Neural Mechanisms of Sensory Integration: Frequency Domain Analysis of Spike and Field Potential Activity During Arm Position Maintenance with and Without Visual

Feedback

By

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#### ABSTRACT

Understanding where our bodies are in space is imperative for motor control, particularly for actions such as goal-directed reaching. Multisensory integration is crucial for reducing uncertainty in arm position estimates. This dissertation examines time and frequency-domain correlates of visual-proprioceptive integration during an arm-position maintenance task. Neural recordings were obtained from two different cortical areas as non-human primates performed a center-out reaching task in a virtual reality environment. Following a reach, animals maintained the end-point position of their arm under unimodal (proprioception only) and bimodal (proprioception and vision) conditions. In both areas, time domain and multi-taper spectral analysis methods were used to quantify changes in the spiking, local field potential (LFP), and spike-field coherence during arm-position maintenance.

In both areas, individual neurons were classified based on the spectrum of their spiking patterns. A large proportion of cells in the SPL that exhibited sensory condition-specific oscillatory spiking in the beta (13-30Hz) frequency band. Cells in the IPL typically had a more diverse mix of oscillatory and refractory spiking patterns during the task in response to changing sensory condition. Contrary to the assumptions made in many modelling studies, none of the cells exhibited Poisson-spiking statistics in SPL or IPL.

Evoked LFPs in both areas exhibited greater effects of target location than visual condition, though the evoked responses in the preferred reach direction were generally suppressed in the bimodal condition relative to the unimodal condition. Significant effects of target location on evoked responses were observed during the movement period of the task well.

In the frequency domain, LFP power in both cortical areas was enhanced in the beta band during the position estimation epoch of the task, indicating that LFP beta oscillations may be important for maintaining the ongoing state. This was particularly evident at the population level, with clear increase in alpha and beta power. Differences in spectral power between conditions also became apparent at the population level, with power during bimodal trials being suppressed relative to unimodal. The spike-field coherence showed confounding results in both the SPL and IPL, with no clear correlation between incidence of beta oscillations and significant beta coherence.

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#### **CHAPTER 1 INTRODUCTION**

### Overview

Moving and interacting with our environment is a fundamental part of daily life that is often taken for granted, but it is a product of complex interaction between the sensory and motor systems. Every volitional movement involves sensing, planning, and executionrelated neural processes that, while seemingly sequential in nature, are continuously influencing each other throughout the course of movement. Something as simple as reaching for a glass of water involves understanding where the glass is located, where our arm is located in space relative to the glass, and computing the motor commands needed to accurately reach for it. One movement is initiated, the location of the arm must be continuously updated to account for unanticipated changes in arm or target location. It is therefore essential for the motor system to have an accurate 'arm state estimate' - or information about the position and velocity of the arm in space - in order to both initiate and successfully execute reaches. This state estimate is generally thought to comprise sensory information from vision and proprioception, as well as predictions derived from ongoing motor commands and an internal model of the arm. Inherent noise in sensorimotor processes arising from network and cellular mechanisms (Faisal et al., 2008) can impact the reliability of these state estimates, resulting in neural or behavioral variability. In order to overcome this uncertainty, there is a growing body of evidence from behavioral and modeling studies that suggests the brain may employ a strategy of combing sensory information from multiple feedback streams in a process known as multimodal integration, wherein the combined feedback improves the accuracy and reliability of arm state estimates (Angelaki et al., 2009).

Traditionally, neural correlates of multimodal (or multisensory) integration have been assessed using approaches that looked at changes in mean firing rates of neurons during presentations of uni- and multisensory stimuli. These studies have described enhancement or suppression of spike rates during multimodal stimulation of single cells, both subcortically (Stein and Meredith, 1993; Wallace and Stein, 1997; Jiang et al., 2001) and in higher-order sensory association areas in non-human primates (NHP) (Avillac et al., 2007; Morgan et al., 2008; McGuire and Sabes, 2011; Shi et al., 2013). Recent evidence indicates that multimodal integration can manifest in the brain through other mechanisms as well. Changes in spike timing or variability (Koehler et al., 2011; Shi et al., 2013; Chabrol et al., 2015; VanGilder et al., 2016) and spike synchrony (Engel et al., 2001a; Sarko et al., 2013) have been observed in response to multisensory stimuli. Larger network responses to multisensory tasks have shown that certain frequency bands in LFPs (Belitski et al., 2010; Sarko et al., 2013) and EEG signals (Engel et al., 2007; Womelsdorf et al., 2007) play a role in multisensory processing, and coherent oscillations have been implicated as means of communication between sensory and motor areas during visual feature linking (Eckhorn et al., 1988), fixation and movement planning (Stetson and Andersen, 2014), and maintaining the current sensorimotor state (Engel and Fries, 2010).(Eckhorn et al., 1988; Engel and Fries, 2010; Stetson and Andersen, 2014).

It has become clear that multisensory interactions cannot be explained solely by changes in the firing rate, especially for behaviors such as reaching that involve multiple cognitive, motor, and sensory ensembles across cortical areas. This dissertation is focused on how the brain computes state estimates of the arm for reaching movements and the neural correlates of this process that extend beyond measures of firing rate. To this end, several analyses were conducted to examine how visuo-proprioceptive interactions may modulate spike train dynamics, and how these changes could be reflected in LFP activity and spike-field interactions.

The first set of analyses focused on changes in spike train dynamics between unimodal and bimodal feedback conditions during an arm position maintenance task. The overarching hypothesis behind this study is that changes in spike timing and variability, expressed as enhanced spectral power in the beta band, are a mechanism underlying multimodal integration in parietal cortex. Spectral analysis techniques were used to identify neural populations in the superior and inferior parietal lobules (SPL/IPL) of NHPs that exhibit changes in temporal spiking regularity in response to changes in visual and proprioceptive feedback about arm position.

The second set of analyses quantified changes in local field potential (LFP) activity during the same task and conditions. LFPs represent the pooled synaptic activity of a small population of neurons, and therefore spiking and LFP activity can mutually influence each other. Changes in individual unit spike timing could be reflected in the LFP response, though LFP oscillations could influence the spiking activity. Enhanced power in the 13-30Hz band, indicating beta oscillations, has been proposed as a mechanism to synchronize functional cortical networks during multimodal integration or a mechanism of modulating the spike timing. To assess these hypotheses, spectral analysis techniques were used to measure changes in the spectral power of LFPs in the SPL and IPL of NHPs in response to changes in visual and proprioceptive feedback about arm position.

The final set of analyses focused on changes in spike-field measures due to changes in sensory feedback conditions. Intuitively speaking, complimentary changes in spike timing and the LFP oscillatory activity could have interactive effects. To explore this hypothesis, spike-field coherence measures were used to characterize the temporal coordination of action potentials with LFP activity in the two parietal areas during the task.

This dissertation comprises six chapters. This chapter (Chapter 1) provides a brief introduction and motivation for the work. Chapter 2 will outline important background information and previous work that forms the conceptual foundation of this inquiry. Chapter 3 describes the materials and methods used throughout the studies, including hardware and software, experimental subjects and paradigms, and analytical approaches. Chapter 4 focuses on the spiking responses within the SPL and IPL. A large portion of Chapter 4 has been adapted from a previously published journal paper (VanGilder et al., 2016), with additional experimental results and modifications to improve readability and context. Chapter 5 discusses the LFP responses for both cortical areas as well as spike-field coherence measures. For each of these chapters, additional background and methodology information specific to the given topic will be provided in addition to the experimental results and discussion. The final chapter serves to unify the three analyses through a cohesive discussion about neural responses to visuo-proprioceptive interactions during arm-position estimation.

#### **CHAPTER 2 BACKGROUND**

Every volitional movement is the product of interaction between the sensory and motor systems. A prevailing theoretical framework proposes that the central nervous system uses an efference copy of motor commands and a learned internal model of the dynamic behavior of the motor system to create predictions about the state of the system (Miall and Wolpert, 1996). The predictions derived from the internal model are then combined with sensory feedback to create a more robust state estimate. This chapter reviews what is known about the sensory component of the state estimate during reaching movements. Sensory feedback, provided through visual and proprioceptive cues, are combined to form a unified sense of arm position in a process known as multimodal integration. This phenomenon is important not only for understanding how the sensorimotor system functions, but also for applications such as neural prosthetics, sensory substitution, and rehabilitation.

### **Multimodal Integration and State Estimation**

The human body is equipped with an array of sensors that are constantly providing information about the outside world and the body's place within it. Vision, audition, and touch are just some of the modalities that are being continuously processed and analyzed in order to create perceptual estimates of the environment. The brain also uses information from a variety of sensory cues within and across modalities to form estimates about the body. Through a process known as multimodal integration, sensory cues are combined to form unified, robust percepts that can be used for movement planning, interacting with the environment, or just observing our surroundings. Combining multiple cues in this manner can reduce perceptual ambiguities (e.g. self-motion vs. other-motion) and strengthen the reliability of these estimates across different contexts and conditions (Ernst and Bülthoff, 2004).

There is a large and growing body of work examining how the brain combines different cues ('cue integration') across a variety of behaviors and sensory conditions to reduce the overall variability in sensory estimates. One construct used in studies of perception and multimodal integration is the 'ideal observer' framework. In this framework, researchers aim to understand computational strategies for combining cues in a way that is 'optimal' within a given situation (Landy et al., 2011). Thus, 'optimal cue integration', predicts that the optimal estimate of the current state is calculated from individual sensory estimates that are weighted according to their relative reliability, or the inverse of variance (van Beers, 1999; Ernst and Banks, 2002; Ernst and Bülthoff, 2004; Tassinari et al., 2006; Angelaki et al., 2009; Fetsch et al., 2013). How the brain weights different sensory cues can be highly dependent on a number of factors, including the sensorimotor context, stage of movement planning, or even a priori probability distributions of previous sensory states (Sober and Sabes, 2003; Scheidt, Robert A, Conditt, Michael A, Secco, Emanuele L, Mussa-Ivaldi, 2005; Körding and Wolpert, 2006; Sabes, 2011). The reliability of different sensory cues can also be affected by noise within the

sensory system, which has been shown to produce errors in position and velocity estimates that manifest in behavioral variability (Faisal et al., 2008).

These principles can and have been tested in behavioral studies. Different sensory modalities are experimentally given stimuli that can be independently manipulated, often producing conflicting or mixed perceptual estimates. Using a Bayesian statistics framework, uncertain sensory information from multiple cues can be combined in a manner that takes into account the probability of the individual cues being "true." In this model sensory cues are averaged with the most reliable being given more weight, forming an optimal perceptual estimate. This Bayesian model of sensory integration has been shown through a variety of psychophysics tasks involving visual and haptic cues (Ernst and Banks, 2002) and visual and auditory cues (Körding et al., 2007). Of particular relevance to this dissertation is work demonstrating visual and proprioceptive cue weighting during reaching tasks (van Beers, 1999; Sober and Sabes, 2005).

#### **Forward Models**

It is important to understand how sensory information is used within the overall context of reaching movements. A reliable sense of hand and arm position is imperative for not only the initial planning stage of reaches toward a target, but also for corrections of the ongoing movement. It is these online motor corrections that make reaching movements unique from static multisensory integration situations involving the arm. The dynamic nature of reaching movements means state estimates of the arm involve time-varying computations. "Motor cues," internal signals analogous to sensory cues but arising from efferent copies of the motor commands, can be combined with sensory information to

create more accurate state estimates. As stated above, a prevailing theoretical framework proposes that the central nervous system uses a learned internal model of motor dynamics to create predictions about the state of the system using efference copy, or corollary discharge, of motor commands (Wolpert, 1995; Miall and Wolpert, 1996). Figure 2.1 outlines how this process works.



#### Figure 2.1 Flow diagram of the computations involved in visually guided reaching.

Similar to the framework for sensory cue integration, dynamic state estimation using a forward model can be considered within the context of Bayesian statistics as well. In this scenario, the previous state estimate or 'prior' and the efferent motor command are used as inputs to the forward model to estimate the next state. This simulated, or feedforward predictive state estimate is then combined with sensory feedback in a Bayesian manner to form a more accurate state estimate (Wolpert, 2007; Shadmehr and Krakauer, 2008; Franklin and Wolpert, 2011). This scheme is analogous to a Kalman filter, a common recursive Bayesian algorithm used across a wide range of technical applications such as control theory, signal processing, and economics (Kalman, 1960). The forward model has become an integral part of theoretical work regarding motor control, as it addresses several computational problems. In addition to state estimation, a forward model explains how the CNS can anticipate and cancel the sensory effects of movements (e.g., which explains why you are unable to tickle yourself) and provides a mechanism to facilitate motor learning (Wolpert, 1995). Forward models also overcome inherent sensory feedback delays that would otherwise preclude stable control of movements (Franklin and Wolpert, 2011). These computational and theoretical advantages of the forward model are predicated upon accurate sensory feedback of the arm for the motor learning needed to generate the model – sensory information about arm endpoint must be associated with the motor commands that moved it there. Despite theoretical and behavioral evidence for the forward model, neurophysiological evidence is sparse. The involvement of both sensory and motor processing in this theoretical framework support the idea that neural correlates for this process may occur at the functional interface of these representations in the brain. Thus, studies have focused largely on cortical association areas such as the parietal and premotor cortices.

#### **Anatomical Areas of Sensorimotor Processing**

In the case of arm position, cortical areas responsible for calculating state estimates would need to process visual and proprioceptive sensory feedback, as well as motor signals in the form of efferent copy. One prime area of interest that meets these criteria is the Posterior Parietal Cortex (PPC), considered a cortical association area. Located between the visual cortex in the occipital lobe and the somatosensory cortex in the postcentral gyrus, it is ideally positioned to receive both visual and somatosensory signals and send information to the motor and premotor cortices (Mountcastle et al., 1975; Georgopoulos et al., 1984; Andersen, 1987; Andersen et al., 1997; Wise et al., 1997; Culham et al., 2006). In non-human primates, the prominent intraparietal sulcus (IPS) divides the PPC into the Superior and Inferior Parietal Lobules (S/IPL).

Neurophysiology studies in non-human primates have found that various divisions around the IPS are involved in multimodal sensory processing. The different subregions of the PPC have been linked to movement planning related to specific body parts or combinations of body parts, such as the lateral intraparietal area (LIP) for eye movements (Andersen, 1989; Bremmer et al., 1997), ventral intraparietal area (VIP) for vestibular coding of movement heading (Wise et al., 1997; Bremmer et al., 2002a), the 'parietal reach region' (PRR) and area 5 for arm movements (Batista et al., 1999; Buneo and Andersen, 2006), and the anterior intraparietal (AIP) for grasping and manipulation (Culham et al., 2006). Subregions of the IPL, such as 7a (posterior IPL) and 7b (anterior IPL), have been implicated in visual and somatosensory tasks, respectively (Andersen et al., 1990).

Much of the initial basis for neurophysiological investigations was based on observations of humans and primates with PPC lesions. Such lesions can result in optic ataxia, characterized by poor control over visually guided reaching, apraxia, characterized by deficits in motor planning, hemispatial neglect, characterized by deficient contralateral spatial awareness, as well as other disorders (Caminiti et al., 1996; Andersen and Buneo, 2002). Conclusions about functional localization drawn from lesions studies are stronger when a double dissociation can be shown (Shadmehr and Krakauer, 2008). For example, cortical lesions to a particular cortical area may cause sensorimotor deficits in one task, while normal functioning persists in another. To demonstrate a double dissociation, lesions to different cortical areas should have opposing sensorimotor outcomes. For example, Rushworth et al. (1997) conducted lesion experiments in monkeys during reaching tasks and found that proprioceptively-guided reaches were not affected by IPL lesions, but were inaccurate in monkeys with SPL lesions. In another study, subjects with isolated IPL lesions were contrasted with subjects with IPL and inferior frontal lobe (IFL) lesions. Using both IFL and normal elderly subjects as control, the researchers demonstrated that IPL lesions cause both perceptual and motor deficits in spatial representations, suggesting the IPL acts a sensorimotor interface rather than exclusively a sensory area (Mattingly et al., 2004).

Neurophysiological recordings support observations from lesions studies that the PPC is involved in the formation of multimodal spatial representations that support reach planning. The PPC is a central node in the "dorsal stream" of visual processing – a pathway thought to involved in processing the spatial characteristics of a visual scene, information that is essential for visuomotor behaviors, including reaching. There are a number of areas of PPC that respond specifically to different aspects of reach-related planning of movements. Neurons in the medial intraparietal area (MIP) (Johnson et al., 1996; Rushworth et al., 1997; Andersen and Buneo, 2002) areas 7a and 7b (Andersen, 1987; MacKay, 1992; Battaglia-Mayer et al., 2000) and area 5 (Kalaska et al., 1997; Ferraina et

al., 2001; Shi et al., 2013) reflect both sensory and motor parameters of upcoming reaches. Another area, defined more functionally than anatomically, is the Parietal Reach Region (PRR) that includes parts of MIP and V6a (Batista and Andersen, 2001; Andersen and Buneo, 2002; Buneo et al., 2002). Figure 2.2 shows the relative locations of these parietal areas in macaque cortex.



Figure 2.2 Lateral view of the rhesus monkey brain showing cortical areas implicated in visuomotor processes related to reaching.

For this dissertation, neurophysiological recordings were made during an arm positioning task involving visual and proprioceptive cues, and focused on areas thought to be functionally relevant in both the SPL and IPL, i.e. areas 5 and 7. Previous neurophysiology studies have identified neurons whose responses are modulated during

active static position of the arm across the IPS, including area 5 (Lacquaniti et al., 1995; Caminiti et al., 1996; Buneo et al., 2002; Shi et al., 2013). One of the first direct investigations into the roles of visual and proprioceptive cues in the coding of arm position was performed by Graziano and colleagues (2000). A small but statistically significant number of neurons' responses were found to be modulated by visuo-proprioceptive cues, providing some evidence that area 5 may be involved in multimodal integration for the It should be noted though that this experimental paradigm involved passive arm. movement of the arm, so efference copy signals of the motor commands were not addressed. Other studies have indirectly probed the role of area 5 in multimodal representations of arm position. One such study showed that hand position was encoded relative to eye position, even in the absence of vision of the hand. This is an indication of a coordinate transformation of arm position from body- (somatic) to eve-centered coordinates (Buneo and Andersen, 2006; Buneo et al., 2011) – a computation that would require access to both proprioceptive and visual sensory information.

There have not been any direct examinations into the roles of visual and proprioceptive cues in arm position coding in area 7, but this area has been implicated more generally in visuomotor tasks (Andersen et al., 1987; Barash et al., 1991; Bremmer et al., 1997). There is a much larger body of anatomical evidence supporting visual and somatosensory interactions in area 7 of the IPL. Area 7a (caudal) has many reciprocal connections to vision related multisensory areas, e.g., the superior temporal polysensory area (STP), area V2, and the parieto-occipital area (PO). Area 7b, in addition to

connections to vision related areas, has interconnections with somatosensory areas, as well as area 5 (Cavada and Goldman-Rakic, 1989).

Through more recent anatomical studies, 7a and 7b have been further subdivided based on cytoarchitectonic structure and corticocortical connections. Rozzi et al. (2006) found 4 subdivisions with distinct connectivity divisions - Opt, PG, PFG, and PF (from rostral to caudal). Areas OPT and PG, in caudal area of the IPL, are both connected within the dorsal stream visual pathway, while PG is also a target of somatosensory areas. The anatomical connections of area Opt are consistent with neurophysiological findings by Andersen et. al. (1997) that area 7a neurons are involved in processing visual optic flow and representations of space in body-, head-, or world-centered coordinates (Rozzi et al., 2006, 2008). There are tightly linked lateral reciprocal connections between area Opt and area PG in the IPL. PG connections are largely with AIP, MIP, V6A – areas involved in visual and somatosensory guidance of arm movements (Johnson et al., 1996; Andersen et al., 1997; Rushworth et al., 1997; Wise et al., 1997; Rozzi et al., 2006). This points to a convergence of connections in PG-Opt of sensory information related to eye- and armrelated motor signals. PF is primarily connected with arm-related somatosensory areas, and its strong lateral connections with PFG, which receives input from temporal visual areas, suggest these areas may be involved in somatomotor transformations in the guidance of goal directed movements. All four areas show a high degree of connectivity with other areas of PPC, particularly MIP and area 5 (Rozzi et al., 2006). Neurophysiological investigation using multi- and single unit recording of neurons across PF, PFG, and PG found sensory and motor responses to visual and somatosensory information that were generally somatotopically organized. All three areas showed responses to somatosensory, visual, and motor stimuli to some degree, with a transition from somatomotor to visuomotor being the dominant responses observed as you move from rostral to caudal. Regarding possible representations of arm position, passive movement of the arm by the experimenters while the monkey's eyes were opened and closed suggest proprioception is minimally represented as well, with a small number of neurons responding to joint position across the three areas (Rozzi et al., 2008). The recordings were mostly exploratory in nature and not task specific, where neural activity was recorded during a variety of naturalistic behaviors and passive arm manipulations by the researchers.

The results of anatomical, neurophysiological, and lesion studies point to the PPC as an interface between sensory and motor areas of the brain (Buneo and Andersen, 2006; Mulliken and Andersen, 2009). More specifically, due to its downstream connections to motor and premotor areas, as well as its role in reach planning, some researchers have proposed that one role of the PPC is state estimation, i.e. integration of predictions from a forward model with visual and proprioceptive feedback (Wolpert et al., 1998; Buneo and Andersen, 2006; Mulliken et al., 2008; Shadmehr and Krakauer, 2008). In further support of this idea, TMS studies have shown that disruptions of PPC activity can impair subjects' ability to use anticipatory mechanisms, such as efference copy of motor signals in a forward model, to detect time differences in real and virtual hand position, relying instead solely on visual feedback (MacDonald and Paus, 2003). In another related study, Desmurget and Colleagues (1999) used TMS to disrupt subject's ability to correct movement trajectories

that were altered at the time of movement onset -a key piece of experimental evidence for the existence of forward models.

Despite differences in size and greater anatomical complexity, the human PPC is largely homologous to that of the macaque. Functional magnetic resonance imaging (fMRI) studies show that there is clear parallel functional organization of cortex around the IPS in humans and monkeys (Grefkes and Fink, 2005). Human fMRI studies focused on the IPS, particularly visual areas of PPC, suggest this area is involved in motor planning, spatial representations and coordinate transformations (Orban et al., 2006). fMRI studies have found areas of the human brain analogous to the PRR of NHP cortex (Connolly et al., 2003; Parkinson et al., 2010). Other studies using fMRI to investigate brain regions in humans involved in reaching or maintaining postural representations of the upper arm found enhanced BOLD response in the SPL of the PPC (Pellijeff et al., 2006; Parkinson et al., 2010; Medendorp et al., 2011). These physiological parallels are important for adapting our understanding of sensory guided reaching to development of neuroprosthetic devices, brain-computer interfaces, and improved neuro-rehabilitation methods and protocols.

The results of these anatomical and physiological studies paint a picture of the PPC as a central hub where sensory inputs converge to be integrated before being further processing in the downstream motor areas. The large interconnectivity of different areas of parietal cortex may mean that even areas classically considered to be unimodal may actually appear multimodal within certain contexts. Visual and somatosensory responsive areas are distributed across both the SPL and IPL, making possible multiple representations of extra-personal space and state estimates. Experimental results seem to imply that there

may not be clear divisions between functional areas, but instead support the idea of a distributed network of neural populations with different response characteristics based on available sensory information and task context. But what might these responses look like?

#### **Correlates of Multisensory Integration: Single Unit and Neural Oscillations**

As mentioned above, neural correlates of cue integration have previously been examined using electrophysiology methods. Classical studies of the subcortical superior colliculus by Stein and colleagues have demonstrated that integration of visual, auditory, and/or somatosensory inputs at the single cell level follow several empirical principles, namely spatial and temporal congruency and inverse effectiveness (Stein and Stanford, 2008). The basis for these principles are the enhancement and suppression of firing rates that have been observed in response to multisensory stimuli. Spatial and temporal congruency posit that firing rates can be enhanced or suppressed depending on the relative presentation of two or more stimuli in space and time. Inverse effectiveness is refers to the observation that the effects of multisensory integration are stronger for weak responses unimodal stimuli than for strong stimuli and can be super or subadditive, i.e., responses to multimodal stimuli can be greater (or smaller) than the sum of unimodal responses. Modelling studies have demonstrated that these principles are consistent with network models of optimal cue integration (Ma et al., 2006).

Enhancement and suppression of spiking during multimodal integration have been demonstrated in cortical areas as well (Graziano et al., 2000; Zhou and Fuster, 2000; Bremmer et al., 2002a; Ghazanfar and Schroeder, 2006; Sugihara et al., 2006; Ogawa et al., 2007; Shi et al., 2013). In a particularly elegant study, Angelaki and colleagues found

that responses of neurons in the dorsal medial superior temporal area to multimodal stimuli varied in a linear or subadditive manner based on the relative reliabilities of the unimodal sensory cues (Morgan et al., 2008). This physiological evidence coincides well with human behavioral studies that suggest a Bayesian model for cue integration (Ernst and Banks, 2002; Battaglia et al., 2003; Alais and Burr, 2004). In addition, a computational model by Ma and colleagues showed that Poisson-like variability in neural responses made Bayes-optimal calculations possible through simple linear summation of activity within the population (Ma et al., 2006). Though this could be a potential mechanism underlying multisensory integration in certain cortical regions, it is becoming increasingly clear that the Poisson assumption does not hold for all areas of cortex (Amarasingham, 2006; Maimon and Assad, 2009) and that more complex oscillatory, bursty, or refractory spiking patterns can be observed under certain task conditions (Buneo et al., 2003; Compte et al., 2003; Joelving et al., 2007). Thus it is not clear how to resolve the Bayesian model of integration for multimodal areas exhibiting non-Poisson spike trains.

The highly regular nature of oscillatory spike trains raises questions about the importance of spike timing, as opposed to spike rate, for encoding multimodal information. Several recent studies suggest that changes in spike train dynamics in response to multimodal stimuli could be indicative of a temporal code underlying sensory integration. A recent study of the mouse vestibulocerebellum found evidence of a mechanism for encoding coincident multisensory inputs by the timing of spike responses (Chabrol et al., 2015). Multisensory pyramidal cells in the dorsal cochlear nucleus of the guinea pig have characteristic spike timing patterns in response to auditory stimuli that are

altered during integration of somatosensory information (Koehler et al., 2011). In NHPs, it has been demonstrated that during arm position maintenance in 3D space, spike train variability is reduced in bimodal (proprioception and vision) trials relative to the unimodal (proprioception) trials (Shi et al., 2013). Similarly, in a study of audio-visual integration, it was found that spike trains clearly displayed temporal modulation during multimodal trials, and the responses to weak and strong stimuli followed the principle of inverse effectiveness. Visual stimuli also influenced the reliability of the spike trains, eliciting responses with less variability than would be expected from a Poisson model of firing (Belitski et al., 2010).

Oscillations and synchrony in cortex have been proposed as means for regulating and coordinating spike timing into a temporal code. These oscillatory changes can be observed in changes in spectral power and in phase coherence within or across neural populations, and have been noted in primary motor and sensory areas, as well as higher order association areas such as parietal and prefrontal cortex, indicating that this may be a widespread phenomenon (Engel et al., 2001a; Womelsdorf et al., 2007; Senkowski et al., 2008; Engel and Fries, 2010; Buzsaki and Draguhn, 2014). Synchronized oscillations are implicated in a variety of cognitive and sensorimotor functions, including feature binding, perceptual stimulus selection, attention, and movement preparation (Pöppel et al., 1990; von Stein et al., 1999; Compte et al., 2003; Engel et al., 2007; Engel and Fries, 2010). Following the convention of EEG studies, the spectrum is typically broken up into delta (0-6Hz), alpha (~8-12Hz), beta (~13-30Hz) and gamma (~30-100Hz) frequency bands. Though it is still unresolved if the different frequency bands subserve distinct

functional roles in cognitive, sensory, and motor processing, it is well established that oscillations reflect synchronized changes in neural population activity. Beta band oscillations, which are relatively unexplored relative to gamma, delta, and alpha, have recently been proposed as a mechanism of linking functionally-related neural ensembles together during the processing of multimodal information relevant for motor performance. Brovelli et al. examined the role of beta oscillations in a large scale sensorimotor network during a motor maintenance task, and found beta band synchronization across several cortical areas (Brovelli et al., 2004a). Another study found a correlation between evoked beta activity (oscillatory activity phase-locked to stimulus onset) and decreased reaction times during multisensory audio-visual trials. Higher amplitude beta activity correlated with lower reaction times in areas of multisensory convergence, implicating beta activity in multisensory processing of behaviorally relevant stimuli (Senkowski et al., 2006). Another EEG study of audio-visual integration showed increased beta band coherence between the temporal and parietal cortices during multisensory trials (von Stein et al., 1999). beta band activity has also been exploited for decoding of EEG based brain computer interface applications in sensorimotor areas (Bai et al., 2008).

Of particular relevance to the current study is the hypothesis that beta band activity may underlie what Engel and Fries refer to as a "maintenance of the status quo", i.e. beta activity may be a hallmark of maintaining an existing motor plan (Engel and Fries, 2010). It is proposed that beta band activity is enhanced during periods where sensorimotor or cognitive maintenance is given priority, such as during working memory tasks, instructed delay periods or task periods requiring postural control. This idea is supported by a recent study showing more effective corrective responses in a visuallyguided postural task during periods of enhanced beta activity in motor cortex (Androulidakis et al., 2006). In another study, field potentials from motor cortex were found to have oscillatory activity in the beta band that was coherent with peripheral EMG recordings from contralateral muscles during steady state contractions following movement. This coherence is thought to manifest not just from cortical motor output, but also from feedback from the periphery. More specifically, the phase relationship between motor and peripheral oscillations was less than half the conduction time between the two locations, meaning the coherency could not arise solely from motor output (Baker, 2007). This study also found that muscle spindle and dorsal root ganglion afferent activity from NHPs showed bidirectional (from afferents to muscle and vice versa) coherent oscillations in the beta band, further indicating a possible role for beta oscillations in the processing of proprioceptive information (Baker 2007). These studies suggest that sensorimotor processing may be expressed as oscillatory activity, at present this relationship in parietal cortex remains relatively unexplored.

It is unclear how proprioceptive and visual feedback are integrated in cortical association areas during reaching tasks. Investigation of multisensory integration have primarily focused on auditory, visual, vestibular, or tactile cues, while proprioceptive sense has remained largely unexplored despite direct involvement of parietal cortex during proprioceptively guided movements (Barraclough et al., 2005; Sugihara et al., 2006; Avillac et al., 2007; Gu et al., 2008). A study by Graziano and colleagues found evidence

that visual and somatic signals regarding arm position were integrated in SPL, but their study relied on passive movement of the arm and therefore did not account for motor signals (Graziano et al., 2000). In the present study, which is partly a continuation of work by Shi et al. (2013), NHPs make volitional reaches to targets in 3D space, rendering visual, proprioceptive, and motor signals relevant to the task. In general, investigations of multisensory integration have focused on enhancement or suppression of firing rates, and the relationship between integration and spike timing has gone relatively unexplored. For this study, the focus was on the oscillatory nature of neurons during a multimodal reaching task. The spike spectrum, LFP spectrum, and spike-field coherence were used to quantify neural oscillations during arm position estimation. This approach examined three important aspects: single-cell modulation of spike timing, the local network response, and how changes in spike timing influence the local network.

Based on the previous work mentioned above, the focus was on oscillations in the beta band (13-30Hz). Previous studies that directly examined multisensory integration in the beta band utilized non-invasive EEG or fMRI measures, or didn't directly examine individual sensory contributions. In the present study, single unit and microarray recordings were made during an arm position maintenance task under variable sensory feedback conditions to probe the contribution of beta oscillations during multimodal integration. Of particular significance is the spectral analysis of spike trains during the arm position estimation task. From a comprehensive literature search, it appears this is the first time this analysis has been applied to cortical spiking during a multisensory integration task, visual-proprioceptive or otherwise, to examine changes in spike timing in relation to

multimodal integration. beta oscillations were apparent in distinct neural subpopulations in response to unimodal, bimodal, or both sensory conditions. These oscillations, observed as spectral peaks in spike and LFP power, may serve to synchronize intra-parietal or crosscortical networks for conveying multimodal information.
#### **CHAPTER 3 MATERIALS AND METHODS**

Many studies of multimodal integration are tested using sensory modalities that can be independently manipulated, providing a means for testing optimal cue integration principles. However, visual and proprioceptive cues regarding the position of the arm cannot be presented in isolation – visual feedback of the arm will necessarily be accompanied by somatic feedback. As a result, in this work neural responses were characterized during unimodal (proprioception only) and bimodal (vision and proprioception) trials of a center-out reaching task. Non-human primates (NHP) were trained to make reaches in a virtual reality environment where visual feedback of the arm could be controlled, and the neural responses were recorded using standard neurophysiological techniques. This chapter will outline the general experimental paradigm, recording techniques, and data analysis methods. Methodological approaches relevant to specific data analysis techniques will be addressed in later chapters.

# **Experimental Paradigm**

Two rhesus monkeys (Macaca mulatta) were subjects in the studies that comprise this work. All animal welfare and experimental procedures were conducted according to the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals (Public Law 99-158) and the Guide for the Care and Use of Laboratory Animals (National Academy Press, 1996) and were approved by the Arizona State University Institutional Animal Care and Use Committee. Two different recording methods were utilized, but the same experimental paradigm was used for both. The NHPs (monkey B and monkey X) were trained to make eye and arm movements within a 3D virtual environment. A 3D monitor (Dimension Technologies Inc.) projected the virtual environment onto an angled mirror in the NHP's field of vision. An active LED tracking system (Phoenix Technologies Inc.) monitored arm movements via LED markers placed on the monkey's wrist. The mirror blocked views of the monkey's actual arm, but visual feedback of arm position was provided as a sphere ('arm cursor') within the virtual environment. Eye movements were tracked using a remote optical tracking system (Applied Science Laboratories Inc.). A schematic of this virtual reality setup can be observed in Figure 3.1



Figure 3.1 Experimental apparatus (Shi et al., 2013)

At the start of each trial, the animal had to align the arm cursor with the starting position which was a green sphere presented in the center of the virtual workspace. Once this position had been maintained for 500ms, the starting position was extinguished and one of eight peripheral reach targets (green spheres) was presented and served as the "go" cue to begin the reach. This center-out design ensured that all reaches were made from the

same starting position, minimizing any postural variation across trials that could confound the results. The animal had up to 1400 msec to acquire the target before the trial would abort and a new trial would begin. After the animal had acquired the peripheral target and maintained position for a short period of time (300 msec monkey X, 400 msec monkey B), the peripheral target was extinguished, and a fixation target was presented in the center of the workspace cueing a saccadic movement back to the starting position. This began the "static holding period," where the animal maintained its arm position at the peripheral target while fixating at the starting position for 800-1200ms. During the static holding period, visual feedback of the arm cursor was allowed on half the trials (bimodal somatic/vision [V] condition) and blanked on others (unimodal somatic/no-vision [NV] condition). Behavioral windows surrounded the reach and saccade targets, and successful trials required the animals to maintain their arm position within these windows for the duration of the trial. The window radii for the peripheral targets were 2 and 2.4 cm for Monkey X and Monkey B, respectively. Water or juice rewards were provided for successful trials. Each block of trials during a recording session consisted of five pseudorandomly interleaved reaches to each target in each sensory condition, resulting in a total number of 80 trials for each recording session. A schematic of this experimental paradigm can be observed in figure 3.2



Figure 3.2 Sequence of events in experimental paradigm for vision and nonvision trials (Shi, 2011)

# Virtual Reality Environment

The virtual reality (VR) environment used in the experiment was based on a C++ program that generated 3D graphical objects to represent the starting and peripheral targets, as well as the arm cursor for visual feedback. A cube framework was also rendered to give additional spatial cues about the workspace environment. The arm cursor location was

updated in real-time during the experiment in order to provide an accurate sense of hand position and movement. Display of the arm cursor could be controlled within the VR environment, and was removed for the NV trials. The VR environment was displayed on a stereoscopic 3D monitor, providing a 3D image without the need for a head-mounted visor or other accessories. This monitor was mounted horizontally and the image was projected downward onto a mirror angled at 45°, providing a clear vision of the 3D environment for the animal while also allowing free movement of the arm within the workspace.

# **Motion Tracking**

An active LED-based motion tracking system (Visualeyez 3000; Phoenix Technologies, Inc.) was used to track the monkeys' 3D arm movements in real-time during the task. This was done for several reasons. The experimental paradigm is based on a series of behavioral tasks, and successful trials were dependent upon the animal reaching specific spatial locations within the workspace. Monitoring hand position in real-time also allowed the animals' movements to be correlated with the neural recordings, which allowed examination of the relationship between behavioral activity and neural responses. Lastly, tracking arm location was also essential for providing visual feedback to the animals.

In the experimental setup, a tracking unit consisting of three horizontally arranged cameras was set on a tripod and placed lateral to the reaching workspace. A bracelet with LED markers was attached to the wrist of the monkeys during the experiment. The tracking unit monitored the location of these markers in space during the experiment, and positional data was relayed to a behavioral PC that controlled the VR environment and experimental task. The motion tracker had a sampling rate of 250Hz with a spatial resolution of 0.015mm.

Eye movements were tracked using an optical eye tracking system (ASL Inc.). The camera was placed perpendicular to the monkeys' field of vision and a reflective hot mirror placed near the monkeys' left eye and angled at approximately 45° was used to capture a clear image of the eye. Infrared LEDs were used to illuminate the eye and an Eye-Trac 6000 control unit (ASL Inc.) computed point of gaze based on a combination of corneal and pupillary reflection.

## **Neurophysiological Recording**

Microelectrodes recorded high frequency (600-6000Hz) extracellular action potentials from single neurons, as well as the lower frequency (<~300Hz) local field potentials (LFP) from neural ensembles located near the electrode tip. The neural signals were amplified, and a multichannel acquisition system (MAP, Plexon Inc.) was used to filter and record the cortical neural spiking data. The continuous analog data (LFP and eye position data) was separated from the spike data after amplification and recorded using a National Instruments Data Acquisition (NIDAQ) board. An A/D clock on the MAP box ensured that the spike and continuous signals were synchronized. This hardware system and complementary software suite made it possible to monitor waveform shapes and oscilloscope output of the amplified and filtered signal as well as to sort spikes in real-time during the acute recordings or using the offline-sorter. A dedicated "data PC" received the output from the MAP system, as well as 8-bit strobed data from the NIDAQ device encoding behavioral data and experimental events for synchronization with the neural data. Two different recording methods, acute and chronic, were employed for collecting action potential and LFP data.

#### **Acute Recording**

Acute recordings were made using single varnish-coated tungsten microelectrodes that were inserted into the superficial cortex of the SPL prior to each recording session. Two NHPs (monkey X, monkey B) had a recording chamber surgically implanted over the posterior parietal cortex contralateral to the working hand (left hemisphere). The recording chamber provided access to the dura for recording purposes, but could be sealed off for hygienic purposes when the monkeys were not working. A microdrive (NaN Instruments Ltd.) was attached to the recording chamber and used to precisely control the positioning of the microelectrodes. During each recording session, a microelectrode ( $\sim 1-2M\Omega$ ) was fixed to the microdrive system to be driven through the dura into superficial cortex. This system allowed manual positioning of the electrodes independently in the X and Y directions with a precision of 0.1mm. Electrodes were driven in the Z-direction (into the cortex) through a computer-controlled mechanical drive with variable speeds of 0.001-0.2 mm/sec. The precision of electrode placement within the cortex affords acute recordings the distinct advantage of optimizing the neural signal being recorded. The electrode tip can be moved within cortex to isolate the action potential waveforms from background noise, improving the signal fidelity. Microelectrodes could record both action potential and LFP data simultaneously. For the acute recordings, single action potentials were isolated in real-time from the amplified and filtered signal via time-amplitude window discriminators implemented in software (Plexon Inc.). Spike times were sampled at 2.5 kHz. The low frequency LFPs were recorded on a separate continuous channel that was sampled at 1 kHz.

One disadvantage of this acute recording method is that only a single recording channel can be utilized, meaning that only a small number of individual neurons and a single channel of LFP can be recorded simultaneously. In addition, driving electrodes into cortex and isolating neurons can also be time-consuming process, requiring a cooperative animal. Lastly, in general, microelectrodes can only be driven into a cortical location once, so in order to record behaviorally relevant neural data the animal needed to perform the experimental task during the recording session. For these and other reasons, many neurophysiologists have moved to chronic recording methods, the advantages and disadvantages of which are discussed below.

# **Chronic Recording**

For chronic recordings, a Utah array (BlackRock Microsystems) was surgically implanted in monkey B in the superficial cortex of the IPL. The array had 96 microelectrodes that were permanently embedded into the cortex. An external headstage connector was affixed to the skull with bone screws and served as the interface between the MAP system and the electrode array. Essentially the microelectrode array interface allowed for plug-and-play operation, and recording could commence whenever the monkey was seated within the experimental rig. This eliminated some of the behavioral issues that could arise from the long setup times associated with acute recording methods. The 96 electrodes provided the capability to record many neurons simultaneously during the experiment, but electrode placement within cortex was fixed, obviating optimization of the signal-to-noise ratio of the recordings. Amplification parameters and filtering for the chronic recording sessions were the same as for the acute recordings. Waveforms recorded on all 96 channels were initially fit to a template for online spike sorting (Plexon) during the experiment. These templates could be adjusted to accommodate day-to-day changes in signal or noise, if necessary, before the recording session began. Post-recording verification of spike waveforms was performed using Plexon Offline Sorter. This software made it possible to examine all the waveforms recorded on a given channel during the recording session and allowed for manual adjustments to the spike sorting parameters as well. Due to hardware limitations, there were only 50 analog channels available for recording. Two channels were reserved for horizontal and vertical eye position signals, leaving 48 LFP channels. These channels could be selectively assigned to different microelectrodes on the array. In order to have the greatest spatial distribution of analog recordings, the odd-numbered microelectrodes were designated as LFP channels, recording digital and analog signals simultaneously.

### **Data Analysis**

Neurophysiological analysis focused on temporal changes in three distinct but related domains of neural data from both the SPL and IPL: 1) action potentials (spike data), 2) LFPs, and 3) spike-field interactions, all from the last 800ms the static holding period. This section will give a brief overview of the analysis methods; further details will be provided for each data domain in subsequent chapters of this dissertation.

Data analyses in this dissertation were focused on identifying temporal structure in neural activity and how they relate to ongoing sensory and motor processes. Spectral

analysis an ideal tool for this undertaking. Both spiking and LFP activity are time series, and though they differ in type (point vs. continuous processes), spectral analysis can be used to characterize both signals in the frequency domain (Pesaran, 2008). The spectrum of a time series is an important tool for examining relationships between and within data that may occur as a function of frequency. It can often provide information that is not apparent from analysis in the time domain, particularly for signals with a periodic component. The power spectrum of a signal essentially captures the distribution of variance within a signal. White noise, for example, is a signal with evenly distributed variance and its resulting power spectrum is flat. The absence of spectral peaks indicates there is no frequency-dependent variance. Other signals may have variance centered on a certain frequency or frequency band, indicated by significant peaks in the power spectrum. These peaks represent oscillatory components of the signal (Watts and Jenkins, 1968). In relation to spiking activity, oscillations indicate a more regular firing pattern, with variations in the actual spike timing centered on the peak of the power spectrum; i.e., the probability of the cell firing is greater within the time-window corresponding to the oscillatory frequency.

The LFP is composed of a series of voltage measurements changing in time (a continuous process) and the spiking activity is a series of delta functions occurring at each spike time (a point process). An important assumption of spectral analysis of neural signals is that these time series are specific realizations of the underlying stochastic process generating the data, and that by transforming the data into the frequency domain it is possible to characterize the properties of these signals (Pesaran, 2008). Transforming time

series data into the frequency domain is done through a process called the Fourier transform, which decomposes the time series data into a series of sinusoidal functions with an amplitude and phase (i.e., a complex number) at each frequency. Ideal Fourier transforms are performed on time series of infinite length, and in practice a straightforward Fourier transform will impart distortions of the signal. Several strategies have been developed to overcome these distortions and the inherent bias of simple Fourier transformed spectral estimates. One such strategy is multitaper spectral estimation, which can be used for both continuous and point processes (Percival and Walden, 1993).

Multitaper spectral estimation methods were used to quantify the power spectrum of spike trains from individual cells and LFPs in the frequency domain. The advantage of multitaper methods is a reduction in both wideband bias and variance in the spectral estimate, and it is a commonly used technique for spectral analysis applications (Jarvis and Mitra, 2001; Pesaran, 2008; Wong et al., 2012). Wideband bias arises from distant frequencies influencing the estimate, sometimes referred to as leakage. Utilizing data tapers concentrates the spectral estimate within a range of frequency space, reducing the effects of wideband bias. The multitaper spectral estimate can be computed using the following generalized equations:

$$\tilde{x}_k(f) = \sum_{t=1}^N w_t(k) x_t \exp(-2\pi i f t) \quad (1)$$

$$S_{MT}(f) = \frac{1}{K} \sum_{k=1}^{K} |\tilde{x}_k(f)|^2 \quad (2)$$

In this method, the Fourier transform (1) of the time domain signal ( $x_i$ ) is multiplied by a set of windowed sequences ( $w_t(k)$ ). These windowed sequences, or orthogonal taper functions, provide optimal spectral concentration properties. For taper sequences of a given length *N*, and a chosen bandwidth parameter *W* (i.e., frequency resolution), *K*=2*NW*-1 taper sequences will have their energy concentrated within the [-W, W] frequency space, reducing the effects of wideband bias. The overall multitaper spectral estimate (2) of the signal is the constituent tapered spectral estimates averaged over *K* orthogonal taper functions (Percival and Walden, 1993). Variance of the estimate (not to be confused with variance of the original signal) can also be easily addressed through the multitaper method. Jackknife error bars can be computed by leaving out a data taper and creating a distribution of spectral estimates from which the variance can be determined (Pesaran, 2008). A Matlab toolbox, Chronux, was used for all power spectrum computations (Bokil et al., 2010).

#### **Spike Data**

The power spectrum was used to quantify temporal structure in the spike trains recorded from individual cells. In addition to spectral analysis, autocorrelation functions were also be used to quantify spike trains. The autocorrelation function is a time-domain counterpart to the spectrum, and computes the correlation of a signal with itself. It is a commonly used tool for examining the distribution of variance within a signal and finding periodic signals that could be obscured by noise. It is a complementary method to spectral analysis for examining regularity within spike trains that can expose oscillatory activity. Rather than examining the variance distribution as a function of frequency, the autocorrelation is expressed in terms of the time lag between observations. More specifically, autocorrelograms are histogram representations of the correlation values versus binned time lags. Peaks on autocorrelograms can be interpreted as representing time delays where the probability of a neuron firing is greater. In many instances of spike train analysis (Compte et al., 2003; Joelving et al., 2007), a shuffle correction is applied to autocorrelation calculations in order to remove spurious periodicity due to an increase in firing rate. The shuffle correction is computed from the cross-correlation of spike trains from the same neuron, but on different trials. It represents the distribution of covariance across trials that could arise from changes in firing rate, rather than an induced regularity of firing due to oscillatory components. That is, a higher firing rate would increase the probability of spikes firing within time lags, even without an oscillatory component. By subtracting the shuffle correction from the raw autocorrelation, the "corrected" autocorrelogram will capture any periodic components of a signal that are not confounded by an increase in firing rate (Aertsen et al., 1989).

Together, the spike spectrum and autocorrelogram were used to classify neurons from the SPL and IPL during the sensory integration task. Using a method based on previously published criteria (Compte et al., 2003; Joelving et al., 2007), neurons were classified as oscillatory, bursty, refractory, Poisson, or "other" based on the spike train properties during the static holding period. The rate-normalized spectrum of a neuron with a firing pattern that follows an ideal Poisson-process would have power centered on one (Buneo et al., 2003). Significant deviations in the power spectrum from this value are indicative of temporal structure in the spike trains. For example, in this work if the power spectrum exceeds the expected Poisson power by 1 standard deviation in the 12-30Hz range (beta band), that would be classified as a beta oscillation. Further details about the classification scheme can be found in chapter 4 of this dissertation.

#### **LFP Data**

LFPs, in contrast to spikes, are thought to be representative of summation of local synaptic inputs and can reflect subthreshold activity of local neurons, providing information unavailable in the analysis of spikes alone (Einevoll et al., 2013). From a network perspective, LFP analysis is complementary to spike analysis in characterizing the dynamics of sensory information processing, as the underlying synaptic inputs (LFP) generated in response to the sensory stimuli during the task influence the output (spikes). Unlike spikes, the LFP signal is a continuous process with the amplitude (voltage) changing as a function of time during the experiment. In addition to changes in amplitude of the raw voltage signal, some tuning features of the LFP can be frequency-dependent, with different sensory or motor information encoded across voltage frequency bands. In this study, the raw LFP was subdivided by band-pass filtering into slow (0-13Hz) intermediate (13-30Hz) and fast (30-60Hz) frequency bands, corresponding approximately to the alpha, beta, and low gamma bands, respectively, in accordance with previous sensorimotor studies of LFP activity (Scherberger et al., 2005; Heldman et al., 2006; O'Leary and Hatsopoulos, 2006). A fourth-order Butterworth filter, run bi-directionally to remove time lags, was used to separate the LFP signal (in  $\mu V$ ) into the constituent frequency bands. These evoked LFP responses, both filtered and raw, we used to examine the sensory and directional tuning properties of the LFP response during the experiment. Further details of these procedures can be found in Chapter 6.

Evoked responses that are not phase-locked can have the effect of cancelling each other out when averaged across trials, a deficiency that can be overcome by looking at the power of the signal (O'Leary and Hatsopoulos, 2006). So in addition to the evoked voltage response, temporal structure in LFP was analyzed using the spectral analysis techniques outlined above. By computing the spectrum within sliding time windows of short duration and averaging across the total trial duration, it was possible to visualize changes in the power spectrum. Prior studies have shown that LFP power can be modulated by task or sensory related activity (Pesaran et al., 2002; Hwang and Andersen, 2011; Hagan et al., 2012; Lehmann and Scherberger, 2015) and we expected such modulations would be evident in our limb position maintenance task. Of particular interest we anticipated beta band oscillations during the holding period of our task, as indicated by peaks in the power spectrum. Determining the significance of these oscillations is not as straightforward for LFPs as for spiking activity, which has a standard (the expected value of a Poisson process) against which the spectrum can be compared. LFP oscillations are still evident from peaks in the power spectrum, but the significance of these increases in power are determined differently. A random permutation test was used to determine significance between experimental conditions for frequency bands of interest. A permutation test is a nonparametric procedure that generates a sample distribution of the test statistic (in this case, spectral power) through a resampling process that computes the sample mean with one observation (trial) left out. This process is repeated many times (1000+) in order to generate the sample statistics necessary to determine significance (Pesaran, 2008).

Previous studies have shown that the different frequency bands for both evoked responses and LFP power can carry different information about a signal, which can be used to improve decoding accuracy for BCI applications (Pesaran et al., 2002; Andersen et al., 2004; Scherberger et al., 2005; Belitski et al., 2010; Lehmann and Scherberger, 2015). Even though beta band oscillations were a main focus of this dissertation, due to their implication in multisensory interactions in the PPC, analyses were extended to other frequency bands as well, particularly low frequency alpha and gamma band.

## **Spike-Field Coherence**

The spike-field coherence (SFC) is a measure of the relative phase between two time series in the frequency domain. It was computed using multitaper methods, and therefore has the same advantages mentioned above (reduced bias and variance). The direct estimate of the coherence between two signals is outlined in equation (3):

$$C_{xy}(f) = \frac{\frac{1}{K} \sum_{k} \tilde{x}_{k}(f) \tilde{y}_{k}(f)}{\sqrt{S_{x}(f)S_{y}(f)}}$$

Here, the numerator is the tapered Fourier transforms of the two signals (spike and LFP). This is the cross-spectrum of the two processes, a frequency domain equivalent to the covariance of the signals. The cross-spectrum is then normalized by the square root of the product of the spectrum of each signal. The coherence  $[(C_{xy}(f))]$  is therefore just the correlation coefficient between the two signals at each frequency. The coherence is unaffected by changes in firing rate meaning it can be averaged across different time series (Jarvis and Mitra, 2001; Pesaran et al., 2002). The magnitude of the coherence at each frequency has a value between zero and one, indicating how correlated the signals are with

one being perfectly correlated and zero being uncorrelated. High coherence at a given frequency occurs if the phase of one signal is fixed relative to the other. The coherence can be thought of as estimating how two signals are changing relative to each other in the frequency domain. The SFC was calculated for both SPL and IPL activity in order to relate oscillatory spiking activity to the concurrent local population inputs (i.e. LFPs) in a given sensory condition. By computing the spike-field coherence for activity recorded on nearby electrodes, it was possible to see how oscillatory spiking patterns related to local pooled synaptic activity. This approach assumed that coherency patterns would reflect differences in functional connectivity of between unimodal and bimodal neural ensembles underlying limb position maintenance.

The acutely recorded SPL data used only a single electrode during recording sessions, meaning the spike-field analyses were limited to a small number of isolated units and a single LFP channel at each cortical location. The IPL data recorded from the array allowed for much more complex combinations of spike-field interactions between the 96 spike channels and 48 LFP channels, including larger scale spatial relations between LFP and spiking oscillatory activity spanning the cortical footprint of the array.

# CHAPTER 4 MULTISENSORY INTERACTIONS INFLUENCE NEURONAL SPIKE TRAIN DYNAMICS IN THE POSTERIOR PARIETAL CORTEX

## Abstract

Although significant progress has been made in understanding multisensory interactions at the behavioral level, their underlying neural mechanisms remain relatively poorly understood in cortical areas, particularly during the control of action. In recent experiments where animals reached to and actively maintained their arm position at multiple spatial locations while receiving either proprioceptive or visual-proprioceptive position feedback, multisensory interactions were shown to be associated with reduced spiking (i.e. subadditivity) as well as reduced intra-trial and across-trial spiking variability in the superior parietal lobule (SPL) and, to a lesser degree, the inferior parietal lobule (IPL). To further explore the nature of such interaction-induced changes in spiking variability we quantified the spike train dynamics of 231 acutely recorded SPL neurons and a collective of IPL neurons recorded on a chronically implanted array. Neurons were classified as Poisson, bursty, refractory, or oscillatory (in the 13-30 Hz "beta-band") based on their spike train power spectra and autocorrelograms. No neurons were classified as Poisson-like in either the proprioceptive or visual-proprioceptive conditions. Instead, oscillatory spiking was most commonly observed with many neurons exhibiting these oscillations under only one set of feedback conditions. The results suggest that areas of the posterior parietal cortex may belong to a putative beta-synchronized network for arm position maintenance and that position estimation may be subserved by different subsets of neurons within this network depending on available sensory information. In addition, the nature of the observed spiking variability suggests that models of multisensory interactions in the SPL and IPL should account for both Poisson-like and non-Poisson variability.

# Introduction

Multisensory interactions are critical to both perceptual and motor function. Under certain spatial and temporal constraints, such interactions can result in the fusion of sensory information from different streams, a phenomenon known as multisensory (or multimodal) integration. Such integration is thought to be necessary in part because sensory information is inherently noisy, which can lead to uncertainty in estimating the state of the environment and our own bodies, including the positions and velocities of our arms. Computational and behavioral studies have demonstrated that combining information from different senses through integration can improve such state estimates (Ernst and Bülthoff, 2004). Moreover, several studies have shown that sensory signals are combined in a Bayes-optimal (or nearly optimal) manner, i.e. sensory inputs are weighted according to their relative reliabilities and combined with prior information to maximize the precision of state estimates (Knill and Pouget, 2004; Körding and Wolpert, 2004; Tassinari et al., 2006).

Despite significant progress in understanding multisensory interactions at the behavioral level, their underlying neural mechanisms remain relatively poorly understood. Until fairly recently, most of what is known comes from studies of a subcortical structure, the superior colliculus (SC), during the interaction of visual, auditory and/or somatosensory inputs. Seminal work by Stein and colleagues established several empirically-derived

principles based on studies of the SC, including those of spatial and temporal congruency and the principle of inverse effectiveness (Stein and Stanford, 2008). The spatial and temporal congruency principles state that the responses of multisensory neurons will be enhanced in the presence of multiple stimuli provided these stimuli occur close together in space and time, otherwise responses will be suppressed. The principle of inverse effectiveness summarizes the observation that effects at the single cell level are proportionately stronger to the combined presentation of weak stimuli than to the combined presentation of strong stimuli. The combined response to weak stimuli can in some cases be superadditive, i.e. greater than the sum of the responses to individual stimuli, while responses to strong stimuli can actually be less than the sum of the responses to each individual stimulus (i.e. subadditive). Recently, a ubiquitous network-level phenomenon known as divisive normalization has been shown to account for these empirically-derived principles as well as others (Ohshiro et al., 2011).

As in the SC, multisensory interactions in the cortex are associated with both enhancement and suppression of spiking activity (Graziano et al., 2000; Zhou and Fuster, 2000; Bremmer et al., 2002b; Ghazanfar et al., 2005; Sugihara et al., 2006; Shi et al., 2013). However, the relation between such single-cell level phenomena, larger scale networklevel operations and principles of optimal integration derived from theoretical and behavioral studies have only recently been addressed. Ma and colleagues showed that if neural variability in the cortex is assumed to be Poisson-like, Bayes-optimal multisensory integration can conceivably be implemented via a simple linear summation of population responses (Ma et al., 2006). This study and others also predict that cortical areas should

exhibit largely additive or subadditive responses to multisensory inputs. Interestingly, studies designed to test for optimal integration of visual-vestibular inputs in the dorsal medial superior temporal area showed a predominance of subadditivity (Morgan et al., 2008). However, although neural variability appears Poisson-like in some parts of the cortex, particularly those situated relatively early in the visual processing stream (Bair et al., 1994), other areas have been shown to demonstrate more complex patterns of spiking variability under certain task conditions (Buneo et al., 2003; Joelving et al., 2007; Maimon and Assad, 2009). For example, a previous study of the posterior parietal cortex (PPC) found evidence for strong, spatially-tuned, oscillatory spiking during the memory period of an instructed delay reaching task, with spectral power peaking at approximately 25 Hz Although prevailing computational models of multisensory (Buneo et al., 2003). integration may be insensitive to minor violations of spike-train irregularity, it is not entirely clear how well these models can account for integration in areas and/or tasks where spike trains are highly regular or even oscillatory, such as those described above. As a result, the extent to which neural spike trains are Poisson-like in multisensory areas, particularly during motor tasks, remain an important open question.

The importance of variability in spike timing for multisensory integration has also recently been highlighted by experimentalists, leading to the suggestion that some aspects of integration might even be expressed as a temporal code, e.g. as changes in spike train dynamics and/or oscillatory activity within or across functionally-related neural ensembles (Ghazanfar et al., 2008; Senkowski et al., 2008; Wang, 2010). For example, multisensory interactions have been associated with altered spike timing in the vestibulocerebellum of the mouse (Chabrol et al., 2015) and in the dorsal cochlea nucleus of the guinea pig (Koehler et al., 2011). In non-human primates, multisensory interactions result in reduced spiking variability (Kayser et al., 2010; Shi et al., 2013) and are associated with changes in the phase of ongoing oscillations within a given area (Lakatos et al., 2007), as well as changes in inter-areal LFP and spike-field coherence in the gamma band (Ghazanfar et al., 2008; Maier et al., 2008). Regarding the possible role of temporal coding in multisensory state estimation, work in non-human primates suggests that synchronized LFP beta band oscillations serve to bind multiple cortical areas into a large-scale network subserving the maintenance of arm position (Brovelli et al., 2004a). Although the roles of different sensory signals were not addressed by Brovelli and colleagues, fMRI work in humans suggests that the different nodes of this putative network could contribute differentially to the maintenance of arm position depending on available sensory information (Lloyd et al., 2003).

The activity of two populations of posterior parietal neurons was characterized during multisensory interactions. Neural activity in the SPL and IPL was recorded during a reach and hold task performed with unimodal (proprioceptive) or bimodal (visualproprioceptive) sensory feedback. The initial study focused on the SPL (Shi et al., 2013). Firing rates were largely suppressed under bimodal conditions, consistent with a subadditive interaction of visual and proprioceptive inputs. Average arm endpoint positions and variability in endpoint positions did not differ between unimodal and bimodal conditions however, suggesting that interactions at the single cell level were associated with differences in perceptual and/or motor related variables which were not monitored in these experiments, such as arm configuration (Scott et al., 1997; Torres et al., 2009). In this study, both across trial and intra-trial variability in spike timing was reduced under bimodal conditions as measured by the Fano factor and Coefficient of Variation, respectively. Given that reduced intra-trial variability can result from the induction or enhancement of oscillatory spiking (Maimon and Assad, 2009) and that oscillations have been proposed to play an important role in multisensory interactions in the cortex (Senkowski et al., 2008), it was hypothesized that this population of cortical neurons would show evidence of induced or enhanced oscillatory activity under bimodal conditions. This hypothesis was examined in a follow up study by comparing the power spectra and autocorrelograms of the recorded spike trains between the unimodal and bimodal conditions. An additional population of neurons in the IPL was recorded using a chronically implanted microelectrode array in this follow up study.

#### **Materials and Methods**

# **Experimental Subjects and Paradigm**

Two rhesus monkeys (Macaca mulatta) were subjects in the SPL study. One of these animals was also a subject for the IPL recordings used in the follow up. All animal welfare and experimental procedures were conducted according to the U.S. Public Health Service Policy on Humane Care and Use of Laboratory Animals (Public Law 99-158) and the Guide for the Care and Use of Laboratory Animals (National Academy Press, 1996) and were approved by the Arizona State University Institutional Animal Care and Use Committee. Great care was taken to minimize any pain or discomfort during any medical procedures, using proper anesthesia and analgesia under veterinary care when necessary. All housing, feeding, and environmental social enrichment conformed to institutional standards which are AAALAC International accredited.

The experimental apparatus and paradigm have been described in detail elsewhere (Shi et al., 2013). Briefly, two Rhesus monkeys (X and B) were trained to reach to targets in a semi-immersive 3D virtual reality environment and to maintain their arm position at these targets either with or without vision of the endpoint of the arm, which was provided as a virtual sphere ('arm cursor'). The virtual environment was displayed on a 3D monitor (Dimension Technologies Inc.) and was projected onto a mirror embedded in a metal shield that blocked the real arm from view (Figure 1). Arm position was tracked using an active LED based system (Phoenix Technologies Inc.) and eye position was monitored using a remote optical tracking system (Applied Science Laboratories Inc.).



Figure 4.1 Experimental apparatus and paradigm(Shi et al. 2013). A. Schematic of virtual reality setup. B. Sequence of events on a single trial. Grey rectangle indicates the 800 ms analysis epoch that was the focus of this study. During this time period, animals were required to fixate at the center of the display (S) while maintaining their arm position at the peripherally located targets (T).

At the beginning of each trial, an animal first acquired a spherical starting position that was presented at the center of the vertically oriented workspace. After maintaining this position for 500 ms, a spherical green target was presented at one of eight locations arranged in a square (monkey B) or rectangle (monkey X) and up to 6.4 -7.1 cm from the center of the workspace. Onset of the target instructed the animals where to reach and also served as the 'go' signal. Once the target was acquired it was extinguished after 300-400 ms and a yellow sphere was presented at the center of the workspace, cueing the fixation position. Once the fixation position was acquired a holding period commenced during which time animals continued to fixate the center of the display while maintaining their arm position at the target for 800-1200 msec. During the holding period, animals viewed their arm on half of the trials (bimodal condition) while on the remaining trials vision was prevented by blanking the arm cursor (unimodal condition). In summary, on a given trial animals executed a center-out, reaction-time reach and saccade to one of eight peripheral targets, made a saccade back to a central fixation point, then maintained their arm position at the target for a variable period in the presence of proprioceptive feedback or both visual and proprioceptive feedback. Five (5) trials were performed for each target in each sensory condition, which were pseudorandomly selected.

# **Neurophysiological Procedures and Analysis**

All experimental procedures were conducted according to the "Principles of laboratory animal care" (NIH publication no. 86-23, revised 1985) and were approved by the Arizona State University Institutional Animal Care and Use Committee. Extracellular recordings (N= 343; 219 from X and 124 from B) were made using varnish-coated tungsten microelectrodes in the superficial cortex of the SPL (area 5), as judged by recording depth and similarity to previous recordings made in this area (Buneo et al., 2003; Buneo and Andersen, 2012). Spikes were isolated from the amplified and filtered (600-6000 Hz)

signal via a time-amplitude window discriminator (Plexon Inc.). Spike times were sampled at 2.5 kHz.

A chronically implanted 96-channel Blackrock microelectrode array was used for recording extracellular activity and field potentials in the superficial cortex of the IPL of one NHP (monkey B). Amplification parameters and filtering were the same for the array recording sessions as the acute. Waveforms were initially fit to a template for online spike sorting (Plexon) that was adjusted to accommodate day-to-day changes in signal or noise, if necessary, before the recording session began. Due to the difficulties in monitoring 96 channels in real-time, post-recording verification of spike waveforms was performed using Plexon Offline Sorter.

## Analysis of Neurophysiological Data

Data analyses focused on an 800 ms long section of the holding period beginning 400 ms after target acquisition. Firing rates during this period were compared statistically between conditions using the Mann-Whitney U test using a significance level of  $\alpha = 0.05$ . Peristimulus time histograms (PSTHs) of the trial averaged rate were constructed using data from each neuron's preferred and non-preferred locations during the holding period (based on mean firing rates) and were smoothed with a Gaussian kernel ( $\sigma = 50$  ms).

We previously quantified the effects of multisensory integration on spiking variability using the Fano factor and coefficient of variation of the interspike intervals (Nawrot et al., 2008; Shi et al., 2013). Here, we used the power spectra and autocorrelograms of the recorded spike trains to provide further insights. Power spectra were computed from the spike times on each trial using multitaper spectral methods (Jarvis

and Mitra, 2001; Bokil et al., 2010; <u>http://chronux.org/</u>). Spectra were computed with a 6.25Hz resolution and nine Slepian data tapers. Single trial spectra were normalized by the mean firing rate during the 800ms window before averaging across trials and cells. The variance of the normalized single cell and population spectra were estimated using a Jackknife procedure that involved leaving out a data taper and creating a distribution of spectral estimates from which the variance was determined. We also computed the variance distribution of individual cells using the autocorrelation function, the time domain counterpart to the spectrum, to look for regularity (oscillations) in the spike trains. Autocorrelograms were computed for each trial by subtracting the shuffle predictor (i.e. the average cross-correlogram of the spike trains from one cell during different trials) from a histogram of the intervals between spikes. The resulting autocorrelogram for all five trials was then normalized by the standard deviation (SD) of the shuffle predictor at each time lag (Aertsen et al., 1989; Joelving et al., 2007) putting them in units of shuffle predictor SDs.

Power spectra and autocorrelograms were used to classify the neural spike trains recorded during the 800 ms holding period using previously published criteria (Compte et al., 2003; Joelving et al., 2007). To classify the spectra from individual cells, we first defined an index A as the average height of the central autocorrelogram bins corresponding to time lags < 5 ms (Joelving et al., 2007). Spike trains were classified as "bursty" if they exhibited a peak in their power spectrum that exceeded the expected Poisson spectrum by 1 SD in the 5-60 Hz frequency band and had a value of A > 1 (1 SD higher than the shuffle predictor). We classified spike trains as "refractory" if they exhibited a spectral trough that

deviated from the expected Poisson power by 1 SD and had a value of A < -1. Spike trains were classified as "Poisson" if their power spectrum showed no deviations from the expected Poisson power and -1 < A < 1. Spike trains were classified as "oscillatory" if their power spectra exceeded the expected Poisson power by 1 SD in the 13-30Hz range and exhibited a value of A < 1. This sorting paradigm, which is based on previous work (Compte et al., 2003; Joelving et al., 2007), utilizes complementary but mathematically equivalent time and frequency domain functions to examine temporal structure in spike trains. Time domain correlation functions are known to suffer from estimation bias and variance, and are particularly susceptible to violations of the non-stationarity assumption (Pesaran et al., 2002). Frequency domain analyses, particularly multitaper spectral methods, greatly reduces the problems associated with estimation bias and variance, and is able to detect subtle changes in temporal structure better than their time-domain counterpart (Jarvis and Mitra, 2001). Owing to these advantages and the ability to construct accurate spectral confidence intervals to assess significant structural features, we also sorted the cells using only the spectral criteria.

Regarding the oscillatory classification, we chose to focus on the 13-30 Hz range for two reasons. First, previous work from the PPC showed strong oscillations in this range during performance of various tasks (Buneo et al., 2003; Joelving et al., 2007; Witham and Baker, 2007). In addition, the 13-30 Hz band corresponds to the 'beta' band of EEG, LFP, and MEG signals, which has been implicated in the maintenance of sensorimotor state (Engel and Fries, 2010), including arm position (Brovelli et al., 2004a), one of the independent variables in the current study. Although the term "beta oscillations" is typically used to refer to oscillations observed in EEG and other continuous time signals, for convenience we will use this term to refer to rhythmic spiking in the same frequency band. Oscillatory population spectra were computed for both for the preferred and non-preferred locations in each condition. Power in the beta-band was compared between conditions using the Mann-Whitney U test and a significance level of  $\alpha = 0.05$ .

# Results

#### SPL

As described previously, firing rates during the hold period of the bimodal condition were generally suppressed relative to corresponding rates in the unimodal condition. Figure 2 shows PSTHs for both conditions for the SPL population (N=343), aligned to reach target acquisition (t = 0), the onset of the static holding period. Rates were generally indistinguishable between conditions both before and during the movement (i.e. from -0.5s - 0 s), though in both conditions static positional discharge and movement related modulation of activity was clearly evident. During the hold period (0.4s -1.2s), rates were largely stationary but deviated in magnitude between conditions, with activity under bimodal conditions being significantly less than activity under unimodal conditions (p<0.05). Note that the hold period is the only part of the task where the arm feedback conditions differed, i.e. vision of the arm was provided prior to and slightly after arrival at the target and was removed at the time of the saccade to the central fixation position. Given that previous analyses established that neither the mean fixation positions nor the variances of the spatial components of eye position differed between conditions (Shi et al., 2013),

the deviation in firing rates during the hold period can be attributed largely to differences in visual feedback regarding the position of the arm.



Figure 4.2 Population PSTHs for all SPL cells(N=343) in the unimodal (U) and bimodal (B) conditions. Data from the preferred and non-preferred locations are shown aligned to target acquire (Time = 0). Grey rectangle indicates the 800 ms analysis epoch that was the focus of this study. During this time period, animals were required to fixate at the center of a visual display while maintaining their arm position at peripherally located targets.

Approximately 67% of the neurons (231/343) had a sufficient number of spikes during the holding period in both conditions to compute a spectrum. Figure 3 shows the power spectra and autocorrelograms (insets) for example neurons classified as bursty (A), refractory (B) and oscillatory (C). The spectrum for the bursty neuron shows the enhanced low frequency power (relative to that expected of Poisson spiking) that was representative of this spike train classification as well as an autocorrelogram with the expected peak around zero lag (Joelving et al., 2007). In contrast, the spectrum for the refractory neuron demonstrates suppressed power at low frequencies (<20 Hz) and an autocorrelogram with a broad central trough. As discussed by Bair et al (1994) and others, spectral suppression is consistent with a relative refractory period, i.e. a decreased likelihood of additional spiking shortly after the occurrence of a spike. The oscillatory neuron (C) also demonstrates a low frequency spectral suppression consistent with a refractory period in addition to broad-band enhancement of spectral power from ~15-30 Hz that peaks at approximately 20 Hz. The autocorrelogram for this cell also shows evidence of temporal structure, with several peaks at relatively equally-spaced time lags on either side of zero lag (Joelving et al., 2007).



Figure 4.3 Example SPL rate-normalized spike spectra and autocorrelograms(insets) for three neurons. Data for the preferred location during the holding period of the unimodal condition are shown. Bursty (A), Refractory (B) and Oscillatory (C) neurons are shown. For the autocorrelograms, histogram bars are expressed in units of the shuffle predictor (see Methods for details). Horizontal lines at 1 indicate the power spectrum expected of a Poisson spike train.

The distributions of spike train classifications were highly non-uniform in both the unimodal and bimodal conditions. Table 1 shows the cell classifications for both conditions. In the unimodal condition, few cells were classified as bursty (~4%; 9/231) but refractory spike trains were slightly more common (~17%; 39/231). Oscillatory spike trains were far more common however, with ~38% of the cells (88/231) in the unimodal condition being classified as oscillatory in the 13-30 Hz (beta) frequency band. Notably, no neurons were classified as Poisson-like when both the spectrum and autocorrelation criteria were considered. It should be noted however that the power spectra of some cells were often consistent with oscillatory, bursty, or refractory spike trains but failed to meet the corresponding autocorrelation criteria and were therefore classified as 'other'. In the unimodal condition, cells in the 'other' classification constituted approximately 41% (95/231) of the population of neurons for which a spectrum could be computed.

	Bimodal Condition					
Unimodal	Oscillatory	Bursty	Refractory	Poisson	Other	Unclassified
Oscillatory	47	1	3	0	37	11
Bursty	2	5	0	0	2	3
Refractory	3	0	32	0	4	0
Poisson	0	0	0	0	0	0
Other	44	1	3	0	47	21
Unclassified	0	0	0	0	12	65

Figure 4.4 SPL cell classifications in the unimodal and bimodal conditions based on the spectrum and autocorrelation criteria.

Gray boxes indicate the neurons that maintained their classifications between conditions. 'Unclassified' refers to cells which did not have a sufficient number of spikes to compute a spectrum in either or both conditions, therefore these cells do not factor into the percentages of spike train classifications reported in the text.

In the bimodal condition, the distribution of spike train classifications was similar to that in the unimodal condition. Here again bursty spike trains were relatively few in number (~3%, 7/231), as were refractory ones (~16%, 38/231). Most of the cells classified as refractory in the bimodal condition were also classified as refractory in the unimodal condition (32/38) suggesting that the spike train dynamics of these neurons were invariant to changes in sensory conditions in this task. This was also true of a large number of the neurons that were classified as oscillatory in the bimodal condition (~42%; 96/231); approximately half of these 96 neurons were also identified as oscillatory in the unimodal condition, again suggesting that their spike train dynamics were invariant to the presence/absence of visual information about the position of the arm. Lastly, as in the unimodal condition, no neurons were classified as Poisson-like in the bimodal condition when both their spectra and autocorrelograms were taken into account.

Although many neurons retained their spike train classifications between conditions, the spike train dynamics of a substantial number of 'other' neurons (100/231;

43%) changed. The most commonly observed difference in spike timing was the presence of beta oscillations in one condition but not the other. Figure 4 shows spectra for one of these neurons in both conditions. On trials where both visual and proprioceptive feedback was provided (A), the spectrum exhibited low frequency suppression up to  $\sim$  20 Hz, consistent with refractoriness, but at frequencies greater than 20 Hz the spectrum showed only very small deviations from that expected of a Poisson process. On trials where only proprioceptive feedback was available (B), low frequency suppression up to  $\sim$ 20 Hz could also be observed. However, this was followed by a substantial peak in the spectrum that was centered at approximately 25 Hz, i.e. in the beta band of frequencies. It's important to reiterate that unimodal and bimodal trials were interleaved in this task. Thus, on a trial by trial basis beta-band oscillations would alternately appear or disappear from the spike trains of this cell and many others, and this was directly related to the nature of the feedback the animal was receiving.


Figure 4.5 Rate-normalized spike spectra for a single SPL neuron.(A) Bimodal condition and (B) unimodal condition. Horizontal lines at 1 indicate the power spectrum expected of a Poisson spike train.

Approximately equal numbers of neurons showed evidence of beta oscillations in the unimodal condition, bimodal condition, or both conditions. Figure 5 shows population spectra for the preferred location for neurons classified as oscillatory in both conditions (A), oscillatory in the bimodal condition only (B) and oscillatory in the unimodal condition only (C). In Figure 5A a broad-band peak centered at ~25 Hz is apparent in the spectra for both conditions. Power in the beta-band (inset) did not differ significantly between conditions for this group of cells (p=0.56). Thus, the spike train dynamics of these neurons were invariant to changes in the sensory conditions in this task. In contrast, in Figure 5B a similar spectral peak in the beta-band can be observed for the bimodal condition but not the unimodal condition; for this group of neurons power in the beta-band did in fact differ significantly between conditions (p < 0.05). Although a smaller peak in the beta-band is apparent for the unimodal condition in Figure 5C, power also differed significantly between conditions for this group of cells (p < 0.05). Thus, for the subsets of neurons shown in Figs. 5B and 5C, beta-band oscillations were apparent in one set of sensory conditions but not the other.



Figure 4.6 SPL population spike spectra for oscillatory cells in the unimodal and bimodal conditions. Spectra for the preferred location for neurons classified as oscillatory in both conditions (A; N=47), oscillatory in the bimodal condition only (B; N=49) and oscillatory in the unimodal condition only (C; N=41).

It should be noted, that when sorting the neurons using only the power spectrum criterion, none were classified as "other," indicating that the autocorrelogram-based criteria served only to exclude cells from one of the classifications. The most apparent change when sorting cells based solely on their spectra was a much more even distribution of cells. Aside from a single bursty cell in the bimodal condition, all other classifiable cells fell into either the oscillatory or refractory categories and did so in similar proportions (Table 2). In the bimodal condition, 54% of neurons were classified as oscillatory (125/231) and 45% (105/231) were refractory. For the unimodal condition the proportions were nearly equivalent, with 49% (114/231) being oscillatory and 50% (116/231) being refractory. There was an increase in the number of cells that were oscillatory in both conditions (76/231, 33%) relative to those that were oscillatory only in the unimodal (38/231, 16%) or bimodal (49/231, 21%) conditions, but the majority of cells that had been previously classified as "other" were reclassified as refractory in one or both conditions.

	<b>Bimodal Condition</b>							
Unimodal	Oscillatory	Bursty	Refractory	Poisson	Other	Unclassified		
Oscillatory	76	1	38	0	0	24		
Bursty	0	0	0	0	0	0		
Refractory	49	0	67	0	0	11		
Poisson	0	0	0	0	0	0		
Other	0	0	0	0	0	0		
Unclassified	7	0	5	0	0	65		

Figure 4.7 SPL alternative cell classifications in the unimodal and bimodal conditions, based on the spectrum criteria only for SPL neurons.

IPL

The IPL data was recorded from a chronically implanted array, and there are over 30 days of recording sessions. The analysis focused on ten sessions recorded 1-2 months post-surgery that show well-isolated and stable neurons. The number of units varied slightly from day-to-day across the ten sessions, but on average 97 neurons were recorded each day, with a range of 87-108. The number of recorded neurons became more constant as data collection progressed, with later recording sessions having more consistent numbers of units. Despite differences in the number of units, the neural responses showed consistent trends across recording sessions. The firing rates of cells in the IPL had marked differences than what was observed in the SPL. Figure 4.6 shows PSTHs for both conditions for the population (n=105) aligned to reach target acquisition (t=0) from a stereotypical recording session. Results from this dataset will be used throughout this section, unless otherwise noted.



Figure 4.8 Population PSTH for all IPL cells recorded in a single recording session (n=105).

Overall, firing rates were much lower throughout the duration of the trial for this population of cells – approximately half the magnitude of the rates observed in the SPL neurons. Another difference from the SPL is the rate response to task epochs. In the SPL there was a clear increase in firing during the movement phase of the task. In contrast, the IPL neurons showed a rather stationary response, with gradual increases in firing rate for both conditions during the trial, and the highest firing rates occurring during the static holding period. Like the SPL though, the rates were nearly indistinguishable for most of the movement portion of the task and higher rates for the bimodal condition during the

static holding period. This becomes more apparent in Figure 4.8 which shows the PSTHs for cells with activity during all recording sessions (n=84); e.g.: this figure represents the average response of these cells across 50 trials. Just like the SPL, the deviation in firing rate arises during the portion of the trial where the sensory conditions differed – implicating a difference in visual feedback modulating firing rate.



Figure 4.9 Population PSTH for all recorded IPL cells with activity, averaged across trials and all recording sessions (n=84) from the unimodal (red) and bimodal (blue) conditions. Data is for the preferred direction, aligned to target acquire (t=0).

One drawback of a low firing rate is an inability to create a spike spectrum.

In many cases in the IPL, there were insufficient action potentials throughout the course of

a trial to create an accurate spectrum for classification purposes. Using the dataset from above as an example, 49% (51/105) cells did not have enough spikes in either condition to compute a spectrum. These cells were therefore excluded from analysis. Slightly more than half (51%, 53/105) had enough spikes to compute a spectrum. Despite the large number of cells that were excluded, the distribution of spike train classifications largely resembled that of the SPL. Table 3 summarizes IPL classifications for both conditions from the example dataset, but this represents stereotypical results across all recording sessions.

	Bimodal Condition							
Unimodal	Oscillatory	Bursty	Refractory	Poisson	Other	Unclassified		
Oscillatory	16	2	8	0	1	2		
Bursty	0	0	0	0	0	0		
Refractory	7	0	10	0	2	0		
Poisson	0	0	0	0	0	0		
Other	1	0	0	0	6	10		
Unclassified	0	0	3	0	3	34		

Figure 4.10 IPL Cell classifications in the unimodal and bimodal conditions for a stereotypical recording session

There were no Poisson-like cells, in this example or across all the other recording sessions. Bursty cells were similarly rare, with never more than 2% of cells being classified

as such in either condition. Like the SPL, oscillatory cells were the most common classification. Across recording sessions, 21-36% of cells exhibited oscillatory spiking response in the beta band during bimodal trials. Oscillatory spiking was somewhat more common in the unimodal trials, with 25-39% of cells exhibiting oscillatory responses. The number of refractory cells had a greater variability across recording sessions, with 12-27% of cells exhibiting refractory spiking patterns during bimodal trials. This was even more pronounced for the unimodal condition, with 8-34% of neurons being classified as refractory. In general, neurons in the PPC, both SPL and IPL, tended to fall into one of three categories. Cells were either oscillatory in both conditions, or oscillatory in one condition and refractory in the other. Thus, there may be populations of cells within the PPC that have firing patterns that are selectively modulated based on available sensory cues.

In order to rule out cortical cell-type being responsible for any variability in the spike responses the waveform shapes were examined across recording sites. Some models of conjunctive encoding from the hippocampus suggest that inhibitory neurons would be required for cells to fire in response to specific presentation of multiple stimuli, which could then provide a potential framework for multisensory integration. In order to rule out this mechanism, the spike widths of recorded neurons were quantified. Previous studies have suggested that spike waveform widths can be used to distinguish inhibitory interneurons from pyramidal cells (Mitchell et al., 2007; Maimon and Assad, 2009; Torres et al., 2009). To test whether inhibitory cells could be providing the necessary inhibition for conjunctive encoding, the relationship between the waveform widths of the cells and

their responses under the multisensory condition was examined. After computing the average waveform width for each cell, Hartigan's dip test of unimodality (statistical mode, not sensory modality) was used on the distribution of waveforms widths to determine if there are distinct groups of waveform shapes. Spike widths were measured as the time interval between the trough and peak of the recorded spike waveforms. The spike amplitude was computed as the difference between the voltage at the peak and trough of a given waveform. Spike widths and amplitudes were then averaged across all waveforms for a given cell. A Kruskal-Wallis test showed no significant differences in width or amplitude across the three groups of oscillatory cells, suggesting the oscillatory spiking responses didn't arise from different cell types, at least not as can be differentiated by waveform

# Discussion

Although several studies have shown that the interaction of different sensory processing streams alters neuronal firing rates in the primate brain, the relationship between such interactions and action potential timing has remained relatively unexplored. Based on previous work (Buneo et al., 2003; Lloyd et al., 2003; Brovelli et al., 2004a; Senkowski et al., 2008) we hypothesized that SPL neurons would show evidence of oscillatory activity in the beta band during the sustained maintenance of arm position, and that these oscillations would be enhanced under bimodal conditions. Given that more regular (e.g. oscillatory) spiking leads to reduced spike timing variability (Maimon and Assad, 2009), enhanced spiking oscillations under bimodal conditions would also be consistent with our

previous findings of reduced intra-trial spiking variability under bimodal conditions (Shi et al., 2013). Although oscillatory spiking was commonly observed here, we did not find evidence that these oscillations were consistently enhanced under bimodal conditions. Instead some neurons fired rhythmically in the beta band under only one set of sensory conditions (unimodal or bimodal), while others did so under both conditions. The results suggest that the SPL and IPL may belong to a putative beta-synchronized network for arm position maintenance (Brovelli et al., 2004a) and that position estimation could be subserved by different subsets of neurons within this network depending on available sensory information. In addition, the nature of the observed spiking variability observed in this study suggests that computational models of multisensory interactions in the PPC and elsewhere should account for both Poisson-like and non-Poisson variability.

#### Behavior

In the experimental sessions described here, animals performed a reach and hold task while receiving either unimodal (proprioceptive) or bimodal (visual-proprioceptive) sensory feedback. Despite consistent difference in firing rates between the two conditions (described below; see also Figure 2), average arm endpoint positions and variability in endpoint positions did not differ between unimodal and bimodal conditions. It has also previously reported no differences in average eye position or variability in eye position during this task (Shi et al., 2013). No difference in arm endpoint position was an expected consequence of our experimental design. In this initial exploration of multisensory interactions it was desirable to ensure that any differences in firing rates that were observed did not reflect the fact that animals held their arms at slightly different positions in the two

tasks and were instead due to the different visual conditions. As a result, animals were trained to maintain their arm position within a very tight behavioral window in both tasks. However, this behavioral constraint also resulted in endpoint variability being roughly equivalent between the two conditions. It's currently unclear how to interpret difference in firing rate during multisensory interactions without a concomitant change in behavior. It should be noted however that other studies exploring the neural correlates of multisensory integration have also not observed a concomitant change in perceptual or action-related variables mainly because such variables were not monitored. For example, work by Graziano and colleagues have previously shown differences in firing rates with and without arm vision in a task where the animal was not required to move or make a perceptual judgement (Graziano et al., 2000). Since it is impossible to monitor all possible behavioral variables in a single experiment, the most logical explanation for the observation of a neural correlate without a corresponding behavioral correlate is a perceptual or behavioral change that is not observed simply because it is not monitored. Given the known sensitivity of SPL neurons to differences in arm configuration (Scott et al., 1997; Torres et al., 2009), the most likely explanation for those results is that animals used either a slightly different arm configuration while maintaining their position with and without visual feedback, or they used roughly the same configuration but exhibited differing degrees of variability in configuration between conditions. The IPL has been implicated in processing perceptual attention, such as in neglect (Mattingly et al., 2004), and in other attentional-related motor tasks (Andersen et al., 1990; Clower et al., 2001; Culham et al., 2006). Despite controlling for attention-related modulation by having the

monkeys fixate during the static holding period, it could be possible that increased cognitive functioning is required to maintain position during proprioceptive only trials. In that case there would be no outward behavioral correlate. Additional experiments will be necessary to distinguish between these and other potential explanations for the changes in neural activity reported here and elsewhere.

# **Effects of Multisensory Interactions on Firing Rates**

As described previously by Shi et al (2013) for SPL, and here for IPL, firing rates were suppressed under bimodal conditions, consistent with a subadditive interaction of visual and proprioceptive inputs. Early work by Stein and colleagues in the SC described additive, subadditive and superadditive responses to multisensory interactions depending on factors such as spatial and temporal congruency. More recent experimental work however suggests that superadditive responses are less common than initially believed, being observed generally for weak responses to unimodal stimuli (Stanford, 2005; Fetsch et al., 2013). This finding is more in line with computational modeling studies employing a probabilistic population coding framework which predicts that cortical areas should exhibit largely additive or subadditive responses (Ma et al., 2006). Interestingly, recent studies of visual-vestibular interactions under conditions designed to test for optimal integration of these inputs showed a predominance of subadditivity in the dorsal medial superior temporal area (Morgan et al., 2008). Similarly, studies of other cortical regions employing different experimental paradigms (Dehner et al., 2004; Barraclough et al., 2005; Sugihara et al., 2006; Avillac et al., 2007) have reported substantial degrees of multisensory suppression (and therefore subadditivity). Although the significance of this relatively ubiquitous suppression is still not entirely clear, it is noteworthy that some studies have provided evidence that suppression of spiking and reduced spiking variability resulting from multisensory integration is associated with greater encoded stimulus information and greater population decoding accuracy (Kayser et al., 2010; Shi et al., 2013).

## **Spike Train Dynamics**

A relatively large number of neurons in this study could not be classified as Poisson, bursty, refractory, or oscillatory and were therefore classified as 'other', particularly in the SPL. This is due in part to the fact that the employed spike train classification scheme relies on meeting two separate criteria, one based on the power spectrum and the other on the autocorrelation function. Many cells exhibited power spectra that were consistent with bursty, refractory or oscillatory spike trains but did not meet the corresponding autocorrelation criteria or vice-versa. Of the cells with internally consistent spectra and autocorrelations, the vast majority were classified as oscillatory in the beta-band in one or both conditions. This preponderance of oscillatory spiking in the beta-band is consistent with other studies of the PPC using different tasks and behavioral epochs (Buneo et al., 2003; Joelving et al., 2007). It should be noted that virtually all of the oscillatory spike trains were accompanied by a spectral trough at low frequencies. Although somewhat nonintuitive, this suppression is consistent with a refractory period, i.e. a decreased probability of spiking shortly after the occurrence of a spike (Bair et al., 1994). A substantial number of cells in our population also showed evidence of refractoriness without accompanying oscillations, also consistent with previous investigations (Bair et al., 1994; Buneo et al., 2003; Compte et al., 2003; Joelving et al., 2007).

Although some neurons demonstrated power spectra that appeared Poisson-like, none were classified as Poisson when the corresponding autocorrelograms were considered. Although Poisson-like spiking has been reported in several subdivisions of the PPC, the percentage of cells classified as such appears to be task-, epoch-, and areadependent (Joelving et al., 2007; Maimon and Assad, 2009). The relative dearth of Poisson-like spike trains reported here has important implications for computational models of multisensory integration. That is, recent studies have demonstrated that Bayesoptimal multisensory integration can be implemented as a simple linear summation of cortical activity assuming that neural variability in the cortex is approximately Poissonlike (Ma et al., 2006). The present findings however reinforce previous studies that this assumption does not hold for all cortical regions. Although the model of Ma et al. is at least somewhat insensitive to violations of Poisson-like variability, it is not clear how well the model can accommodate neural variability which is highly regular, as observed here. As a result, it may be necessary for future modeling efforts to account for both Poissonlike and non-Poisson neural variability.

## **Temporal Coding of Multisensory Information During Limb Position Maintenance**

Although the basic premise of temporal coding, i.e. that information is encoded not only in spike rates but also in the precise timing of action potentials and/or ongoing neuronal (LFP) oscillations, has been postulated to play a role in phenomena such as feature binding, its relevance to multisensory interactions has been addressed only relatively recently (Senkowski et al., 2008). Some of the strongest evidence in support of this idea comes from analyses of neural data obtained from non-human primates engaged in tasks involving somato-auditory and audio-visual interactions. For example, interaction of somatosensory and auditory inputs has been shown to result in changes in the relative phase of ongoing oscillations within primary auditory cortex (Lakatos et al., 2007). Similarly, audio-visual interactions are associated with enhanced LFP and spike-field gamma coherence between auditory cortex and the superior temporal sulcus (Ghazanfar et al., 2008; Maier et al., 2008). Regarding changes in spiking, multisensory interactions have been shown to alter spike timing in the vestibulocerebellum of the mouse (Chabrol et al., 2015), in the dorsal cochlea nucleus of the guinea pig (Koehler et al., 2011), and in the cortex of non-human primates engaged in tasks involving audio-visual and visual-proprioceptive interactions(Shi and Buneo, 2009; Kayser et al., 2010) . The current findings extend those of Shi et al (2013) by showing that changes in spike timing can manifest differently in different subpopulations within a given cortical area, with potentially important implications for transcortical representations of perceptual and motor-related phenomena.

The present findings are consistent with the idea that the PPC is involved in estimating the state of the arm, as suggested by clinical and functional imaging studies in humans (Wolpert et al., 1998; Lloyd et al., 2003; Pellijeff et al., 2006; Parkinson et al., 2010) as well as neurophysiological studies in monkeys (Georgopoulos et al., 1984; Lacquaniti et al., 1995; Scott et al., 1997; Graziano et al., 2000; Torres et al., 2009; Buneo and Andersen, 2012; Shi et al., 2013). Previous work in monkeys, has also shown that static maintenance of arm position involves a beta-synchronized cortical network that includes the somatosensory cortex, inferior parietal lobule, and primary motor cortex

(Brovelli et al., 2004a). The strong beta oscillations observed in the present study suggest that the SPL and IPL are also a part of this network and support the idea that beta oscillations serve to functionally link ensembles of neurons in cortical and subcortical regions that are believed to be involved in the maintenance of current motor state (Womelsdorf et al., 2007; Senkowski et al., 2008; Engel and Fries, 2010; Wang, 2010).

Contrary to the stated hypothesis, there was no evidence that beta oscillations were consistently enhanced under bimodal conditions. Instead roughly equal numbers of neurons fired rhythmically in the beta band under only one set of sensory conditions (unimodal or bimodal) or both conditions and in the latter case, beta band power was the same magnitude in the two conditions. The fact that the beta oscillations of some cells were modulated by the presence/absence of visual input at all suggests that these oscillations are associated not only with sustained muscle activation and somatosensory feedback, as has previously been suggested (Baker, 2007), but also with ongoing visual feedback used for limb position maintenance. However, the lack of a consistent bias in the population raises the question as to the functional significance of these findings. One possible interpretation is that different subsets of neurons exhibiting beta oscillations during proprioceptive, visuo-proprioceptive, and both conditions, reflects the differential recruitment of partially overlapping neural ensembles devoted to these respective modes of sensorimotor control during the maintenance of arm position (Harris and Mrsic-Flogel, 2013). The idea that control mechanisms for the arm may differ in the presence and absence of vision is supported by numerous psychophysical studies in humans (Rossetti et al., 1995; McIntyre, 1997; McIntyre et al., 1998; Bagesteiro et al., 2006; Apker et al., 2011;

Apker and Buneo, 2012). In further support of this idea, functional imaging studies in humans indicate that the recruited nodes of a cortical network for arm position vary depending on available sensory information. For example, in the absence of vision, interaction of tactile and proprioceptive inputs has been shown to involve the right PPC, whereas in the presence of vision, interaction recruits a network of areas including the parietal and premotor cortices (Lloyd et al., 2003). Validating this hypothesis more directly would require recording from single neurons in multiple nodes of the state estimation network simultaneously and looking for evidence of functional coupling between subsets of neurons only under a prescribed set of sensory conditions. Such manipulations are intended to be the focus of future planned series of studies.

# CHAPTER 5 LFP AND SPIKE FIELD COHERENCE DURING ARM POSITION ESTIMATION IN TWO POSTERIOR PARIETAL AREAS

## Introduction

The local field potential (LFP) is a measure of the electric potential, or voltage, of a given volume of neural tissue. Unlike an action potential, which is the electrical output of a single neuron, the LFP signal represents the summed electrical activity of a local ensemble of neurons, and is thought to represent the synchronized input into the cortical area surrounding the recording electrode (Einevoll et al., 2013). Whereas the action potential is an all-or-nothing phenomenon that is treated as a discrete event during analysis, the LFP response is a continuous signal akin to magneto- or electroencephalography (M/EEG) where fluctuations in voltage are monitored in response to stimuli. Typically LFPs are low-pass filtered at  $\sim$ 300Hz from the electrophysiological signal recorded on microelectrodes, isolating them from the major components of the action potential. The resulting signal reflects the excitatory and inhibitory postsynaptic changes in electric potential, as well as subthreshold membrane oscillations (Sarko et al., 2013) – thus action potentials and LFPs represent functionally distinct neural processes. This functional difference can manifest in differences in signal response to a given stimulus, for example, modulations in LFP voltage response can occur with or without a concurrent change in spiking (e.g.: firing rate, temporal pattern). Because LFP captures synaptic processes that cannot be reflected in spiking activity, such as membrane fluctuations or subthreshold voltage changes, there is an inherent ambiguity in the LFP signal. Changes observed in

LFP response without a change in spiking behavior has led some researchers to view the LFP as having a modulatory role in neural processing (Schroeder et al., 2001; Ghazanfar et al., 2005; Schroeder and Foxe, 2005; Lakatos et al., 2007). For example, Ghose et al. found that small changes in LFP amplitude in response to an auditory stimulus facilitated visual discrimination during a multisensory task, implying the LFP signal may contribute to multisensory interaction and processing in a modulatory manner (Ghose et al., 2014).

LFPs can be examined in both the time and frequency domains. In time domain analysis, the LFP voltage signal is typically filtered using common signal processing techniques such as the Butterworth filter to separate the voltage response into different frequency bands. In this type of analysis, the LFP response is characterized by changes in voltage amplitude, often termed the 'evoked response'. The evoked response conveys information about underlying synaptic activity, and is often treated similarly to the spiking activity; e.g. characterized by its tuning to movement and/or stimulus direction. Differences in the enhancement or suppression of evoked potentials has been shown across frequency bands, indicating that different components of the LFP signal may uniquely contribute to information processing (Ghazanfar et al., 2005; Scherberger et al., 2005; Liu and Newsome, 2006; O'Leary and Hatsopoulos, 2006; Einevoll et al., 2013; Lehmann and Scherberger, 2015).

Frequency domain analysis is another approach to evaluate LFPs. This approach involves transforming the LFP signal using an appropriate method, such as the multitaper method discussed previously in this dissertation. The changes in spectral power within distinct frequency bands, such as alpha, beta, or gamma bands from the EEG literature, are then examined relative to a provided stimulus. There is growing evidence that these different frequency bands may subserve distinct neural processes relevant to multisensory integration (Ghazanfar and Schroeder, 2006; Ghazanfar and Chandrasekaran, 2007; Lakatos et al., 2007; Belitski et al., 2008; Ghazanfar et al., 2008).

The LFP signal has been studied in relation to sensory processing (Liu and Newsome, 2006; Berens et al., 2008; Belitski et al., 2010; Lee et al., 2011), motor planning (Scherberger et al., 2005; Heldman et al., 2006; Kilavik et al., 2012), cognitive processes such as attention (Berens et al., 2008) and memory (Pesaran et al., 2002), and as a control signal for neuroprosthetic devices (Andersen et al., 2004; Kilavik et al., 2012; Lehmann and Scherberger, 2015). The framework of many LFP studies in NHPs are based on the conventions of less invasive methods such as MEG and EEG, where the spectrum is divided into distinct frequency bands. The LFP is also thought to relate well to the blood oxygenation level-dependent (BOLD) signal of MRI in humans (Logothetis et al., 2001; Ghazanfar et al., 2008; Logothetis, 2008; Stevenson et al., 2014). M/EEG signals have been used extensively to detect rhythmic shifts, or oscillations, in large areas of cortex during multimodal interaction in different spectral bands (Engel et al., 2001c; Fries, 2005; Lakatos et al., 2005; Magri et al., 2012; Buzsaki and Draguhn, 2014). Large-scale oscillations are thought to be an important mechanism for modulating neuronal firing and coordinating activity across cortical regions.

There are a growing number of studies investigating what role oscillatory LFP activity plays in multisensory interaction in parietal cortex. It has been observed that visual stimuli can modulate the LFP power in the auditory cortex of non-human primates during

multi-modal tasks (Kayser et al., 2008). Studies indicate evoked responses may be involved in multisensory processing in parallel with oscillatory activity. Sieben et al. examined evoked LFP and oscillations in rat cortex in response to multisensory visual and tactile stimuli. Evoked responses were augmented during bimodal stimulation (presentation of bright light and a whisker deflection), and were phase locked to the stimulus presentation, indicating a local network response to the presentation of both stimuli. Bimodal stimulation modulated the spectral power as well by resetting the phase of ongoing oscillatory spectral activity (Sieben et al., 2013).

A number studies that looked at EEG or spiking activity have implicated beta oscillations may be linked to sensorimotor and visual processing, postural control, or "maintenance of the status quo" (Brovelli et al., 2004a; Barraclough et al., 2005; Androulidakis et al., 2006; Senkowski et al., 2006, 2008; Baker, 2007; Engel and Fries, 2010; VanGilder et al., 2016). In light of these results, beta oscillations in the LFP were the main focus of this study, but both alpha and gamma bands were examined as well for a number of reasons. Gamma band has been implicated in somatosensory processing (Bauer et al. 2006) and sensorimotor integration and movement planning (Sanes and Donoghue, 1993; Roelfsema et al., 1997). Furthermore, previous studies have shown that the different LFP frequency bands in both the evoked response and spectral power can carry different information about a stimulus (Pesaran et al., 2002; Scherberger et al., 2005; Belitski et al., 2010; Lehmann and Scherberger, 2015) or be used as separate decoding streams in BCI applications (Andersen et al., 2004). There is some evidence that gamma band has been implicated for somatosensory processing (Pesaran et al., 2002; Andersen et al., 2002; Andersen et al., 2002; Andersen et al., 2004).

al., 2004; Scherberger et al., 2005; Belitski et al., 2010; Lehmann and Scherberger, 2015) and sensorimotor integration and movement planning (Sanes and Donoghue, 1993; Roelfsema et al., 1997) and it is still unclear if these different frequency bands may serve different roles in processing sensory information in concert, though it is still unclear the extent to which this occurs. In an MEG study in humans, beta-band activity in posterior parietal areas during a reach planning task was shown to be related to reach targets encoded relative to spatial location of the body, whereas high gamma (>60Hz) was shown to be related to visual coding of reach targets (Buchholz et al., 2013).

An emerging area of interest is spike-field coherence, a measure of the synchronization of pooled synaptic activity of the LFP and neuronal spike firing. It has been proposed that neural coherence – a measure of the phase coupling between two signals – may provide information about long-range communication between brain areas that are anatomically separated (Fries, 2005; Canolty et al. 2010). Studies have reported correlations between spiking activity and LFPs that may reflect the underlying connectivity of local neural populations. Within local brain regions, the spike-field coherence is a measure of the synchronization of pooled synaptic activity of the LFP and neuronal spike firing. Coherent oscillatory activity may therefore be a potential mechanism for combining neural processes within and across brain areas, supporting the idea of "integration by coherence" – where different sensory modalities may link disparate cortical areas in a context-dependent manner through coherent oscillatory activity (Engel et al., 1992, 2001a; Gray, 1999; Salinas and Sejnowski, 2001; Fries, 2005; Womelsdorf et al., 2007; Senkowski et al., 2008; Benchenane et al., 2010; Singer, 2011; Sarko et al., 2013). A study by Romei

et al. was able to directly link synchronized oscillatory activity in visual cortex to behavioral outcomes, demonstrating that a cross-modal auditory stimulus affected visual perception (Romei et al., 2012). In a similar audio-visual study, when stimuli were presented simultaneously, coherence between the auditory and visual cortices rose significantly – signifying that coherence may be a signature of multisensory integration across cortical regions (Ghazanfar et al., 2008).

Traditionally, multisensory integration has been assessed from the perspective of the single neuron within a framework of converging inputs mediating firing rate. The generality of this model of integration has been challenged recently, as spike timing, oscillatory activity, and neural coherence have emerged as potentially important mechanisms underlying multisensory processing. To summarize, larger network responses to multisensory tasks have shown that evoked responses and the modulation of spectral power may play a role in multisensory processing, and coherent oscillations may facilitate communication between sensory areas. In light of these studies, spectral analysis techniques were used to measure changes in the spectral power of LFPs in the SPL and IPL of NHPs in response to changes in visual and proprioceptive feedback about arm position. Changes in spike timing as discussed in Chapter 4, and oscillatory LFP activity could have interactive effects. To explore this hypothesis, spike-field coherence measures were used to characterize the temporal coordination of action potentials with LFP activity in the two parietal areas during the task.

## Methods

## **Experimental Subjects and Paradigm**

Two rhesus macaques were trained to make eye and arm movements within a 3D virtual environment that was projected onto a mirror in the NHP's field of vision. An active LED tracking system monitored arm movements via LED markers placed on the monkey's wrist. A mirror blocked the view of the monkey's actual arm, but visual feedback of arm position was provided as a green cursor within the virtual environment. Eye movements were tracked using a remote optical tracking system. At the start of each trial, the animal had to align the arm cursor with the starting position, a green sphere presented in the center of the virtual workspace. Once this position had been maintained for 500ms, one of eight peripheral reach targets was presented and served as the "go" cue to begin the reach. When the peripheral target was acquired, the animal performed a saccadic movement back to the starting position. This began the "static holding period," where the animal maintained its arm position at the peripheral target while fixating at the starting position for 800-1200ms. During the static holding period, visual feedback of the arm cursor was allowed on half the trials (bimodal Vision [V] condition) and blanked on others (unimodal Nonvision [NV] condition). Behavioral windows surrounded the reach and saccade targets, and successful trials required the animals to maintain position within these windows for the duration of the trial. Each block of trials during a recording session consists of five pseudorandomly interleaved reaches to each target in each sensory condition.

## **Data Acquisition**

Similar to the experimental paradigm used to record spiking activity, LFPs were recorded using a different method for each cortical area. In SPL, LFPs were recorded using acutely-driven single microelectrodes. The SPL LFP data come from previous work that was focused on the spiking activity during multisensory interaction. As such, the LFP was not recorded during all recording sessions from this area, although overall there were 178/343 LFP recordings from SPL available for analysis.

The IPL activity was recorded using a chronically implanted array with 96 microelectrodes (BlackRock Microsystems). Hardware limitations made it possible to record 48 channels of LFP simultaneously. These 48 channels were assigned as the odd numbered microelectrodes on array, providing more distributed spatial coverage of LFP recordings in superficial cortex of the IPL.

In both SPL and IPL, LFPs and spike data was recorded simultaneously on the microelectrodes. The neural signals were amplified, and a multichannel acquisition system (MAP, Plexon Inc.) was used to filter and record the neural spiking data. The continuous analog data (LFP and eye position data) were separated from the spike data after amplification, and were recorded using a National Instruments Data Acquisition (NIDAQ) board. An A/D clock on the multichannel acquisition processor (MAP) box ensured that the spike and continuous signals were synchronized. A dedicated "data PC" received the output from the MAP system, as well as 8-bit strobed data from the NIDAQ device encoding the analog data and experimental events for synchronization. The LFP signals were low-pass filtered at 300Hz to remove components of the action potential and sampled at 1kHz to disk.

#### **Data Analysis**

## Evoked Potentials

From previous work in SPL (Shi et al., 2013) it was observed that population firing rates in the preferred direction were similar for the two sensory conditions, but the firing rate during the bimodal task was suppressed at the onset of the holding period. The spiking data also implicated that many cells were tuned to arm position, or the direction of reaching. In this study, time-domain analysis of the LFP examined whether these changes in firing rate were reflected in the evoked responses. LFP data underwent two stages of preprocessing. The Chronux toolbox (Bokil et al., 2010, http://chronux.org) was used to remove any 60Hz line noise or slow voltage fluctuations caused by electrical transients that may cause a slow "drift" of the signal. Using a sliding window linear regression, a leastsquares trend line is fit to the samples within each window, and each window is then weighted to fit a sinusoidal curve to the data representing the slow fluctuation which was removed. Line noise was removed using Thomson's regression method to detect and remove 60Hz sinusoids and any harmonics from the data. The raw LFP was subdivided by band-pass filtering into slow (0-13Hz) intermediate (13-30Hz) and fast (30-60Hz) frequency bands for each condition and reach direction, and were averaged across trials to compute the evoked response. A fourth-order Butterworth filter, run bi-directionally to remove time lags, was used to separate the LFP signal, in  $\mu V$ , into the aforementioned frequency bands. These frequency bands were created to approximate the alpha, beta, and low gamma bands, respectively. Within the literature there is a very fluid definition of where the cutoff lies for each these bands and where to subdivide the LFP for analysis of the evoked response (Rickert, 2005; Scherberger et al., 2005; Heldman et al., 2006; O'Leary and Hatsopoulos, 2006; Sridharan et al., 2011; Lehmann and Scherberger, 2015) but the frequency bands outlined here are consistent with the general grouping.

Changes in LFP amplitude could reflect directional tuning properties of LFPs as well. To quantify this, the filtered LFP signals were aligned to the start of the hold period. For each reach direction, the mean LFP response for each reach direction and sensory condition was squared, and then averaged over the holding period time window. Taking the square root of this value yields a response value, in  $\mu$ V, that can be compared for each reach direction and sensory condition) was used to assess whether significant differences in LFP response are tuned for arm position and/or sensory feedback.

Using the same framework from previous experiments (Shi et al., 2013) the enhancement/suppression index was computed based on evoked LFP response to changing sensory conditions. The reach direction eliciting the maximum LFP response (the preferred direction) may not coincide with the preferred direction found in the spiking analysis. Because it is thought that different components of the LFP may carry different information, the preferred direction may change across filtered frequency bands, and so was determined for all four response bins. The value of the LFP response was averaged across trials in the preferred direction for both V and NV conditions for each of the filtered response bands and the raw LFP signal. The preferred direction was defined as the reach direction with the largest trial-averaged evoked response in the NV condition, as was the convention in

previous studies (O'Leary and Hatsopoulos, 2006; Shi et al., 2013). The enhancement/suppression index was computed as follows:

$$I = \frac{V_{peak_NV} - NV_{peak_NV}}{NV_{peak_NV}}$$
(1)

Where V and NV refer to the trial-averaged evoked response for the preferred direction as defined by the NV condition. Positive index values indicate enhancement and negative values indicate suppression of LFP response across sensory conditions. Index values are considered to be significant at locations with significant differences in sensory condition as determined by ANOVA.

# Spectral Analysis of LFP signal

If the evoked responses are not phase-locked to a stimulus, information about the signal can be lost when the responses averaged across trials. are This deficiency that can be overcome by looking at the power spectrum of the signal, and prior studies have shown on LFP power can be modulated by movement or sensory related activity (Pesaran et al., 2002; Hwang and Andersen, 2011; Hagan et al., 2012; Lehmann and Scherberger, 2015). Temporal structure in LFPs was analyzed using the multitaper spectral analysis technique outlined in previous chapters of this dissertation. Briefly, a Fourier transform was applied to the tapered, continuous LFP time series to convert LFP data from the time domain into the frequency domain. Multiple orthogonal data tapers, characterized by their time length and bandwidth were used. Using the multitaper method reduces estimation bias and variance in the spectral estimate (Pesaran et al., 2002). In this

study 9 data tapers with time-bandwidth parameter of 5 were used, providing a spectral resolution of 6.25Hz. Significance levels of the multitaper spectral estimates for individual recording sites were computed across trials using the jackknife method, and population spectra error bars were derived from the standard error of the mean across recording sites. All spectral calculations were performed using custom programs in Matlab supplemented by the Chronux toolbox (Bokil et al., 2010). The power spectrum was computed for the static holding period and the baseline period (500ms where the animal arm was at the start position in the center of the workspace before a reach target was presented). For each reach direction and in each sensory condition, the spectral power in the holding period was averaged across trials and then normalized by the baseline power. After the power spectrum was divided into the alpha, beta, and gamma bands, oscillatory activity was indicated by peaks in the power spectrum. Significant differences between the spectra of different sensory conditions and task epochs were tested using permutation tests in each frequency band. Spectral differences between the baseline and holding period epochs to were examined for each frequency band to reveal any induced oscillations related to the maintenance of arm position. The power spectrum between sensory conditions during the holding period was also analyzed to evaluate sensory-related spectral differences for each frequency band.

# Spike Field Coherence

Spike field coherence can be thought of as the counterpart to the time-domain measure of cross-correlation. The SFC is a measure of the relative phase between two timeseries, a frequency-domain representation of the similarity of dynamics between a spike train and the voltage fluctuations produced by activity in the spiking neuron's local neural environment. SFC was computed using multitaper methods, and has the same bias and variance advantages as the spectral computations mentioned above:

$$C_{xy}(f) = \frac{S_{xy}(f)}{\sqrt{S_x}(f)S_y(f)}$$
(2)

The coherence  $(C_{xy}(f))$  is the cross-spectrum  $(S_{xy}(f))$  between two signals, normalized by the spectrum of each signal. It is unaffected by changes in firing rate, meaning it can be averaged across different time series (Jarvis and Mitra, 2001). This is an advantage over the cross-correlation, which is normalized in an *ad hoc* fashion and is dependent on the bin size of time lags (Pesaran et al., 2002). The magnitude of coherence takes a value between zero and one, and indicates the degree of correlation between signals, with a value of one indicating the two signals are perfectly correlated, and zero indicating the signals are completely unrelated. The confidence level for SFC is determined was the following formula: The coherence  $(C_{xy}(f))$  is the cross-spectrum  $(S_{xy}(f))$  between two signals, normalized by the spectrum of each signal. It is unaffected by changes in firing rate, meaning it can be averaged across different time series (Jarvis and Mitra, 2001; Pesaran et al., 2002). This is an advantage over the cross-correlation, which is normalized in an *ad hoc* fashion and is dependent on the bin size of time lags. The magnitude of coherence takes a value between zero and one, and indicates how correlated the signals are, with one being perfectly correlated and zero being completely unrelated. The confidence level for SFC is determined was the following formula:

$$CL = 1 - \alpha^{1/(K-1)}$$
 (3)

Where K is the number of data tapers used and alpha is significance level; for this study alpha was set at 0.05. Frequencies with coherence values that exceeds this confidence level are considered to have significant coherence.

From the previous chapter, it was noted that cells were grouped into categories based on sorting criteria using the spike train power spectrum and autocorrelation. Cells were classified as bursty, refractory, oscillatory, or "other," wherein "other" cells did not meet both criteria for one of the other groups. Cells without a sufficient number of spikes to compute a spectrum were omitted. None of the cells were classified as Poisson-like. The largest classification group comprised cells with spike trains that exhibited oscillatory activity in the beta band and therefore analysis focused primarily on significant spike-field coherence measures within this frequency range. According to the hypothesis that LFP oscillations may be related to enhanced spike timing, it was expected that significant spike field coherence would be observed between cells with beta oscillatory spiking patterns and recording areas with LFP oscillations.

The acutely recorded SPL data used only a single electrode during recording sessions, meaning the spike-field relations are limited to a single spike and LFP channel. Unfortunately, LFP were not recorded during all recording sessions, so some spike-field coherence values could not be determined. Spike-field coherence was computed for all beta oscillatory cells in the SPL, at recording sites where LFP data was available, for both

conditions during the baseline and holding periods. Because the IPL data were recorded simultaneously from the array, more combinations of spike-field interactions between the 96 spike channels and 48 LFP channels could be computed for the same conditions. The array also made it possible to seek coherent relationships across the full spatial area of the array.

## Results

## Behavior

Behavioral data was analyzed during the initial investigation into SPL neural activity (Shi et al., 2013) but will be summarized here. To ensure consistent behavioral results across recording sessions, IPL data was collected during the same task and from an animal who was also a subject during the SPL data collection. The experimental paradigm maximized the likelihood that arm endpoint positions would be the same during both unimodal and bimodal conditions of the task. This was to ensure that changes in the neural response would be due to differences in sensory processing and not behavioral differences. From the previous study, the average percentage of recording sessions with significant differences in mean endpoint position of the arm was  $6.9 \pm 1.5\%$  (MANOVA, P < 0.05), and average percentages for endpoint differences along the individual axes (horizontal, vertical, and depth) axes were lower than this (Levene's test, P<0.05). Shi's results suggest the static holding period behavior was largely the same between sensory conditions. The results of the current study were interpreted within this context.

# SPL

# Time Domain Analysis

#### Tuning of Evoked Responses to Location and Condition

Not all of the spike recordings from SPL also included LFP. Overall, there were 178/343 (52%) recording sessions in the SPL with LFP data available for analysis. LFP analysis had two main approaches in both cortical areas: evoked responses in the timedomain and spectral analysis frequency-domain. Figure 5.1 shows the "raw" LFP evoked responses for both sensory conditions from a single recording site. Each panel corresponds to one of the 8 reach targets, arranged by reach direction. Responses from the bimodal V condition are blue, unimodal NV condition are red. Responses are aligned to when the animal acquired the reach target location within the workspace, and the static holding period that is the focus of this analysis occurs from 0.4-1.2s of the trial. The static holding period is the trial epoch where the animal must maintain target endpoint position while the sensory feedback is manipulated. The responses in Figure 5.1 are averaged across trials (n=5). There is a similar response pattern across directions for this recording site, with a sharp dip in evoked response amplitude preceding and up to the target acquire event (t=0s), with this dip being the most pronounced to reaches to targets that are located to the left directions. Amplitude appears to increase again during the holding period, reaching a maximum around the onset of the static holding period before a general decrease in amplitude throughout the remainder of the holding period. Though there are some slight variations in the magnitude of the amplitude across directions, they follow this same basic trend. For a majority of recording sites the general shape of the raw voltage trace was similar for both conditions and reach directions, though not necessarily always resembling the traces in Figure 5.1

At the center of the 8 panels is a polar plot illustrating the trial-averaged RMS voltage activity during the holding period for each reach direction, showing a strong similarity in response amplitude for all reach directions. Notable is the uniformity between sensory conditions as well. At this recording site, the overall LFP response does not appear to be modulated by changes in sensory feedback during the static holding period; i.e.: the LFP responses were generally the same during both bimodal and unimodal trials. A 2-way ANOVA (factors: reach direction, sensory condition) for the evoked responses at this site showed no significant main or interaction effects (p<0.5). Thus the raw LFP response at this recording site was not sensitive to reach direction or sensory condition. Overall, this was representative of a majority of recording sites in the SPL for the raw LFP response, as only 8.43% of sites had significant effects of vision and 16.29% of recording sites had significant effects.



Time (s)

Figure 5.1 Raw evoked LFP response from an SPL site.Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by target direction. For each reach direction, responses were averaged across trials (n=5). Polar plot in the center of the panels is mean response voltage during the holding period for each reach direction and sensory condition. Dotted lines are baseline tuning, dashed lines are movement period tuning, and solid lines are holding period tuning.

To investigate whether different components of the LFP may have different responses, the raw LFP signal was filtered into slow, intermediate, and fast frequency
bands. Figure **5.2** shows the slow band evoked responses from the same recording site as Figure **5.1**.



Figure 5.2 Slow evoked LFP response from an SPL site.Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by target direction. For each reach direction, responses were averaged across trials (n=5). Polar plot in the center of the panels is mean response during the holding period for each reach direction and sensory condition. Same conventions are used as in Figure 2.1.

Referring to Figure **5.2**, the shape of the response of the slow frequency band is very similar to the raw evoked LFP with slow, wide peaks in the activity. There is a prominent downward peak around t=0, corresponding to the time at which the monkey acquired the target, before the static holding period began. There is a slight increase in amplitude during the early holding period (before sensory feedback is manipulated), reaching a maximum around the onset of the static holding period before a general decrease in amplitude throughout the remainder of the holding period.

Significant effects of reach direction were more common for the slow, intermediate, and fast responses as determined by ANOVA. For the slow frequency band, only 12.36% of sites showed directional tuning, which is slightly greater than the raw signal, though similar numbers of sites show significant vision (8.43%) and interaction (3.93%) effects as was seen in the raw LFP responses.

Directional effects were much more prevalent for the intermediate and fast bands, with nearly a quarter of the sites (22.47%, 23.03% respectively) having directional effects. The intermediate and high bands depicted in Figures 5.3 and 5.4 are centered around the zero axis rather than large, broad changes observed in the slow and raw bands.



Figure 5.3 Intermediate evoked LFP response from an SPL site.Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by target direction. For each reach direction, responses were averaged across trials (n=5). A polar plot in the center of the panels is the mean voltage response during the holding period for each reach direction in each sensory condition. Same conventions are used as in Figure 2.1.

In the intermediate band, evoked responses increase during the static holding period, as evidenced by higher peak-to-trough amplitudes. Though the bimodal V and unimodal NV responses do not have the same uniformity observed in the raw and slow bands, the evoked responses for both conditions increases during the holding period. In the fast band, trends are more difficult to observe, as response amplitude is inversely correlated with frequency. In order to quantify changes in evoked response and account for the oscillations, the square root of the squared evoked responses was used. The changes in response amplitude during the holding period did not appear to be spatially tuned. Polar plots in the center of the eight panels show the mean evoked responses for all frequency bands versus reach direction during the static hold period for both sensory conditions. The activity at this recording site did not show clear spatial tuning during the hold period, and the raw and filtered (slow, intermediate, and fast) bands all appeared to have a similar within-band responses to reach direction. In the fast band, the responses at this site to reach direction are nearly uniform across target and visual condition. Though intermediate and fast bands in general showed greater sensitivity to reach direction according to ANOVA (22.5% and 23%, respectively) the responses at this site are representative of the responses at a majority of LFP recording sites.



Time (s)

Figure 5.4 Fast evoked LFP response from an SPL site.Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by target direction. For each reach direction, responses were averaged across trials (n=5). Polar plot in the center of the panels is mean response during the holding period for each reach direction and sensory condition. Same conventions are used as in Figure 2.1

SPL	Raw	Slow	Intermediate	Fast
Reach Direction	16.29%	12.36%	22.47%	23.03%
Visual Condition	8.43%	8.43%	7.87%	2.25%
Interaction	2.81%	3.93%	6.74%	2.25%

Table 5.1 Summary of 2-way ANOVA results from SPL evoked LFP responses for raw, slow, intermediate, and fast bands during the holding period.

SPL	Raw	Slow	Intermediate	Fast
Target	2.81%	3.93%	6.18%	3.93%
Visual Condition	5.62%	5.06%	3.93%	8.43%
Interaction	1.69%	1.69%	2.81%	3.93%

Table 5.2 Summary of 2-way ANOVA results from SPL evoked LFP responses for raw, slow, intermediate, and fast bands during the baseline period.

SPL	Raw	Slow	Intermediate	Fast
Target	38.20%	40.45%	9.55%	9.55%
Visual Condition	4.49%	4.49%	6.18%	5.06%
Interaction	1.69%	2.25%	7.30%	7.30%

 Table 5.3 Summary of the 2-way ANOVA results from SPL evoked LFP responses

 for raw, slow, intermediate, and fast bands during the movement period.

As summarized in Table 5.1-3, overall very few recordings sites showed sensory or spatial tuning characteristics, particularly for the raw and slow bands. The LFP voltage

response in the intermediate and fast bands showed greater sensitivity to reach direction, though less than a quarter of recording sites showed significant effects of target location.

## Quantification of Multisensory Enhancement/Suppression of Evoked Response

It is possible that small effects of direction or condition may be overlooked when applying the 2-way ANOVA for all target locations and sensory condition. In accordance with other multisensory integration studies that focus on the peak response for a given receptive field, changes in evoked LFP responses were examined for the preferred and nonpreferred directions of a given recording site using the multisensory integration index to calculate the magnitude of enhancement or suppression. This method had been applied frequently for other brain areas, animal models, and behavioral paradigms (Stein et al., 1989; Barraclough et al., 2005; Ghazanfar et al., 2005). Previous studies defined the preferred direction for the LFP as the direction of maximum firing rate of a neuron recorded on the same electrode (Pesaran et al., 2002). In the current study, there were multiple neurons recorded on a single electrode, each with independent preferred directions that were not in alignment in many instances. Additionally, the LFP represents the summed neural activity of an area of cortex that may comprise many neurons. For these reasons, it was prudent to define the preferred direction as the direction that elicited the maximum trial-averaged evoked response during the static holding period during the unimodal task. The unimodal condition was chosen in accordance with previous conventions in studies of multisensory interaction in the posterior parietal cortex (Shi et al., 2013) and other areas (Stein et al., 1989; Ghazanfar et al., 2005).

An analysis of the differences in evoked responses between conditions for the raw LFP response indicated that a vast majority of recording sites had a reduction in LFP response amplitude during multisensory trials. Figure 5.5 is a figure of the population mean evoked response for both conditions in the preferred and nonpreferred directions. Since the LFP can take positive or negative voltage values, to prevent the evoked responses from washing out when averaged across SPL recording sites, the voltage traces in Figure 5.5 are the square root of the squared evoked responses. In the preferred direction, bimodal and unimodal responses were very similar in amplitude during the movement period, and diverge as the holding period begins (t=0.4), with bimodal responses suppressed relative to the unimodal responses. This is very similar to the spiking patterns observed in this area (see Figure 4.2 in Chapter 4). The responses in the non-preferred direction follow a similar pattern to the preferred direction, though exhibit further suppression, as expected. Notable is that in the unimodal responses in the non-preferred direction, were more suppressed than the bimodal responses.



Figure 5.5 Population evoked raw LFP responses for the preferred and nonpreferred directions for both bimodal and unimodal trials. Preferred direction was defined as the target location with the greatest LFP response during the holding period for unimodal trials. The mean response for the preferred direction in unimodal (red) and bimodal (blue) trials, as well as the mean response for the nonpreferred direction for unimodal (magenta) and bimodal (green) with jackknife error bars.

The enhancement/suppression index that is commonly used for quantifying multisensory responses single cells was computed for all sites in the SPL during the hold period for the raw LFP response, as well as each of the three filtered response bands. LFP responses were suppressed across nearly all SPL recording sites during the bimodal V task, indicating that responses were greater during trials with only proprioceptive feedback. Figure **5.6** shows bar plots of the enhancement/suppression index (*Eq. 1*). The x-axis represents the sites where LFP were recorded (n=178) and the y-axis is the percent

enhanced (values>0) or suppressed (values<0). Figure **5.6** shows the enhancement/suppression indices for the raw LFP, slow (0-13Hz), intermediate (13-30Hz) and fast (30-60Hz) (clockwise from top left, respectively). Sites with significant effects of sensory condition, as determined by t-test (p<0.05) are represented with green bars.



Figure 5.6 SPL Multisensory Enhancement and Suppression Indices.LFP responses were suppressed across nearly all SPL recording sites during the bimodal task. Green bars indicate sites with significant effects of sensory condition (t-test, p<0.5). Clockwise from top left: raw, slow, intermediate, fast. Each bar in the graph represents an LFP recording site.

At 90.4% of sites, the raw LFP response was suppressed, with similar numbers for the other filtered bands: 91.1% of sites for slow, 89.3% of sites for intermediate, and 89.3% of sites for the fast responses showed suppression. Though the number of sites showing suppression is similar across bands, it is notable that the sites that did show enhancement during the bimodal task was differed for many of the frequency bands; i.e.; a single site may show suppression in some frequency bands, but enhancement in another. A t-test (p<0.05) was computed for the LFP responses in the preferred direction for each visual condition. A significant difference in unimodal/bimodal response at a recording site was considered to have significant suppression/enhancement. Few sites showed a significantly different response to different sensory stimuli. Of the ones that did, none showed enhanced responses. All significant LFP responses were suppressed.

	Raw		Slow		Intermediate		Fast	
_	Enhance	Supp.	Enhance	Supp.	Enhance	Supp.	Enhance	Supp.
% Responses	8.43%	91.57%	10.11%	89.89%	13.48%	86.52%	10.67%	89.33%
% Significant	0.00%	8.43%	0.00%	6.18%	0.00%	11.80%	0.00%	9.55%

Table 5.4 Table summarizing the percentage of recording sites in SPL with enhancement or suppression of LFP activity during the multisensory portion of the task. (n=178). The bottom row are the percent of sites with a significant difference (t-test, p<0.5) between unimodal and bimodal LFP voltage response for the preferred direction.

The suppression of LFP responses during the bimodal condition coincides with the spiking responses recorded in the same area. During bimodal trials, spiking was suppressed during the holding period as well. Figure **5**.7 is a scatter plot illustrating the enhancement and suppression of LFP and spiking responses during the holding period for all LFP recording

sites. There is a large cluster in the third quadrant, indicating all the sites with suppression for both LFP and spike responses. Colored dots on the figure represent sites that had significant differences in responses during the unimodal and bimodal conditions, according to a t-test (p<0.05). All the LFP recording sites with significant differences in evoked response showed suppression, and nearly all (12/13) also had suppression in the spiking response. Only two sites had significant differences for both spiking and LFP responses, with suppressed responses in both locations.



Figure 5.7 Scatter plot of LFP and Spiking Enhancement/Suppression during the holding period. Each dot represents a site where LFP and spiking were recorded simultaneously. Green dots are sites where a t-test indicated a significant difference (p<0.05) between the LFP response in the bimodal and unimodal conditions. Pink dots are sites with significant differences in spiking responses. Cyan dots are sites with significantly different responses for spiking and LFP.

#### Frequency Domain Analysis

The LFP power spectrum was computed during the static holding period for each trial and analyzed separately in alpha, beta, and gamma bands. Across individual recording sites, there was very little difference in spectral power between unimodal and bimodal

conditions during the holding period, particularly for beta band frequencies. Figure 5.8 is an example of LFP spectra from an SPL recording site.



Figure 5.8 LFP spectra for bimodal (blue) and unimodal (red) for each target location in the SPL during the holding period (t=0.4-1.2s).

According to a 2-way ANOVA, the beta band had the fewest number of recording sites that showed sensory condition-dependent power changes, a surprising result in light of the single cell spiking responses observed in the same cortical area (Chapter 4). Additional analysis focused on the preferred and nonpreferred directions. Randomized permutation tests were used to determine significant differences between the power spectrum during bimodal V and unimodal NV trials for each recording site, with 95.51% of sites (n=178) showing no significant difference in beta power. When there was a difference, 1.12% of sites had significantly greater power in the unimodal NV condition, and 3.37% in the bimodal V condition. Figure 5.8 is an exemplary figure representing typical spectra of recording sites in the SPL, with very little difference in the power spectrum between visual conditions, and slightly greater power for reaches up and to the right. For the other spectral bands, power in the gamma band had similar results, with 88.77% of sites showing no significant differences in spectral power between the conditions, with greater power being more common during bimodal trials (6.74% of sites) than unimodal (4.5%). The alpha band showed more modulation in spectral power between conditions, with 39.89% of recording sites showing a significantly greater beta power during either bimodal V (17.42%) or unimodal NV (22.47%) trials. Table 5.5 summarizes the differences in power spectrum between sensory conditions during the holding period.

	Alpha	Beta	Gamma
Greater Power Unimodal Trials	22.47%	1.12%	4.49%
Greater Power Bimodal Trials	17.42%	3.37%	6.74%

Table 5.5 Summary of the percentage of recording sites in the SPL with greater spectral power during the holding period for each frequency band.

The largely similar power spectra during the holding period, excepting the alpha band, prompted a look at differences in power between task epochs. Randomized permutation tests were used to compare the difference in the power spectrum during the static holding period and a 500ms baseline period at the start of each trial beginning when the animal reaches the starting position. Induced oscillations were observed across all three frequency bands during the holding period, regardless of sensory condition, for a majority of the recording sites; i.e. spectral power increased significantly from baseline during the holding period. Induced oscillations appeared more commonly during unimodal NV trials than bimodal V trials, but it was still a widespread phenomenon.



Figure 5.9 Example LFP power spectra from a recording site in SPL. Spectrum averaged across trials for the preferred reach direction during the baseline period and static holding period. The blue line represents spectra from bimodal V trials, and the red line represents spectra from unimodal NV trials. There is a clear peak in beta power during the holding period that is indicative of the induced oscillations.

Beta power in the LFP increased during the holding period in both the bimodal V and unimodal NV conditions at a large majority of sites (75.28% and 84.27%, respectively). Taken in context with the previous results where only 1% of sites saw a greater increase in the unimodal condition, and only 3% of sites saw a greater increase in the bimodal power, for a large majority of the recording sites the change in spectral power from baseline to holding period was just an overall increase in beta band spectral power. Thus it appears that beta power in the LFP is modulated more by maintaining position of the arm than by the available sensory feedback during the task. The alpha band had very similar numbers (78.09% and 83.71%, respectively) when comparing induced oscillations during the holding period, but the results are not as straightforward as in beta band. Alpha band power at nearly 40% of sites was significantly greater in one or the other sensory conditions during the holding period. A further analysis showed that these differences in power during the holding period arose from the amplitude of the induced oscillations; i.e. even though spectral power tended to increase from baseline to holding period, at many recording sites the increase was greater under one sensory condition than the other. Gamma band had very similar numbers for bimodal and unimodal trials (81.46% and 82.02%, respectively)

	Holding Power > Baseline Power				
	Bimodal Trials	Unimodal Trials			
Alpha Band	78.09%	83.71%			
Beta Band	75.28%	84.27%			
Gamma Band	81.46%	82.02%			

Table 5.6 Percentage of recording sites in the SPL that had greater spectral power during the holding period than the baseline for each sensory condition.

The mean power at the central frequency for each band was compared using a 2way ANOVA (factors: arm location, sensory conditions). For beta and gamma band power during the holding period, more sites showed significant effects of target location than effects of sensory condition or interaction effects. Overall only a small proportion of sites showed significant changes in beta band, with 18.54% showing effects of target location, 6.18% for visual condition, and 5.06% for interaction effects. Similar trend was observed for the gamma band as well (22%, 4.5%, and 4.5% respectively). The small number of sites showing significant effects of sensory condition is consistent with the finding from the permutation test, where the bimodal V and unimodal NV conditions had very similar power spectra.

In the low frequency alpha band, more sites showed significant effects of the sensory condition than position or interaction, but it was only 6.18% of recording locations. Only 3.93% sites showed significant effects of target location in the alpha band, and only 1.69% showed interaction effects. Overall, only a small minority of recording sites in SPL showed significant effects according to ANOVA for visual condition during the holding period across frequency bands.

#### IPL

## Time Domain Analyses

#### Tuning of Evoked Responses to Location and Condition

There were over 30 days of recording sessions, but analysis has focused on ten sessions recorded 1-2 months post-surgery. For continuity purposes, unless otherwise noted the figures and analysis in this chapter come from the same recording session that was the focus of spiking analysis in the previous chapter. Overall there were 48 LFP channels available for recording in the IPL, approximately a quarter of the number of recording sites that were available in the SPL. Despite the smaller number of recording sites, there was a greater variety of responses that were modulated by visual condition or reach direction across the raw, slow, intermediate, and fast bands of evoked responses.

The different reach directions show different responses during the static holding period as well, with some reach directions showing large deflections much earlier in the trial than what was observed in the SPL ( $\sim$ t=0.5s) while in other directions peaks, both positive and negative, appear near the end of the hold period ( $\sim$ t=1.0s). Similar to the LFP response for the SPL, the responses for each sensory condition are remarkably similar. The changes in evoked responses observed across directions occur for both sensory conditions, which seems to suggest that changes in evoked response are due more to reach direction than changes in sensory feedback during the task.

Error! Reference source not found. IPL Trial averaged raw evoked LFP responses from a single recording site. Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by reach direction. For each reach direction, responses were averaged across trials (n=5). Polar plots in the center represent tuning for different task epochs using the same conventions as Figure 5.1.

Unlike the example recording site from the SPL (and SPL responses in general), the shape of the voltage trace is different across the eight reach directions. There evoked response during the movement period (t=-0.5-0) shows positive and negative peaks, depending on movement direction, with the largest amplitudes for target directions up and to the right. There is a second amplitude peak shortly after the onset of the static holding period (t=0.4) which is most pronounced for target locations downward and to the left. A visual inspection of the raw evoked potentials revealed that the voltage traces were dissimilar across target locations for an individual recording site, but were generally consistent for the same target location across all IPL recording sites; e.g.: the prominent amplitude peak during the movement period for the target location at  $45\Box$  in Error! Reference source not found..

A two-way ANOVA (factors: reach direction, visual condition, p<0.05) for this recording site indicated a significant main effect of target location but not visual condition during the static holding period (t=0.4-1.2). A polar plot in the center of the target panels indicates the mean response during the static holding period for each reach direction. In this example, the mean response for the unimodal trials (red) was slightly greater than that for the bimodal (blue) for most target locations during the holding period. For the overall population, half (n=24) of the recording sites showed significant effects of reach direction in the raw evoked LFP responses, whereas 31% (n=15) showed significant effects of the visual condition. Only 6.25% (n=3) showed interaction effects.

The evoked responses in the slow band in Figure 5.10 are very similar to the results observed in the raw evoked response, with large wide peaks that follow the similar patterns (e.g. prominent peaks during the movement period for some target locations). There are large deflections during the movement epoch for target locations upward and to the right, while movement related responses to other directions appear relatively flat. The evoked responses in the slow band for this recording site also had a significant main effect of target location, but not visual condition, as was observed for the raw LFP responses. For the overall population, there were similar numbers of recording sites with significant effects

of target location (n=24, 50%), visual condition (n=17, 35%) and interaction effects (n=3, 6.25%) between the raw and slow bands.



Figure 5.10 IPL Trial averaged slow evoked LFP responses from a single recording site. Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by reach direction. For each reach direction, responses were averaged across trials (n=5). Polar plot in the center of the panels is mean response during the holding period for each reach direction and sensory condition.

The large amplitude deflections of the raw and slow bands are not present in the intermediate band (Figure 5.11). Instead, the largest amplitude responses appear to occur

during the holding period for most target locations and sensory conditions. This site did not have significant main or interaction effects. For the overall population, few (n=8; 16%) of the recording sites showed significant effects of reach direction in the intermediate band of evoked LFP responses, whereas 10% (n=5) showed significant effects of the visual condition. Interaction effects were the most common for the intermediate band (n=9; 18.75%).



Time (S)

Figure 5.11 IPL Trial averaged intermediate evoked LFP responses from a single recording site. Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by reach direction. For each reach direction, responses were averaged across trials (n=5). Polar plot in the center of the panels is mean response during the holding period for each reach direction and sensory condition.

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In the fast band, depicted in Figure 5.12Figure 5.11, there are no clear changes in amplitude of the response that appear to occur in relation to trial epochs in either condition. The unimodal and bimodal trials elicit largely the same responses, as well, with the central polar plot overlapping for a majority of target locations. This site also showed now main or interaction effects, as was the case with a majority of the recording locations in the fast band. Only three (6.25%) of recording sites showed main effects of target location. None of the recording locations showed any effects of the visual condition. Interaction effects were also observed on very few trials (n=4; 8.33%).



Figure 5.12 IPL Trial averaged fast evoked LFP responses from a single recording site. Blue lines indicate bimodal V trials, and red lines indicate unimodal NV trials. Responses are aligned to target acquire (t=0s). The static holding period, where sensory conditions were manipulated, occurs from 0.4-1.2s. The figure includes data from all eight reach targets, arranged by reach direction. For each reach direction, responses were averaged across trials (n=5). Polar plot in the center of the panels is mean response during the holding period for each reach direction and sensory condition.

In general the 2-way ANOVA (factors: reach direction, sensory condition) for the evoked responses in IPL showed that the raw and slow bands were more sensitive to target location and sensory condition than the intermediate and fast bands, with 87.5% and 90.5% of recording sites, respectively, showing some main or interaction effect. A greater percentage of recording sites had significant differences due to sensory condition in the raw and slow bands, with 31.25% and 35.42% of sites showing significant effects, respectively. These results are in contrast to the SPL, where the raw and slow bands were largely insensitive to the visual condition during the task. The intermediate and fast bands on the other hand were largely consistent with what was observed in the SPL: only a small percentage of sites showed significant effects of sensory condition. In fact, none of the voltage responses in the fast band appeared to be modulated by sensory condition.

A large percentage of recording sites, nearly half, showed significant effects of differences in reach direction for the raw and slow bands, whereas these dropped considerably for the intermediate (4.17%) and fast (12.5%) bands. This seems to be clearly reflected looking at **Error! Reference source not found.**-Figure 5.12 which show the filtered evoked responses across reach directions for each sensory condition. Compared to the SPL, more recording sites showed significant effects of sensory condition and reach direction in the raw and slow bands, whereas as the intermediate and fast bands in SPL showed greater response effects.

		Raw	Slow	Intermediate	Fast
	Target	16.29%	12.36%	22.47%	23.03%
Ide	Visual Condition	8.43%	8.43%	7.87%	2.25%
	Interaction	2.81%	3.93%	6.74%	2.25%
	Target	50.00%	50.00%	16.67%	6.25%
IdI	Visual condition	31.25%	35.42%	10.42%	0.00%
	Interaction	6.25%	6.25%	18.75%	8.33%

Table 5.7 Percentage of recording sites showing significant effects of target location, visual condition, or interaction for SPL and IPL cortical areas per 2-way ANOVA (factors: target location, sensory condition; p<0.05).

	Raw	Slow	Intermediate	Fast
Target	0.00%	2.00%	0.00%	0.04%
Visual condition	25.00%	22.92%	43.75%	2.08%
Interaction	0.00%	0.00%	0.00%	4.17%

 Table 5.8 Summary of 2-way ANOVA results from IPL evoked LFP responses for raw, slow, intermediate, and fast bands during the baseline period.

	Raw	Slow	Intermediate	Fast
Target	52.08%	70.83%	14.58%	0.02%
Visual condition	0.00%	0.00%	0.02%	16.67%
Interaction	2.08%	6.25%	31.25%	0.00%

Table 5.9 Summary of 2-way ANOVA results from IPL evoked LFP responses for raw, slow, intermediate, and fast bands during the movement period.

## Quantification of Multisensory Enhancement/Suppression of Evoked Response

An analysis of the differences in evoked responses between conditions for the evoked LFP response in the preferred and nonpreferred directions did not have clear separation between conditions as was seen in the SPL. Figure 5.13 is a figure of the population mean evoked response for both conditions in the preferred and nonpreferred directions. The voltage traces in Figure 5.13 are the square root of squared voltage responses averaged across recording sites.

Figure 5.13 are the square root of the squared evoked responses. In the preferred direction, bimodal and unimodal responses were very similar in amplitude during the movement period, and diverge as the holding period begins (t=0.4), with bimodal responses suppressed relative to the unimodal responses. This is very similar to the spiking patterns observed in this area (see Figure 4.2 in Chapter 4). The responses in the non-preferred direction follow a similar pattern to the preferred direction, though exhibit further suppression, as expected. Notable is that the unimodal responses in the non-preferred direction, were more suppressed than the bimodal responses.



Figure 5.13 Population evoked raw LFP responses for the preferred and nonpreferred directions for both bimodal and unimodal trials. Preferred direction was defined as the target location with the greatest LFP response during the holding period for unimodal trials. The mean response for the preferred direction in unimodal (red) and bimodal (blue) trials, as well as the mean response for the nonpreferred direction for unimodal (magenta) and bimodal (green) with jackknife error bars.

Results in the IPL for the multisensory enhancement/suppression indices were more mixed (Fig. 5.15). For the raw LFP, only 43.75% of sites showed suppressed responses in the multisensory condition, a stark contrast to the near ubiquitous suppression observed in the SPL. A similar trend was observed for the slow band as well, though the incidence of suppression was higher at 58.33%. Interestingly, there were more than twice the number of sites with significant effects of condition that showed enhancement than suppression;

i.e.: even though a small majority of sites showed suppression, more significant sites showed enhancements. For the intermediate and fast bands, the rate of suppression resembled that observed in the SPL, with large majorities (75% for both) showing suppression. There were very few sites in these two bands that had significant effects of condition; only 3 significant sites in the intermediate band, 2 of which showed suppression. Across the different bands, some sites showed enhancement in one band and suppression in another, indicating that the evoked response within the different bands could be dependent on the frequency response. Bar graphs for the enhancement/suppression indices can be observed in Figure 5.14, where positive values indicate enhancement and negative values represent suppression. Indices are shown for the raw, slow, intermediate, and fast (clockwise from top left). Green bars indicate sites with significant effects of vision as determined by t-test (p<0.05).



Figure 5.14 IPL Enhancement/Suppression Indices - LFP responses were suppressed across nearly all IPL recording sites during the bimodal task. Green bars indicate sites with significant effects of sensory condition (t-test, p<0.05). Clockwise from top left: raw, slow, intermediate, fast. Each bar in the graph represents an LFP recording site.

Compared to the SPL, there was a greater incidence of enhancement of responses in the IPL, particularly for the raw and slow bands. Enhancement was more common for the raw LFP response, with 62.5% of sites (n=48) exhibiting enhanced responses. In the slow, intermediate, and fast bands suppression predominated, with 54.17% of sites for slow, 81.25% of sites for intermediate, and 75% of sites for the fast responses showing suppression. It is notable that the enhancement or suppression of responses was not consistent across frequency bands for a given recording site; i.e.; a single site may show suppression in some frequency bands, but enhancement in another. A t-test (p<0.05) was computed for the LFP responses in the preferred direction for each visual condition. A significant difference in unimodal/bimodal response at a recording site was considered to have significant suppression/enhancement. Similarly to the SPL, none of the recording sites showed significant enhancement of responses, all significant LFP responses were suppressed.

	Raw		Slow		Intermediate		Fast	
	Enhance	Supp.	Enhance	Supp.	Enhance	Supp.	Enhance	Supp.
% Responses	62.50%	37.50%	45.83%	54.17%	18.75%	81.25%	25.00%	75.00%
% Significant	0.00%	0.10%	0.00%	10.42%	0.00%	0.06%	0.00%	10.42%

Table 5.10 Table summarizing the percentage of recording sites in IPL (n=48) with enhancement or suppression of LFP activity during the multisensory portion of the task. The bottom row are the percent of sites with a significant difference (t-test, p<0.5) between unimodal and bimodal LFP voltage responses for the prefferred direction.

# Frequency Domain Analysis

The LFP power spectrum was computed during the static holding period for each trial and analyzed separately for the alpha, beta, and gamma bands. Similar to what was observed in SPL LFP responses, the IPL had only a small percentage of sites that showed sensory-dependent power changes during the holding period in the beta band. None of the



sites showed significant increase in beta power during the bimodal condition, and only 2% of sites showed an increase in unimodal power.

Figure 5.15 LFP spectra for bimodal (blue) and unimodal (red) for each target location in the IPL during the holding period (t=0.4-1.2s).

In contrast, power in the alpha band was significantly modulated for the unimodal condition, with about a third of recording sites (31.25%) showing significant sensory-dependent changes in spectral power during the holding period. Like the beta band, none of the sites showed an increase in power during bimodal trials, indicating the alpha band

power may be selectively sensitive to arm position signals rather than visual input. Though only a small portion of recording sites showed a significant increase in spectral power based on sensory condition, the response was mixed. Gamma band showed significant increases in spectral power for the unimodal condition in a small proportion of recording sites (12.5%), and even fewer (4.17%) sites showed significant increases in the bimodal condition. The largely similar power spectra during the holding period, particularly in the beta band, prompted a look at differences in power between task epochs. Randomized permutation tests were used to compare the difference in the power spectrum during the static holding period and a 500ms baseline period at the start of each trial.

Induced oscillations during the static holding period were observed in the IPL across all three frequency bands. Permutation tests comparing spectral power during the baseline and holding periods showed that a majority of recording sites showed an epoch-dependent increase in power during the holding period relative to baseline period. Figure 5.10 shows example spectra from a recording site in the IPL. This is from the same recording session that has been the focus of most of the analysis in this dissertation, and depicts an example site typical of the beta band, where power showed a significant increase in both conditions during the holding period relative to baseline. The beta peak in Figure 5.16 is rather prominent during the holding period, but the baseline beta power shows a slight peak as well. At this particular site, permutation tests showed that this was a significant increase in beta power. This was common across all the recording sites, with permutation tests showing beta power being significantly greater during the holding period for 81.25% of sites in the bimodal condition and 79.2% of sites in the unimodal condition.


Figure 5.16 Example LFP power spectra from a recording site in IPL. Spectrum averaged across trials for the preferred reach direction during the baseline period and static holding period. The blue line represents spectra from bimodal V trials, and the red line represents spectra from unimodal NV trials. There is a clear peak in beta power during the holding period that is indicative of the induced oscillations.

Taken in context with the previous results where only 2% of sites saw a greater increase in spectral power during the unimodal condition, it appears that an increase in LFP beta power from baseline to holding period is not sensory dependent.

Though a slightly higher number of recording sites showed an increase in power during the bimodal condition, it appears that beta power in the LFP is modulated more by maintenance of arm position than sensory feedback, which is consistent with the results from the SPL. Permutation tests showed a similar trend for the other frequency bands as well, with 79.2% and 89.6% of sites in the bimodal and unimodal conditions, respectively, showing increased alpha band power during the holding period. For gamma band, 77.08%

of sites showed an increase in power during the holding period for both bimodal and unimodal conditions, though it was not all the same sites showing the increase. Though all three frequency bands had a large majority of sites that exhibited increased power in the holding period for both sensory conditions, the sites where these increases were observed were not uniform across the distribution; i.e.: some recording sites only saw significant increase in beta or alpha power, and not in all three frequency bands. This is an indication that the induced spectral power may not just be a generalized increase in wideband power across the spectrum. The combined results observed in alpha band, where spectral power increased in an epoch- and sensory dependent manner for some sites indicates that alpha band may be modulated in a mixed fashion, with a bias toward the unimodal condition. An analysis of the amplitude of the induced oscillations showed that differences arose between the sensory conditions. Alpha band power increases were associated with the holding period (i.e.: spectral power increased relative to baseline), the degree to which the power increased was sensory dependent. Gamma band on the other hand, appears to have spectral power modulated by both sensory and task-related parameters, though the effects of sensory condition seem to be mixed and only minimal. The same number of recording sites showed increases in spectral power during the holding period for both conditions in the gamma band, though the sensory condition did influence this at a small number of sites. Whereas alpha band, on average, had higher spectral power during the unimodal condition, with nearly a third of sites showing significant increases, the gamma band exhibited mixed responses, with some sites having higher unimodal spectral power and some sites having

higher bimodal spectral power. This was only significant for a small number of sites, though significantly higher unimodal responses were more prevalent.

To look more into how task or sensory related parameters may affect spectral power across the three frequency bands, a 2-way ANOVA was conducted for reach direction and sensory condition. Power at the central frequency for each band was averaged across trials for a given recording site. The 2-way ANOVA (factors: arm location, sensory condition) had mixed results across frequency bands. Only a small portion (<2%) of recording sites (n=48) showed significant effects of sensory condition on spectral power in the beta band, which is consistent with prior analyses in SPL. A larger number of sites (12.5%) showed significant effects of reach direction, though it is still a small proportion of sites overall. No sites showed interaction effects in the beta band. The small number of sites showing significant effects of sensory condition is consistent with the finding from the permutation test, where the bimodal V and unimodal NV conditions had very similar power spectra.

The alpha band also showed no significant interaction effects. Despite the large number of sites that had higher spectral power in the unimodal condition for the preferred direction in the alpha band, only 12.5% of sites showed significant effects of sensory condition. In contrast, half (50%) of the recording sites showed significant effects of reach direction. Though not intuitive, this is consistent with results from the permutation test. Whereas the permutation test only included spectral power in the preferred direction, the ANOVA looked at spectral power in all directions. Visual inspection and subsequent permutation tests across all directions indicate that alpha band power was generally elevated in the preferred direction, with the unimodal response being higher at a small

portion of recording sites; i.e.: recording sites may be direction specific as related to spectral power, but the sensory condition further modulates the spectral power for a minority portion of the recording sites. In gamma band, it was notable that none of the sites had significant effects of sensory condition. In gamma band 12.5% of sites saw significant effects of reach direction, and 10.42% of sites saw significant interaction effects. These interaction effects could explain the permutation tests, where despite an equal number of recording sites showing greater power in the holding period for both unimodal and bimodal conditions, there were mixed results regarding sensory-dependent changes spectral power.

# **Spike-Field Coherence**

## SPL

Spiking and field potential data was recorded in the SPL from two rhesus macaques performing an arm-position maintenance task in a virtual reality environment. The acute recording technique for recording SPL activity used only a single electrode during each recording sessions, meaning spike-field coherence can only be computed for a single LFP channel and spiking data for each recording session. Spiking data results were reported in the previous chapter and in the literature (VanGilder et al., 2016) and comprised 343 individual neurons across a number of months. LFP recordings were made using the same microelectrode used for spiking data, and were captured during approximately half of the recording sessions. Due to an incomplete LFP dataset, the number of LFP channels recorded from the SPL was limited to 178. Unfortunately, not all of these sites also had neurons with sufficient spike counts to classify their spiking dynamics. Therefore the

spike-field coherence analysis was limited to recording sessions where robust LFP and spike data were recorded simultaneously.

The analysis focused on the cells with temporal structure in the beta band during the arm position maintenance portion of the task. The cells that exhibited beta oscillatory spiking activity were broken up into three groups: those that were oscillatory in unimodal condition only, cells that were oscillatory in the bimodal condition only, and cells that were oscillatory in both. The three groups had roughly equal numbers of cells (49, 41, and 47, respectively). Due to the limited number of LFP recordings, coherence values could only be computed for about half of the total number beta oscillatory cells. Of the cells that had beta oscillatory spiking in bimodal, unimodal, and both conditions, there were only 23 (46%), 25 (61%), and 23 (46%) sites, respectively, where LFP data was also recorded. At each of these sites, the spike-field coherence was computed for the baseline and holding period epochs of the trial for each of the sensory conditions. To examine whether LFP activity was driving beta oscillatory spiking activity in a sensory dependent way, spikefield coherence was first examined during unimodal and bimodal periods of the task when the animal was maintaining arm position in space (i.e. the holding period). An example of the typical spike-field coherence response during the holding period of a bimodal task is depicted in Figure 5.17. The red and blue lines indicate the magnitude of spike-field coherence, a measure of the linear correlation between spikes and LFP at each frequency. Error bars are Jackknife error bars. The horizontal line indicates a 95% confidence level, and magnitude coherence values above this line are considered significant.



Figure 5.17 Example SPL recording site with no significant spike-field coherence in the beta band.

Figure 5.17 is an example of typical coherence observed for cells that exhibited beta oscillatory spiking activity. The magnitude coherence values did not exceed the 95% confidence level, indicating no frequencies with significant coherence. During the holding period of the task, significant spike-field coherence in the beta band was only observed at a small number of sites. Somewhat counterintuitively, in the SPL cells that exhibited oscillatory spiking only under one sensory condition often had significant spike-field coherence for the condition without oscillatory spiking.

Table 5.11 Summary of spike-field coherence in the beta band during the holding period. Cells were classified as beta oscillatory cells under bimodal, unimodal, or both conditions depending on their spiking dynamics. Each column lists the number of cells from each of the three groups of oscillatory cells that had significant spike-field coherence. Not all oscillatory cells had LFP data for comparison; the percentage of sites is reflective of the available LFP data for each group of oscillatory cells.

Table 5.11 summarizes these findings. For the cells that were beta oscillatory in the bimodal condition only (i.e.: during unimodal trials spike trains were *not* beta oscillatory) only two sites had significant spike-field coherence during bimodal trials. In contrast, cells with non-oscillatory spiking in the beta band during the unimodal condition had significant beta coherence at five sites. A similar trend was observed for cells that were beta oscillatory in the unimodal condition only - only a small number of sites had significant spike-field coherence during bimodal trials, spike trains that were *not* beta oscillatory had significant spike-field coherence in the beta band at four sites. In other words, significant spike-field coherence in the beta band was more prevalent with cells that exhibited non-oscillatory spiking. This trend continued when looking at the cells that were beta oscillatory in both sensory conditions, where only three sites showed significant beta coherence for unimodal and bimodal conditions.

	SFC during Bimodal Trials	SFC during Unimodal Trials
Oscillatory Spiking Bimodal Task	2 (8%)	5 (22%)
Oscillatory Spiking Unimodal Task	4 (16%)	2 (8%)

Oscillatory Spiking in both	3 (13%)	3 (13%)

Table 5.11 Summary of spike-field coherence in the beta band during the holding period. Cells were classified as beta oscillatory cells under bimodal, unimodal, or both conditions depending on their spiking dynamics. Each column lists the number of cells from each of the three groups of oscillatory cells that had significant spike-field coherence. Not all oscillatory cells had LFP data for comparison; the percentage of sites is reflective of the available LFP data for each group of oscillatory cells.

A further examination of the cells that were oscillatory in both conditions did reveal an interesting pattern. There were no sites that had significant beta coherence during both unimodal and bimodal trials, despite all the cells exhibiting beta oscillatory spiking activity; i.e.; all sites that exhibited significant beta coherence did so during only one sensory condition. This prompted a further look at the cells with bimodal only or unimodal only oscillatory spiking. For cells that were oscillatory in bimodal only condition, only two sites had significant beta coherence during both sensory conditions; for unimodal only cells, there was only one site. Beta coherence was therefore typically only associated with one sensory condition for a given cell/LFP recording site combo, and was overall more common during trials with non-oscillatory spiking activity.

In order to determine if the significant spike-field coherence arose in a task-related manner, spike-field coherence during the baseline period of the task was also examined. Surprisingly, there were a larger number of sites that exhibited significant beta coherence during baseline relative to the holding period, a trend that was observed across sensory conditions and all three groups of cells with oscillatory spiking dynamics. Though overall the percentage of sites that showed significant spike-field coherence is still only about half. The disparity between the number of sites with significant coherence between oscillatory and non-oscillatory cells was not as pronounced.

	SFC during Bimodal Trials	SFC during Unimodal Trials
Oscillatory Spiking Bimodal Task	9 (39%)	13 (56%)
Oscillatory Spiking Unimodal Task	14 (56%)	13 (52%)
Oscillatory Spiking in both	12 (52%)	10 (43%)

Table 5.12 Summary of spike-field coherence in the beta band during the baseline period for beta oscillatory cells in the bimodal, unimodal, and both conditions.

It should be noted that the results from the previous chapter (VanGilder et. al, 2016), oscillatory spiking arose in response to the sensory condition. During baseline epoch of the task, cells did not generally exhibit oscillatory spiking behavior. In this context, it appears that during the baseline period of the task there is higher beta coherence despite a dearth of oscillatory spike trains, and during the holding period when oscillatory spiking arises in some cells, the beta coherence subsides. This also seems counterintuitive

in the context of the LFP results, wherein LFP power in the beta band increased during the holding period relative to baseline for a large majority of recording sites. These results seem to suggest that significant beta coherence is more prevalent during periods of the task when spiking and LFP beta oscillatory activity is absent.

# IPL

Spike-field coherence was measured in the IPL using 96-channel microelectrode array. Spiking data was recorded on all 96 digital channels during the task. LFP data was recorded simultaneously on 48 analog channels that were evenly distributed about the spatial footprint of the recording array; i.e.: every other channel on the array recorded analog LFP data. Spiking and LFP activity was recorded from the IPL in one rhesus macaque. Spiking data for this analysis was reported in the previous chapter, and is from the same recording session reported there. One ubiquitous trend in the spiking data from the IPL was very low firing rates. One drawback of a low firing rate is an inability to create a spike spectrum. In many cases in the IPL, there were insufficient action potentials during the holding period to create an accurate spectrum for classification purposes. For the spike data from the recording session that has been used throughout this dissertation, 49% (51/105) cells did not have enough spikes in either condition to compute a spectrum. These cells were therefore excluded from analysis, as computing spike-field coherence is contingent on being able to compute the spectrum. Slightly more than half (51%, 53/105)had enough spikes to compute a spectrum; the majority of cells with a spectrum were classified as beta oscillatory under unimodal, bimodal, or both conditions during the holding period, with 13 (31%), 8 (15%), and 16 (25%) cells, respectively.

The spike-field coherence was computed for each cell classified as beta oscillatory and all 48 LFP channels. The apparent task-dependent effects seen in the spike-field coherence in the SPL motivated an examination of the spike-field coherence for both the holding period and baseline period of the task under unimodal and bimodal sensory conditions. In general, significant spike-field coherence in the beta band of frequencies was more common in the IPL than was observed in the SPL, with nearly all of the beta oscillatory cells having significant coherence during the holding period for at least one sensory condition.

The IPL exhibited a similar trend as was seen in SPL, where trials with nonoscillatory spiking activity had higher incidence of coherence than the oscillatory counterpart in the same neuron. On a cell-to-cell basis among the subpopulation of cells with oscillatory spiking in the bimodal only condition, the prevalence of LFP channels with significant beta coherence varied between unimodal and bimodal trials; i.e.: some cells had significant coherence with more LFP channels during unimodal trials, and some cells had significant coherence with more LFP channels during bimodal trials. Though the average number of channels that had significant coherence was greater under the unimodal condition, Mann-Whitney U-test showed that across the subpopulation there was not a significant difference in single-cell responses to bimodal and unimodal trials (p=.52).

When the spike-field coherence for the baseline epoch in this group of cells was examined, there was a general increase in the number of sites that had significant beta coherence. This was particularly true for like-condition trials; where the number of sites with baseline coherence for a given sensory condition was more common than coherence during the holding period, and Mann-Whitney U-test showed that beta coherence was significantly more common during the holding period (p-0.04, bimodal trials; p=.049 unimodal trials). The number of beta oscillatory cells for the unimodal condition had a very similar distribution of coherence values as in the bimodal cells. Notable though is that the number of channels was generally greater during unimodal trials, though only slightly and a Mann-Whitney U-test showed no significance (p=0.47). There were more channels with coherent activity during baseline period than the holding period; significantly more so under bimodal conditions (p=0.04) than unimodal.

Beta oscillatory cells under both sensory conditions had the highest variability in the number of channels with significant beta coherence. Like the other two subpopulations of oscillatory cells, some cells had greater incidence of coherence during under one sensory condition, and the opposite for others. Figures 5.20-5.22 illustrate this, with the number of LFP channels with significant spike field coherence shown for each category of beta oscillatory cell, for all conditions and task epochs.



Figure 5.18 IPL Coherent channels in bimodal oscillatory cells during the baseline and holding periods. Each oscillatory neuron is represented on the x-axis, and the number of LFP channels with significant spike-field coherence in the beta band is on the y-axis.



Figure 5.19 IPL Coherent channels in unimodal oscillatory cells during the baseline and holding periods. Each oscillatory neuron is represented on the x-axis, and the number of LFP channels with significant spike-field coherence in the beta band is on the y-axis.



Figure 5.20 IPL Coherent channels in oscillatory cells under both conditions during the baseline and holding periods. Each oscillatory neuron is represented on the y-axis, and the number of LFP channels with significant spike-field coherence in the beta band is on the x-axis.

Looking at the median number of beta coherent channels across each of the three subpopulations of oscillatory neurons in Figure 5.21 does show some clear trends. In general, coherent activity is more common during unimodal trials, regardless of cell-type. During baseline for cells that are oscillatory in both conditions is the only exception. As was seen in the SPL, coherent activity is more common during the baseline period, with the median number of coherent channels being greater than half for all combinations of sensory condition and cell type.



Figure 5.21 Median Coherent Channels of beta oscillatory cells in the IPL

In addition to looking at the number of sites where coherent activity occurs, analysis looked at where those sites were and if they change across trials for a given cell. One advantage of the microelectrode array is the ability to record from a large number of channels simultaneously. This enables examination of how spike field coherence is spatially distributed in cortex, and if coherent activity changes between conditions or task epochs. One way to visualize these changes was to plot beta coherence as a heat map showing the approximate spatial location of the analog channels in the electrode. In reality the analog channels formed a checkerboard pattern on the electrode array, with every other one of the 96 electrodes also recording analog LFP data. Figure 5.22 shows an example 147

heat map as a 7x7 grid representing the LFP recording channels in the array. The digital channels omitted for visualization purposes. Pixels with a zero value represent recording channels where the magnitude of coherence did not surpass the 95% confidence level for significance. In this particular example, the bimodal oscillatory cell was recorded on an electrode at approximately location [2,2]. The grid represents trial-averaged coherent activity between a single cell and the 48 LFP channels during unimodal and bimodal trials. Color intensity represents the magnitude of coherence for a given cell-LFP combination, with the red and yellow map for unimodal trials and blue and green for bimodal trials. This exemplary map was chosen because it shows clearly distinct spatial patterns of coherent activity between the cell and LFP under different sensory conditions. Patterns of coherent activity across the spatial footprint of the array showed a general variability between sensory conditions in the holding period, so despite similar a quantity of synchronized channels between trial conditions, the underlying patterns of synchronization changed in a sensory dependent manner.



Figure 5.22 Spatial Distribution of Spike-Field Coherence in biomodal and unimodal trials for a beta oscillatory cell. X- and y-axis are grid numbers representing LFP channel locations. Higher intensity colors correspond to magnitude of coherence values for the given channel.

Inspection of these heat maps and the underlying patterns of which areas of the IPL selectively synchronize in response to task parameters, there was a large disparity between sensory conditions, as seen in Figure 5.22. Additional changes were observed as between the baseline and holding periods of the task as well. Figure 5.23 depicts this same cell shown in Figure 5.22, but includes the baseline period coherent activity.



Figure 5.23 IPL Spatial Distribution of Spike-Field Coherence in Bimodal and Unimodal trials for a beta oscillatory cell. X- and y-axis are grid numbers representing LFP channel locations. Higher intensity colors correspond to magnitude of coherence value. Left hand figures are for baseline period of the task and right-hand figures are for the holding period.



Figure 5.24 IPL Distribution of unique sites of coherent activity within the IPL under different sensory conditions. Along the x-axis is the percentage of sites that were beta coherent under only one sensory condition, and the y-axis is the number of spike recording sites.

Analysis of the different channels with coherent beta activity under different sensory conditions revealed that a majority of sites were unique for each condition. For example, the cell in Figure 5.22 had 17 and 15 channels with coherent activity during the bimodal and unimodal trials, respectively, but only two of those channels were coherent under both conditions. Across the population, no fewer than 35% of cells were different between the two conditions, with most having a large majority of sites that were coherent

only under one sensory condition – indicating that for any given cell, the areas of cortex that show synchronization vary depending on the sensory conditions of the trial. Figure 5.24 shows the distribution of unique beta coherence locations between the unimodal and bimodal trials.

#### Discussion

The common framework of multisensory integration rests on the idea that different unimodal sensory signals must converge in some manner for multisensory processing to occur. Early studies focused on the response characteristics of single neurons (Stein and Stanford, 2008) where "multisensory" cells would receive direct input from different sensory modalities. A complementary idea is the convergence of multisensory inputs into groups of neurons, where even neurons that are overtly responsive to a single sensory modality can be modulated by LFP activity related to multisensory interactions (Schroeder et al., 2001; Schroeder and Foxe, 2005; Allman et al., 2009; Meredith and Allman, 2010; Sarko et al., 2013). This idea of ensembles of multisensory neurons that are modulated by LFP activity coincides well with what is known about the posterior parietal cortex as a multisensory association area. As mentioned previously in this dissertation, there is a wealth of anatomical evidence pointing to the SPL and IPL being sites of converging sensory inputs from primary visual, somatosensory, auditory, and vestibular sensory areas, as well as a large degree of interconnectedness within the PPC (Andersen, 1987; Cavada and Goldman-Rakic, 1989; Martin et al., 1989; Andersen et al., 1990; Johnson et al., 1996; Wallace and Stein, 1997; Wise et al., 1997; Lewis and Essen, 2000; Orban et al., 2006; Rozzi et al., 2006). It could therefore be possible that different intermingled ensembles of neurons form networks to process sensory information, with LFP activity having a modulatory effect depending on the sensory sources. As was observed in Chapter 4, oscillatory spiking patterns arose in different groups of neurons depending on the visual and proprioceptive sensory conditions of the task. Subthreshold input currents to nearby neurons are a large component of the LFP signal, whereas the spiking reflect the output of single neurons (Tiesinga et al., 2008; Buzsaki and Draguhn, 2014). It was thought that LFPs may serve as a possible neural substrate for linking these neural subpopulations, either through a modulatory role or by directly driving action potential activity, e.g. through oscillatory LFP activity (Fu et al., 2004; Gail et al., 2004; Ghazanfar and Chandrasekaran, 2007). For the SPL, it was hypothesized that LFP responses would be sensitive to sensory conditions, wherein LFP evoked potentials would be modulated by the presence or absence of visual feedback. The spiking patterns observed in SPL, and to a lesser extent the IPL, suggest that beta oscillations may be involved in processing arm position estimates, with different subsets of neurons exhibiting oscillatory spiking depending on available sensory information. It was hypothesized that oscillatory LFP activity may be a mechanism for modulating the observed variability by linking these subsets of neurons in a functional network.

## **Evoked LFP Responses**

#### Effects of Multisensory Interactions on LFP Activity

SPL

Time-domain analysis of LFPs focused on changes in amplitude of the evoked potential in response to changing sensory conditions during the holding period. The trialaveraged evoked LFP potential was filtered into four different response bands. ANOVA testing showed that across all recording sites in the SPL, only a small percentage showed significant effects of sensory condition across the four response bands. Visual inspection of LFP potentials across reach directions showed similar response patterns during the holding period in both the unimodal and bimodal trials. Since the ANOVA may mask small effects of the sensory condition when the data was compared across target reach direction, analysis was also performed that focused on the evoked responses in the preferred and nonpreferred directions, a common practice in studies of motion control and multisensory integration (Barash et al., 1991; Flash and Sejnowski, 2001; Morgan et al., 2008; Dean et al., 2012; Shi et al., 2013; VanGilder et al., 2016)

LFP evoked responses in the preferred direction were examined using multisensory enhancement/suppression indices introduced by Stein and colleagues. Consistent with previous work in this area examining the single-cell responses to multisensory interaction (Shi et al., 2013) evoked LFP responses were suppressed under bimodal conditions across a majority of sites in the SPL. Though only a small portion of sites showed significant effects of sensory condition when using a t-test, all sites with significant effects showed suppression. The suppression of LFP activity in the SPL during bimodal arm position estimation may account for the subadditive firing rates previously observed in the SPL during bimodal trials.

The LFP activity is thought to be reflective of synaptic output within a localized area of cortex. The widespread suppression of LFP activity during bimodal tasks could be an influence on the suppressed firing rates seen during bimodal tasks in the prior study. Suppression of neural activity in response to multisensory stimuli, particularly a visual stimulus, has been previously demonstrated. The suppression of firing rates during bimodal tasks, particularly in response to a visual stimulus, has been shown in association areas such as parietal cortex (Shi et al., 2013), as well as primary auditory cortex (Kayser et al., 2010). Studies of crossmodal binding have shown that large-scale cortical activity (EEG) is suppressed when a visual stimulus is presented during an ongoing tactile stimulation (Senkowski et al., 2008). A study of multisensory speech perception found that responses to auditory stimuli were suppressed when accompanied by a concurrent visual stimulus (Stekelenburg and Vroomen, 2007). The temporal relation between audio and visual stimulus was important, as suppression only occurred when the visual stimulus was close enough in time to the auditory stimulus, a result interpreted as reflecting a temporal rule of multisensory integration mechanisms. Both of these studies were focused on how multisensory interactions were expressed in EEG event related potentials. Much less common are studies of multisensory integration in the evoked responses of the LFP. A study from Ghazanfar et. al. (2005) examined evoked LFP responses to audiovisual interaction in the auditory cortex of primates during passive stimulus presentation. This study found significantly more instances of enhancement than suppression during bimodal trials, and that suppression was more correlated with greater temporal disparity between the two stimuli (i.e.: duration between presentation of audio and visual stimuli was greater). In the current study, visual and proprioceptive cues were actively used for a task relevant behavior (limb-position maintenance). Though the importance of suppression during bimodal limb position estimation is still unclear, it is consistent with the spiking results (Shi et al., 2013) and supports the notion that the SPL is involved in limb position estimation from other neurophysiological studies in primates (Georgopoulos et al., 1984; Scott and Kalaska, 1997; Lacquaniti, 1998; Graziano et al., 2000; Torres et al., 2009; Buneo and Andersen, 2012)

# IPL

Multisensory interaction had different effects in the IPL. Across the population, the evoked potentials did not exhibit a clearly stereotyped response shape across reach directions as was seen in the SPL, indicating wholly different response to the task. Additionally, IPL LFP responses had greater effects of condition than was seen in the SPL, particularly for the slower bands. Furthermore, the raw and low frequency filtered IPL bands were more sensitive to sensory condition. Results from a 2-way ANOVA show that nearly a third of recording sites showed significant effects of sensory condition in the raw and low bands. In contrast though, the intermediate and fast bands had little or no effects from sensory condition, indicating that different bands may play different roles in sensory encoding. The enhancement/suppression indices in IPL seem to support this notion as well. For the intermediate and fast bands, widespread suppression was observed for the bimodal condition, consistent with results from the SPL. The raw and low bands, on the other hand, had mostly mixed responses, with some channels being enhanced and others suppressed during the bimodal condition. The number of sites with significant effects of vision was nearly split evenly between enhancement and suppression. There was a clear difference between LFP response in the intermediate and fast bands relative to the raw and low bands, with the raw and low bands having more sites with significant effects of sensory condition. These differences across filtered LFP bands are not unique in the literature. It has been noted that modelling studies have shown different components of LFP may carry distinct information (Einevoll et al., 2013) and different frequency bands have been observed having different tuning properties for motor actions (O'Leary and Hatsopoulos, 2006) and in anterior and posterior parietal cortex (Scherberger et al., 2005; Lehmann and Scherberger, 2015). Ghazanfar and colleagues have noted differences in multisensory enhancement and suppression of LFP responses in response to different auditory stimulus signals (Ghazanfar et al., 2005) and found distinct differences in responses to facial and auditory stimuli across LFP bands (Chandrasekaran et al., 2011). The LFP comprises a number of neural processes, including summed synaptic potentials, subthreshold potentials and various voltage- and ligand-gated membrane potentials that occur on slow timescales (Buzsáki, 2002; Mazzoni et al., 2008) so it isn't surprising that different components of the LFP signal may represent different processes and independent stimulus response activity (Belitski et al., 2010).

#### **Temporal Structure in the LFP**

There is rising interest in temporal structure of neural activity, particularly for LFP activity in relation to sensorimotor processing (Pesaran et al., 2002; Scherberger et al., 2005; Sridharan et al., 2011). Frequency domain analysis is complementary to the timedomain, and can provide additional information about neural activity, particularly when evoked potentials are not clearly phase-locked to stimulus onset (O'Leary and Hatsopoulos, 2006) as was the case in most recording sites here. Spectral analysis, particularly multitaper methods, are well suited for studying neural dynamics, and can overcome some of the bias and variance problems reportedly associated with time-domain analysis (Jarvis and Mitra, 2001; Pesaran, 2008). In this study the power spectrum of LFP frequency bands were examined in both superior and inferior parietal areas during a multisensory arm position estimation task. beta band activity was the initial focus of LFP temporal dynamics in both parietal areas in this study based on previous results. Spike train dynamics in these areas showed that temporal structure arose in subsets of neurons based on available sensory information, particularly manifesting as beta (13-30Hz) oscillations (VanGilder et al., 2016). It was therefore hypothesized that LFP activity would follow a similar pattern, with beta oscillations occurring selectively depending on available sensory stimuli. Instead, the results for both IPL and SPL show that beta band LFP spectral power is not particularly sensitive to multisensory inputs, where differences in temporal structure between unimodal and bimodal conditions occurred in fewer than 4.5% of recording sites in SPL and 2% of recording sites in the IPL. Instead beta oscillations appeared to contain information about the task epoch. Significant beta oscillations arose in LFP during the holding period of the task, where the animal maintained a position in 3D

space with and without visual feedback of the arm. These induced oscillations were not sensory specific, meaning that the presence of absence of visual feedback did not have modulatory effects on the temporal structure of the LFP. Compared to the baseline condition, the power during the holding period in the beta band increased in a large majority of the recording locations, with 75% or more recording sites showing increases during unimodal and bimodal trials in both the SPL and IPL. A 2-way ANOVA showed similar results, with a very low number of recording sites having significant effects of sensory condition. These results were not expected, particularly based on the spiking dynamics seen in these areas during the same task. There is a large body of evidence showing that the PPC is involved in sensory association and motor planning, with converging sensory inputs from proprioceptive, visual, and other areas (Bolognini and Maravita, 2007; Buneo and Batista, 2008; Hagan et al., 2012; Shi et al., 2013). These results may indicate that different mechanisms underlie the oscillatory LFP and spiking activity, or that the underlying neural networks responsible for coding sensory information related to limb position estimation influence LFP and spike response differently. Within the parietal cortex, networks of neurons that respond selectively to visual or proprioceptive inputs may be in close proximity. A sample of the general activity within an area, such as through LFP, may reflect beta activity in responses to the holding period. Individual samples, as measured by extracellular spike recordings, would only reflect a single node of that network with its own beta response properties. The near ubiquity of beta activity in LFP during arm position maintenance, and the relatively low number of recording sites where beta oscillations show significant effects of target direction support the notion that oscillatory beta activity is a mechanism for "maintaining the status quo" (Engel and Fries, 2010).

In order to determine if the increase in power during the static holding period was task-specific for the beta band, or just the result of wideband increase in spectral power, the alpha and gamma bands were also examined. The power increases observed in alpha and gamma bands followed a similar trend that was seen in beta band for both parietal areas, though there were some distinct differences. In beta band, induced oscillations had approximately the same spectral power under both the unimodal and bimodal conditions. gamma band and alpha band both had a greater number of recording sites where sensory condition influenced the magnitude of spectral power during the holding period, though alpha band was the most prominent. A majority of recording sites had higher alpha band power during the holding period (relative to the baseline) in both conditions and parietal areas, the response magnitude was sensory dependent for a number of recording sites. About a 35% of recording sites had significantly higher spectral power in one sensory condition or the other, even if both conditions had induced oscillations during the holding period; i.e.: power increased during the holding period, but the degree to which the power increased at some sites was dependent on the sensory condition. A similar effect was observed in the IPL as well, though responses were biased toward the unimodal condition: 31.25% of recording sites showed significantly higher spectral power under unimodal conditions. It has been suggested that modulation of alpha band power during multisensory interaction is related to crossmodal binding and intersensory attentional shifts (Senkowski et al., 2008). A number of studies have linked ongoing EEG alpha oscillations to visual

perception (van Dijk et al., 2008; Busch et al., 2009; Mathewson et al., 2009). Other evidence of alpha band being involved in sensory perception comes from a multisensory study where parieto-occipital alpha activity had pronounced responses to audiovisual stimuli (Sakowitz et al., 2005). alpha oscillations have been suspected of linking largescale neural populations, as the power density of electrical potentials are inversely proportional to the frequency (Buzsaki and Draguhn, 2014); i.e. lower frequency signals have greater cortical spatial reach. The higher incidence of sensory-dependent induced power may be related to activity from a large number of multisensory inputs across the parietal cortices. The number of recording sites with sensory-dependent shifts in gamma band power were diminished relative to alpha band, but followed the same pattern. Both unimodal and bimodal spectral power showed greater magnitude increase at select recording sites in the SPL, and in the IPL more sites had greater power under unimodal conditions than bimodal. Studies have implicated gamma band for somatosensory processing (Bauer et al. 2006) and sensorimotor integration and movement planning (Sanes and Donoghue, 1993; Roelfsema et al., 1997) though in those studies gamma band involvement was significantly more widespread.

## **Spike Field Coherence in Parietal Cortex**

#### SPL

A number of studies have looked at spike-field coherence in the parietal cortex in relation to reach or saccade planning (Hagan et al., 2012; Stetson and Andersen, 2014). This is the first study to specifically investigate coherent activity during multisensory interaction with respect to vision and proprioception during arm position estimation. This

investigation sought to link the subsets of beta oscillatory spiking activity previously seen in the SPL (VanGilder et al., 2016) with LFP oscillations using spike-field coherence measures. One limiting factor to the investigation was the number of LFP channels recorded in the SPL. Spike-field measures were only computed for spike and LFP data recorded during the same recording session. Unfortunately on a number of sessions the LFPs were not recorded, and consequently there were LFP data for only about 46-61% of the beta oscillatory cells (depending on classification), so the spike-field relations could not be fully characterized for the whole population of beta oscillatory cells.

It was hypothesized that the beta oscillations in the LFPs would be highly correlated with oscillatory spike trains during the holding period of the task. A number of theoretical studies have postulated that cortical oscillations in activity measured in interstitial space (such as EEG, ECoG, or LFP) may be a mechanism for linking neural populations for synchronized functional output (Engel et al., 2001b; Womelsdorf et al., 2007; Engel and Fries, 2010; Wang et al., 2015). Under this hypothesis, it was expected that spike-field coherence at beta frequencies would be greatest during the holding period between cells that exhibited beta oscillatory spike trains and LFPs with induced beta oscillations. Cells that were only beta oscillatory during unimodal trials would only be coherent with concomitant LFPs during unimodal tasks, and the opposite for cells with beta oscillatory spiking only during bimodal trials. The results of this study were quite the opposite from expectations. Looking only at the holding period, coherence activity were the most commonly observed between the LFPs and the non-oscillatory cells for a given classification; e.g.: of the cells classified as beta oscillatory in the bimodal condition only,

more than twice as many had significant beta coherence under unimodal conditions. This trend of fewer cells having significant beta coherence despite having oscillatory spike trains held for the other two classifications as well (oscillatory under unimodal/both conditions). This is notable especially because LFP activity was oscillatory at nearly all the sites with where cells with oscillatory spiking activity were recorded. Of all the cells that had significant beta coherence, for the vast majority it was significant under only one sensory condition; i.e.: only three cells were beta coherent under both unimodal and bimodal task conditions, regardless of the cell's classification. Though it would be expected that beta oscillatory LFP and spiking activity would intuitively be coherent, this does not appear to be the case. In the SPL, Spike-field coherence in the beta band may be a sensory-dependent measure, independent of the oscillatory (or non-oscillatory) spiking patterns of a given cell.

More interestingly though is the finding that significant spike field coherence was more common during the baseline period than the holding period. Even cells with disparate spiking characteristics under different sensory conditions (e.g.: oscillatory in unimodal only) had roughly the same number of sites with significant spike-field coherence. Notably during the baseline period, LFP beta power is suppressed relative to the holding period. During the baseline period the occurrence of significant spike-field coherence was more evenly distributed among cells with different sensory-response properties. beta coherence during the baseline period is more prevalent among all three subpopulations of oscillatory-spiking cells, and is extinguished during the holding period when betaoscillatory spiking arises. This result does not preclude the oscillatory spiking from being a mechanism of linking cells for processing relevant sensory data, but these findings suggest that beta coherence is not a driving factor of the oscillatory spiking patterns seen in the SPL during arm position maintenance.

IPL

Neural activity in the IPL was marked by very low firing rates during the task. Nearly half of the cells could not be examined for coherent activity due to spike counts, wherein the dearth of spiking activity prevented a spectrum from being computed. Over half of the cells in the IPL had beta-oscillatory spiking patterns, and it was hypothesized these spiking patterns were the result of intra-areal synchronization mediated by LFP and measurable through spike-field coherence. Despite temporal structure in the beta band during the sensory epoch of the task, spike-field coherence measures were remarkably different. Similar to what was seen in the SPL, the median number of LFP channels with coherent beta activity was greater during the baseline period than the holding period across all three groups of cells.

The different patterns of coherent activity relative to individual cells showed distinct differences under different sensory task conditions. LFPs reflect the average synaptic activity of neurons nearby the recording electrode. As the patterns of spike-field coherence relative to an individual cell change it is indicative of the neural environment responding differently to the sensory stimulus. Despise a greater median number of channels showing significant coherent activity during the baseline period, there are clear differences in how the neurons of the IPL respond to changing sensory conditions during the holding period. It is presently unclear how these patterns of coherent activity are

involved in multisensory integration, but nonetheless there are distinct sensory-dependent responses. The fact that the responses were modulated by the absence or presence of visual input on concert with proprioception implies that some degree of multisensory interaction is occurring.

Though the results here did not support the hypothesis that enhanced beta coherency would arise between oscillatory LFP and spiking activity during the holding period, it does not necessarily negate the idea that different subpopulations of neurons are selectively involved in the maintenance of arm position. Studies of coherence in sensory processing are common, particularly in the EEG and MEG literature. Due to the spatial resolution of EEG and MEG, many of these studies look at coherence across cortical areas during multisensory experimental paradigms, particularly between primary sensory processing areas and association areas such as parietal and premotor cortices. Increase coherent EEG activity in the beta band (13-18Hz, in this particular study) was found between the temporal and parietal cortices during audiovisual multimodal stimulus presentation, a finding the authors interpreted as a mechanism for binding multimodal neural ensembles (von Stein et al., 1999). Another audiovisual study found that long-range synchrony through neural coherence in the gamma band was associated with accurate speech perception (Doesburg et. al. 2008). Tactile and visual stimulus interactions enhanced EEG gamma band coherence, and phase synchrony was related to more accurate behavioral outcomes in a rubber hand illusion paradigm in humans (Kanayama et al 2007). These studies focused on the importance of coherence in perception, rather than state estimation for behavioral outcomes, but they indicate that neural coherence during
multisensory interaction may be a phenomenon that occurs across cortical areas rather than within. The coherence patterns that arise in the SPL and IPL under different sensory conditions could be a mechanism for enhancing communication between the parietal cortex and downstream areas such as premotor or motor cortices. The intra-cortical coherence patterns observed in SPL and IPL do not appear to be directly relate the LFP and beta oscillations, and the oscillatory spiking activity may be related to long-range communication from other cortical areas. Previous studies have indicated that coherence may arise between different cortical areas during multisensory or sensorimotor tasks (Engel et al., 2001a; Senkowski et al., 2008; Wang, 2010). For example, beta-synchronized networks may link parietal and motor cortices during sensorimotor tasks (Brovelli et al., 2004a). Cortico-cortical synchrony through neural coherence has been reported to arise in a frequency-specific manner between motor and sensorimotor cortices in pre- and postmovement generation task epochs (Arce-McShane et al., 2016), and increased coherence between auditory and superior temporal sulcus was related to multisensory interaction of heading signals (Ghazanfar et al., 2008).

The activity patterns observed during the baseline period indicate that beta coherence may play a role in internal processing states, rather than being directly stimulus driven. These findings seem to implicate spike-field coherence in the beta band may be involved with cognitive aspects of a task, such as attention or planning, rather than overt sensory or motor behaviors. There is some support for this in the literature. It has been reported that beta oscillations that increased coherence was associated with the engagement of attention. Enhanced synchrony was observed in area V4 during attended visual stimulus

responses, and coherency was diverted to distractors during attentional errors (Taylor et al., 2005). A study of interaction in prefrontal and parietal cortices during a top-down processing attentional paradigm showed enhanced coherency between the areas (Buschman and Miller, 2007). Another study proposed that coherence between visual areas V1 and V4 is modulated during attention to task-relevant information (Bosman et al., 2012)(Bosman et al., 2012).

There is evidence here that LFP oscillations are induced during the static holding period of an arm position estimation task two parietal areas. Spike-field coherence in both the IPL and SPL was more common during the baseline period, but there were sensory=dependent aspects to their activity during the holding period. Recent studies have shown that coherent and oscillatory activity may be an important mechanism for corticocortical communication. The nature of parietal cortex and its interconnectedness with cognitive, sensory, and motor function make it a primary area for examining long-range communication in the sensing, planning, and execution of volitional reaches. To validate the functional importance of LFP and spike-field coherence to arm position estimation in parietal cortex, it would be important to record from multiple cortical areas involved in the limb position maintenance process, including posterior parietal cortex, premotor cortex, and possibly even primary sensory and motor cortices.

### **CHAPTER 6 SUMMARY AND FUTURE WORK**

There work detailed here has focused on multimodal limb position maintenance of the arm, particularly the functional interaction of visual and proprioceptive cues during limb position maintenance. Although significant progress has been made in understanding multisensory interactions at the behavioral level, their underlying neural mechanisms remain relatively poorly understood in cortical areas, particularly during the control of the limb. To this end, neuronal and local field potential responses in the superior and inferior parietal lobules were recorded while non-human primates maintained their arm position in a 3D virtual reality space. Time- and frequency-domain analyses were used to quantify changes in spiking and LFP responses in response to different sensory condition.

Most of what is known about multisensory interaction at the single cell level comes from studies of the superior colliculus (SC) during the interaction of visual, auditory and/or somatosensory inputs. Several empirically-derived principles of multisensory integration are based on studies of the SC, such as super/subadditivity, where responses to strong stimuli can actually be greater/less than the sum of the responses to each individual stimulus. Super/subadditivity can be quantified through the enhancement or suppression of neural activity during multimodal tasks. The results from a number of neurophysiological and computational studies predict that cortical areas should exhibit largely additive or subadditive responses to multisensory inputs (Graziano et al., 2000; Ghazanfar et al., 2005; Ma et al., 2006; Sugihara et al., 2006; Shi et al., 2013). The importance of variability in spike timing for multisensory integration has also emerged as an area of interest, wherein a temporal code and/or oscillatory spiking activity within or across functionally-related neural ensembles may facilitate multisensory integration (Ghazanfar et al., 2008; Senkowski et al., 2008; Wang, 2010).

The LFP captures synaptic processes that cannot be reflected in spiking activity, such as membrane fluctuations or subthreshold voltage changes (Buzsaki et al., 2012; Sarko et al., 2013). This functional difference can manifest in differences in signal response to a given stimulus, for example, modulations in LFP voltage response can occur with or without a concurrent change in spiking (e.g.: firing rate, temporal pattern). Changes observed in LFP response without a change in spiking behavior has led some researchers to view the LFP as having a modulatory role in neural processing (Schroeder et al., 2001; Ghazanfar et al., 2005; Schroeder and Foxe, 2005; Lakatos et al., 2007). LFP has been studied in relation to sensory processing (Liu and Newsome, 2006; Berens et al., 2008; Belitski et al., 2010; Lee et al., 2011), motor planning (Scherberger et al., 2005; Heldman et al., 2006; Kilavik et al., 2012), cognitive processes such as attention (Berens et al., 2008) and memory (Pesaran et al., 2002), and as a control signal for neuroprosthetic devices (Andersen et al., 2004; Kilavik et al., 2012; Lehmann and Scherberger, 2015).

It has been proposed that neural coherence – a measure of the phase coupling between two signals – may be a method of communication between brain (Fries, 2005; Canolty et al. 2010). Coherent oscillatory activity is gaining attention as a potential mechanism for combining neural processes within and across brain areas, supporting the idea of "integration by coherence" – where different sensory modalities may link disparate cortical areas in a context-dependent manner through coherent oscillatory activity (Engel et al., 1992, 2001a; Womelsdorf et al., 2007; Ghazanfar et al., 2008; Senkowski et al., 2008; Sarko et al., 2013).

Recent multimodal work using EEG has led to a hypothesis that beta band activity may underlie "maintenance of the status quo", i.e. beta activity may be a hallmark of maintaining an existing motor plan (Engel and Fries, 2010). A number of studies focusing on beta band (~13-30Hz) have implicated oscillations may be a mechanism of linking functionally-related neural ensembles during the processing of multimodal information (von Stein et al., 1999; Brovelli et al., 2004b; Senkowski et al., 2006; Haegens et al., 2011). Of particular relevance to the current study is the hypothesis that beta band activity may underlie what Engel and Fries refer to as a "maintenance of the status quo", i.e. beta activity may be a hallmark of maintaining an existing motor plan (Engel and Fries, 2010). It is proposed that beta band activity is enhanced during periods where sensorimotor or cognitive maintenance is given priority, such as during working memory tasks, instructed delay periods or task periods requiring postural control (Engel et al., 2001a, 2001c; Androulidakis et al., 2006; Baker, 2007).

It is unclear how proprioceptive and visual feedback are integrated in cortical association areas during reaching tasks. Investigation of multisensory integration have primarily focused on auditory, visual, vestibular, or tactile cues, while proprioceptive sense has remained largely unexplored despite direct involvement of parietal cortex during

proprioceptively guided movements (Barraclough et al., 2005; Sugihara et al., 2006; Avillac et al., 2007; Gu et al., 2008). A study by Graziano and colleagues found evidence that visual and somatic signals regarding arm position were integrated in SPL, but their study relied on passive movement of the arm and therefore did not account for motor signals (Graziano et al., 2000). In this study, non-human primates made center-out reaches to peripheral targets presented in a virtual reality environment, and maintained the endpoint position of their limb with and without visual feedback during a static holding period in the task.

Prior analysis (Shi et al., 2013) found that firing rates were largely suppressed under bimodal conditions, consistent with a subadditive interaction of visual and proprioceptive inputs. Furthermore, both across trial and intra-trial variability in spike timing was reduced under bimodal conditions as measured by the Fano factor and Coefficient of Variation, respectively. Given that reduced intra-trial variability can result from the induction or enhancement of oscillatory spiking (Maimon and Assad, 2009) and that oscillations have been proposed to play an important role in multisensory interactions in the cortex (Senkowski et al., 2008), it was hypothesized that this population of cortical neurons would show evidence of induced or enhanced oscillatory activity under bimodal conditions.

A paradigm from earlier studies (Compte et al., 2003; Joelving et al., 2007) was adapted for classifying cells based on their spiking patterns. Sorting criteria based on the power spectrum and autocorrelation functions were used to classify spike trains as bursty, refractory, beta oscillatory, or Poisson-like during the holding period of the task. It was observed that a majority of cells in the SPL could be classified as beta oscillatory. Power in the beta band increased during the holding period of the task, but in an idiosyncratic way. Of the cells classified as beta oscillatory, about one-third exhibited oscillatory spiking in only the bimodal condition; about one-third in the unimodal condition, and about one-third in both conditions, forming three subpopulations of neurons that respond with oscillatory spiking patterns depending on task parameters. These three groups of cells may represent beta-synchronized subnetworks for arm position maintenance that are selectively activated depending on available sensory cues. Interestingly, none of the cells in the SPL were classified as Poisson-like, contrary to a general assumption of many modelling studies of neurons in this area.

In the IPL, firing rates were much lower than what was observed in the SPL, with mayn neurons unable to be classified due lacking an adequate number of spikes for computing a spectrum. Of the cells that could be classified, similar results to SPL were observed, with a majority of cells being oscillatory in the beta band. There was also a relatively high number of refractory cells. Again, none of the cells were classified as Poisson.

It was hypothesized that the changes observed in the firing rates of neurons may be explained to some degree by the LFP. Evoked LFP responses were recorded on the same electrodes as the spiking data. Enhancement or suppression of evoked potentials can reflect stimulus-driven tuning responses, and different components of the LFP signal may uniquely contribute to information processing (Ghazanfar et al., 2005; Scherberger et al., 2005; Liu and Newsome, 2006; O'Leary and Hatsopoulos, 2006; Einevoll et al., 2013; Lehmann and Scherberger, 2015). The time-domain LFP response was filtered into four activity bands (raw, slow, intermediate, and fast), though the responses in the SPL were generally the same. Overall the magnitude of the evoked potentials were suppressed during bimodal tasks. Only a small portion of evoked responses during the holding period were tuned to reach direction or visual condition. During the movement period of the task, magnitude of the evoked response was greater than during the holding period, and tuning for reach direction was much more common, though differences between sensory conditions were minimal. This also parallels the spiking patterns seen in this area (see Figure 4.2, Chapter 4). This intuitively makes sense, as an increase in the extracellular potential may increase the likelihood of a cell to fire, and vice versa.

Evoked responses in the IPL were more varied across reach direction, with a greater influence of the movement period on the response amplitude. Recording sites in the IPL appeared to have greater tuning for reach direction than was observed in the SPL. Responses were generally suppressed during the holding period, though enhancement was somewhat more common for the raw and slow frequency bands than was observed in the SPL.

In the frequency domain, the power in the beta band increased during the holding period for both conditions in the SPL and IPL, meaning maintenance of limb position may induce LFP beta oscillations. In the SPL, power did not appear to have strong spatial tuning properties, as the increase in power was common for all reach directions in both conditions. At individual recording sites, the difference in spectral power appeared similar between the sensory condition, with similar power increase for bimodal and unimodal trials. The induced beta oscillations in LFP during the holding period may therefore be related to

maintenance of arm position in a non-sensory dependent way, e.g. maintenance of an ongoing postural state. Looking at spectral responses for the preferred direction across the population revealed that power during unimodal tasks was generally greater than during the bimodal task, particularly in the alpha and beta bands. Alpha power showed significant increases during the holding period relative to baseline, as well as clear suppression of power during bimodal trials relative to unimodal. Sensory differences in beta band were present as well, though not as pronounced as what was observed in the alpha band. Spikefield coherence was rarely significant for beta oscillatory cells and simultaneously recorded LFP activity. The changes spike power during the holding period cannot be explained by the oscillatory activity of the LFP. The power density of LFP activity is thought to be inversely proportional to frequency (Buzsaki and Draguhn, 2004) and therefore slower LFP oscillations, such as alpha, theta, or beta band may have more long-range influence than the local networks examined here. The results of this study provide support for analyses that suggest that intra-cortical neural populations may form a number of subnetworks that are selectively activated depending on the sensory input (Harris and Mrsic-Flogel, 2013). In the SPL, this manifests as subpopulations of neurons that fire in beta-oscillatory patterns in response to different visuomotor cues.

Future work is needed to see if long-range oscillatory activity from other cortical areas involved in visuomotor processing influence the spiking patterns seen here. Other multimodal areas in premotor and parietal cortices have been implicated in visuomotor function or state estimation. Neurons in the medial intraparietal area (MIP) (Johnson et al., 1996; Rushworth et al., 1997; Andersen and Buneo, 2002) areas 7a and 7b (Andersen,

1987; MacKay, 1992; Battaglia-Mayer et al., 2000) and area 5 (Kalaska et al., 1997; Ferraina et al., 2001; Shi et al., 2013) reflect both sensory and motor parameters of upcoming reaches. Another area, defined more functionally than anatomically, is the Parietal Reach Region (PRR) that includes parts of MIP and V6a (Batista and Andersen, 2001; Andersen and Buneo, 2002; Buneo et al., 2002). Most of these studies have focused on firing rates within a specific area of cortex during multimodal tasks. Despite a large number of EEG studies relating oscillations to multisensory integration across large brain areas (Senkowski et al., 2006, 2008; Wang et al., 2015) examinations of cross-cortical spectral relationships between spiking and LFP lacking, particularly for visuoproprioceptive interactions. Functional connectivity between different cortical areas may be revealed through simultaneous recording of spiking and LFP activity during a limb position maintenance task. Cross-cortical neural coherence may arise linking long-range LFP oscillations to local subpopulations of neurons. Previous multisensory integration work was instrumental in establishing principles at the single-cell level, however, future work would need to focus on how the numerous multisensory cortical areas are linked to create accurate sense of limb position during reaching, particularly with respect to oscillatory spiking and LFP activity as mechanism for inter-areal synchronization.

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# APPENDIX A PERMISSIONS

## PERMISSION FROM SCIENTIFIC JOURNAL

Chapter 4 is adapted from a published article in *PLoS One*. It has been updated to include additional results and analysis that best fit, in the context of this dissertation, within this chapter. Some language has been slightly modified for readability, but previous results and conclusions have not been materially changed from their published form.

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# APPENDIX B

# INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE FORMS

#### Institutional Animal Care and Use Committee (IACUC) Office of Research Integrity and Assurance Arizona State University 660 South Mill Avenue, Suite 315

Tempe, Arizona 85287-6111 Phona: (480) 965-4387 FAX: (480) 965-7772

#### Animal Protocol Review

ASU Protocol Number:	
Protocol Title:	tle:
Principal Investigator:	
Date of Action:	

15-1429R Cortical Mechanisms of Sensorimotor Integration Christopher Buneo 04/23/2015

The animal protocol review was considered by the Committee and the following decisions were made:

### The protocol was approved by Full Committee Review as presented.

If you have not already done so, documentation of Level III Training (i.e., procedure-specific training) will need to be provided to the IACUC office before participants can perform procedures independently. For more information on Level III requirements see <u>https://researchintegrity.asu.edu/training/animals/levelthree.</u>

Total # of Animals: Species: Protocol Approval Period:

Macaca mulatta 04/23/2015 - 04/22/2018

6

Pain Level: D

Sponsor: ASU Proposal/Award #: Title: ABRC 028286 Neural Correlates of Cooperative Manipulative Actions

Signature: IACUC Chair or Designee

Date: 4/31

Cc:

IACUC Office IACUC Chair