. To reduce biases for both the location and identities of the objects, the object locations were rotated by 180 degrees on alternate days and each day a new set of objects was selected. All object positions and identities were presented with equal probability in a pseudo random sequence. In monkey B, 10% of the trials did not include stimuli and the monkey simply had to maintain fixation throughout the trial to receive a reward. The eye position signals were acquired using the scleral search coil method in monkey A and an infrared eye-tracking system in monkey B. Both custom software and the publicly available MonkeyLogic software (<http://www.monkeylogic.net/>) were used to display the stimuli

and provide experimental control (Asaad and Eskandar, 2008a; Asaad and Eskandar, 2008b).

Recording Techniques. Broadband neuronal activity (1 Hz – 10 kHz) was recorded simultaneously from multiple electrodes in both chambers using acute (Monkey A) and semi-chronic (Monkey B) recording techniques. The signal from each electrode was amplified (5k), filtered (1.0 Hz – 10 kHz), digitized (30 kHz) and stored for later, off-line analysis. In the acute method (Gray et al., 2007), recordings were made by passing 4-8 independently controlled microelectrodes (Tungsten-in-glass, 0.5-1.5 M Ω impedance) through the dura in both chambers on a daily basis. The separation between electrodes in each chamber was at least 0.86 mm (range 0.86 – 6.08 mm) and each electrode was advanced until unit activity was encountered. The recording locations were varied each day by using different holes in an 8x8 guide array and the recording depths ranged from the point of initial detection of unit activity in the superficial layers to a maximum of 5 mm.

In the semi-chronic method, Monkey B was implanted with two miniature mechanical microdrives, each containing 32 independently movable microelectrodes spaced 1.5 mm apart. Recordings were made by slowly advancing a subset of electrodes in each chamber each day. Electrode movement typically ranged from 0.1 to 0.5 mm and some electrodes were left in a fixed position for several days. All redundant measurements of activity (i.e. those in which a pair of electrodes was left in a fixed position for multiple sessions) were accounted for in the analysis by reducing the sample size and degrees of freedom accordingly. The deepest recordings were made roughly 10

mm from the surface of the cortex. These recordings spanned a total duration of 14 months. To identify the recording locations in Monkey B, electrolytic lesions were made at the final position of each electrode (10 μ A, 25 sec.) prior to the perfusion.

In both recording methods, the reference and ground connections of the amplifiers were tied to a connection linking the two recording chambers. The reference signal was thus obtained from a distributed source.

Histology. When recording was completed, each monkey was euthanized (Pentobarbital, 100mg/kg; i.v.) and perfused through the heart with phosphate buffered saline (PBS) followed by a solution of 5% paraformaldehyde in PBS. The brain was removed and relevant portions blocked and sunk in a solution of fixative with 30% sucrose several days before being sectioned (60 μ m) and stained for Nissl substance to identify electrode tracks. Prior to blocking and sectioning, the brain was photographed to confirm the location of the chambers relative to major cortical sulci.

Data Analysis. In the present study, all of our analysis was performed on blocks of trials sampled during the identity matching rule of the task.

Preprocessing The broadband signal from each recording was bandpass filtered in two steps to separate the local field potential (LFP, 1-100 Hz) and the highpass unit activity (500 Hz – 7 kHz). The LFP was down sampled to a rate of 200 Hz. The highpass signal was further processed to extract all spike waveforms. For this, local minima in the original signal (i.e., negative peaks in the spike waveforms) were identified if they exceeded 4 standard deviations (SD; Monkey A) or 5 SD (Monkey B) of the background

signal. Spike waveforms were extracted by storing 32 data points (11 points prior to and including the minimum, and 21 points following the minimum), from each channel (Yen et al., 2007).

Spike Sorting. The methods for spike sorting closely followed those described in an earlier study (Yen et al., 2007). Automated clustering of waveforms was performed using the KlustaKwik software package and inspected using the MClust software package (<http://redishlab.neuroscience.umn.edu/MClust/MClust.html>). Single unit activity (sua) was identified when each candidate waveform cluster was stable over time, nonoverlapping with all other clusters in at least one classification dimension, and the interspike interval histogram (ISIH) displayed a clear refractory period. Multiunit activity (mua) was recovered by applying an amplitude threshold to the highpass signal and recording the time of each negative threshold crossing. The data were carefully screened to eliminate artifactual waveforms prior to saving the final spike trains.

Selection of Channels. In order to insure that all measurements were coming from cortical grey matter, subsequent analyses of the LFP were done only if spiking activity from the same electrode had been visually detected during the sorting procedure and the signal-to-noise ratio (SNR) of the highpass signal was ≥ 1.8 .

Detection of Artifacts. Occasionally, we found instances in which the LFP signals were contaminated by electrical artifacts. These artifacts showed up as large deviations in the amplitude distributions of the signals and were generally either transient (such as a spike) or sustained (such as line noise or movement artifacts). Trials with transient

artifacts were excluded from subsequent analyses when the maximum amplitude of the LFP exceeded 12 SD computed from all trials. We used an iterative procedure to detect more sustained artifacts. For this, we calculated the Kurtosis of the distribution of spectral power at each frequency across all trials. When the Kurtosis of the distribution exceeded a predefined threshold of eight, the trial with the largest power value was removed and the Kurtosis recomputed. This procedure was repeated until the residual distribution either dropped below the Kurtosis threshold or the rate of change of the Kurtosis evaluated over all previous iterations was not significantly different from zero ($p > .0001$). By applying this method to each frequency in the spectrum, we were able to remove trials with narrow and broadband artifacts. Finally, selected channels were rejected from further analysis when more than four percent of the trials were contaminated with artifacts.

Data Selection Based on Behavioral Performance. In addition to the rejection of trials containing artifacts, we implemented several measures to identify periods of stable behavioral performance and applied the subsequent analysis to these periods. First, the initial 25 trials at the beginning of a session and following each non-instructed rule switch were excluded to avoid drops in performance that occur in these conditions. Second, trials in which the reaction time was less than 80 ms were excluded from the analysis. Third, behavioral performance was calculated on the remaining trials. If the performance was below 75% correct responses (CR) the first trial was removed using an iterative procedure until performance was $\geq 75\%$ CR. Short periods within the session where performance dropped below 55% CR (using a sliding window of 50 trials, stepped

in one trial increments) were also excluded. When these events occurred, the block of 50 trials used to calculate performance was rejected from further analysis. This had the effect of further increasing the overall performance above 75% CR.

After application of all selection criteria, our analysis included sessions with a mean of 498 trials per session (min = 219; max = 1038) and on average the minimum number of trials per stimulus condition was 66 ± 23 (mean $\pm$ std).

Multi-Taper Spectral Power and Coherency Analysis. To evaluate the time course of the amplitude and synchronization between simultaneously recorded fronto-parietal LFPs, we calculated the time-frequency power and coherency spectra (200 msec. sliding window stepped at 50 ms) using multi-taper spectral analysis (Mitra and Pesaran, 1999) implemented in the Chronux toolbox (Bokil et al., 2010) (<http://www.chronux.org/chronux/>) with three tapers and a time-bandwidth product of two (frequency resolution of 3.12 Hz and frequency smoothing of 12 Hz). The coherency spectrum was estimated using equation 1,

$$(1) \text{ coherency} = \left| \frac{S_{12}}{\sqrt{S_1 S_2}} \right|$$

where S_1 and S_2 are the mean auto-spectra of the two time series and S_{12} is the mean cross-spectrum. For simplicity, we use the term coherence instead of coherency.

For each session, we estimated the coherence between each fronto-parietal pair using three different combinations of trials; one for trials acquired in response to each of

the 9 stimuli, a second in which we combined the trials for all objects at each location, and a third in which we combined the trials for all locations for each object. We used the first set of measurements to estimate the location and identity specificity of coherence and the latter two to determine the incidence of significant coherence at each location and for each object, respectively, across the entire sample (see below). The test for significance was applied to four separate windows of equal duration (500 ms) during the presample, sample, early delay and late delay periods of the task. A pair was considered to have significant coherence if at least 15% of the time-frequency bins exceeded the surrogate threshold ($p < 10^{-3}$) (see below).

Detection of Significance Using Surrogate Distributions. To evaluate the statistical significance of the spectral metrics (coherence, Mutual Information and Wiener-Granger causality), we computed significance thresholds from randomized surrogate distributions. A distribution of surrogates was created by shuffling the trial sequence, the stimulus assignment in the case of the mutual information (see below), or the causal direction in the case of Wiener-Granger causality (see below), for each channel in the pair and repeatedly computing the spectral quantity with a new random number seed for a large number of iterations ($n = 1000$). The method yields a distribution of values at each time-frequency bin that are expected to occur by chance when the signal fluctuations are not locked to the events in the task. A significance threshold was chosen by selecting the value that lies at the n^{th} percentile of each distribution. Because the time needed to generate a surrogate distribution scales approximately with the square ($n(n-1)/2$) of the number of signal pairs (n), it became necessary to implement a generalized

method for computing surrogate distributions. For this, we computed a surrogate distribution for each day of recording by randomly shuffling the trial sequence and channel selection across the entire data set. For each iteration one channel was taken from PPC and the other from PFC. Thus we refer to this method as a semi-generalized surrogate procedure. We used this approach for testing the statistical significance of all the metrics utilized in this study.

Mutual Information. We used Shannon's mutual information (Ince et al., 2010) to quantify how well the neuronal responses enabled us to discriminate among the different sample stimuli (equation 2). For the LFP-coherence, mutual information ($I(S;R)_{coh}$) was estimated as a function of time and frequency (see below). For cellular firing rates, mutual information ($I(S;R)_{FR}$) was calculated as a function of time (bin size = 100 ms).

$$(2) \quad I(S; R) = \sum_{r,s} P(s)P(r|s) \log_2 \frac{P(r|s)}{P(r)}$$

with

$$(3) \quad P(r) = \sum_s P(r|s)P(s)$$

where $P(r)$, $P(s)$ and $P(r|s)$ are the probabilities of the response, the stimulus ($1/\#\text{stimuli} = 1/3$) and the conditional probability of the response on the stimulus, respectively. This measure is straightforward for cellular firing rates because we have a direct measure of $P(r|s)$ from the firing rate measured on each trial. However, coherence is an average measure across a set of trials, making it necessary to estimate $P(r|s)$ when coherence is the response. Using the Chronux toolbox, we computed the standard deviation of the

coherence at each time and frequency using a Jackknife resampling method on the tapered Fourier transforms (Pesaran et al., 2002; Bokil et al., 2007). We generated $P(r|s)$ using a normal probability density function (mean = magnitude of coherence, std = standard deviation of coherence) for values ranging from 0 to 1 in .01 increments and divided by the cumulative sum. We then computed $I(S;R)_{coh}$ with respect to stimulus identity at each of the three sample locations, and with respect to stimulus location for each of the three sample identities. This yielded 6 separate measures of $I(S;R)_{coh}$ as a function of time and frequency.

Some further comments are warranted regarding $I(S;R)_{coh}$. Because coherence is an average measure, $I(S;R)_{coh}$ quantifies the degree to which the coherence, measured across a set of trials, reduces the uncertainty about the stimulus associated with that set of trials, rather than quantifying the reduction in uncertainty associated with single trials. A related measure has been used previously to quantify the average mutual information of a population of neurons in motor cortex (Maynard et al., 1999). The metric is thus not directly comparable to $I(S;R)_{FR}$. We therefore refer to $I(S;R)_{coh}$ as the coherence selectivity index (*CSI*) and utilize the measure solely as a means to quantify stimulus related differences in coherence.

In order to estimate the statistical significance of *CSI* at each time-frequency bin, we computed the semi-generalized surrogate distribution of *CSI* (CSI_{sur}) for each of the 6 conditions being evaluated (see above). On each of 1000 iterations a pair of signals is randomly chosen, one from PFC and one from PPC, the trials are shuffled with respect to the stimuli, $P(r|s)$ is estimated with a normal pdf and CSI_{sur} is calculated using equation 2.

This procedure maintains the number of trials for each stimulus condition while generalizing the surrogate across channels. The statistical significance of each time-frequency bin can then be evaluated using the corresponding CSI_{sur} distribution.

Because it is well established that $I(S;R)$ can be biased when the number of observations is small (Panzeri et al., 2007), it was necessary to implement a bias-correction procedure by subtracting the expected value of CSI_{sur} ($E[CSI_{sur}]$) from the measured value of CSI .

$$(4) \quad E[CSI_{sur}] = \sum_n CSI_{sur}(n) * P(CSI_{sur}(n))$$

and

$n = 500$ bins

However, because CSI_{sur} is a semi-generalized estimate, it is unlikely to fully account for the true bias over all times and frequencies for each channel pair. Moreover, significant values of CSI may occur during the presample period due to unexplained sources of variance such as eye movements occurring at the onset of fixation. Therefore, there was a need to adjust the bias obtained from the CSI_{sur} for each pair to compensate for these deviations. To accomplish this, we implemented a scaling factor (α_i) on each channel pair (equation 5), which yields an average value of $CSI=0$ during the presample period. This measure also served to increase the stringency of the statistical test (equation 6) for significant CSI .

$$(5) \quad \alpha_i = \frac{\sum_{t,f} CSI}{\sum_{t,f} E[CSI_{sur}]}$$

$$(6) \quad CSI_{sur_a_i} = \alpha_i * CSI_{sur}$$

where t and f correspond to all times (0.1-0.4 sec) and frequencies (0-50 Hz) in the presample period.

The CSI values within each of four equal time windows [presample (0.1 – 0.4 sec); sample (0.6 – 0.9 sec); early delay (1.1 – 1.4 sec); and late delay (1.4 – 1.7 sec)] were considered significant if i) two adjacent bins (either in time or frequency (10-42 Hz)) exceeded CSI_{sur_a} at $p < .02$, and ii) the coherence values (estimated across the 3 stimuli at each location) in the same adjacent time bins were significant with respect to their generalized surrogate at $p < 10^{-3}$.

For plotting purposes (Fig. 2B and C) the CSI values were bias corrected according to equation 7.

$$(7) \quad CSI_{corr} = CSI - \alpha E[CSI_{sur}]$$

Finally, for cellular firing rates $I(S;R)_{FR}$ was corrected by subtracting the bias (i.e. expected value) at each time bin.

$$(8) \quad I(S;R)_{FR_corr} = I(S;R)_{FR} - E[I(S;R)_{FR_sur}]$$

where $I(S;R)_{FR_sur}$ is the mutual information for cellular firing rate after shuffling the trial sequence of the spike train responses.

Wiener-Granger Causality Analysis Directional interactions between PFC and PPC LFP signals were evaluated in the time-frequency domain using the spectral Wiener-Granger causality (WGC) calculated from autoregressive models (sliding window of 200 ms stepped each 50 ms), as previously described (Bernasconi and Konig, 1999; Salazar et al., 2004; Bressler and Seth, 2011). We used the Bayes information criterion (BIC) on a few pairs to select our model order of 20. Because our main focus was to detect significant differences in directional interactions, we developed a statistical test to compare the two directions and applied this to the data sampled during the last 400 ms preceding the match onset (Fig. S7). For this, we compared the difference between the two WGC directions against a distribution of shuffled directional differences. The surrogate population of directional differences was created by randomizing the assignment of the channel to either PFC or PPC, before creating the autoregressive model over all the trials (1000 iterations). In this analysis, the trial sequence remains the same as the real data. The difference between the two WGC directions at each frequency was considered significant if i) it exceeded a threshold p-value of 0.01 (two-tailed, Fig.S7B, dashed lines), and ii) the WGC value at the same frequency also exceeded its respective significance threshold ($p < .001$, one tailed) in either of the two directions (Fig. S7A, dashed lines).

Firing Rate Analysis. To evaluate the stimulus selectivity of the unit activity, we calculated the time course of $I(S;R)_{FR}$ using equation 2 (100 ms window with no overlap) where the conditional probabilities $P(r|s)$ were estimated from all the selected trials (Peng et al., 2005). The mutual information was calculated for either the three sample objects combined over all locations or vice versa to increase the number of trials used to estimate the probability distributions. Significance was evaluated for each unit by a shuffling procedure (10,000 iterations; $p < .01$). A unit was considered selective during the sample and/or delay if there was at least one significant bin during either of these periods.

Spike Field Coherence. The spike field coherence was estimated only during the delay period (1.0 to 1.8 sec from the start of the fixation) between spike trains recorded in either PFC or PPC and the LFPs recorded from the other cortical region. This method was preferred to a sliding window method because of the sparse activity during the delay for a majority of neurons. In addition, we applied a minimum criterion of 5 spikes per trial to avoid differences due to small spike counts. Nine tapers were used resulting in a time-bandwidth product of five. Statistical significance was evaluated using a surrogate distribution (1000 iterations; $p < .01$) calculated for each spike-LFP pair separately.

Additional Results

Selective Unit Activity. We evaluated the identity and location selectivity of cellular responses by calculating $I(S;R)_{FR}$ as a function of time and compared this measure to a surrogate distribution at a p-value less than .01. An example of an identity selective cell, recorded in LIP, is shown in Fig. S8A and B. To assess the overall time

course of PFC and PPC response selectivity, we pooled the selective cells from frontal and parietal regions and plotted the average $I(S;R)_{FR}$ ($\pm$ SEM) for each population as a function of time (Fig. S8C). This revealed a rapid onset in selectivity following the sample that occurred earlier in the parietal areas and extended into the delay period with a gradual decay.

The incidence of identity and location selectivity for all sampled areas is shown in table S3. Interestingly, the highest incidence of identity selective responses occurred in areas PG (26%) and LIP (49%) of parietal cortex and areas 8AD (33%) and vPFC (40%) of prefrontal cortex.

Comparison of Two Methods for Calculating CSI. We compared our method for computing CSI to a bootstrap procedure that directly generates a probability distribution of coherence values at each time-frequency bin (500 iterations). This method assumes that the probability distribution of coherence can be estimated by random resampling of trials with replacement. Because this approach is computationally intensive, we applied the measure to a randomly selected set of 100 LFP pairs from the population of pairs that exhibited significant delay period CSI (Fig. 2D). The results of this analysis are shown in Fig. S9. In A and B, we compare two examples, applied to the data from Figs. 2A and B, of CSI calculated using the two methods. There was very little difference between the two measures at all time-frequency bins. The plots in C and D show the average of the differences across the population and the resulting p-values derived from a two-sample Kolmogorov-Smirnov test, respectively. We found no time-frequency bins where the p-

value was less than .05. Thus, the two methods for measuring CSI yielded comparable values.

Additional Discussion

Cognitive Processes Contributing to Fronto-Parietal Coherence. It is likely that cognitive processes other than working memory, such as anticipation, spatial and object-based attention, and movement preparation, also contribute to the patterns of fronto-parietal coherence we have observed. The presence of significant coherence during the pre-sample period could be related to the allocation of attention to the fixation target as well as anticipation of the sample onset. The buildup of coherence during the delay period and its reduction at the time of match onset could be related to spatial and object-based attention, anticipation of the match onset, and preparation for a motor response. Multiple lines of evidence indicate that these processes are related to the coordination of activity in a variety of cortical structures (Sanes and Donoghue, 1993; Vaadia et al., 1995; Riehle et al., 1997; Donoghue et al., 1998; Fries et al., 2001; Liang et al., 2002; Buschman and Miller, 2007; Gregoriou et al., 2009). However, our finding of differential coherence related to the sample stimulus is unlikely to be accounted for by processes such as anticipation, motor planning and spatial attention. While the sample is presented at one of three possible locations, the locations of the match stimuli are randomized and unpredictable. Thus, spatial attention or different motor plans are unlikely to account for the observed identity selectivity. Similarly, since the time course of the task is identical for all stimuli, there is no apparent reason that the different object identities would induce

different levels of anticipation. Thus, our results reveal a stimulus specific memory component of fronto-parietal coherence that may be co-occurring with other processes necessary for carrying out the task. We can only speculate on how these different processes interact, but it would appear that the memory component primarily modulates the coherence rather than being a primary generator of it.

Volume Conduction Effects. Because neuronal tissue is electrically conductive, and we used monopolar recording methods, volume conducted signals may have contributed to our estimates of LFP coherence. This phenomenon is well known in studies of the scalp recorded EEG and a variety of methods have been implemented to correct for its effects (Nolte et al., 2004; Stam et al., 2007; Vinck et al., 2011). Volume conduction of intracranially recorded field potentials is also detectable, particularly within and around neural structures, such as the hippocampus and pyriform cortex, which produce a dipolar open field (Sirota et al., 2008). The conventional approach to this problem is to use transcortical bipolar recording techniques to remove the common mode signals transmitted from other structures (Bressler, 2003). This method was not appropriate for our study since we recorded unit activity as well as the LFP and we advanced the electrodes through many millimeters of cortex, often at angles oblique to the cortical lamination.

While it is difficult to estimate the contribution of volume conduction to our findings, several factors suggest that its effects are minimal. First, compared to scalp recorded EEG, intracortical microelectrodes are known to record highly local signals. This was demonstrated by an earlier study in which the local field potential was tuned for

the orientation and direction of visual stimuli (Gray and Singer, 1989). A number of subsequent studies have confirmed and extended these findings (Jia et al., 2011), demonstrating that the LFP can be restricted to columnar domains (Wang and Roe, 2012) and greater in amplitude in superficial layers of visual cortex (Xing et al., 2012). Second, all of the reported measurements of coherence were between pairs of electrodes where one channel was in the prefrontal cortex and the other channel was in the posterior parietal cortex. The large distance between measurements greatly reduces the likelihood of volume conduction effects on the measured fronto-parietal coherence. Third, if volume conduction were making a significant contribution to our findings, we would not necessarily expect to find task and time-dependent phase differences between sites. Fourth, we calculated the spike-triggered average of the LFP at each recording site in our data set and found that extracellular spiking activity was primarily correlated with the negative phase of the LFP recorded on the same electrode (Dotson et al.; in preparation). Fifth, we discovered a distinct set of phase relationships between the medial and lateral banks of the intraparietal sulcus. LFPs recorded on the same side of the sulcus (i.e. lateral-vs-lateral and medial-vs medial) tended to be in phase, whereas LFPs recorded on opposite sides of the sulcus (i.e. lateral-vs-medial) tended to show large phase differences (Dotson et al., 2012). Finally, the occurrence of significant spike-field coherence between units in one region (PPC or PFC) and the LFP in another region precludes an explanation of volume conduction for long-range coherence. Together this evidence argues against a significant contribution of volume conduction to the coherence measured between prefrontal and posterior parietal cortex.

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CHAPTER THREE

SPATIOTEMPORAL ACTIVITY PATTERNS REVEAL
THE INTERPLAY BETWEEN INTEGRATION AND
SEGREGATION DURING VISUAL WORKING MEMORY

Contribution of Authors and Co-Authors

Manuscript in Chapter 3

Author: Nicholas M. Dotson

Contributions: data collection, data analysis, and preparing manuscript.

Co-Author: Rodrigo F. Salazar

Contributions: study design, data collection, and editing manuscript.

Co-Author: Charles M. Gray

Contributions: study design, and preparing manuscript.

Manuscript Information Page

Nicholas M. Dotson, Rodrigo F. Salazar, Charles M. Gray

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Abstract

Working memory requires the appropriate balance between functional integration and segregation across widespread cortical and sub-cortical brain regions. Task-specific synchronization of activity across distributed networks has been proposed as a mechanism for functional integration, but segregation is less well defined. In order to identify functional activity patterns related to functional integration and segregation, we estimate the incidence, magnitude, and relative phase angle of beta-band activity from simultaneous recordings in prefrontal (PFC) and posterior parietal (PPC) cortex in monkeys performing a visual working memory task. Intra-parietal and fronto-parietal correlations reveal a bimodal distribution of relative phase angles concentrated near 0° and 180° . Furthermore, fronto-parietal correlation patterns exhibit rapid changes in magnitude and relative phase that are task dependent, including nearly 180° shifts in the relative phase angle. These findings suggest that distinct functional networks, defined by the properties of synchronization, provide a mechanism for modulating the interplay between integration and segregation.

Introduction

The realization that the primate cerebral cortex is composed of a large number of anatomically and functionally distinct cortical areas (Brodmann, 1909; Zeki, 1978; Livingstone and Hubel, 1988; DeYoe and Van Essen, 1988; Goldman-Rakic, 1988; Desimone and Ungerleider, 1989; Paxinos et al., 1999; Saleem and Logothetis, 2007; Van Essen et al., 2012) widely linked by weak cortico-cortical connections (Zeki and

Shipp, 1988; Felleman and Van Essen, 1991; Markov et al., 2011,2012), poses a well recognized challenge to theories of perception, action and cognition. Somehow, large populations of neurons, distributed across widespread regions of the cortex, must rapidly and selectively cooperate in a flexible manner to enable a vast repertoire of possible functions (Mesulam, 1990; Tononi et al., 1992,1998; Bressler, 1995; Varela et a., 2001; Bressler and Menon, 2010). A large body of evidence indicates that this functional integration occurs when distributed populations of neurons transiently form large-scale networks, defined by the spatiotemporal patterns of coordination among the participating neurons (Bressler et al., 1993; Gray, 1994; Bressler, 1995; Singer and Gray, 1995; Roelfsema et al., 1997; Varela et al., 2001; Buzsaki, 2006; Fell and Axmacher, 2011; Siegel et al, 2012). However, this functional integration must be balanced by a competing demand for segregation in order to avoid false associations and globally cooperative states (Zeki and Shipp, 1988; Kelso, 1995; Bressler and Kelso, 2001). Segregation, could occur when competing networks are inhibited (Desimone, 1998), display statistical independence (Singer and Gray, 1995), or operate at different phases or frequencies (Bressler and Kelso, 2001; Popa et al., 2009).

Working memory has the hallmark features of a cognitive process, requiring both functional integration and segregation. Endogenous and/or exogenous information no longer available in the environment, must be maintained, manipulated, and integrated with behavioral goals and decisions, while resisting interference from competing representations (Miller, 2013). Recently, we reported a high incidence of task-dependent and content-specific synchronization of activity between prefrontal (PFC) and posterior

parietal (PPC) cortical areas in the beta frequency range (Salazar et al., 2012). While these findings demonstrate that fronto-parietal synchronization reflects the integration of distributed activity, the properties of the relative phase relationships and the patterns of correlation within PFC and PPC were not analyzed. Here, we use cross-correlation analysis to estimate the incidence, magnitude and relative phase angle among pairs of LFP signals (bandpass filtered at 8 - 25 Hz) sampled from 63 different intra- and inter-areal combinations within and between PPC and PFC. We find widespread patterns of task-dependent correlation that vary in magnitude and incidence of occurrence, and fall into two distinct phase relationships centered near 0° and 180° . Moreover, the phase relationships are dynamic and can display rapid transitions by as much as 180° that are linked to task events. These findings suggest that dynamic phase relationships, in addition to inhibition and statistical independence may contribute to the interplay between functional integration and segregation of distributed networks.

Results

We recorded broadband neuronal activity from multiple electrodes in multiple areas of the PFC and the PPC in two monkeys (Monkey A and Monkey B), while the animals performed an oculomotor, delayed match-to-sample task (**Fig. 1**). A total of 342 PFC and 437 PPC recordings were acquired (**Table S1**). The task involved an initial fixation period (pre-sample, 500 ms), followed by the presentation of sample stimulus, consisting of one of three possible objects presented at one of three possible locations (sample, 500 ms), a variable delay period (delay, 800 - 1200 ms, or 1000 – 3000 ms) and

a match stimulus, consisting of the target object and a distractor object presented at two of three possible locations (**Fig. 1b**, identity task). The animals successfully completed the trial by making a saccade to the target object and maintaining gaze for a minimum of 300 milliseconds. If the distractor was chosen the trial immediately ended. The animals performed either an identity-matching rule or a location-matching rule in blocks, with a non-cued rule switch (see Online Methods and Salazar et. al., 2012, for more details). Trials were pooled across stimuli, and only trials recorded during the identity-matching rule were used for this analysis.

Working Memory Activity Patterns

To determine the patterns of functional connectivity across the fronto-parietal network, we used cross-correlation analysis to estimate the incidence, magnitude and relative phase angle of correlation between all combinations of simultaneously recorded LFPs (bandpass filtered at 8 - 25 Hz) during the delay period of the task. We found significant correlations in 60% and 48% of the signal pairs in Monkeys A and B, respectively - resulting in 1644 significantly correlated signal pairs sampled from 63 different intra- and inter-areal combinations (**Table S2**). Figure 2 shows four examples of the signal correlations we observed in the data from figure 1c. During the task, the correlation magnitude peaks prior to the sample, transiently declines, and then increases again during the delay (**Fig. 2a-d**). These magnitude changes are accompanied by subtle shifts in the relative phase angle, especially during the response to the sample when the correlation magnitude is at its minimum. Notably, the correlation magnitudes and phase relationships are related to the cortical locations of the recording sites. In these examples,

the PEC-PEC signal pair, recorded from the medial bank of the IPS, exhibits a strong, in-phase correlation (**Fig. 2a,e**), while the PG-PEC signal pair, recorded from opposite sides of the IPS, displays a weaker, but nearly anti-phase correlation (**Fig. 2b,f**). Moreover, similar phase relationships are present in the long distance fronto-parietal signal pairs. The dPFC-PEC (**Fig. 2c,g**) and dPFC-PG (**Fig. 2d,h**) signal pairs display weaker correlations while maintaining a striking difference in relative phase.

An analysis of the relationship between incidence and magnitude of correlation and the separation between recording sites revealed distinct patterns of functional connectivity. We evaluated these effects by grouping signal pairs with significant correlations into 6 categories: those in which both signals were recorded i) within PFC, ii) within the medial bank of the IPS (mPPC), iii) within the lateral bank of the IPS (IPPC), and those in which signals were recorded iv) in the medial and lateral banks of the IPS (mPPC-IPPC), v) prefrontal and medial parietal pairs (PFC-mPPC), and vi) prefrontal and lateral parietal pairs (PFC- IPPC). As shown in table S3, the incidence and magnitude of correlation were highest among signal pairs recorded on the same bank of the IPS (i.e. mPPC-mPPC, IPPC-IPPC), somewhat lower within PFC, and markedly lower for signal pairs separated by larger distances (i.e. mPPC-IPPC and PFC-m/IPPC). To assess the effect of inter-electrode separation on correlation magnitude within PFC and PPC, we plotted the correlation magnitude vs. distance for all pairs within PFC, and together for all pairs within the same bank of the IPS (i.e. mPPC-mPPC and IPPC-IPPC combined) (*Supplementary Figure 2*). This revealed a fall off of correlation magnitude as a function of distance for electrode separations less than 6 mm. Thus, the magnitude of

correlation decreases with distance within and between adjacent areas of the PFC and PPC (Murthy and Fetz, 1996; Destexhe et al., 1999) while both the incidence and magnitude of correlation plateau to lower levels over distances that span widely separated areas of the cortex (Roelfsema et al., 1997).

Consistent with the results shown in figure 2, we found a clear bimodal distribution of relative phase angles among significantly correlated signal pairs in both Monkeys (**Fig. 3**). With all data combined, the distributions of relative phase angles were split into approximately in-phase and anti-phase modes, with a dividing line centered at $\pm 90^\circ$ (**Fig. 3a,e**). To identify the source of these distinct modes, we separated the data into PFC, PPC and fronto-parietal categories. Within PFC, the vast majority of phase values are centered near 0° in both monkeys (**Fig. 3b,f**). Within PPC, the relative phase distributions are distinctly bimodal in both monkeys, with the dominant mode centered near 0° and the secondary mode centered near 180° (**Fig. 3c,g**). These phase relations also exist in the fronto-parietal correlations, with clear bimodal phase distributions present in both animals (**Fig. 3d,h**). The dominant mode, centered near -16° in both Monkeys, displays a prefrontal phase lead, as previously reported (Salazar et al., 2012), while the secondary mode is more broadly distributed and centered at -179.5° and -148° in monkeys A and B, respectively (**Table S4**).

To gain further insight into these processes, we subdivided the correlation analysis with respect to each intra- and inter-areal combination of signals. The magnitude and relative phase relationships of the correlations are shown in figure 4. (*The incidence of significant correlations for all intra- and inter-areal signal pairs is provided in*

supplementary figure 3 and table S2.) Since the sign of the relative phase angle - indicating which channel is “leading” the other – can be ambiguous, we report the absolute value of the relative phase angles. The results reveal that the patterns of correlation are anatomically specific. Within PFC the correlations among signals vary widely in magnitude with respect to areal combination (and thus distance) and are dominated by in-phase relationships, with a small percentage of values scattered around 100° in Monkey B (**Fig. 4a**). Within PPC, signal pairs recorded on either the medial (**Fig. 4b**) or the lateral (**Fig. 4c**) bank of the IPS have a broad distribution of correlation magnitudes and are highly clustered in-phase, with only one value exceeding a 90° phase angle. In contrast, the long distance correlations, measured between signals recorded in the medial and lateral banks of the IPS and between these areas and the PFC, are smaller in magnitude and exhibit a clear bimodal distribution of phase values (**Fig. 4d-f**). Signal pairs recorded on opposite sides of the IPS are dominated, with few exceptions, by near anti-phase relationships (**Fig. 4d**). Signal pairs recorded in PFC and the medial bank of the IPS (**Fig. 4e**) are dominated by in-phase relationships, with the exception of signals sampled from areas 8B and MIP in Monkey B that are almost entirely out-of-phase (shaded region in **Fig. 4e**). In contrast, signal pairs recorded in PFC and the lateral bank of the IPS (**Fig. 4f**) exhibit both unimodal and bimodal phase distributions that are anatomically specific. In Monkey A, all signal pairs, except one, have phase values $>90^\circ$. In Monkey B, correlations between prefrontal and lateral parietal signals are either exclusively out-of-phase (8B-LIP), exclusively in-phase (8AD-PG), or bimodally distributed (8B-PG, dPFC-PG, dPFC-LIP). In addition to the abundance of correlated

interactions, we also found a number of inter-areal pairings with significant correlation occurring $\leq 10\%$ of the time (*see supplementary Figure 3 and Table S2*). While some of this effect could be related to small sample sizes (e.g. 6DR-PG, 8AD-LIP, vPFC-LIP), and thus reflect an experimental bias, other inter-areal combinations (e.g. MIP-LIP, 6DR-PEC, 6DR-PE, 8B-MIP, vPFC-MIP) have 50 or more signal pairs and show a very low probability of correlation. For example, none of the cross-correlograms computed from the 60 MIP-LIP signal pairs in Monkey B reached significance. This indicates that these and other areas are functioning largely independently under the conditions of this experiment.

To further illustrate the complexity of these interactions, Figure 5 shows the correlation patterns obtained from a single recording session in Monkey B. Within PFC the signal correlations have values less than 0.5 and, with one exception, display relative phase values less than 45° (thin green lines in **Fig. 5c**). The intra-parietal signals exhibit stronger correlations having relative phase values less than 45° when the electrodes are located on the same sides of the IPS (thick green lines in **Fig. 5d**), and weaker correlations with relative phases greater than 135° for recordings on opposite sides of the IPS (thin red lines in **Fig. 5d**). The fronto-parietal correlations are weaker and display relative phase values that are clustered into two groups (**Fig. 5e**), those less than 45° (thin green lines) and those greater than 135° (thin red lines). This segregation of phases, as in Figure 2 (Monkey A), displays some anatomical boundaries. The signals in area 8B exhibit near anti-phase relationships with signals recorded in areas LIP and MIP, even though the signals in LIP and MIP are statistically independent (**Fig. 4d**). The remaining prefrontal

signals in areas 8AD, dPFC and vPFC have in-phase relationships with parietal signals recorded in areas that are medial to the IPS, but are statistically independent from signals recorded lateral to the IPS, even though significant anti-phase correlations occur between signals that span the IPS (i.e. signals in LIP show anti-phase correlations with signals in PGM and PE). In contrast to these non-overlapping interactions, we found numerous instances in which simultaneous in-phase and anti-phase correlations occurred between fronto-parietal signals during the delay period (1.2-1.8 s) (see **Fig. 2c,d**, and Supplementary Materials for more details), which suggests that these activity patterns are not entirely parallel, but overlapping to some extent.

Task Dependent Activity Patterns

So far, we have provided evidence that the incidence, magnitude, and relative phase angle of correlated interactions provide a mechanism for modulating cortical coordination. Next, we examined the task-dependence of fronto-parietal correlations by comparing the pre-sample period (0.1 - 0.5 s) with a window of the same size in the delay period that is locked to the first possible match (1.4 - 1.8 s). Signal pairs were selected using the same criteria as above, but for both task periods, resulting in a new set of signal pairs that were not exclusively determined by the delay period (see Table S2 for areal counts). To determine the task dependence of the correlation magnitude, and to highlight the relevant areal combinations, we tested whether changes in the correlation magnitude increased or decreased between the pre-sample period and the delay period (Sign test, paired, two-sided). Figure 6 shows the difference distributions for each areal combination, with at least 5 signal pairs, pooled across both animals. Several trends

emerge from this analysis. Within PFC, a small, but significant increase in correlation occurred for areal combinations 8B-8B, 8B-8AD and 8B-dPFC (**Fig. 6a**). Within PPC correlations displayed a distinct pattern of changes: areas medial to the IPS displayed a robust increase in correlation (**Fig. 6b**), those lateral to the IPS showed no change (**Fig. 6c**), and areas separated by the IPS tended to decrease (**Fig. 6d**). A related pattern of changes was apparent in the fronto-parietal correlations. Significant increases occurred between dPFC and medial parietal areas PEC, PE and MIP (**Fig. 6e**), and between prefrontal areas dPFC and 8B and lateral parietal areas PG and LIP (**Fig. 6f**). In addition to the task-dependent changes in correlation magnitude, we found substantial changes in relative phase (**Fig. 6**, lower plots). Shifts in relative phase between the two task periods ranged from 0 to 45°, with the largest shifts occurring most often between fronto-parietal areal combinations (**Fig. 6e,f**).

To further explore the potential for these activity patterns to re-organize, we compared the delay period of the task (1.4 - 1.8 s), using the same correct trials used in the previous analyses, to the inter-trial interval (ITI) shortly after the match period on error trials (For technical reasons, the ITI period was only recorded after incorrect trials in Monkey B.). This was partially motivated by a previous study that described large shifts in the relative phase during the reward period of a discrimination task in behaving cats (Roelfsema et al., 1997). During the ITI, we observed a strong oscillatory response, visible in the band-passed LFP, which showed a marked change in relative phase among the signals compared to the delay period (**Fig. 7a**). An analysis of the peak amplitude of these beta oscillations revealed that they occurred earlier in PPC (671 ms $\pm$ 96 std, after

match onset) than PFC ($769 \text{ ms} \pm 137 \text{ std}$, after match onset) (Wilcoxon rank sum test, $p < .001$). Using this timing information, we centered the ITI analysis epoch over the peak amplitudes of the observed beta bursts (0.5 to 0.9 s after match onset). Signal pairs were once again subjected to the fitting criteria for both task periods, resulting in a slightly different set of pairs (see **Table S2** for areal counts). Figure 7b and c shows the time course of the trial-averaged cross-correlation for two of the signal pairs from figure 7a. In these examples, the relative phase is near 180° for the duration of the task and then abruptly flips to an in-phase relationship after the decision period during the ITI. This effect, accompanied by an increase in correlation strength, occurs between the prefrontal and parietal signals (**Fig. 7b**) and between the parietal signals on opposite sides of the IPS (**Fig. 7c**), demonstrating its widespread nature. Figure 7d shows the third fronto-parietal signal pair, which is weakly correlated in-phase prior to the sample, largely un-correlated during the delay, and then highly correlated during the ITI, without a flip in the relative phase angle.

We quantified this task-dependent re-organization in the same manner as the previous comparison of the pre-sample with the delay. We first tested whether changes in the correlation magnitude increased or decreased between the delay period and the ITI (Sign test, paired, two-sided). The upper plots in figure 8a-f show the difference distributions for each areal combination (outliers are not shown). In general, correlation strength increased during the ITI, but the range of change was much larger than that seen during the task, indicating widespread activation and, with few exceptions, increased synchronization across the fronto-parietal network. Correlation strength increased within

and between areas 8B and dPFC (**Fig. 8a**), among parietal areas medial to the IPS (**Fig. 8b**), and somewhat heterogeneously among the other prefrontal and parietal areas (**Fig. 8c-f**). We also found a striking change in relative phase relationships that occurred predominantly among signals separated by large distances (i.e. fronto-parietal and medio-lateral parietal) (**Fig. 8a-f**, lower plots). Whereas the changes in phase during the task were all less than 50° (**Fig. 6**), during the ITI we found numerous changes in phase exceeding 90° . Also, changes in correlation strength and relative phase were not obligatorily coupled. We found multiple areal combinations where correlation strength increased while relative phase remained stable (i.e. 8AD-dPFC, PEC-MIP, PG-LIP) and other combinations where correlation strength showed little or no change while relative phase changed substantially (i.e. PEC-PG, dPFC-PE, 8B-LIP).

Discussion

We found that within and between adjacent areas of the PFC and PPC the magnitude of correlation decreases with distance, while both the incidence and magnitude of correlation plateau to lower levels over larger distances. This agrees with what might be predicted from recent anatomical work (Markov et. al., 2011,2012), and suggests that a substantial contribution to the magnitude of correlation is from anatomy. However, the magnitude of correlation is contingent upon tasks demands, indicating that these interactions are not hard coded, but simply constrained by anatomy. Another component influencing the magnitude of correlation is the intrinsic frequencies of the individual signals (see Supplementary Materials). An additional analysis revealed that signal pairs

with high correlations also have similar dominant frequencies (**Supplementary Fig. 4**). These results provide evidence that the incidence and magnitude of correlated interactions are mechanisms for modulating the interplay between integration and segregation.

An analysis of the relative phase angles revealed a clear bimodal distribution among significantly correlated signal pairs in both Monkeys (see Fig. 3). While this is not the first report of anti-phase correlations (Gregoriou et al., 2009), it is to our knowledge, the first report of simultaneous in-phase and anti-phase correlations, and 180° phase transitions. It could be argued that the distinct inter-areal phase differences we observe are due to variations in the cortical depth of our recordings. Since it is well known that some cortical areas exhibit phase differences, and polarity reversals, in the LFP as a function of depth (Mitzdorf & Singer, 1978; Murthy and Fetz, 1996; Bollimunta et al., 2008), this behavior would be expected to lead to some dispersion of our measured phase values. Careful examination of the phase distributions in the bottom row of Figure 4, however, indicate that biased sampling across a cortical dipole cannot fully account for our observations. For example, in order to account for the exclusively anti-phase correlations between areas PE and LIP in Monkey B (**Fig. 4d**), and the exclusively in-phase correlations within areas PE (**Fig. 4b**) and LIP (**Fig. 4c**) would require that all the measurements were made within supra-granular layers in one area and the infragranular granular layers in the other area. Similar arguments apply to all the paired recordings within the medial and lateral banks of the IPS (**Fig. 4b,c**). The phase distributions are somewhat dispersed, but there is no evidence of polarity reversals, or anti-phase

relationships, as are seen in the correlations between the medial and lateral banks of the IPS. These data argue against the notion that a laminar sampling bias can account for the anti-phase relationships we observe. It might also be argued that the anti-phase correlations we observe are occurring among signals that are weakly correlated and thus represent another form of sampling bias. Further examination of the results in Figure 4 (d,e,f) also rule out this explanation. The long-range, in-phase ($<90^\circ$) correlations are not significantly different in magnitude from the anti-phase ($>90^\circ$) correlations (Wilcoxon rank sum test, two-sided, Monkey A: $p = 0.8$, Monkey B: $p = 0.5$). Additional evidence in support of this argument is presented in Figures 7 and 8. The large and rapid changes in relative phase provide strong evidence against the notion that the bimodal distribution of relative phase angles (see **Fig. 3**) can be explained by a sampling bias across a cortical dipole field.

When considering the relevance of the relative phase angle, the timing between synchronous oscillations is suggested to provide the requisite delay for maximal postsynaptic efficacy (Fries, 2005; Gregoriou et al., 2009; Verhoef et al., 2011; Liebe et al., 2012). Our results, however, suggest that the relationship between distant neuronal populations may not be strictly related by a simple time delay, especially in light of the 180° degree phase shifts we observe during the ITI period. A more favorable explanation is that these dynamics are a product of global co-operation across the brain and that the changes in correlation magnitude and phase could reflect shifts in global coordination states (Bressler and Kelso, 2001).

Collectively, our results demonstrate that the incidence, magnitude, and relative phase angle of correlated activity within and between cortical areas may provide the substrate for balancing integration and segregation, and while they appear to be constrained by anatomy, they are not enslaved by it. The role of the relative phase angle with respect to long-range cortico-cortical interactions is still somewhat ambiguous; however, spontaneous transitions in coordination have been observed in several biological systems (Kelso, 1995; see Supplementary Materials for a further discussion). Subsequently, the implications for these findings are of great general importance to understanding the coordination dynamics of the brain. Future studies, including ones involving multiple tasks, and levels of attentional demand, will be crucial to better understanding the mechanisms underlying integration and segregation.

Online Methods

Animals and Recordings

Two female rhesus macaque monkeys (Monkey A and Monkey B) were each implanted with a cranial post for head restraint, scleral search coils to track eye positions (Judge et al., 1980), and two recording chambers (Gray et al., 2007) located above the prefrontal and posterior parietal cortices (for more details see Salazar et. al., 2012). All procedures were performed in accordance with NIH guidelines and the Institutional Animal Care and Use Committee of Montana State University.

Broadband neuronal activity was recorded simultaneously from multiple electrodes in both the prefrontal and posterior parietal cortex. The signal from each

electrode was amplified (5k), filtered (1 Hz-10 kHz), digitized (30 kHz) and stored for off-line analysis. In Monkey A, an acute recording method (Gray et al., 2007) was used that involved passing 4-8 independently positioned microelectrodes (Tungsten-in-glass, 0.5-1.5 M Ω) through the dura on a daily basis. The horizontal separation between electrodes was at least 0.86 mm (range 0.86 – 6.08 mm) and the recording depths ranged from the point of initial detection of unit activity to a maximum of 5 mm. Monkey B was implanted with two miniature mechanical microdrives containing 32 independently movable electrodes with a horizontal spacing of 1.5 mm and a maximum travel of 20 mm. The maximum recording depths were ~10 mm from the surface of the cortex. There was no attempt to identify the response properties of recorded neurons prior to recording. In both sets of recordings the reference and ground connections were tied together and connected to both of the recording chambers.

The broadband signal from each electrode was bandpass filtered (1-100 Hz) and down-sampled to 1 kHz to obtain the local field potential (LFP). To extract the unit activity the broadband signal was highpass filtered (500 Hz - 7 kHz). Spike waveforms were extracted by detecting local minima in the highpass signal that exceeded 4 and 5 standard deviations of the noise level in Monkey A and Monkey B, respectively. These waveforms were clustered using the KlustaKwik software package and further sorted using MClust (<http://redishlab.neuroscience.umn.edu/MClust/MClust.html>). Only channels with detectable unit activity were considered for further analysis. Due to the recording technique in Monkey B, a low percentage of signals were recorded at the same

depth during recording sessions occurring at least 24 hours apart (see Supplementary Material).

Behavioral Procedures

The monkeys were trained to perform an oculomotor, delayed match-to-sample task involving a non-instructed rule switch. The results from this study are only from trials during the identity rule. In this task, each trial is initiated with the appearance of a central fixation spot presented on a grey background. The monkey, seated in a primate chair in front of a 19-inch monitor (85 Hz refresh rate, 57 cm distance), is required to maintain visual fixation within a three-degree window throughout the trial until an appropriate oculomotor response is made. At a latency of 500 ms, one of three possible sample objects (size: 3x3 deg., eccentricity: 5 deg.) is presented for 500 ms at one of three possible locations lying at the vertices of an invisible triangle. This design resulted in 9 unique sample stimuli on each session. The sample stimulus is followed by a randomized delay, ranging from 800-1200 ms in one set of experiments and 1 to 3 sec in a second set of experiments, in which no stimulus is present. At the end of the delay period, the fixation target is extinguished and a match stimulus is presented that consists of a target and a distracter object positioned at two of the three possible locations. While the match stimulus is visible, the monkey must make a saccadic eye movement to the target object and maintain gaze on the object for 300 msec. The target object is defined by the matching rule in effect, either location or identity. After the monkey had reached criterion performance (>80% correct responses for at least 300 consecutive trials using a sliding-window of 100 trials), the rule was switched without cueing the animal. Several

rule switches could occur each day, but in general only one to two switches were achieved. Correct trials were rewarded with a drop of juice. To reduce biases for both the location and identities of the objects, the object locations were rotated by 180 degrees on alternate days and each day a new set of objects was selected. All object positions and identities were presented with equal probability in a pseudo random sequence. In monkey B, 10% of the trials did not include stimuli and the monkey simply had to maintain fixation throughout the trial to receive a reward. The eye position signals were acquired using the scleral search coil method in monkey A and an infrared eye-tracking system in monkey B. Both custom software and the publicly available MonkeyLogic software (<http://www.monkeylogic.net/>) were used to display the stimuli and provide experimental control (Asaad and Eskandar, 2008). Only trials recorded during the identity-matching rule were used for this analysis.

Histology

When recording was completed, each monkey was euthanized (Pentobarbital, 100mg/kg; i.v.) and perfused through the heart with phosphate buffered saline (PBS) followed by a solution of 5% paraformaldehyde in PBS. The brain was removed and relevant portions blocked and sunk in a solution of fixative with 30% sucrose several days before being sectioned (60 μ m) and stained for Nissl substance to identify electrode tracks (FD Neurotechnologies, Columbia, MD). Prior to blocking and sectioning, the brain was photographed to confirm the location of the chambers relative to major cortical sulci. Recording locations were identified from the reconstructed electrode tracks and classified according to the nomenclature of Paxinos et al. (1999).

Data Selection, Filtering and Spike-Field Analysis

All data analysis was carried out using Matlab (The Mathworks, Natick, MA). We determined the relevant frequency band for the correlation analysis by calculating the prevalence of peaks in the power spectrum of each LFP signal. The spectral power was estimated using multi-taper spectral analysis (time-bandwidth product of 2, 3 tapers, Matlab Chronux Toolbox). The mean power during the delay period (1.2 to 1.8 s) was calculated for each channel using all correct trials. The spectra were smoothed (3 point moving average, 1 point step) then investigated for peaks by finding local maxima. At each peak the corresponding frequency was recorded. This provided us with a histogram of peak frequencies that showed the incidence of spectral power that deviates from the typical $1/f$ distribution that is commonly observed in long duration recordings of the LFP or EEG (Buzsaki and Draguhn, 2004). Based on the results of this analysis (**Supplementary Fig. 1a**), and our previous analysis of task dependent coherence (Salazar et al., 2012), we bandpass filtered the LFP signal from 8 – 25 Hz prior to calculating the cross-correlograms.

The LFP signals were chosen for further analysis if the multi-unit activity (MUA) recorded on the same channel had a preferred phase (Rayleigh test, $p < .05$) within $\pm 90^\circ$ of the LFP trough (**Supplementary Fig. 1b**). To calculate the spike-field relationships, the Hilbert transform was used to estimate the instantaneous phase of the LFP at the time of each spike (bandpass filtered at 8-25 Hz). Then, a distribution of instantaneous phase values was made with respect to the spike times recorded on the same channel. The circular mean of this distribution is what we refer to as the preferred phase. The Rayleigh

test, which is a test for uniform circular distributions, was used to evaluate significance ($p < .05$). These selection criteria insure that the LFP closely reflects the underlying unit activity measured from the same electrode. With these criteria, approximately 79% of the PFC and 75% of the PPC recordings were selected. (**Supplementary Fig. 1c**, and **Table S1**).

Cross-Correlation Analyses

All cross-correlations were performed using the Matlab built-in function “xcorr.m”. The average cross-correlogram (± 50 ms time lag, data down sampled to 1 kHz) of the local field potential (8 - 25 Hz) for each pair of signals was calculated across all correct identity trials and all stimuli during the pre-sample (0.1 to 0.5 s) and the delay period (1.2 to 1.8 sec and 1.4 to 1.8 s). Due to our data acquisition technique at the time of recording, the average cross-correlograms during the ITI (0.5 to 0.9 s after match onset) were calculated from the incorrect trials for Monkey B only. The frequency of each correlogram was determined by fitting an 8 parameter generalized Gabor function (König, 1994) with the minimum squared error used as the criterion for the best fit. The central peak (positive or negative) obtained from the fitted Gabor function was determined by finding the local maximum or minimum that was closest to zero time lag. The relative phase angle between the two local field potentials was calculated using the time lag, polarity of the central peak, and the frequency estimated from the Gabor function. Correlograms that were near 180° out of phase had a distinct trough near zero time lag (**Fig. 2f,h**). We used two criteria to identify signal pairs that were significantly synchronized: 1) the correlation coefficient at the central peak was > 0.1 , and 2) the

correlation coefficient between the original correlogram and the Gabor function was $\geq .99$. To visualize the temporal aspects of these cross-correlations, time-dependent average cross-correlograms were calculated using a 200 ms window, a 50 ms time step, and a ± 50 ms time lag (**Fig. 2a-d**, and **Fig. 7b-c**). To compare the results between task periods we used a Sign test (paired, two-sided, $p < .001$), which tests for no difference in medians. This was used to compare the magnitude and phase angle of correlation between the pre-sample and delay periods. It was also used to compare the magnitude and phase angle of correlation between the delay and ITI periods.

ITI Spectral Power Analysis

To determine the time course of the average power during the ITI, we first calculated the time-frequency power spectra (200 ms sliding window stepped at 50 ms) using multi-taper spectral analysis (time-bandwidth product of 2, 3 tapers, Matlab Chronux Toolbox). Second, the maximum power at ~ 19 Hz (starting 200 ms after the first saccade, with the spectra initially locked to the match onset) was determined for each signal. This provided us with a single value for each signal at the time after match onset where the power at ~ 19 Hz was highest – the center of the beta-burst. As stated in the main text, this analysis revealed a timing difference between PFC ($769 \text{ ms} \pm 137 \text{ std}$, after match onset) and PPC ($671 \text{ ms} \pm 96 \text{ std}$, after match onset), which indicated that the burst of activity occurred earlier in the PPC (Wilcoxon rank sum test, $p < .001$).

Tables

Table S1. Sampling distribution of recording sites in both monkeys. The first column lists the cortical area. The second column is the total number of recording sites for each area. The third column is the number of sites with non-uniform, spike-field phase distributions, indicating a preferred phase (Rayleigh test, $p < .05$). The last column is the count of sites with non-uniform phase distributions and a preferred phase that is within $\pm 90^\circ$ (circular mean) of the LFP trough (180°). Areal abbreviations follow the nomenclature of (Paxinos et al., 1999) with the exception of dPFC and vPFC.

Monkey A			
Area	Sites recorded	Sites with preferred phase	Sites with preferred phase near LFP trough
6DR	0	0	0
8AD	0	0	0
8B	16	13	13
dPFC	55	51	50
vPFC	2	2	2
9L	11	9	9
PEC	45	43	41
PGM	0	0	0
PE	0	0	0
PG	38	32	32
MIP	2	2	2
LIP	5	4	4
TOTALS	174	156	153
Monkey B			
6DR	14	14	14
8AD	44	25	21

Table S1 Continued

8B	98	87	86
dPFC	90	65	62
vPFC	12	12	12
9L	0	0	0
PEC	97	95	84
PGM	2	2	1
PE	91	85	84
PG	30	22	22
MIP	66	65	63
LIP	61	57	33
TOTALS	605	529	482

Areal abbreviations (Paxinos et al., 1999).

6DR - dorsorostral area 6

8AD - anterodorsal area 8

8B - area 8B

dPFC - dorsal prefrontal cortex

vPFC - ventral prefrontal cortex

9L - lateral area 9

PEC - caudal area PE

PGM - medial area PG

PE - area PE

PG - area PG

MIP - medial intraparietal area

LIP - lateral intraparietal area

Table S2. Counts for all areal combinations before any selection criteria, and for 4 different subsets with selection criteria. 1) The total number of signal pairs. 2) The total number of signal pairs during the delay (1.2 - 1.8 s) that pass the cross-correlogram selection criteria. 3) The total number of signal pairs during the delay (1.2 - 1.8 s) that pass the cross-correlogram selection criteria and have a relative phase angle near 180° (abs. phase angle > 90°). 4) The total number of signal pairs that pass the cross-correlogram selection criteria during the delay (1.4 - 1.8 s) and the pre-sample (0.1 - 0.5 s). 5) The total number of signal pairs that pass the cross-correlogram selection criteria during the delay (1.4 - 1.8 s) and the ITI (0.5 - 0.9 s after match onset).

Monkey A		1	2	3	4	5
Area 1	Area 2	Signal pairs	Significant signal pairs	Signal pairs near 180° (out-of-phase)	Significant signal pairs (pre-sample and delay)	Significant signal pairs (ITI and delay)
8B	9L	8	7	0	7	
dPFC	9L	3	2	0	2	
PEC	9L	15	8	1	7	
PG	9L	5	1	1	0	
9L	9L	4	2	0	2	
8B	8B	5	5	0	5	
8B	dPFC	13	12	0	11	
8B	PEC	25	20	2	14	
8B	PG	21	7	7	6	
8B	MIP	1	1	0	1	
8B	LIP	1	0	0	0	
dPFC	dPFC	43	33	0	32	
dPFC	vPFC	7	6	0	5	
dPFC	PEC	74	26	2	18	
dPFC	PG	53	16	15	6	
dPFC	MIP	6	5	0	3	
dPFC	LIP	6	5	5	3	
vPFC	PEC	5	2	0	2	

Table S2 Continued

vPFC	PG	2	2	1	1	
PEC	PEC	29	28	1	27	
PEC	PG	34	23	17	22	
PEC	MIP	4	4	0	4	
PEC	LIP	1	0	0	0	
PG	PG	21	17	0	18	
PG	MIP	2	1	1	2	
PG	LIP	2	2	0	2	
	TOTALS	390	235	53	200	
Monkey B						
6DR	6DR	2	0	0	0	0
6DR	8AD	12	6	1	2	3
6DR	8B	31	12	3	6	7
6DR	dPFC	17	8	2	7	6
6DR	PEC	50	2	1	1	2
6DR	PE	49	2	1	0	1
6DR	PG	10	0	0	0	0
6DR	LIP	17	3	3	3	1
8AD	8AD	6	6	0	6	6
8AD	8B	58	38	4	32	33
8AD	dPFC	36	31	0	31	29
8AD	vPFC	6	4	0	5	4
8AD	PEC	61	17	1	13	6
8AD	PE	69	40	0	32	23
8AD	PG	17	9	0	3	6

Table S2 Continued

8AD	PGM	1	1	0	1	0
8AD	MIP	9	1	0	0	0
8AD	LIP	16	0	0	0	0
8B	8B	75	19	5	16	17
8B	dPFC	135	62	9	51	40
8B	vPFC	31	6	0	7	9
8B	PEC	196	66	1	54	50
8B	PE	191	89	0	84	73
8B	PG	51	30	16	17	21
8B	PGM	2	0	0	0	0
8B	MIP	118	12	10	1	6
8B	LIP	58	34	34	24	28
dPFC	dPFC	35	26	0	26	24
dPFC	vPFC	19	12	0	8	8
dPFC	PEC	128	35	0	19	15
dPFC	PE	143	74	0	62	58
dPFC	PG	42	25	7	13	17
dPFC	PGM	2	1	0	2	2
dPFC	MIP	62	16	0	10	10
dPFC	LIP	47	13	2	8	9
vPFC	vPFC	7	7	0	7	2
vPFC	PEC	5	0	0	0	0
vPFC	PE	16	12	0	9	1
vPFC	MIP	52	4	0	2	0
vPFC	LIP	16	0	0	0	0
vPFC	PGM	3	0	0	0	0

Table S2 Continued

PEC	PEC	92	78	0	63	64
PEC	PE	260	188	0	158	169
PEC	PG	58	23	21	16	9
PEC	MIP	52	47	0	46	48
PEC	LIP	77	31	22	21	9
PE	PE	120	114	0	100	112
PE	PG	56	23	22	20	12
PE	MIP	51	32	0	28	30
PE	LIP	91	37	37	38	20
PG	PG	4	4	0	4	4
PG	LIP	10	7	0	7	7
MIP	MIP	96	80	0	69	71
MIP	LIP	60	0	0	2	1
LIP	LIP	15	14	0	13	13
PGM	PE	2	2	0	2	2
PGM	MIP	6	4	0	3	2
PGM	LIP	2	2	2	2	2
	TOTALS	2953	1409	204	1154	1092

Areal abbreviations (Paxinos et al., 1999).

6DR - dorsorostral area 6

8AD - anterodorsal area 8

8B - area 8B

dPFC - dorsal prefrontal cortex

vPFC - ventral prefrontal cortex

9L - lateral area 9

PEC - caudal area PE

PGM - medial area PG

PE - area PE

PG - area PG

MIP - medial intraparietal area

LIP - lateral intraparietal area

Table S3. The incidence and magnitude of significant correlation is reported as the 25th percentile, median, and 75th percentile and grouped into 6 categories: 1) PFC, 2) mPPC-mPPC, 3) IPPC-IPPC, 4) mPPC-IPPC, 5) PFC-mPPC, and 6) PFC-IPPC. For the incidence of correlation the data is pooled across Monkey A and Monkey B for all combinations with ≥ 10 total signal pairs (matches the data from **Supplementary Fig. 3**). For the magnitude of correlation only areal combinations with ≥ 5 significant signal pairs (independently determined for each Monkey) are included (matches the data from **Fig. 4a-f**).

Combination	Incidence (%)	Magnitude (corr. coef.)
	median (25th / 75th)	median (25th / 75th)
PFC	50 (39/69)	.38 (.27/.51)
mPPC-mPPC	85 (72/91)	.50 (.38/.60)
IPPC-IPPC	84 (77/91)	.72 (.54/.80)
mPPC-IPPC	41 (30/43)	.17 (.13/.22)
PFC-mPPC	31 (11/52)	.15 (.13/.20)
PFC-IPPC	34 (0/52)	.18 (.15/.22)

Table S4. With all data combined, and with the data subdivided into PFC, PPC, and PFC-PPC categories, the distributions of relative phase angles were split into approximately in-phase and anti-phase modes, with a dividing line centered at $\pm 90^\circ$. Here we report the circular mean and circular standard deviation for the in-phase and out-of-phase signal pairs. No out-of-phase data is reported for the PFC combination due to the lack of any distinct mode (matches the data from **Fig. 3**).

Combination	Monkey A				
	Count	In-phase Circular mean	In-phase Circular std	Anti-phase Circular mean	Anti- phase Circular std
All	235	-7.3	20.7	181.7	30.0
PFC	67	-0.2	12.2	NA	NA
PPC	75	-8.0	22.5	185.2	24.4
PFC-PPC	93	-15.2	23.6	-179.5	32.6

Table S4 Continued

	Monkey B				
Combination	Count	In-phase Circular mean	In-phase Circular std	Anti-phase Circular mean	Anti-phase Circular std
All	1409	-5	19.1	199.5	32.1
PFC	237	-5.5	18.9	NA	NA
PPC	686	6.3	13.5	185.3	18.1
PFC-PPC	486	-15.9	18.7	-148.0	30.0

Figures

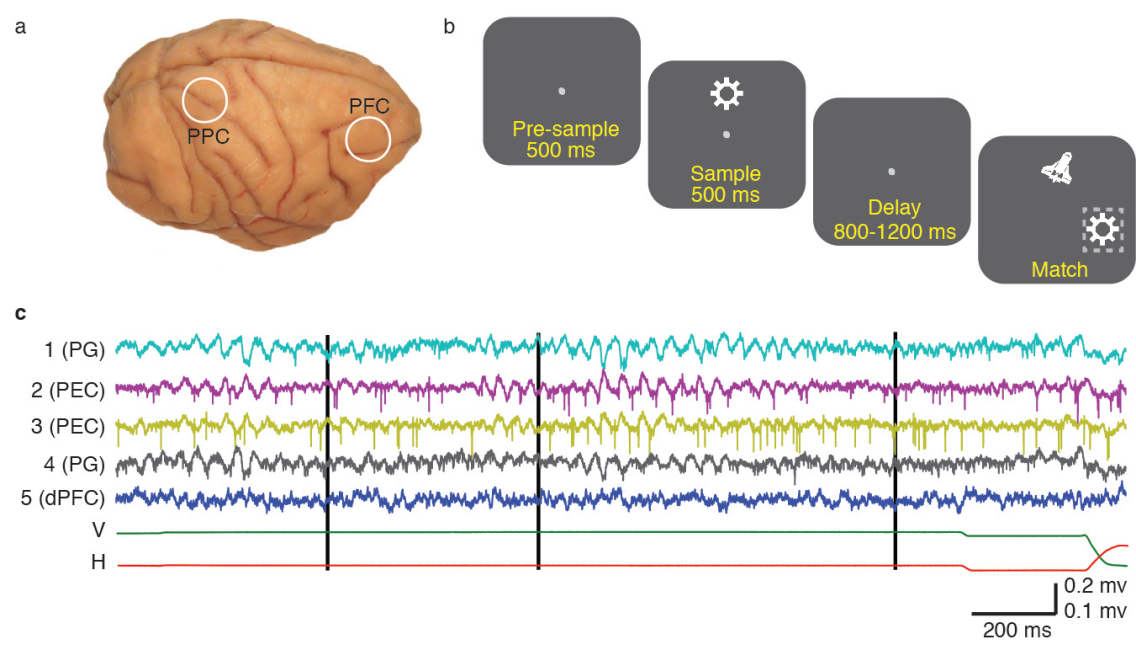


Figure 1. Illustration of recording locations, behavioral task, and an example data set. **(a)** Recording chamber locations in Monkey B superimposed on a photograph of the left hemisphere of a separate macaque brain. The chamber locations in Monkey A were similar. The prefrontal chambers were positioned over the dorsolateral PFC and the parietal chambers were positioned over the posterior intraparietal sulcus. **(b)** Illustration of the delayed match-to-sample task. The dashed box during the match epoch is not visible to the animal and is only included to indicate the correct choice. **(c)** Example of

broadband signals recorded on a single trial from Monkey A. The black vertical lines indicate the sample onset, sample offset and the match onset, respectively. The upper and lower voltage scales correspond to channels 1-4 in PPC and channel 5 in PFC, respectively.

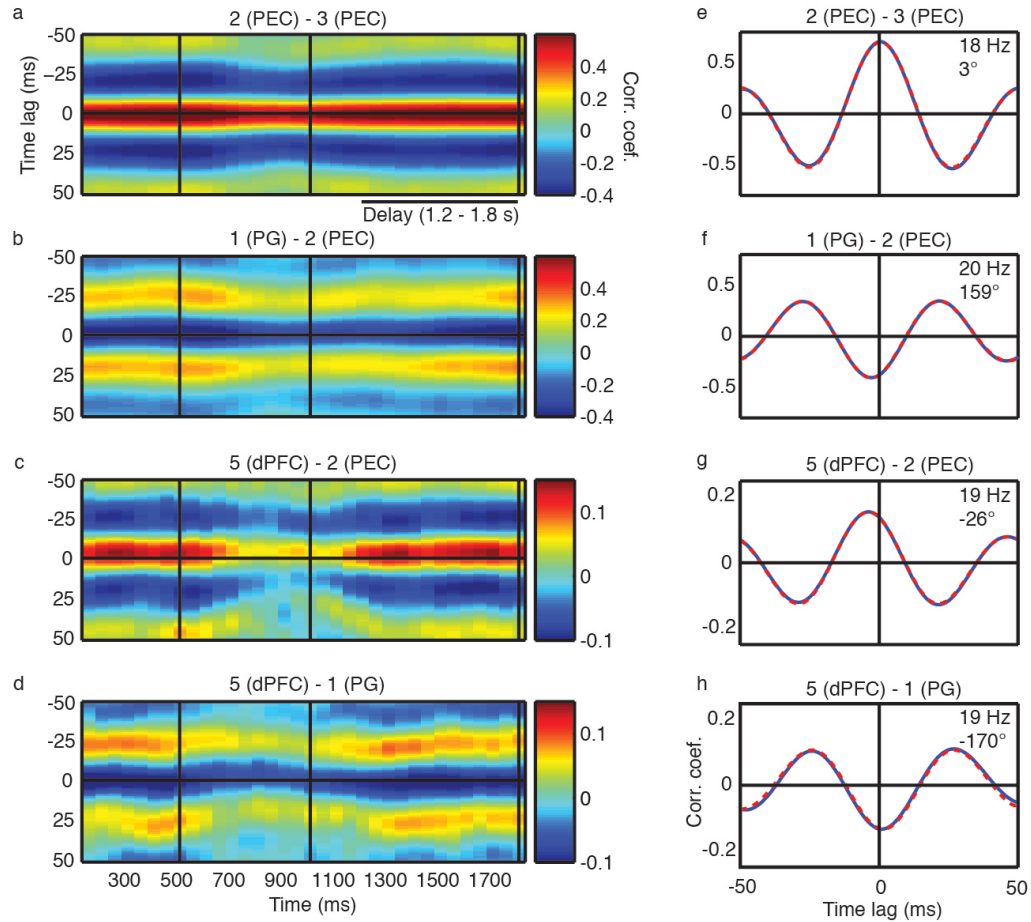


Figure 2. Example of cross-correlation results. **(a-d)** Average cross-correlograms as a function of time (200 ms window, 50 ms step) for four of the signal pairs shown in Figure 1c. Vertical black lines indicate the sample onset, sample offset, and earliest match onset, respectively. **(e-h)** Average cross-correlograms (blue curves) calculated from correct trials during the delay period (1.2 - 1.8 s) and generalized Gabor functions that were fit to the data (dashed red curves). The frequency and phase angle obtained from the Gabor function is indicated in the upper right of each plot.

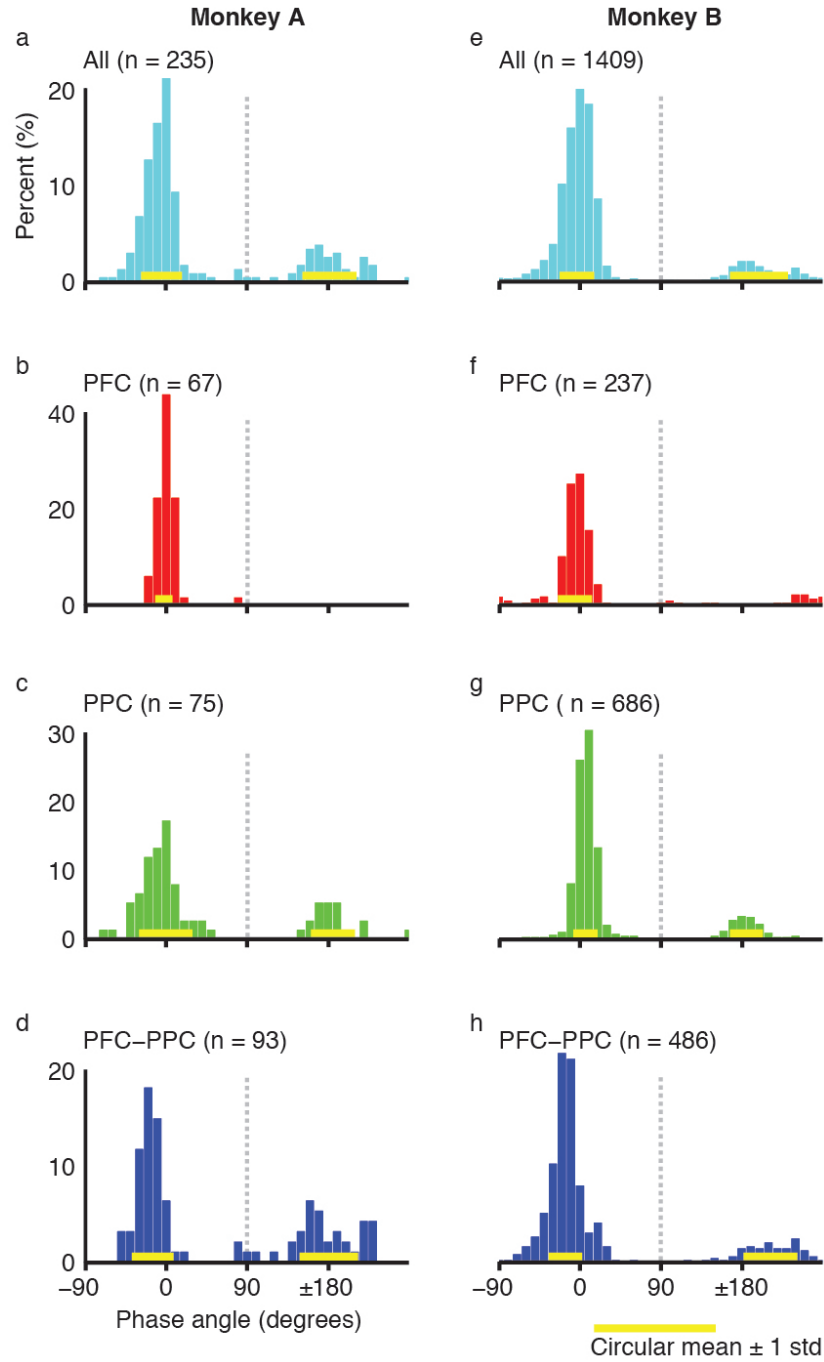


Figure 3. Distributions of the relative phase angles during the delay period (1.2 - 1.8 s) for different combinations of signal pairs recorded from Monkey A (left column) and Monkey B (right). **(a-d)** All, PFC, PPC and PFC-PPC signal pairs for Monkey A. **(e-h)** All, PFC, PPC and PFC-PPC signal pairs for Monkey B. The yellow bars indicate the circular mean ± 1 circular standard deviation for each identifiable mode.

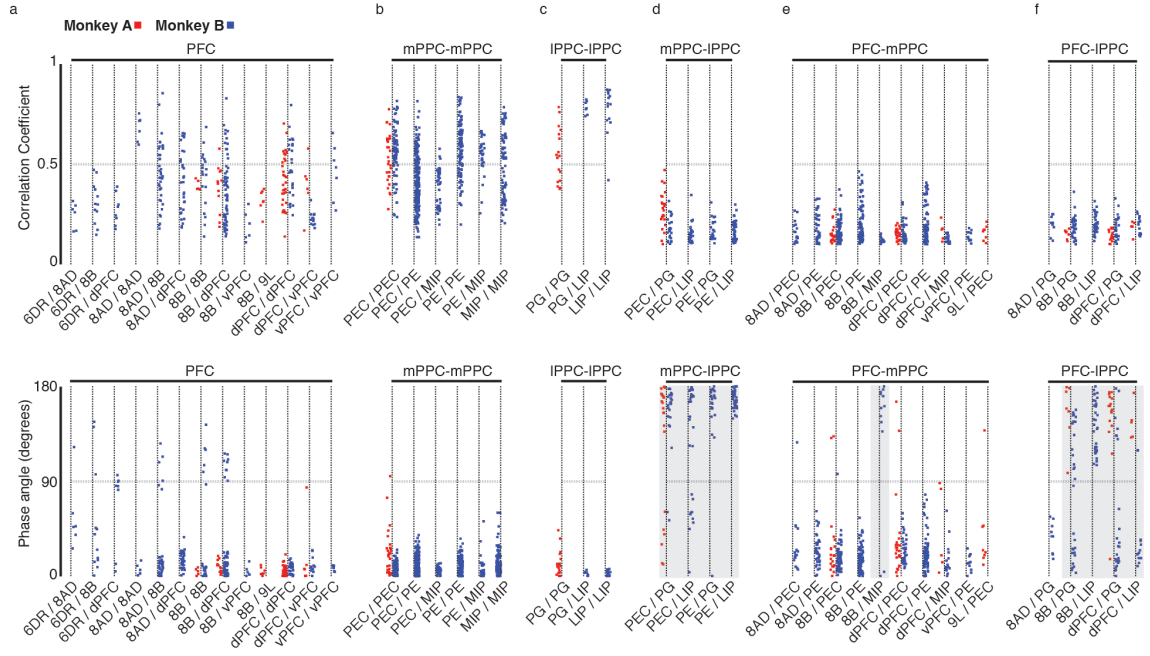


Figure 4. Distributions of the peak correlation coefficients (top row) and absolute values of the relative phase angles (bottom row) during the delay period (1.2 – 1.8 s) for signal pairs recorded in PFC (a), mPPC (b), IPPC (c), mPPC-IPPC (d), PFC-mPPC (e) and PFC-IPPC (f) for Monkey A (red) and Monkey B (blue). Only those areal combinations with five or more observations for at least one of the animals are included in the table. Light gray shading in d, e and f indicates areal combinations with a high percentage of phase values between 90° and 180°. Data points were jittered horizontally for better visualization.

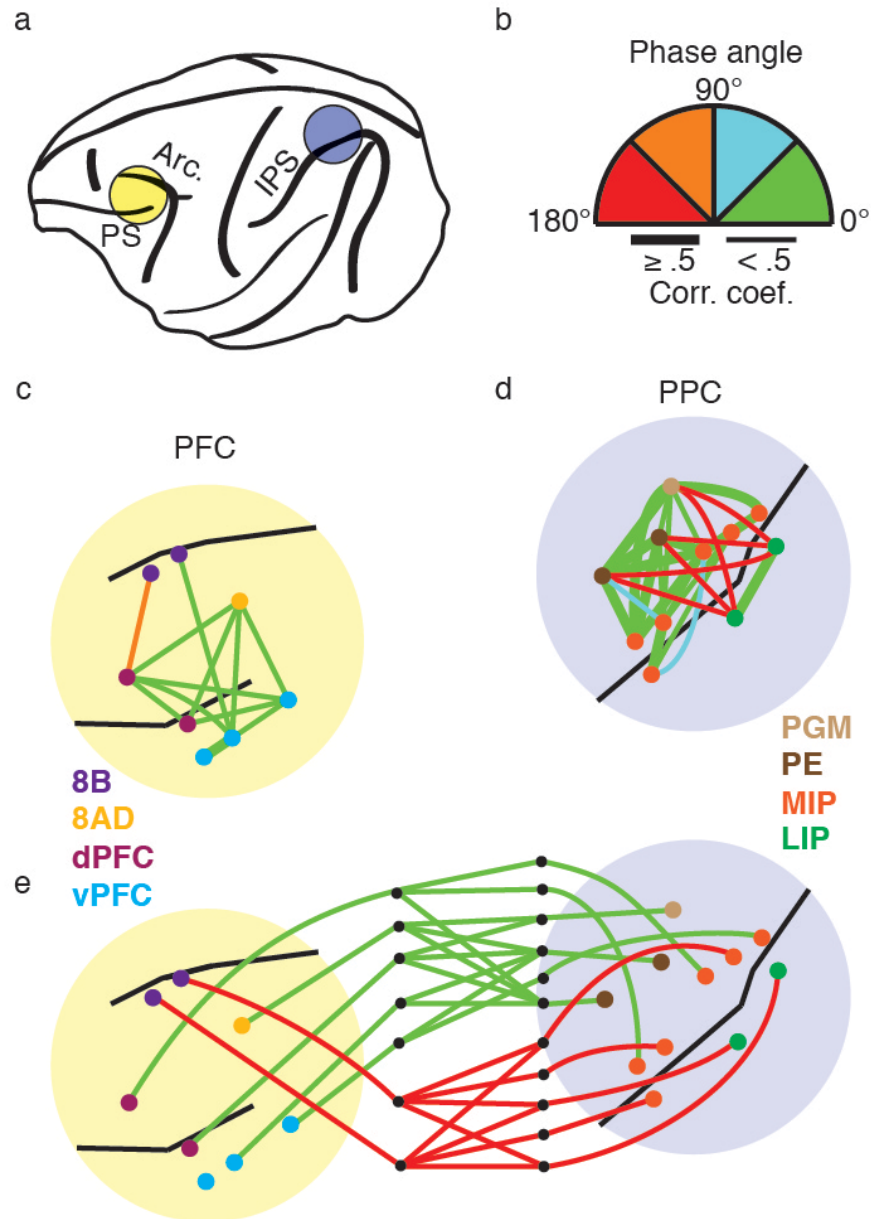


Figure 5. Example of a single recording session from Monkey B. **(a)** Illustration of the recording chamber locations. The names of the sulci are abbreviated as follows: PS (principle sulcus), Arc. (Arcuate Sulcus), and IPS (Intraparietal sulcus). **(b)** Color scale for the relative phase angles (absolute value). The magnitude of correlation is indicated by the line thickness. **(c-e)** Intra- and inter-areal phase angles and magnitudes illustrated on schematics drawings of the PFC (left) and PPC (right). Due to the chamber orientation and the curvature of the sulci the recording locations do not always appear on the appropriate side of the sulcus.

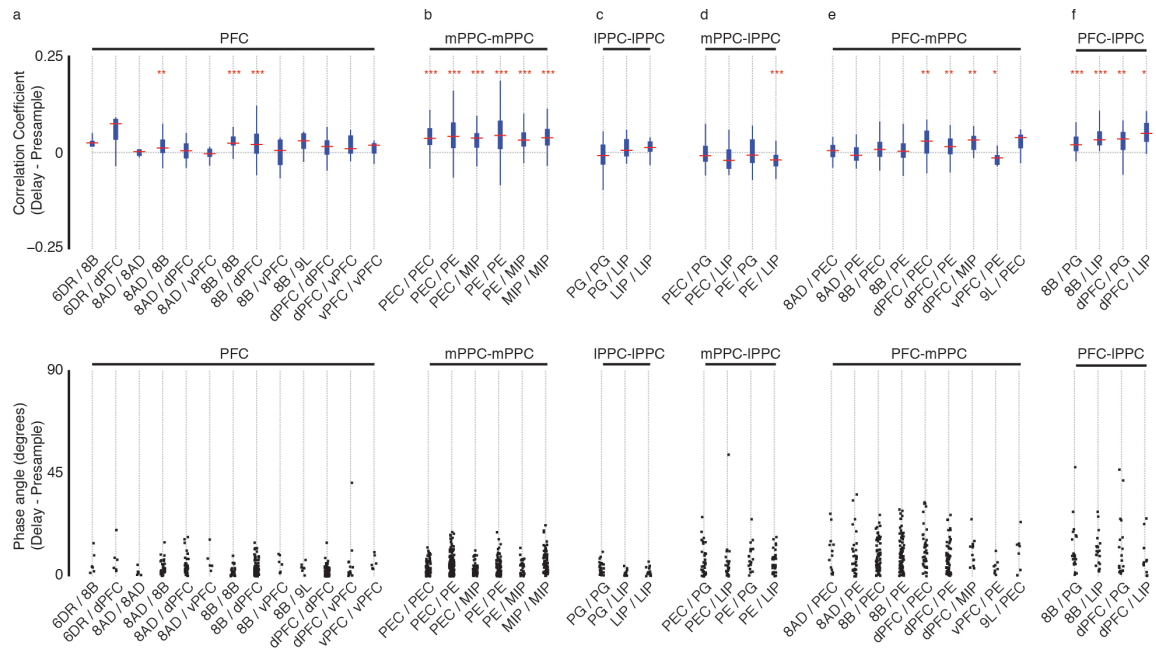


Figure 6. Distributions of the difference in correlation coefficients (top row) and relative phase angles (bottom row) between the delay period (1.4 – 1.8 s) and the pre-sample (.1 - .5 s) for signal pairs recorded in PFC (**a**), mPPC (**b**), lPPC (**c**), mPPC-lPPC (**d**), PFC-mPPC (**e**) and PFC-lPPC (**f**). Data is combined across animals and only those areal combinations with five or more observations included in the table. (Top row) Positive values indicate that the correlation is higher during the delay period. Red asterisks indicate that the median of the difference distribution is non-zero (Sign test, paired, two-sided, * $p < .05$, ** $p < .01$, *** $p < .001$). (Bottom row) For visualization purposes, the relative phase angle is presented as an absolute value and data points were jittered horizontally.

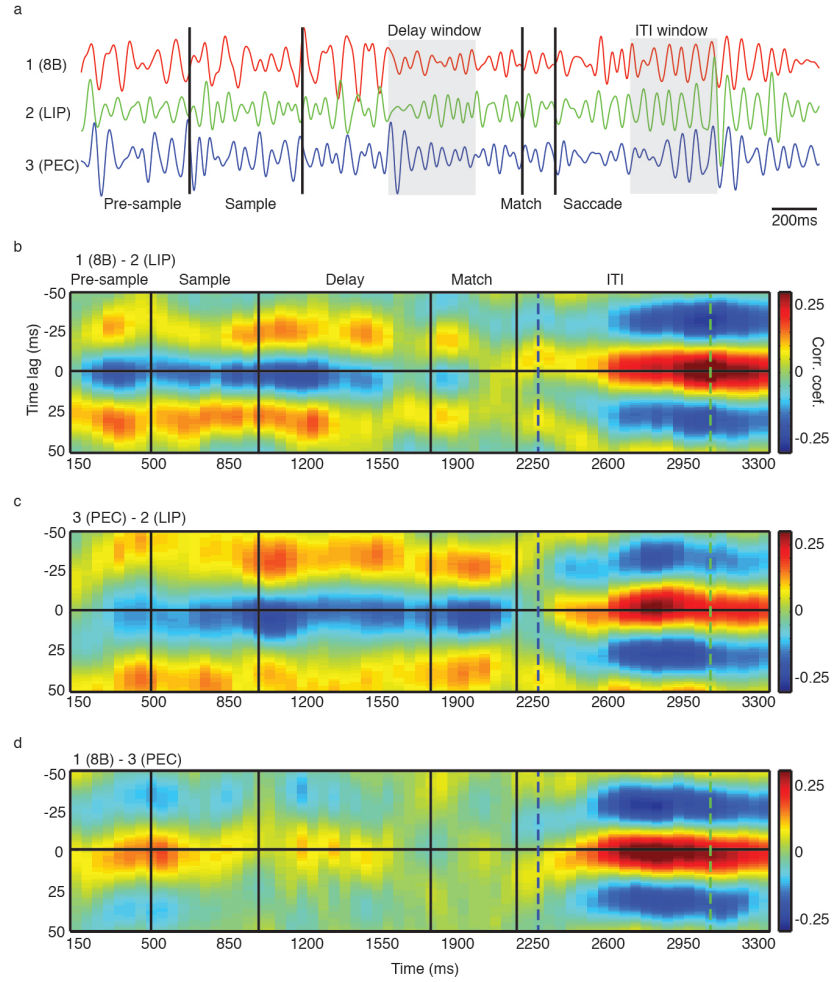


Figure 7. Example of the ITI phase flips during a single trial and averaged over all incorrect trials for a single recording session from Monkey B. **(a)** One PFC (red) and two PPC channels (green and blue) recorded simultaneously. Data is bandpass filtered from 8-25 Hz. Gray shading indicates the time window used during the delay and ITI periods. **(b-d)** Average correlograms as a function of time using a 200 ms sliding window with a 50 ms step for the 8B-LIP, PEC-LIP, and 8B-PEC signals shown above. Vertical black lines indicate the sample onset, sample offset, and earliest match onset, respectively. The dashed vertical blue and green lines indicate the earliest start time and latest end time for the ITI analysis window, respectively.

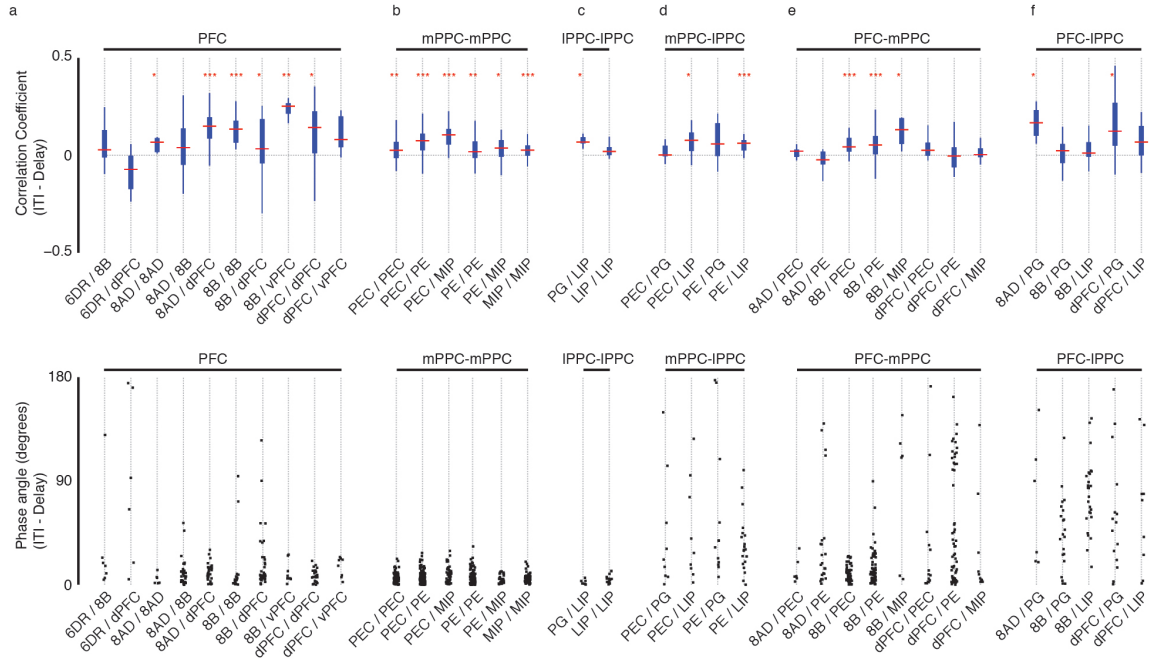
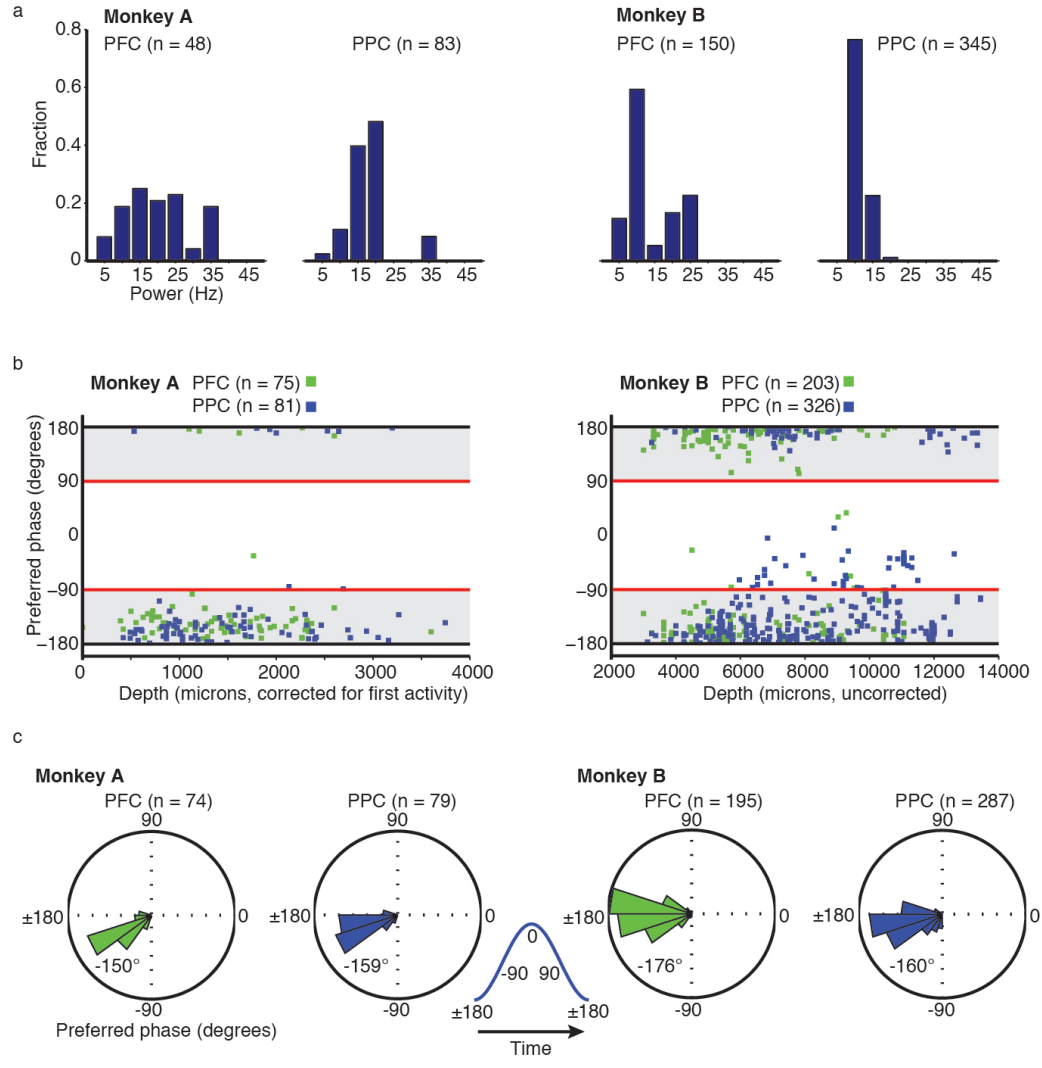


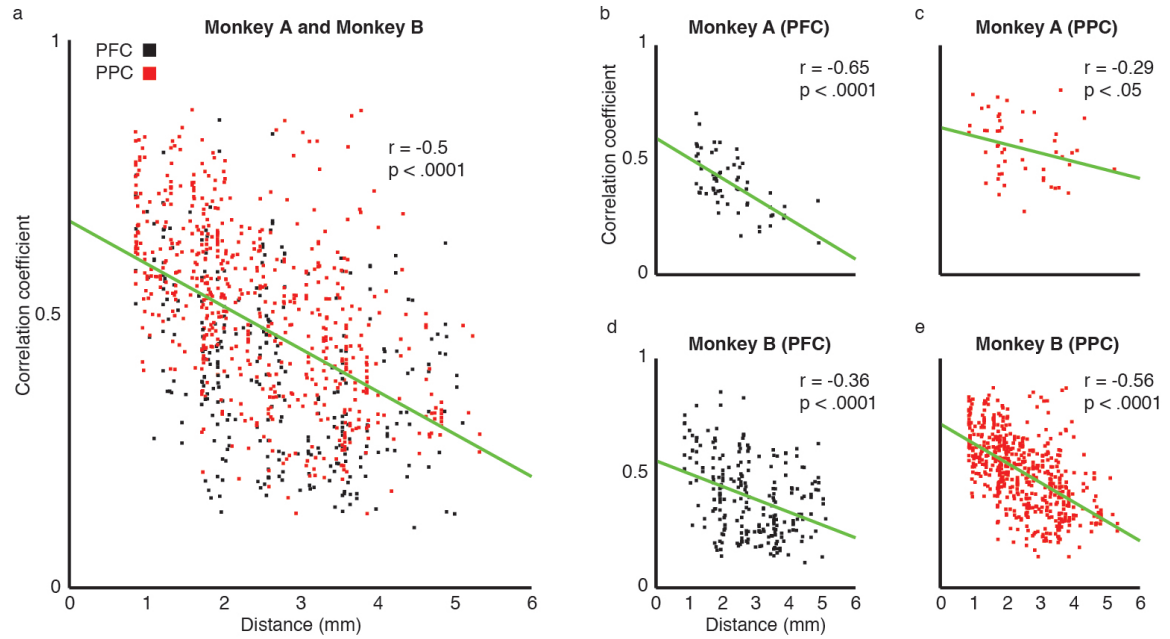
Figure 8. Distributions of the difference in correlation coefficients (top row) and relative phase angles (bottom row) between the ITI period (0.5 - 0.9 s locked to match onset) and the delay period (1.4 – 1.8 s) for signal pairs recorded in PFC (a), mPPC (b), IPPC (c), mPPC-IPPC (d), PFC-mPPC (e) and PFC-IPPC (f). Data is combined across animals and only those areal combinations with five or more observations included in the table. (Top row) Positive values indicate that the correlation is higher during the ITI period. Red asterisks indicate that the median of the difference distribution is non-zero (Sign test, paired, two-sided, * $p < .05$, ** $p < .01$, *** $p < .001$). (Bottom row) Real values of the relative phase angles were used to calculate the difference between task periods, but for visualization purposes, the relative phase angle difference is presented as an absolute value. Also for visualization purposes, data points were jittered horizontally.

Supplementary Figures

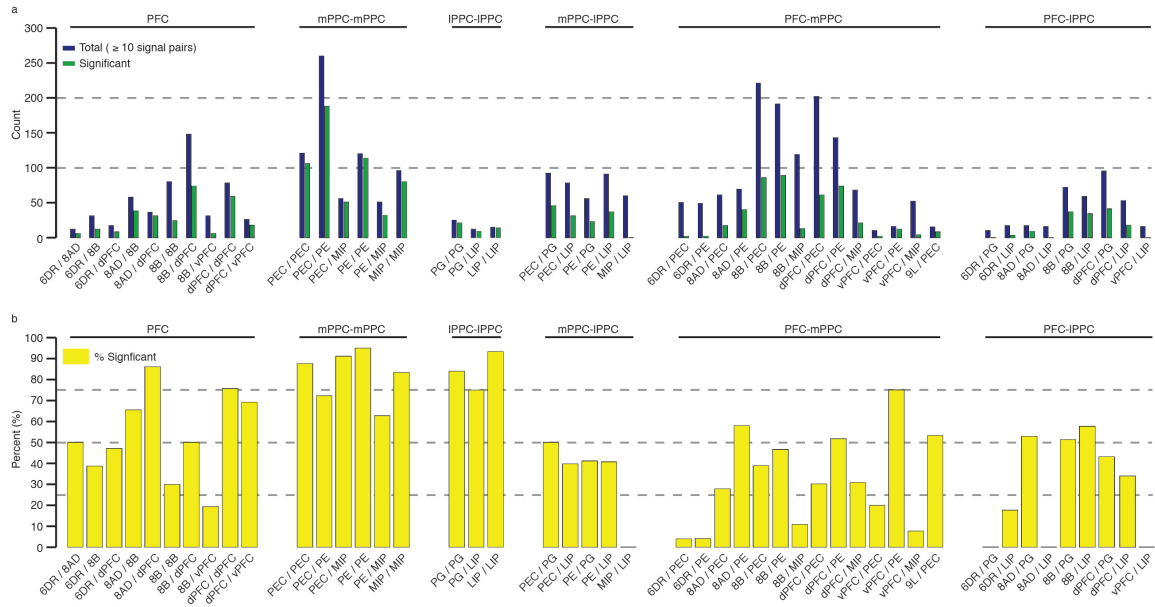


Supp. Figure 1. Summary of the spectral peak analysis and the spike-field phase analysis. **(a)** Distributions of peaks in the spectral power for Monkey A (left) and Monkey B (right) spanning the range of 5-45 Hz in 5 Hz bins. A total of 198 out of 342 PFC signals (Monkey A = 48/84, Monkey B = 150/258) and 428 out of 437 PPC signals (Monkey A = 83/90, Monkey B = 340/347) had peaks in their power spectrum. **(b)** Distributions of the preferred phase (circular mean) of the multi-unit activity (MUA) with respect to the LFP - for those sites passing the Rayleigh test ($p < .05$) - as a function of electrode depth. In Monkey A (left) the recording depth is relative to the first detection of unit activity near the cortical surface. In Monkey B (right) the recording depth is relative to the starting position of the electrodes in the microdrive. A circular mean near 180° indicates that the MUA activity is concentrated near the trough, or negative phase, of the

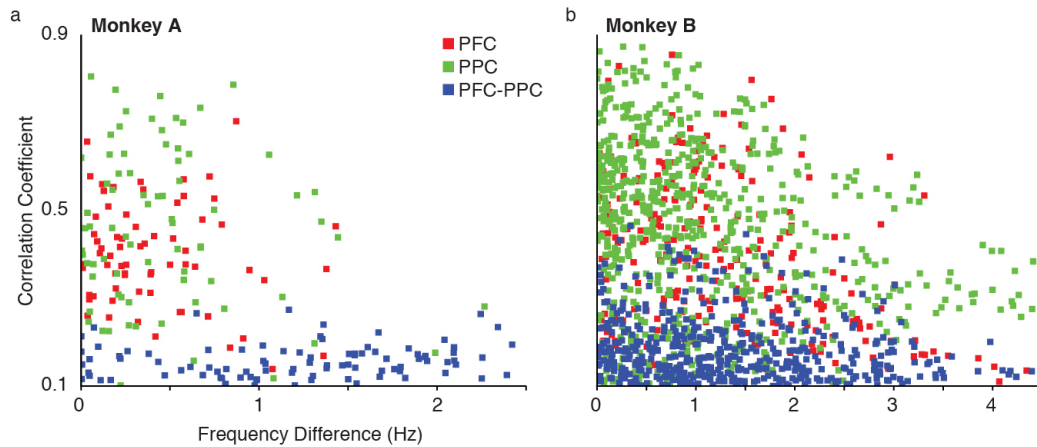
LFP (shaded region). (c) Circular histograms of the preferred phase (circular mean) for all signals that passed the Rayleigh test with a circular mean greater than 90° in absolute value. Inset (middle) indicates the timing of spikes relative to the LFP oscillation, with the negative trough at $\pm 180^\circ$. The grand circular mean is given in the bottom left of each histogram.



Supp. Figure 2. Summary of the relationship between distance and correlation magnitude during the delay period (1.2 - 1.8 s). **(a)** All signal pairs recorded in PFC (black squares) and from the same side of the IPS in PPC (red squares) for both animals. **(b,c)** Signal pairs recorded in PFC and PPC from Monkey A. **(d,e)** Signal pairs recorded in PFC and PPC from Monkey B. Green lines indicate the least-squares fit (Correlation values (r) are provided in the upper right of each plot, along with p values for testing the hypothesis of no correlation, which is computed by transforming the correlation to create a test statistic having $n-2$ degrees of freedom).



Supp. Figure 3. Summary of the counts and incidence of significance for all areal combinations with ≥ 10 signal pairs. **(a)** Counts for the number of signal pairs (blue bars) and the number of significant signal pairs (green bars) during the delay period (1.2 - 1.8 s). **(b)** Percentage of significant signal pairs.



Supp. Figure 4. Summary of the relationship between the intrinsic frequency difference and correlation magnitude during the delay period (1.2 – 1.8s). The intrinsic frequency difference was calculated by estimating the frequency of each signals auto-correlogram and then subtracting the two “intrinsic” frequencies (absolute value used in the figure). The results for Monkey A **(a)** and Monkey B **(b)** indicate that high correlation is typically associated with similar intrinsic frequencies. However, similar intrinsic frequencies do not guarantee high correlation. The data is grouped into three separate categories, PFC (red), PPC (green), and PFC-PPC (blue)

Supplementary MaterialAdditional Analyses

Signal Pair Overlaps. The recording technique for Monkey B involved electrodes that were semi-chronically implanted, which enabled us to sample from similar recording locations across multiple days. Often we chose not to move individual electrodes if unit activity was already prevalent. 325 signal pairs that reached our significance criteria, from Monkey B, were recorded with both electrodes at the same depth. Recordings were made a minimum of ~24 hours apart and between recordings the animal was allowed to freely move in its cage.

175 from PPC-PPC signals pairs

63 from PFC-PFC signal pairs

87 from PFC-PPC signal pairs

23.1% Monkey B signals were overlaps (325/1409)

19.8% of the total signals (pooled over both animals) were overlaps (325/1644)

Analysis of the Relationship Between CorrelationMagnitude and Intrinsic Frequency Differences. To address the relationship

between intrinsic frequency differences and the correlation magnitude between signals we calculated the auto-correlation frequency of each signal during the delay (1.2 – 1.8 s), took the difference, and then compared these values to the correlation magnitude (Supplementary Fig. 4). This analysis indicates that in order for high correlation to occur, the intrinsic frequencies of the two signals must be similar. However, similar intrinsic

frequencies do not ensure a high correlation. One reason for low correlations could be weak anatomical connectivity. This finding is particularly interesting because it illustrates how the spectral content of a signal can influence its relationships with other signals.

Analysis of Simultaneous In-Phase and Anti-Phase Correlations. In Monkey A, of the 45 prefrontal signals showing correlation with a parietal signal, 12 (27%) displayed co-occurring in-phase and anti-phase relationships with a minimum of 2 parietal signals (6 - dPFC, 3 - 8B, 2 - 9L, 1 - vPFC). On the other hand, none of the 46 parietal signals displayed co-occurring in-phase and anti-phase relationships with prefrontal signals. In Monkey B, of the 151 prefrontal signals correlated with a parietal signal, 14 (9%) displayed co-occurring in-phase and anti-phase relationships with parietal signals (11 - 8B, 2 - dPFC, 1 - 8AD). 19 out of the 183 (10%) corresponding parietal signals displayed both phase relationships with prefrontal signals (9 - PG, 6 - LIP, 2 - MIP, 1 - PE, 1 - PEC). In both animals, the majority of prefrontal signals that maintained both phase relationships with parietal signals were from 8B and dPFC. Only Monkey B had parietal signals that maintained both phase relationships with prefrontal signals and these were predominately from PG and LIP. These co-occurring phase relationships indicate that sets of signal pairs with in-phase relationships, and sets of signal pairs with anti-phase relationships, are not mutually exclusive.

Additional Discussion

Methodological Limitations. It could be argued that the use of a time-frequency domain analysis would be more useful because it avoids bandpass filtering the data and provides a better estimate of the relevant frequencies. We chose to use cross-correlation analysis for two reasons. First, the majority of signals recorded had high amplitude components in the alpha and beta frequency bands, suggesting that bandpass filtering would not artificially create a “signal” (Supplementary Fig. 1a). Using the bandpassed signal, we were able to directly assess the relative phase between the dominant components in the signals, rather than a combination of phase and amplitude, which is what coherence analysis does. Second, it provided a single value for the magnitude and phase for the frequency at which the signals were maximally correlated, greatly simplifying the analysis. Another important choice was the use of LFPs rather than unit activity. The LFP was chosen because it provides a robust and continuous signal representing the synaptic activity of a small cortical population – within ~250 μm of the electrode (Katzner et al., 2009) - and has been shown to provide as much or more information than spiking activity (Pesaran et. al., 2002). However, we did utilize the spiking activity to drive our analysis (Supplementary Fig. 1b,c), which we used to verify that a consistent relationship between the LFP and the associated spiking activity existed. A final methodological issue is the use of incorrect trials for the ITI analysis. This occurred because we did not initially intend on analyzing the ITI period, and it was only after the recordings were finished that we recognized the ITI phenomenon. However, we currently have validation that these shifts and flips in the relative phase angle occur

during correct and incorrect trials between many areas of the brain (Dotson and Gray, 2013).

A Discussion of the ITI Beta Bursts. An analysis of the ITI on single signals revealed that bursts of sequentially timed oscillatory activity were present during the ITI in PFC and PPC. These bursts occurred earlier in the PPC than the PFC by ~100ms. This suggests that the task related networks are being re-organized from posterior to anterior, potentially, from a modulatory neurotransmitter such as dopamine. Dopaminergic neurons in the midbrain have been shown to signal the absence of an expected reward by a depression of activity (Schultz et al., 1997). This activity could also be related to an evoked-response, typically measured with scalp EEG recordings, called the error-related negativity (ERN) (see Olvet and Hajcak, 2008, for a review). However, preliminary analyses of a separate data set indicate that these large changes in the relative phase, between distant cortical areas, also occur on correct trials (Dotson and Gray, 2013). An analysis of the extent to which they differ between correct and incorrect trials will have to wait for future studies.

Coordination Dynamics. A potential framework for studying the spatiotemporal patterns we observed is to use the principles considered in coordination dynamics, including metastability and self-organization (Kelso, 1995; Bressler & Kelso, 2001; Kelso & Tognoli, 2009; Kelso, 2012). Work by Kelso and colleagues (Haken et. al., 1985; Schoner & Kelso, 1988; Kelso, 1995) on inter-limb coordination lead to the development and extension of a mathematical model, called the HKB equation (Haken et.

al., 1985), which is used to quantify transitions in the relative phase relationship between two weakly, and non-linearly coupled, non-linear oscillators. A phenomenon they liken to phase transitions in non-equilibrium physical and chemical systems - which exhibit self-organized behavior. Schoner and Kelso (1988) provide a highlight of this work, in which they describe the underlying dynamics of coordinated finger movements. The original experiment required human subjects to oscillate their index fingers from left to right. Subjects were asked to maintain an anti-phase relationship at a specific frequency. The frequency was then slowly increased, either by the subject or an auditory cue. At a certain frequency a spontaneous transition from anti-phase to in-phase would occur. Using the HKB equation, they are able to model the phase transition as a function of frequency. In this study, we demonstrate that inter-areal phase relationships have a tendency to follow some of these dynamics. Including in- and anti-phase relationships and flips between the two. Furthermore, it is noted in that the phase flips we observe are associated with a change in frequency of correlation, providing further evidence that these same principles might be at play between cortical areas. Much work is still needed to accurately capture these dynamics, but the concepts described above appear to be a good candidate (Dotson and Gray, 2013).

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CHAPTER FOUR

LARGE-SCALE SPATIOTEMPORAL DYNAMICS

Abstract

Cognitive processes, such as working memory, involve dynamic and coordinated interactions among very large and heavily distributed populations of neurons. Functional imaging, and non-invasive electrophysiological, techniques have provided great insight into cognitive processes; however, they lack the necessary combination of spatial and temporal resolution to study the dynamics of distributed neuronal interactions. In light of these technical limitations, we developed a device with 256 independently movable microelectrodes (20 mm travel) spanning an entire hemisphere. This technology provided us with an unprecedented look at the real time dynamics underlying working memory. In this Chapter, 1) we analyze the task- and stimulus-dependence of spiking activity, 2) show an example of a large-scale beta network, and 3) extend some of the findings from Chapters 2 and 3, including examples of large shifts in the relative phase angle during the ITI.

Introduction

It is well established that cognitive processes involve dynamic and coordinated interactions among very large and heavily distributed populations of neurons (Mesulam, 1990; Gray, 1994; Bressler, 1995; Singer & Gray, 1995; Friston, 1997; Bressler & Kelso,

2001; Varela et al., 2001; Fell & Axmacher, 2011; Siegel et al., 2012). Even seemingly simple and ubiquitous cognitive functions, such as working memory, involve large-scale interactions among distributed cortical and subcortical networks. How can these brain wide spatiotemporal patterns be empirically quantified? With the use of multi-electrode simultaneous electrophysiological recordings, this can be accomplished by relating different aspects of the recorded signals over repeated observations during a cognitive task or stimulation paradigm. For example, cross-correlation analysis of local field potentials (LFP) has been used to assess the dynamics of area 17 in the anesthetized cat, visuomotor integration and top down processing in the behaving cat, and somatomotor function in the behaving monkey (Gray et. al., 1992; Roelfsema et. al., 1997; von Stein et. al., 2000; Murthy and Fetz, 1996; see Chapter 3 as well). Another method, spectral coherence analysis, which incorporates the amplitude spectrum (Bokil et. al., 2010), has been used to establish the relationships between areas of the fronto-parietal network during attention and decision-making (Buschman & Miller 2007; Pesaran et al., 2008; see Chapter 2 as well).

In Chapters 2 and 3, multiple methods were used to define patterns of stimulus and task related activity from recordings within and between areas of the prefrontal and posterior parietal cortex. While these areas are certainly integral to working memory functions, these studies do not fully address the large-scale nature of cognition. Subsequently, in order to accurately capture large-scale activity patterns, we developed a device with 256 independently movable microelectrodes (20 mm travel) spanning an entire hemisphere. This technology provided us with an unprecedented look at the real

time dynamics underlying working memory. In this Chapter, 1) we analyze the task- and stimulus-dependence of spiking activity, 2) show an example of a large-scale beta network, and 3) extend some of the findings from Chapters 2 and 3. Specifically, we show that a general increase in correlation is observed during the memory delay, and a similar bi-modal relative phase distribution exists across the cortex. We also show that the relative phase is capable of large shifts and 180° flips during the ITI – corroborating the results from Chapter 3

Results

We recorded broadband neuronal activity from multiple electrodes across the left hemisphere of a macaque monkey while it performed an oculomotor, delayed match-to-sample task. The task involved an initial fixation period (pre-sample, 500 ms), followed by a centrally presented sample stimulus (sample, 500 ms), a variable delay period (delay, 800 - 1200 ms), and a match stimulus, consisting of the target object and a distractor object presented to the sides of the central fixation point (Fig. 1a). The animal successfully completed the trial by making a saccade to the target object and maintaining gaze for 300 milliseconds. If the distractor was chosen the trial immediately ended.

Figure 1b shows the recording device attached to a replica of the animal's skull. The electrodes are housed within the recording apparatus and advanced using a simple screw mechanism. Each electrode is independently movable with a total travel of 20 mm. Recordings were made over a 6 month period, and during this time the signals were sampled from widely disparate locations - including several areas of the visual,

somatosensory and motor cortices as well as posterior parietal, prefrontal and cingulate areas. We have analyzed data from 25 separate recording sessions and included only those signals in which at least multiunit activity could be reliably identified. This insured that all signals were obtained from cortical grey matter.

To categorize these data, we first reconstructed the recordings according to cortical location. Figure 1c shows the position of the microelectrodes as they entered into the cortex along with a summary of the active recording sites and sample sizes at each location. Unit and LFP signals were recorded at a total of 817 unique sites from 114 active electrodes. Following histological reconstruction of the electrode tracks, we identified the cortical locations of all 817 recording sites. The results of this analysis revealed that measurements of neuronal activity were made from a total of 46 unique cortical areas (Fig. 1d).

Task and Stimulus Related Spiking Activity

We first sought to evaluate the properties and distribution of task- and stimulus-related spiking activity. To accomplish this, we computed PSTHs of cellular firing rate locked to the sample presentation during the task. Examples of task-related activity from an example session are shown in figure 2. In these plots, the cellular responses on all correct trials of the task are shown in red and the activity recorded on a set of interleaved fixation trials are shown in blue. From these examples alone it is apparent that neuronal activity in widely separated regions of the cortex is modulated in varying ways by the events of the task. Neurons in V1 and V2 (Fig. 2a, c, d), with eccentric receptive field locations, display anticipatory activity prior to the sample, followed by suppression in

response to the sample, and a ramping up of activity during the delay. Moreover, the activity of these neurons, and another recorded at a somatosensory location (Fig. 2e), displays suppression relative to the fixation trials, suggesting that attention to the demands of the task leads to widespread suppression in sensory regions not directly engaged in the task. In contrast, a neuron in a parafoveal location of V1 (Fig. 2b) displays a vigorous response to the sample but no modulation by the memory component of the task. At the same time a neuron recorded in the ventral lateral region of the prefrontal cortex (Fig. 2f) responds to the sample and displays vigorous ramping up of activity during the delay, suggesting a direct involvement in visual working memory (Miller et al., 1996).

To assess the properties of task-related activity across the population, we compared the responses during the match-to-sample task to the activity recorded on the fixation trials (Wilcoxon rank sum test, $p < .001$), and tested for stimulus specific differences in activity across the five sample stimuli (Kruskal-Wallis test, $p < .001$). Figure 3 shows the results of this analysis. Activity is both suppressed and enhanced relative to fixation trials indicating involvement in the working memory task (Fig. 3a). And stimulus selective activity occurs at short latencies following the onset of the sample and continues throughout the delay period of the task (Fig. 3b). Preliminary analysis of the spatial distribution of these data indicates widespread task-related and stimulus selective activity across the cortex (not shown).

A Large-Scale Beta-network

Synchronous beta oscillations have been proposed as a candidate mechanism for large-scale integration (Hipp et. al., 2011). In Chapters 2 and 3 we support this notion. One objective of the current study was to determine the spatial extent of beta coherence. To accomplish this we applied time-frequency coherence analysis to each signal pair and evaluated the coherence spectra for all correct trials. Figure 4 shows the cohgrams for 3 signal pairs recorded during the same session. In this example, the coherence of a V4 signal with signals from MT, PE, and 9L are shown to illustrate distributed beta coherence. Interestingly, the V4 signal is coherent with all three areas; however, there are slightly different frequencies and major differences in the time-dependence. An example of the results of this analysis in the beta frequency band (12-25 Hz) for all pair-wise measurements over an entire session is shown in figure 5. The data reveal widespread coordinated interactions among all major regions of the cortex that change in a task-dependent manner. Visual and posterior parietal areas display widespread coherence that increases during the delay period of the task. These include interactions with the somatosensory and motors areas of the task. Only a small number of prefrontal sites were recorded and these exhibit relatively static interactions with somatomotor areas. While still preliminary, these data, in conjunction with Chapters 2 and 3 demonstrate widespread, task-dependent and content-specific patterns of coordinated interactions across large expanses of the cerebral cortex during visual working memory. These findings support the widely accepted notion that the cortex functions as a distributed

system to flexibly integrate cognitive processes happening in many regions of the brain simultaneously.

Analysis of the Relative Phase During Working Memory

In Chapter 3 we found a largely bimodal distribution of relative phase angles that could be described by anatomy. Consistent with these findings, in this study we find a bimodal distribution of relative phase angles among significantly correlated pairs across a hemisphere (Fig. 6). Figure 6 shows the distribution of relative phase angles from all recording sessions. The relative phase angles are primarily near 0° and 180° . Overall, this re-occurring bimodal distribution is very intriguing, especially because these recordings are very distributed, which makes it difficult to suggest that the relative phase is related solely to anatomical distance. If this were the case, then we would suspect to see a more uniform distribution of relative phase values. This suggests that there are preferred timing relationships between widespread areas of the cortex.

Task Dependence of the Correlation Magnitude

Next, we examined the task-dependence of these correlations, similar to Chapter 3, by comparing the pre-sample period (0.1 - 0.5 s) with a window of the same size in the delay period that is locked to the first possible match (1.4 - 1.8 s). Signal pairs were selected using criteria similar to Chapter 3 (see Methods for more details). To determine the task dependence of the correlation magnitude, we tested whether changes in the correlation magnitude increased or decreased between the pre-sample period and the delay period. Figure 7 shows the difference distributions for all areal combinations. This

revealed a general increase in correlation magnitude from the pre-sample to the delay (Sign test, paired, two-sided, $p < .001$). This result is similar to what was observed in Chapter 3 where there is a general increase in correlation magnitude from the pre-sample to the delay in many areal combinations in the fronto-parietal network. This is also revealed in the previous section using coherence analysis, which shows a general increase the number of significant signal pairs during the delay. Another interesting point is the magnitude of change that is seen, there are increases above 0.15 and decreases near 0.1, which indicates that there is a high degree of variability and that what we are actually seeing is evidence of a highly dynamic process.

Re-organization of the Relative Phase Angle

In Chapter 3 and the previous sections we provided evidence for the coexistence of multiple functional networks defined by relative phase and modulations in correlation strength. To further explore the potential for these large-scale networks to re-organize, we compared the delay period (1.4 - 1.8 s) to the inter-trial interval (ITI) shortly after the match period (see Methods for details on the ITI window). Importantly, in this study the correct trials are used. Figure 8 (top) shows the cross-correlograms, during the delay and ITI, for a pair of signals in the prefrontal areas 6VR and 9/46D. During the delay period these signals are correlated at 19° and then a nearly 180° flip is seen during the ITI where the signals are correlated at -144° . This phase flip is further exhibited in figure 8 (bottom), which shows the time dependence of the cross-correlation. Accompany this phase flip is a change in frequency of correlation, which can be seen by visual inspection. To further explore this finding, and to illustrate these changes across the cortex, the

recording session that the example in figure 8 was taken from was further analyzed. Figure 9 (left) shows the distribution of relative phase angles during the delay (1.4 – 1.8 s) for this recording session. The relative phase values are primarily near 0° and 180° , similar to the cumulative distribution in figure 6. To demonstrate the potential for reorganization, this distribution is compared to the distribution of relative phase angles during the ITI in figure 9 (right). There are several noticeable shifts in the relative phase angle, including the large flip illustrated in figure 8. Figure 10 provides a look at these spatiotemporal patterns during this example recording session. The top row shows the relative phase angles during the delay. The color of the line indicates the relative phase, binned in 45° increments. The middle row shows the signal pairs that exhibit large changes in their relative phase angle ($> 45^\circ$). These are typically distant signal pairs. The bottom row shows the relative phase angle during the ITI. In this example there appear to be sets of areas with in-phase relationships that are linked by anti-phase relationships (compare the primary visual areas with the fronto-temporal areas). Further work will be necessary to fully quantify these networks and the changes during the ITI. Nonetheless, there appear to be large-scale functional networks defined by the relative phase angle.

Discussion

An analysis of the spiking activity revealed widespread task- and stimulus-dependent changes in the firing rate. Signals from V1 to PFC show task dependent changes in firing rate, indicating that working memory processes are very distributed. Moreover, stimulus specific changes in firing rate are also distributed across the cortex.

Further analysis is necessary to determine the contribution of individual areas. Nonetheless, these activity patterns provide an unprecedented look at the large-scale spiking patterns during visual working memory. The coherence analysis further illustrates the distributed nature of working memory and corroborates the findings from Chapters 2 and 3 for a role of the beta band in working memory. This analysis also shows the task dependence, by showing a visible increase in significant signal pairs during the delay. A recent study using non-invasive EEG recordings also describes a large-scale beta-network, which they show is modulated by perception and sensory integration (Hipp et. al., 2011).

In Chapter 3, we observed a general increase in fronto-parietal coherence between the pre-sample and delay period, indicating that the fronto-parietal network as a whole is becomes more coherent during visual working memory. Similar coherence increases have been observed in the theta-frequency band (3-9 Hz) between lateral PFC and V4 during working memory (Liebe et. al., 2012). In the current study, we see a general, hemisphere-wide, increase in correlation from the pre-sample to the delay period, which potentially facilitates the interactions between areas, or in a circular sense, is the product of the interactions between areas. Also, in Chapter 3, when comparing the delay (1.4 – 1.8 s) with the ITI, the phase angles in PFC-PPC pairs changed both from near 0° to near 180° and vice versa, and lPPC-mPPC pairs generally shifted from near 180° to near 0° . In the example session shown in this study we see that signal pairs shifted in both directions as well. These phase angle flips provide a new context for the study of inter-areal relationships. How can this whole network be re-organized? Some insight might be

gained from an analysis of the ITI on single signals in Chapter 3, which revealed that bursts of sequentially timed oscillatory activity were present during the ITI in PFC and PPC. These bursts occurred earlier in the PPC than the PFC by ~ 100 ms. This suggests that the task related networks are being re-organized by outside contributions in a wave of activity moving from posterior to anterior - a hypothesis that we are now capable of testing, but remains outside the objectives of this study.

The results from this study emphasize the distributed nature of working memory. Task- and stimulus-dependent spiking activity and coherent beta activity is widespread. Our results also show that at least two functional networks, defined by the relative phase, coexist in the fronto-parietal network and across the brain, which are enhanced during the memory delay and re-organized during the ITI. Future work will be needed to elucidate the specific areas and combinations of areas that are involved in different aspects of working memory processes. Overall, much work is still needed to fully capture these nebulous spatiotemporal patterns and it will likely require using techniques from non-linear dynamics to model these interactions.

Methods

Animals and Recordings

The objective of this work was to develop a semi-chronic microdrive system capable of recording neuronal activity in behaving macaque monkeys from up to 256 independently moveable microelectrodes spanning an entire cerebral hemisphere at 2 mm intervals. The system needed to be stable, hermetically sealed and implanted for long

periods of time. To accomplish this, we designed and built a form-fitting Titanium chamber and electrode guide array that matched the surface of the skull in an individual monkey. Using the Solidworks CAD software package, we built a 3D model of the animal's skull from structural MRI data and used the coronal sections of the brain to define the boundaries of the intended recording sites. We then designed the chamber and guide array to closely match the surface of the skull (Fig. 1b). The microdrive was built to match the distribution of the intended recording sites and fit within the chamber and guide array. The actuators for bi-directional control of electrode position were based on a simple screw-driven mechanism and electrical connections were established through a printed circuit board that avoided the use of wires.

Once the initial design was fabricated, and all testing completed, we implanted a trained monkey with the microdrive system in a two-step sequence. In the first phase, the chamber was implanted, sealed with a plug and covered with a short cap. The skull was left intact inside the chamber and the animal was given approximately 6 weeks to recover. During this time, we carefully monitored the animal's well being, assessed the wound margins, and occasionally checked the interior of the chamber. The animal recovered very well from the procedure. The skin margins remained healthy and the interior of the chamber was water-tight and showed no signs of infection.

We then loaded the microdrive with 256 microelectrodes, gas sterilized the entire assembly, and sealed the guide tubes with sterile silicone oil. Once all procedures were complete, we implanted the drive after drilling a separate guide hole in the skull for each electrode. This was done using a drill guide having the same shape as the guide array.

The animal was given approximately two weeks to recover from the procedure. Interestingly, the animal learned to avoid bumping the tall protective cap against its home cage and the implant remained stable for more than 8 months.

Following the recovery period, we began recordings on a daily basis. Each day we advanced 20-30 electrodes until they passed through the dura and into the surface cortex. We were careful to note the earliest point at which neural activity could be measured. After two weeks we had advanced all of the functioning electrodes into the brain. We routinely measured electrode impedance and any electrodes with unusually high (> 3 Mohm) or low ($< .1$ Mohm) impedance were considered non-functional.

At the end of approximately 6 months of recording, we made electrolytic lesions on each of the functioning electrodes. The animal was then euthanized, the brain removed for histological analysis and the microdrive removed and carefully disassembled and inspected. We sectioned and stained the entire hemisphere of the brain and reconstructed all of the electrode tracks. This enabled us to identify the cortical area of each of the recording locations (Fig 1c).

Broadband signals (1 Hz – 10 kHz) were digitized at 32 kHz from all active electrodes using a 256-channel Digital Lynx system (Neuralynx, Inc.). The local field potential (LFP, 1 Hz – 100 Hz) and unit activity (600 Hz – 7 kHz) signals were separated off line by band pass filtering. Spike trains from multiunit and single unit signals were sorted using the Klustakwik and MClust software packages (Yen et al., 2007).

Behavioral Procedures

The monkeys performed an oculomotor, delayed match-to-sample task that required the animal to remember the identity of a sample stimulus for 800-1200 ms. The task consisted of four major epochs, referred to as the pre-sample (500 ms), the sample (500 ms), the delay (randomized between 800-1200), and the match (300 ms) epochs. The sample stimulus consisted of 1 out of 5 possible multi-colored images presented centrally. The match and distractor images were presented at to the left and right, randomly. To correctly complete the trial, the animal had to make a saccade to the image that matched the sample image. Each correct trial was rewarded with a drop of juice.

Data Analysis

To analyze the spiking activity we calculated a PSTH for each signal during the match-to-sample task and interleaved fixation trials. Multi- and single-unit activity were analyzed separately. Spikes were binned in 50 ms non-overlapping windows. To assess the properties of task-related activity, we compared the responses during the match-to-sample task to the activity recorded on the fixation trials at each bin (Wilcoxon rank sum test, $p < .001$). To assess the stimulus specific differences in activity across the five sample stimuli a separate PSTH was computed across the trials for each stimulus and then the activity at each bin was tested for significant differences (Kruskal-Wallis test, $p < .001$).

We calculated the coherency spectra (200 ms sliding window stepped at 50 ms) using multi-taper spectral analysis implemented in the Chronux toolbox (Bokil et al., 2010) with three tapers and a time-bandwidth product of two (see Chapter 2 for more

details). The test for significance, used for figure 5, was applied to the delay period (1.4 to 1.8 s, locked to first possible match). A pair was considered to have significant coherence if at least 15% of the time-frequency bins (between 12 and 25 Hz) exceeded the surrogate threshold ($p < .001$). To evaluate the statistical significance, we computed significance thresholds from randomized surrogate distributions ($n = 1000$ iterations).

The average cross-correlogram (± 50 ms time lag, data down sampled to 1 kHz) of the local field potential (8 - 25 Hz) for each pair of signals was calculated across all correct trials during the pre-sample (0.1 to 0.5 s) and the delay period (1.2 to 1.8 s and 1.4 to 1.8 s). The average cross-correlograms during the ITI (0.9 to 1.3 s after match onset) were also calculated. The latency differs from the analysis in Chapter 3 due to a difference in task parameters. Since these are correct trials, the animal must maintain fixation on the target stimulus for 300 ms, thus delaying the ITI response. Further work will be necessary to better determine the ITI time window. The frequency of each cross-correlation was determined by fitting an 8 parameter generalized Gabor function (König 1994). The central peak (positive or negative) obtained from the fit Gabor function was determined by finding the local maximum or minimum that was closest to zero time lag. The relative phase angle between two local field potentials was calculated using the time lag, polarity of the central peak, and the frequency estimated from the Gabor function. Correlograms that were near 180° out of phase had a distinct trough near zero time lag. To identify signal pairs that were significantly synchronized, we used two criteria: 1) The correlation coefficient at the central peak was > 0.05 and 2) The correlation coefficient between the original cross-correlogram and the Gabor function was $\geq .99$. This also

assured that the frequency and phase of correlation was accurately estimated. Time-dependent average cross-correlograms were calculated using a 200 ms window, a 50 ms time step, and a ± 50 ms time lag. To compare the correlation magnitude between the delay and ITI periods we used a Sign test (paired, two-sided, $p < .001$).

Figures

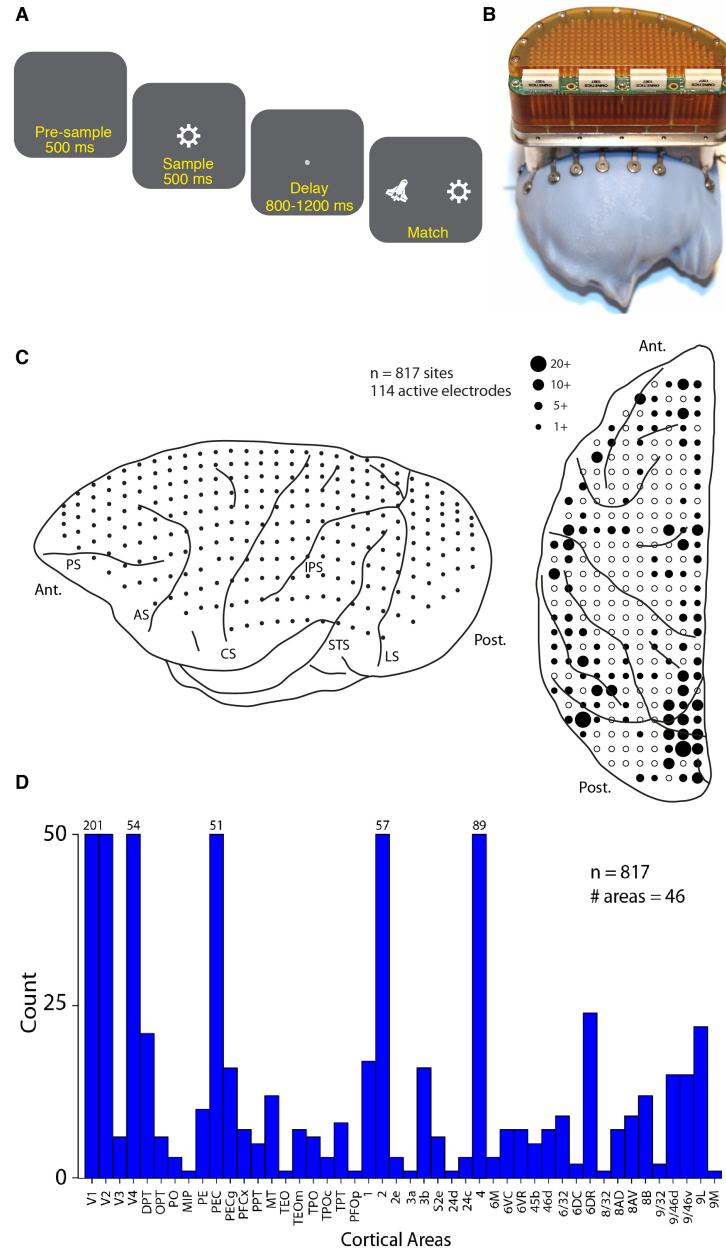


Figure 1: (A) Time line of the match-to-sample task. (B) Recording device positioned on the left hemisphere of a plastic replica of the animal's skull. (C) Reconstruction of the recording locations and sampling distributions. The left plot outlines the major sulci of the left hemisphere along with the entry points of all 256 microelectrodes. The right plot shows the electrode array superimposed on a top view the left hemisphere. Filled circles indicate active electrodes and the sample size is indicated by the diameter. (D) Sample size with respect to cortical area. The numbers above the truncated bars indicate the sample size for that cortical area.

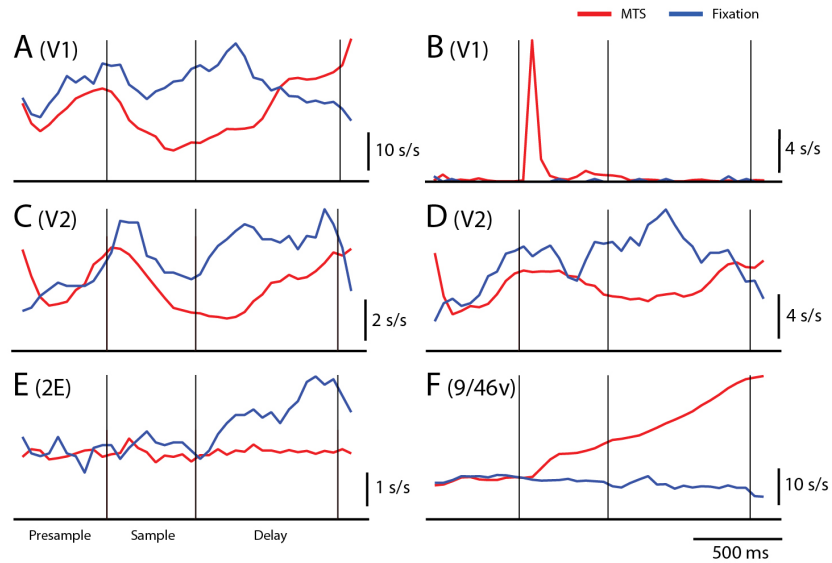


Figure 2: Examples of task-related change in firing rate recorded on a single session from widely disparate cortical locations. The red and blue traces show activity recorded during correct trials of the task and during interleaved fixation trials, respectively.

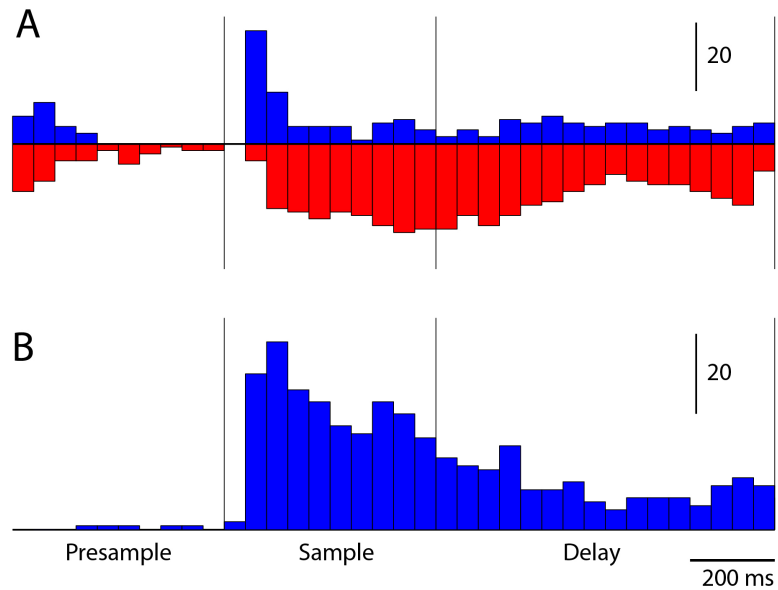


Figure 3: Summary of the incidence of task-related (A) and stimulus selective (B) unit activity over the entire experiment. (A) Number of unique unit recordings in which the task-evoked activity was significantly greater (blue) or less (red) than that recorded on the fixation trials. (B) Number of unique unit recordings in which there was a significant difference in activity for the 5 sample stimuli.

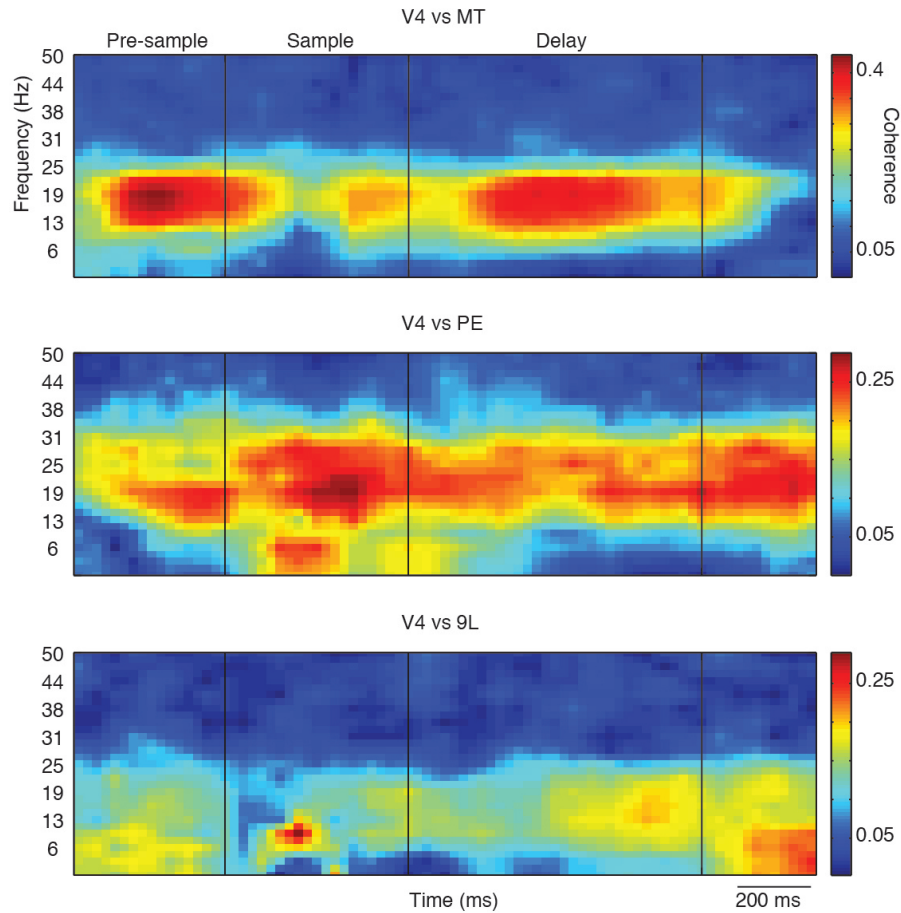


Figure 4: Example cohograms from a single recording session. The V4 signal is the same for all three examples. (Top) A distinct task dependent pattern of coherence is seen between a V4 and a MT signal: a sharp increase occurs prior to the sample, followed by a transient disruption during the sample, and then a sustained elevation during the delay. (Middle, Bottom) The same V4 signal is coherent with both a PE and a 9L signal, but with less obvious task dependence and lower coherence.

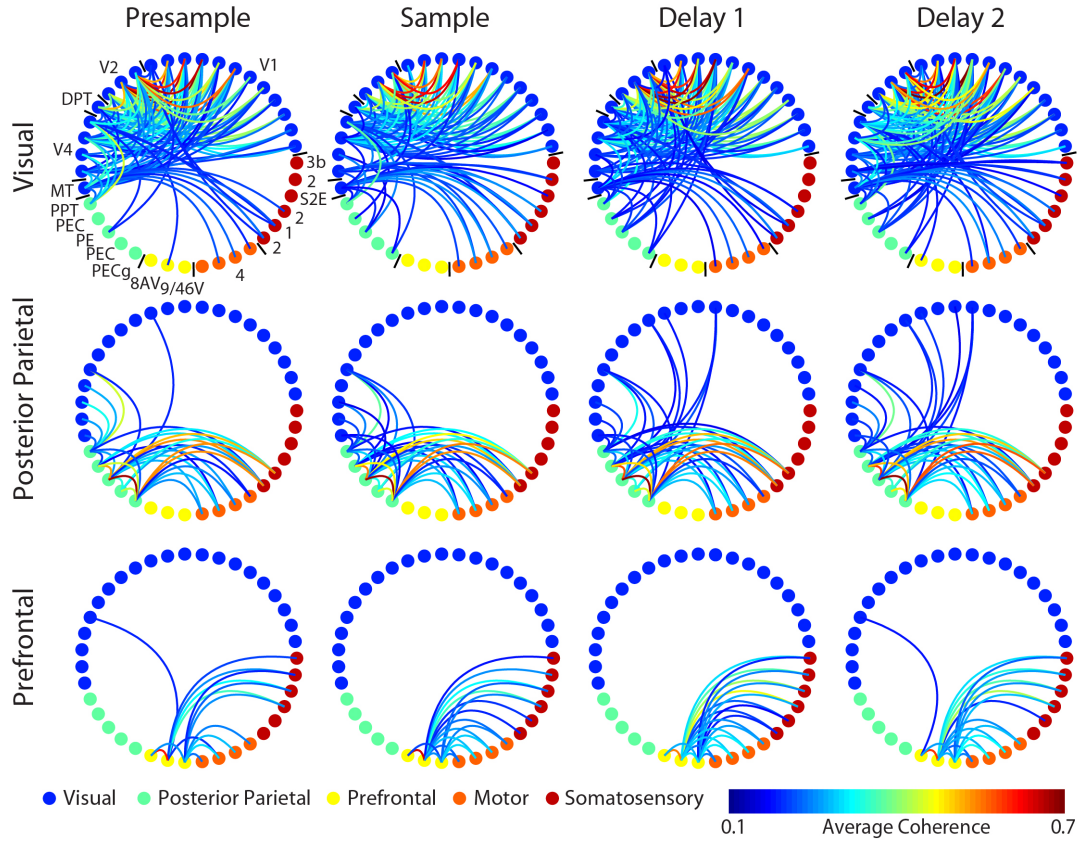


Figure 5: Functional connectivity diagrams for coherence in the 12-25 Hz frequency band for all pairwise combinations of inter-areal signals recorded on the same recording session (same recording session as the examples shown in figure 4). The cortical locations of each signal are shown as filled circles (labeled in the upper left plot) and subdivided with respect to 5 major cortical regions (indicated at the bottom). Each line linking 2 sites shows the mean value of statistically significant coherence ($p < .001$). To facilitate comparison, the plots are subdivided so that all inter-areal interactions are visible for visual, posterior parietal and prefrontal regions. Intra-areal coherence values are excluded.

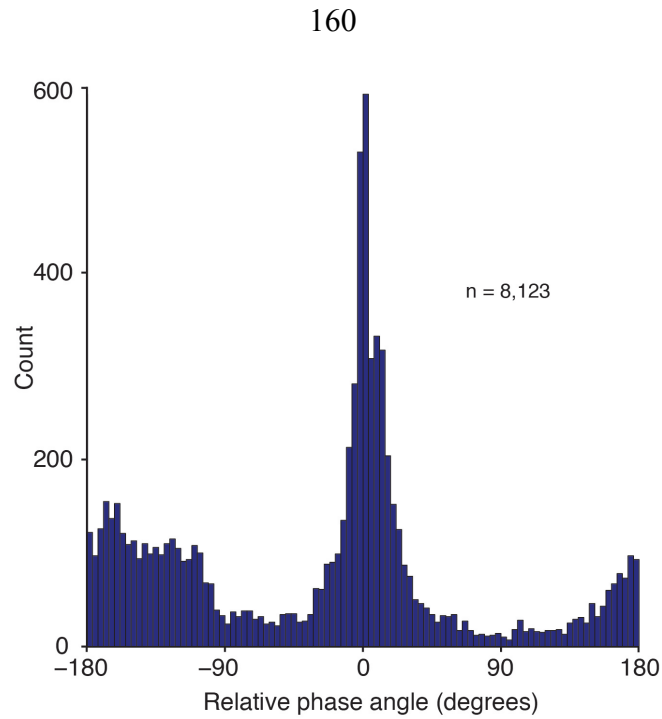


Figure 6: Distribution of relative phase angles across all recording sessions during the delay period. Only signal pairs that are significantly correlated during the delay period are considered. The phase angles are noticeably concentrated near 0° and 180° .

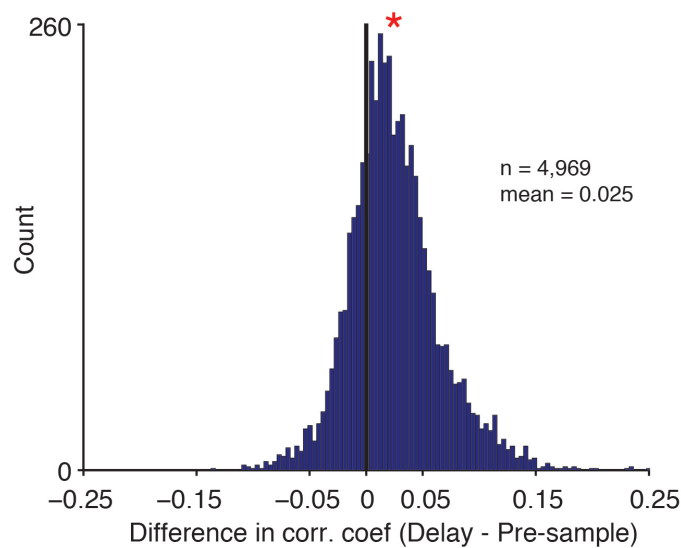


Figure 7: Distribution of the difference in correlation between the pre-sample and the delay period. Only signal pairs that are significantly correlated in both task periods are considered. The red asterisk indicates that the difference distribution is non-zero (Sign test, paired, two-sided, $p < .001$).

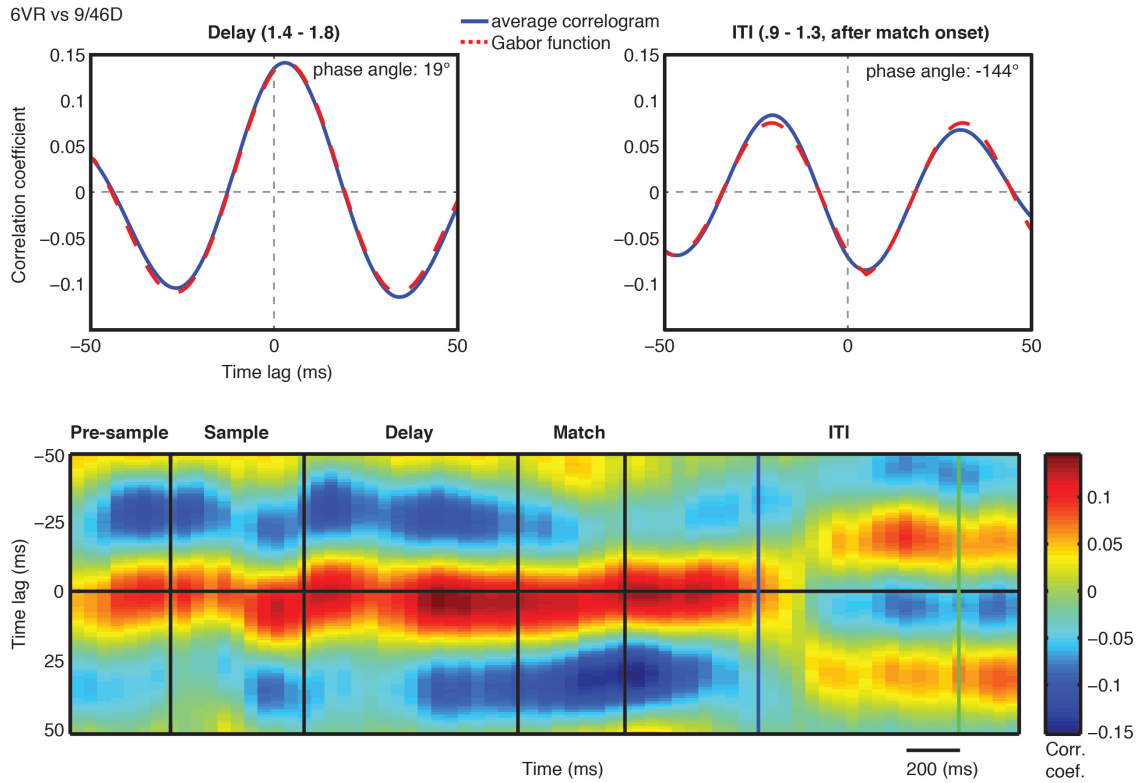


Figure 8: Example of a near 180° phase flip during the ITI. (Top) Cross-correlograms for a 6VR and 9/46D signal pair during the delay and ITI periods. (Bottom) Time dependence of the cross-correlation. The black vertical lines indicate the sample on, sample off, first possible match, and last possible match, respectively. The blue and green lines indicate the ITI window.

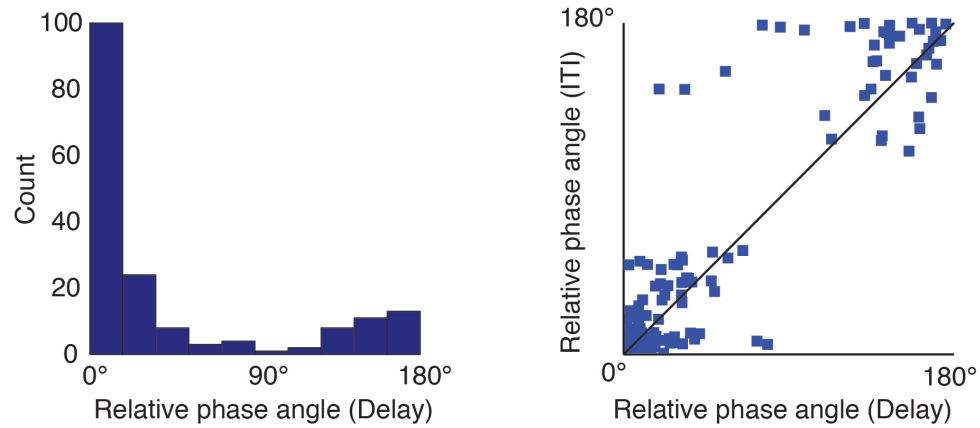


Figure 9: Distribution of the relative phase angles and the potential for re-organization on a single recording session. (Left) The distribution of relative phase angles during the delay (1.4 – 1.8 s) for a single recording session. The relative phase values are primarily near 0° and 180°, similar to the cumulative distribution in figure 6. (Right) The relative phase angles during the delay period are compared to the relative phase angles during the ITI period. There are several noticeable shifts in the relative phase angle, including the large flip illustrated in figure 8.

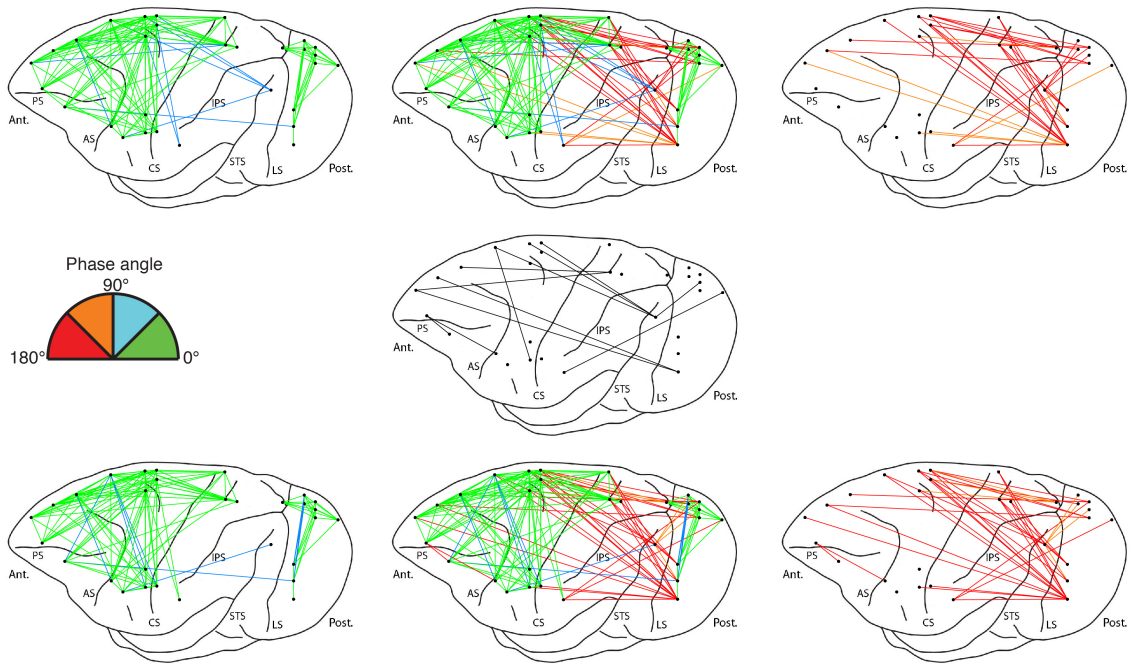


Figure 10: Example of the spatial layout of the relative phase angles (absolute values) during the delay and ITI of a single recording session (same recording session as figures 8 – 10). (Top row) The relative phase angles during the delay. From left to right, the near 0° phase angles, all phase angles, and the near 180° phase angles. (Middle) The signal pairs with > 45° shifts in the relative phase angle. (Bottom row) The relative phase angles during the ITI with the same layout as the top row. The inset in the left middle indicates the color for each phase angle bin.

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CHAPTER FIVE

GENERAL DISCUSSION

Summary of Results

In chapter 2, we demonstrate that fronto-parietal synchronization during visual working memory is 1) widespread, task-dependent, content specific, and 2) potentially driven by PPC influences.

During the working memory task, a common trend in the time course of beta-band (12-25 Hz) coherence was observed: the coherence peaked during the pre-sample period, transiently declined following the sample stimulus onset, and increased again during the delay, reaching a maximum before the match. Content specificity was estimated using the “coherence selectivity index”, which is a mutual information analysis on the coherence spectra. Using this measure we determined that ~25% of fronto-parietal signal pairs, with significant coherence, are selective for the stimuli presented at a specific location during the memory delay. A similar percentage was also found to be selective for location. Thus, our findings demonstrate that short-term memories are represented as stimulus specific patterns of synchronized activity that are widely distributed throughout the fronto-parietal network.

Next, based on time-frequency Wiener-Granger causality (WGC) and spike-field coherence (SFC) we show that fronto-parietal synchronization may be driven by PPC. A more in depth look at the WGC analysis revealed that the area with the highest incidence of “senders” was LIP and the area with the highest incidence of “receivers” was dPFC.

Interestingly, the relative phase of fronto-parietal coherence was lead by PFC; indicating that the relative phase is potentially not a good interpretation of directional influences. Furthermore, we investigated the relationship between multi- and single-unit activity in PPC that is identity selective and SFC ($PPC_{unit}-PFC_{lfp}$). We found that recording sites with and without identity selectivity had significant SFC. However, the majority of the significant SFC pairs involving identity selective units come from cells recorded in areas LIP, PG and to a lesser extent MIP. Indicating that there is some specificity of the areas involved in fronto-parietal interactions.

In chapter 3, we find 1) a general increase in the magnitude of correlation from the pre-sample to the delay period, 2) that the relative phase angles of both intra-parietal and fronto-parietal signals are largely separated into two categories: near 0° and near 180° , and 3) that the relative phase between signals may shift dramatically during the ITI.

Within PFC, an increase in correlation from the pre-sample period to the delay period was primarily seen. Particularly, areal combinations 8B - 8B/8AD/dPFC, were highly significant. Fronto-parietal correlations also increased, predominantly with PFC areas 8B and dPFC. Significant increases between 8B and PPC areas were primarily observed with lateral PPC areas, while dPFC correlations typically increased with both medial and lateral PPC areas. Within PPC correlations displayed a distinct pattern of changes: areas separated by the IPS tended to decrease and areas on the same bank tended to increase. Furthermore, a finer grained analysis, of correlation during the delay period, revealed a fall off of correlation magnitude as a function of distance for electrode separations less than 6 mm. Thus, the magnitude of correlation decreases with distance

within and between adjacent areas of the PFC and PPC while both the incidence and magnitude of correlation plateau to lower levels over distances that span widely separated areas of the cortex.

The relative phase analysis revealed that within PFC, the correlations among signals are dominated by in-phase relationships. Within PPC, signal pairs recorded on either the medial or the lateral bank of the IPS are also predominantly in-phase. In contrast, the long distance correlations, measured between signals recorded in the medial and lateral banks of the IPS and between these areas and the PFC exhibit a clear bimodal distribution of phase values. Furthermore, signal pairs recorded on opposite sides of the IPS are predominantly anti-phase.

Finally, we demonstrate a re-organization of these networks during the ITI. First, we tested whether changes in the correlation magnitude increased or decreased between the delay period and the ITI period. This analysis revealed a large degree of modulation in correlation strength, similar to the changes observed in the previous comparison between the pre-sample and the delay period. However, unlike the bi-directional changes from the previous comparison, the correlations in this analysis all typically increase. Moreover, the degree to which the relative phase changes also differed dramatically from the previous comparison. Between the pre-sample period and the delay period the relative phase angles often shifted, but only up to $\sim 45^\circ$. The phase shifts between the delay period and the ITI are much more drastic, including 180° flips. These large changes were predominately between PFC and PPC areas and the PPC areas on opposite sides of the IPS.

In chapter 4, demonstrate 1) the distributed nature of working memory, by showing widespread task and stimulus related spiking activity, 2) evidence for a large-scale beta network, 3) a general, hemisphere-wide, increase in correlation from the pre-sample to the delay, and 4) that the distribution of relative phase angles are bi-modal and re-organized during the ITI.

An analysis of the task- and stimulus-dependent changes in the firing rate reveal widespread activity changes. Signals from V1 to PFC show task dependent changes in firing rate. Moreover, stimulus specific changes in firing rate are also distributed across the cortex. Further analysis is necessary to determine the contribution of individual areas. Nonetheless, these activity patterns provide an unprecedented look at the large-scale spiking patterns during visual working memory. Next, a coherence analysis was used to illustrate the distributed nature of working memory. This analysis also revealed the task dependence, by showing an increase in significant signal pairs during the delay period. This was further explored using cross correlation analysis, which demonstrated a general, hemisphere-wide, increase in correlation magnitude from the pre-sample to the delay period. Finally, similar to chapter 3, we determined that the distribution of relative phase angles during the delay, across all recordings, was bi-modal with concentrations near 0° and 180° . Also, during the ITI we observed similar 180° flips, and large shifts in the relative phase.

Oscillatory Synchronization Revisited

There have been several roles suggested for the utility of oscillatory synchronization. Very broadly, oscillatory synchronization has been suggested to bind information in large-scale spatiotemporal patterns (see Singer & Gray, 1995; Gray, 1999) and more recently it has been formalized as a routing mechanism (Fries et. al., 2005). This description is far from exhaustive, but it provides some general themes that are useful for discussion. In Chapter 2, we demonstrate that the patterning of oscillatory synchronization contains information about the item in working memory. This result suggests that many ideas, going back to original ideas of cell assemblies (Hebb, 1949; Milner, 1974; Braitenberg, 1978; Edelman & Mountcastle, 1978; von der Malsburg & Willshaw, 1981; von der Malsburg, 1985), are a potential candidate for the utility of oscillatory synchronization. These patterns of co-activated, synchronized, neural populations may provide the neural correlates of cognition and behavior. Furthermore, the malleability of the relative phase relationship, discussed in Chapters 2 and 3, indicate that a more complex relationship exists between cortical areas than those proposed by a simple routing scheme. In general though, these results are likely just the tip of the iceberg, and there is still much more information to be gathered before any solid conclusions can be made.

Discussion of the Relative Phase

In Chapters 3 and 4, we demonstrate that the distribution of relative phase angles across the cortex is largely bimodal. However, this is not the first time that long-range LFP coherence with relative phase angles near 180° has been observed; it is, however, the first to our knowledge that shows both near 0° and near 180° relative phase angles, simultaneously. In a study of visual attention in monkeys, signals in FEF and V4 were synchronized in the gamma frequency range (40 - 60 Hz) with relative phase angles near 180° (Gregoriou et. al., 2009). Beta and alpha coherence were also observed with similar time lags. In this study, the phase difference was taken to be the relevant amount of time for spikes from one area to arrive during the trough of the target areas LFP, and was supported by multiple frequencies maintaining comparable absolute time lags. Similar conclusions have been made between PFC and V4 coherence in the theta frequency range (3-9 Hz) (Liebe et. al., 2012) and between AIP and IT in the beta frequency range (17 - 25 Hz) (Verhoef et. al. 2011). This conclusion assumes that the synaptic delay dictates the relative phase between LFPs and that the LFP-LFP timing relationships dictate - or are at least sufficient to predict - the spike-LFP timing relationships. Our results suggest that a basic timing relationship between areas does not exist in the LFPs. We see small shifts throughout the working memory task and large, even 180° , flips during the ITI. An alternative explanation, is that these LFP phase relationships are acting in a brain-wide network, where the local activity observed in the LFP is subject to varying degrees of segregation and integration with the it's local and long-distance connections.

Coordination Dynamics Revisited

In Chapter 1, the principles considered in coordination dynamics, including metastability and self-organization, were suggested to provide a framework for studying spatiotemporal dynamics (Kelso, 1995; Bressler & Kelso, 2001; Kelso & Tognoli, 2009; Kelso, 2012). While there are several investigators highly interested in the non-linear dynamics of the brain (Friston, 1997; Fingelkurts & Fingelkurts, 2004; Freeman & Holmes, 2005), the work by Kelso and colleagues provides the potential for understanding certain components of the spatiotemporal patterns we have observed; specifically, the flips in relative phase that occur during the ITI (see Chapters 3 and 4). Work by Kelso and colleagues (Haken et. al., 1985; Schoner & Kelso, 1988; Kelso, 1995) on inter-limb coordination lead to the development and extension of a mathematical model, called the HKB equation (Haken et. al., 1985), to quantify transitions in the relative phase relationship between two weakly, and non-linearly coupled, non-linear oscillators. A phenomenon they liken to phase transitions in non-equilibrium physical and chemical systems - which exhibit self-organized behavior. Schoner and Kelso (1988) provide a highlight of this work, in which they describe the underlying dynamics of coordinated finger movements. The original experiment required human subjects to oscillate their index fingers from left to right. Subjects were asked to maintain an anti-phase relationship at a specific frequency. The frequency was then slowly increased, either by the subject or an auditory cue. At a certain frequency a spontaneous transition from anti-phase to in-phase would occur. In order to capture these dynamics, they define the relationship between finger movements by the relative phase,

which they refer to as the “collective variable”. Now, using the HKB equation, they are able to model the phase transition as a function of frequency, which they term the “control parameter” (see Bressler & Kelso (2001) for a review). We demonstrate in chapters 3 and 4 that inter-areal phase relationships have a tendency to follow some of these dynamics. Including in- and anti-phase relationships and flips between the two. Furthermore, it is noted in that the phase flips we observe are associated with a change in frequency of correlation, providing further evidence that these same principles might be at play between cortical areas. Concepts, such as metastability, become relevant when one considers the properties of coherence and anatomical distance between areas. Typically, the phase flips we observe occur between long-range signal pairs, which have very weak anatomical connectivity, and display intermittent coherence. This combination of weak anatomical connectivity and intermittency leads to metastable dynamics, and is thought to reflect the tendency for both integration and segregation (Kelso & Tognoli, 2009). Much work is still needed to accurately capture these dynamics, but the concepts described above appear to be a good candidate.

Concluding Remarks

In Chapter 1, the large-scale nature of visual working memory was illuminated. Task- and stimulus-dependent activity was cited from V1 to PFC, with numerous mechanistic underpinnings. Provided that the brain does not work in a serial manner - like a computer - with specific areas each playing a specific role (storage, maintenance, retrieval, etc.), then a mechanism must be in place to allow for distributed areas, operating as a whole, to integrate information and generate an appropriate response. The results of the studies presented in Chapters 2-4 provide extensive evidence that oscillatory synchronization is a mechanism for distributed integration. We show that the patterns of coherent activity 1) encode working memory items, 2) are indicative of the task period, 3) provide the potential for multiple functional networks, defined by the relative phase and, 4) are highly dynamic, with large fluctuations in magnitude and relative phase. Future studies will be necessary to further investigate the role of oscillatory synchronization. Efforts to perturb oscillatory activity in order to illustrate its utility, rather than simply correlating its activity with stimulus and task components, will be crucial. Finally, efforts must be made to quantify the underlying dynamics of cortico-cortical integration. It is only after we have an accurate description of the dynamical nature of the brain that we will have any hope at understanding cognition.

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