

**THE IMPACT OF LEARNING ON GOAL
ENCODING IN PREMOTOR CORTEX**

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The dorsal aspect of the premotor cortex (PMd) is a key node in the cortical pathway for visually-guided reaching. As such, one of the functions it may contribute to is the conversion from visual (input) to muscle (output) coordinates. My central question is whether or not the task that the animal is trained to perform may affect the tuning properties of PMd neurons. To address this, we recorded from PMd of two Rhesus monkeys while they performed a delayed reaching task. The animals were not trained to fixate. We found that tuning in PMd for reach target location relative to the direction of gaze was quite weak. We recorded neural activity using a 96-channel Blackrock microelectrode array. Nine sessions with 447 well-isolated neurons were analyzed. We first used a planar regression to determine neural tuning. We found that tuning to the location of the target relative to the hand (TH) and target relative to the eye (TE) exhibited statistically significant regression fits (F-test, $p > 0.05$). However, we recognized that our tuning measurements could be overestimates. We found that both animals exhibit consistent gaze behavior patterns during the task, and this meant that at least some of the TH or TE tuning we observed might be an artifact of the nonuniform gaze behavior. To check for this, we performed two additional analyses. We used a partial regression analysis to first remove the tuning due to one reference frame so we could investigate whether the residual variance was tuned in the other reference frame. When the effect of TH was removed, only 36% of our cells exhibited significant but weak tuning to TE. In our second analysis, we built a simulated neural population with TH tuning measured from the real data, but no TE tuning. When those simulated neurons were analyzed like

the real data, using the monkeys' actual gaze behavior, we found they exhibited TE tuning. Our results suggest that neural tuning to the target location relative to the eye is inherently quite weak, weaker still than has been appreciated so far.

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PREFACE

Many people describe the process of earning a PhD as running a marathon. This was definitely true in my experience, although with one addition: I was also trying to break in brand new shoes. When I entered the Bioengineering doctorate program at the University of Pittsburgh, I had a Computer Engineering degree and only one biology course on my undergraduate transcript. And yet, Dr. Aaron Batista took a chance on me. More than that, he showed confidence in me by enlisting me on a project with a heavy concentration in neuroscience. I want to thank Aaron for recognizing my potential, even if my experience was lacking, and for helping that potential become realized. His mentorship, encouragement, patience, and childlike enthusiasm for our work allowed me to make it to the end of this marathon. Aaron also helped to develop me as an educator and communicator. These are skills that I plan to use prominently in my future endeavors.

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1.0 GENERAL INTRODUCTION

The ability to move enables us to interact with our environment. We start off with only rudimentary control of our limbs as infants ([Bower et al., 1970](#)). Over time, our movement repertoire develops through observation and experience. We eventually learn how to perform complex patterns of movements that allow us to locomote from place to place, communicate with one another (speech, handwriting), and use tools. In order to move accurately and efficiently, our nervous system uses sensory stimuli – such as visual, auditory, haptic, or proprioceptive – to guide our movements. In the process of picking up a cup of water, we may determine where the cup is and its shape by how it looks, where our hand is in peripersonal space by proprioception, and what the texture and weight of the glass is by how it feels. All of these sensory signals provide us with the information to accurately move our hand toward the cup, shape our fingers to effectively hold the cup, and apply the correct amount of force to keep it safely in our grasp. In order for movements like that to be accurate and successful, our brain has to be able to perform complex calculations that transform sensory information into movement commands.

1.1 EYE-HAND COORDINATION

From birth, the human brain is primed to coordinate vision and movement of the hand. Newborns as young as 5-days old have been shown to possess rudimentary eye-hand coordination ([Bower et al., 1970](#)). When infants are presented with a moving object, their arm movements are directed forward more frequently than when the object is absent ([von Hofsten, 1982](#)). In addition, their reach endpoints are closer to the object when fixating the object. Neonates

have been shown to follow a moving target with their eyes and head ([Greenman, 1963](#)) and have a changing distribution of arm movements that adapts to the position of an object ([McDonnell, 1979](#)).

Numerous studies have explored the development of eye-hand coordination in adults and nonhuman primates. The sudden appearance of a visual stimulus in a subject's periphery can trigger an automatic saccadic eye movement towards the stimulus ([Todd and Gelder, 1979](#)). This ballistic reflex of the eyes in response to a stimulus is evolutionarily beneficial since quickly identifying potential assets and threats is advantageous. When coupled with a reach, your eye movements tend to lead your arm movement. While making an arm movement to a stationary target, the eyes make a saccade to the target prior to the movement ([Carlton, 1981](#)). Even when the situation demands very rapid and accurate movements to unanticipated targets, the eyes begin moving well before the arm does ([Carnahan and Marteniuk, 1991](#)). Tandem movements of the eyes and the hand allow the visual-motor system to maximize accuracy and precision while minimizing the temporal cost of reach planning and execution. When subjects are not permitted to move their eyes around their environment, movement accuracy worsens ([Mather and Fisk, 1985](#); [Prablanc et al., 1979](#)).

However, continuously performing a visual search for movement goals can sometimes be disadvantageous, especially while in the midst of performing reaches that require a high level of precision. [Neggers and Bekkering \(2002\)](#) asked subjects to perform rapid pointing movements to consecutive visual targets while recording eye behavior. Since the eyes can rapidly foveate and identify salient visual information much faster than the arm can complete a reach, it might be assumed that the eyes would continue to move to the next target in the pattern ahead of the arm. What [Neggers and Bekkering \(2002\)](#) found was that subjects would look at the current reach goal, but did not disengage the eyes and make a saccade to the next reach goal until the ongoing reach was complete. Even though locating movement goals and coordinating an initial reach plan is relatively cheap for the oculomotor system, there is a premium on navigating the limb throughout its movement. Even with proprioception providing information of the location of our hand, the absence of visual feedback produces clear motor deficits. When making reaches without visual feedback of the hand, subjects produce more variability in their reach endpoints ([Keele and Posner, 1968](#); [Carlton, 1981](#);

Zelaznik et al., 1983; Hay and Beaubaton, 1986), undershoot the target (Prablanc et al., 1979; Prablanc and Pélisson, 1990), and perform reaches with greater curvature (Sergio and Scott, 1998; Goodbody and Wolpert, 1999). This visual-motor error correction occurs even when we are not consciously aware of it. Saunders (2003) showed that when humans performed fast reaches with imperceptible visual perturbations to their hand trajectory, vision was continuously used to correctively guide the hand through the entirety of the arm's trajectory.

The integration of eye and hand movement signals in the brain seems apparent considering the mountain of behavioral evidence from reaching studies. But how is eye-hand coordination implemented in the brain?

1.2 REFERENCE FRAMES

Accurately reaching to an object requires knowledge of the spatial location of the movement endpoint, as well as other potentially relevant stimuli. However, there are numerous ways to define an object's location. Imagine giving a group of people directions to a house party. You would need to individually tailor the instructions you give based on where the person is coming from. Each travel plan will be different because the endpoint, your house, is in a different place in relation to each person's origin. In the same way, any object's location is dependent on what coordinate axes, or reference frame, are being used to localize it.

A reference frame is a coordinate system centered on a rigid body used to describe the relative position or orientation of another object. In the previous example, each partygoer had the same movement goal, but their movement plan differed based on the house's location relative to their own position. To expand the example even further, odds are that you define the location of your house in relation to the Earth (longitude and latitude) instead of the Sun. Using a reference frame that is centered on the Earth allows you to define the location of your home as a static position. If you were to center it on the Sun, the location of your home would constantly be shifting.

In much the same way, neurons in the brain that encode spatial location do so relative to some rigid body. This rigid body becomes the common reference point for all salient stimuli. Thus, a spatial encoding framework anchored to the direction of gaze might be labeled as being in a gaze-centered reference frame. More specifically, if a neuron's preferred stimulus position changes in a proportional fashion with changes to the direction of gaze, then it may be using a gaze-centered reference frame to encode position.

Direction and amplitude units are often necessary to accurately investigate the spatial encoding schemes employed by cortical neurons. A reference frame might best define position in a Cartesian coordinate system using horizontal (x) and vertical (y) components or a cylindrical coordinate system using radial (r) and azimuthal (θ) components.

There are two categories of reference frames: egocentric and allocentric. Egocentric reference frames are defined relative to ourselves (e.g. eyes, body, or hand). When you consciously plan a reach to a cup in front of us, typically you will determine the distance and position of the cup in relation to your body or hand. Allocentric reference frames are defined relative to something external (e.g. the room, building) (Olson and Gettner, 1995). The remainder of this chapter will focus on egocentric reference frames used in visually-guided reaching.

1.2.1 Reference Frames In Human Psychophysics

In what reference frame do people plan and execute movements? Our arms execute the planned action, therefore it would make sense that we formulate movements in relation to the hand, arm, or shoulder. We also rely on visual information a great deal for updating reaching plans and guiding online corrections. It is possible that our motor commands are planned in relation to our center of vision. Behavioral studies have given us some insight into this question.

Henriques and colleagues (1998) were the first to demonstrate a gaze-centered remapping scheme in human psychophysics. Subjects performed pointing movements to remembered targets in three separate behavior constraints: maintaining fixation on the target location (control paradigm), maintaining fixation on a peripheral location (static paradigm),

and performing a successive central-to-peripheral fixation pattern before reaching (dynamic paradigm). During the static and dynamic paradigms, subjects overshoot the target, likely due to an overestimation in the angle between the location of gaze and the remembered movement goal. In comparison, subjects had no trouble making accurate movements when fixating the target location. Similar gaze-centered reaching errors were observed for pointing to targets at different distances (Medendorp and Crawford, 2002), after body translations (Van Pelt and Medendorp, 2007), after smooth-pursuit eye movements (Thompson and Henriques, 2008), for pointing to goals inferred from expanding motion patterns (Poljac and Van Den Berg, 2003) and proprioceptive and auditory targets (Pouget et al., 2002; Jones and Henriques, 2010), and for repeated pointing movements to the same remembered target (Sorrento and Henriques, 2008).

However, gaze-centered coordinates are not the only mechanism for updating actions. Sober and Sabes (2005) showed that humans compare a reach target to both the visual and proprioceptive sensation of hand position. These signals are then integrated depending on the stage of motor planning. Additional studies have shown spatial encoding in a combination of gaze and somatosensory reference frames (Khan et al., 2005; Beurze et al., 2006; Blangero et al., 2007).

1.2.2 From sensation to motion in cortex

Movement behavior shows us the results of a completed action. In order to understand the process of generating a reach plan, investigating the cortical mechanisms of reaching is necessary. What do neurophysiology studies tell us about the reference frames used for reaching? What do we observe at the single neuron level?

Motor intention is generated through a network of nerve impulses spanning sensory- and motor-related areas of the brain. The successful completion of a reach relies on the ability of this visual-motor system to use visual stimuli to locate a reach goal and produce the correct motor command to guide the arm. When patterns of light from a stimulus penetrate the retina, visual information is relayed to the lateral geniculate nucleus (LGN) of the thalamus before it arrives in the primary visual cortex (V1), the earliest visual processing

area of the cerebral cortex. Cells in V1 are sensitive to the orientation and position of light (Hubel and Wiesel, 1959, 1962) and have a retinotopic organization. At the other end of the visual-motor pathway, vast corticospinal projections originating in the primary motor cortex (M1) send the finalized motor command to the limbs (Dum and Strick, 2002). Neural activity in M1 is selective for reach direction, preferring to maximally fire for one direction and decrease firing proportionally for directions further away (Georgopoulos et al., 1982, 1986). However, striate and extrastriate areas have no direct corticocortical connections with the frontal lobe (Pandya and Kuypers, 1969; Jones and Powell, 1970). Neither area can explicitly communicate with the other. Therefore, before visual information becomes a motor command, it must move through several areas of cortex for processing and refinement. It is likely that the reference frame transformation for reaching occurs within this network between the parietal and frontal lobes.

1.2.3 Posterior parietal cortex as a visual-motor interface for reaching

Visual processing is commonly separated into two parallel pathways: a "ventral stream" specialized for fine analysis of the qualities of the visual scene, including form, color, and object features, and a "dorsal stream" that encodes the spatial properties of visual perception and motion (Mishkin et al., 1983). The posterior parietal cortex (PPC) is the central node of the dorsal visual stream and receives significant afferents from the occipital lobe and projects to motor areas in the frontal lobe, including premotor cortex, frontal eye fields, and supplementary motor cortex (Cavada and Goldman Rakic, 1989a,b; Tanné et al., 1995). Since the influential work of Mountcastle et al. (1975), the posterior parietal cortex (PPC) has been considered to be a visual-motor interface for action goals.

Lesions to this area produce a number of deficits related to spatial perception and goal-directed movement. One such impairment is hemispatial neglect, a neurophysiological condition in which a person is unaware of stimuli to one side of space (Bisiach et al., 1986). Patients have been observed dressing one side of their body or drawing one side of a picture. Patients with parietal lesions can also suffer from optic ataxia, a difficulty in estimating the

location of stimuli in space, measured by reaching errors (Rondot et al., 1977). Apraxia is a class of deficits characterized by the inability to plan movements (Faglioni and Basso, 1985). This includes an inability to follow verbal commands for simple movements to difficulty in performing sequences of movements. Parietal lesion patients also show difficulty shaping their hands as they prepare to grasp objects. Injury to PPC produces a range of deficits that are not primarily sensory or motor in nature, but that are involved in the integration of sensation and motion. This distinction further supports the role of posterior parietal cortex as an interface for visually-guided movements.

However, earlier work investigating the connections between parietal and frontal lobes discovered what seemed to be an anatomical paradox that undermined the notion of PPC as a visual-motor interface. The intraparietal sulcus splits the PPC into two major areas: the superior parietal lobule (SPL) and the inferior parietal lobule (IPL). Striate cortex was shown to send connections to IPL, making it a likely area to interface with motor areas in the frontal cortex, especially in contrast to the SPL which was regarded as a somatosensory association area (Duffy and Burchfiel, 1971; Sakata et al., 1973) and lacked any visual inputs (Pandya and Kuypers, 1969; Jones and Powell, 1970). However, feedforward projections from IPL did not terminate in motor or premotor cortices, but instead in prefrontal cortex (Petrides and Pandya, 1984; Schwartz and Goldman Rakic, 1984; Cavada and Goldman Rakic, 1989b). No study at the time had identified a connection from the visually-related areas of the IPL to the reach-related areas of motor and premotor cortices. Instead, projections from parietal to premotor cortex were shown to originate in area 5 of the SPL. This gap in the visual-motor pathway, between the sensory-related information entering parietal cortex and the motor-related information being sent to motor cortex, could not be accounted for using the anatomical data available at the time.

As investigations into the PPC continued, the visual-motor gap started to close as more diverse functional areas within SPL were observed. By surgically depriving the brain of visual input, Savaki et al. (1993) observed certain regions in the SPL that showed a decrease in metabolic output. These regions were located in the medial bank of the intraparietal sulcus and overlapped parts of area 5, including the medial intraparietal (MIP) cortex (Colby et al., 1988). Today, the SPL has been shown to include multiple areas with gaze-related responses,

such as MIP and PEa in the medial bank of the sulcus, PE on the dorsal surface, and V6A and PEc on the rostral wall of the parieto-occipital sulcus (Felleman and Van Essen, 1991; Pandya and Seltzer, 1982).

Cells in area MIP, PEa, and PEc show involvement in the control of arm movements (Kalaska and Crammond, 1995; Caminiti et al., 1996; Snyder et al., 2000; Pesaran et al., 2006; Cui and Andersen, 2007), represent target locations relative to the direction of gaze and the position of the arm (Pandya and Seltzer, 1982; Batista et al., 1999; Buneo et al., 2002), and are interconnected with motor areas, such as dorsal premotor cortex (PMd) (Johnson et al., 1996; Wise et al., 1997). The functional properties of these SPL cells showed changes in reference frames as their depth within the intraparietal sulcus changed. Cells closer to the dorsal surface of the intraparietal sulcus, like those in area PEc, respond to somatosensory stimuli, while cells in the fundus, like in area MIP and PEa, respond to visual stimuli; cells at intermediate depths show bimodal properties. The multi-sensory sensitivity of the bimodal cells facilitate a preference for those cells to respond to objects within reaching distance (Colby and Duhamel, 1991). When the reaching distance of the hand or arm are extended (e.g. with a tool), receptive fields update to the larger reach radius. Iriki et al. (1996) trained monkeys to use a rake to retrieve objects beyond their grasp and mapped cell activation before and immediately after tool use. They found that visual receptive fields expanded in response to the tool use.

The parietal reach region (PRR) is a combination of parietal areas in the medial bank of the intraparietal sulcus, likely including areas MIP and V6A. Using a reaching task, Batista et al. (1999) demonstrated that receptive fields in PRR were retinocentric and updated reach plans in a eye-centered reference frame. Reach-related spatial information that is anchored to the eyes may point to PRR, and to a larger extent PPC, as a place that facilitates smooth coordination between the eyes and the hand by using similar coordinates for both effectors. Cells in PRR encode the upcoming movement in a sequential reach task (Batista and Andersen, 2001), show limb-dependence (Chang et al., 2008), and show strong selectivity for reaching when given the choice to autonomously select to perform either a hand or eye movement (Cui and Andersen, 2007). Inactivating PRR causes optic ataxia for reaching actions, but not for saccades (Hwang et al., 2012).

1.2.4 Dorsal premotor cortex and reference frame transformations

The dorsal premotor cortex (PMd) is involved in planning and executing visually-guided reaches (Weinrich and Wise, 1982; He et al., 1993). Neuronal activation in PMd is robust while preparing to make a movement (Weinrich and Wise, 1982) and reflects the direction and amplitude of movement (Riehle and Requin, 1989; Caminiti et al., 1991; Fu et al., 1993, 1995; Crammond and Kalaska, 1994, 1996). PMd possess significant efferentations to the primary motor cortex (M1) and to the spinal cord (He et al., 1993), which require motor commands to be in arm- or limb-centered coordinates. However, it also shares many connections with cortical areas of the superior parietal lobule of PPC. Projections from area MIP (Johnson et al., 1996) and V6A (Tanné et al., 1995) into PMd provide gaze-centered information for reach planning (Batista et al., 1999). The convergence of visual input and motor output in PMd makes it an ideal area to study visual-motor reference frame transformations.

Both premotor and parietal cortices can represent motor plans to instructed targets (Kalaska and Crammond, 1995). However, when instructed to withhold a planned reach, cell modulation in PMd shows a decrease in activity and a loss of directional tuning. In contrast, cells in area 5 of PPC continue to show activation that is similar in reach and non-reach trials. When confronted with multiple potential reach goals, PMd shows activation for both reach directions at once and "releases" one of the reach plans when given instruction on which target to reach to (Cisek and Kalaska, 2002b). Here we see that PMd is only concerned with the spatial encoding of a target as long as it is a potential or upcoming reach goal.

Preparatory activity (during an instructed delay period) in PMd has been shown to change with movement direction and correlate with reach reaction time (Riehle and Requin, 1989). A causal relationship between preparatory activity and movement planning was presumed. Mark Churchland and Krishna Shenoy (2007) tested this hypothesis using subthreshold intracortical microstimulation to disrupt the delay period activity during a reaching task. When microstimulation was given around the time of the go cue, reach reaction time increased, with a smaller effect being observed the earlier the stimulation was given. The microstimulation had no effect on the movement parameters themselves. No reaction

time deficits were seen in saccadic eye movements or when microstimulation was applied to M1. This provides direct evidence that activity in PMd facilitates reach preparation, but also that this preparatory activity is constantly being monitored and updated, even up until the go cue.

Reach goals and instructional cues do not always disseminate information in a spatial manner. Therefore, our visual-motor system has to be able to identify these arbitrary associations between sensory stimuli and motor responses (Wise et al., 1997). Using a delayed match-to-sample task, Wallis and Miller (2003) recorded PMd activity to see how activity would change with nonspatial reaching cues. The task began with a sample image and a cue instructing the monkey what type of task it would be (match or non-match). The cue was given as either an auditory tone or juice drops. After a delay, the monkey had to release a lever when the same image (match task) or a different image (non-match task) appeared. As they expected, activity in PMd increased when a reach was made. Surprisingly, PMd showed selectivity based on perceptual information about the type of task. Higher activation was seen when the cue instructed a non-match task and did not depend on the sensory modality used to give the cue (tone vs juice). Premotor cortical lesions have been shown to impair the ability of a monkey to associate visual information with movement instructions (Halsband and Passingham, 1982). Cells in PMd are able to learn to use nonspatial cues to facilitate accurate movement.

One of the biggest questions we face about PMd and its role in visual-motor reference frame transformations is to what extent gaze affects its activity. PMd is classically known to be influenced by hand position and movement direction within a shoulder- or arm-centered coordinate system (Caminiti et al., 1991; Crammond and Kalaska, 1996). More recently, studies have shown the existence of reach-related activity in PMd modulated by gaze angle (Boussaoud et al., 1998; Cisek and Kalaska, 2002a; Pesaran et al., 2006; Batista et al., 2007), however a consensus has yet to be reached.

Boussaoud et al. (1998) was one of the first studies to document eye-position modulation in PMd during reaching. Monkeys were trained to reach to peripheral touchpoints while maintaining fixation at one of five locations on a screen. What Boussaoud discovered was that activity in PMd varied not only with movement direction, as Caminiti et al. (1991)

showed, but also with gaze direction. A modest amount of cells (34%) showed sensitivity to the location of the instructional stimulus (location did not instruct reach direction), while a larger proportion of cells (79%) showed a gaze effect where activity modulated based on the gaze angle in the orbit. The transformation from sensory coordinates to motor coordinates seems to be incomplete, because of the existence of gaze modulation, by the time a reach plan arrives in PMd.

With evidence of the existence of gaze-related modulation in PMd, previous studies investigating the motor-related tuning properties of PMd were looked at under a new light. These studies allowed their animals to look around freely during their reaching task since they were not under the assumption that eye position had any significant effect on PMd modulation. [Cisek and Kalaska \(2002a\)](#) decided to investigate the strength of this effect during naturalistic (unconstrained) eye behavior. PMd activity was recorded while monkeys performed a center-out task. Eye behavior was unconstrained, but recorded. Using analysis methods similar to [Boussaoud et al. \(1998\)](#), Cisek and Kalaska saw that while half of all cells (51%) showed statistically significant gaze effects, only 11% of those cells had firing rate variance that was well explained by gaze position. By comparison, of the cells tuned to the final hand position, 52% were well explained by hand position. Cisek and Kalaska concluded that gaze-related modulation was evident but weak and that ignoring gaze direction likely did not confound the results from previous PMd studies.

As investigations into reach-related modulation in PMd continued, distinctions between reference frames were commonly defined according to a single body part – typically anchored to the hand or eyes. Evidence of tuning in different reference frames now existed. Reference frame studies in other cortical areas were known to find cells with tuning in complex combinations of reference frames ([Stricanne et al., 1996](#); [Duhamel et al., 1997](#); [Buneo et al., 2002](#)). Motivated by the existence of these combinatory reference frames in cortex, [Pesaran et al. \(2006\)](#) and [Batista et al. \(2007\)](#) investigated this idea in PMd using reference frame dissociation tasks. Both studies observed neurons that were tuned in hand-centered and eye-centered reference frames. Using singular value decomposition, [Pesaran et al. \(2006\)](#) was able to test the separability – the extent of tuning dependent on the relative position of a pair of variables (target, eye, and hand) – of each cell’s response profile. A large portion

of their cells showed tuning that was inseparable in each reference frame (TE - 67%, TH - 60%, HE - 69%). Of the cells that showed inseparability in at least one variable pair, one-fourth encoded all three reference frames. The conclusion was that PMd cells used an encoding scheme that combined the position of the hand, eyes, and target. [Batista et al. \(2007\)](#), employing a similar task paradigm as [Pesaran et al. \(2006\)](#), found that 25-28% of PMd cells were best explained in a reference frame centered on the hand, 12-15% were best explained in a reference frame centered on the eyes, and 50% had modulation that was not better explained using either the position of the hand or eyes. While these complex cells could be employing a reference frame centered on the relative position of the eye and hand, most did not fall under this group. Six percent of the complex cells had activity that was better characterized by the combined position of the hand and eyes than either the hand or eyes alone.

From these four studies, there exists compelling evidence that gaze-related modulation is present at the single-cell level in PMd, whether it is from the eye position in the orbit, target position relative to the direction of gaze, or a combinatorial effect across multiple gaze-related reference frames. However, the extent of gaze-related modulation in PMd is still unclear. Different task paradigms, analyses methods, and interpretational caveats make it difficult to answer the question: what is the role of PMd in visual-motor reference frame transformations and how is this transformation carried out? My work adds relevant insight towards this topic.

1.3 RESEARCH OBJECTIVES AND OUTLINE

The goal of this dissertation is to assess the role of dorsal premotor cortex in visual-motor transformation. In [Chapter 3](#), I investigate the reference frames used by neurons in the dorsal premotor cortex (PMd) during a free-gaze reaching task. In [Chapter 4](#), I describe additional analyses used to study reference frames in PMd. In [Chapter 5](#), I give my thoughts on the future of reference frames studies.

2.0 GENERAL METHODS

In this chapter, I will describe general methods that are used throughout the experiments in [Chapter 3](#). All protocols were approved by the University of Pittsburgh Institutional Animal Care and Use Committee, in accordance with the guidelines of the US Department of Agriculture, International Association for the Assessment and Accreditation of Laboratory Animal Care, and the National Institutes of Health.

2.1 BEHAVIORAL AND ELECTROPHYSIOLOGICAL RECORDINGS

Two adult male Rhesus macaques (*Macaca mulatta*) were used in this study, Monkey L and Monkey I. Each animal was surgically implanted with a Blackrock 96-channel microelectrode array (Blackrock Microsystems, SLC) in the dorsal aspect of the premotor (PMd) cortex. Microelectrode arrays were placed in the contralateral hemisphere to the arm being used to reach (Monkey L: left hemisphere, Monkey I: left hemisphere). MRI scans were used to confirm cortical landmarks used during surgery. Spike times were recorded (Tucker-Davis Technologies) during every experimental session. Threshold crossings above 3.5 times the RMS value were stored for offline spike sorting and analysis.

Monkeys were seated in a custom primate chair. Each monkey had surgery to implant three head posts. The head was braced using a custom halo ([Davis et al., 2009](#)). The ipsilateral arm to the hemisphere of recording was comfortably restrained, while the contralateral (reaching) hand was free to move. A motion capture marker was attached to the third digit of the reaching hand. Hand position was recorded using a Phasespace motion capture system (PhaseSpace Inc., San Leandro, CA) at 120Hz.

Visual targets were projected onto two LCD monitors positioned 30cm away at either side of the animal. Mirrors were used to reflect each monitor's image and project a virtual image to the animal's eyes. Eye position was monitored using a Eyelink 1000 system (SR Research Ltd., Ontario, Canada). Infrared light was reflected from the animal's eyes into the Eyelink tracking camera using an infrared illuminator. Analog output from the camera was digitized at a rate of 1000 Hz with a resolution of 0.05° . Calibration of the eye tracker was done at the beginning of every session; the first 20-30 trials were used to adjust gain and offset values used by our system. Custom software was developed using LabVIEW to control the experimental task and record behavioral data. Behavior was only collected while a trial was active.

3.0 PMD REFERENCE FRAMES DURING FREE GAZE TASK

3.1 INTRODUCTION

The central processes that underlie visually-guided reaching begin with the encoding of reach goals relative to the direction of gaze (Batista et al., 1999) and end with commands to the muscles (Dum and Strick, 2002). Where in the brain this transformation occurs, let alone how, remains largely unknown. The dorsal aspect of the premotor cortex seems to be a key hub in the transition from visual to motor representations of reach goals (Tanné et al., 1995) and neural circuitry within PMd might actually perform the needed transformations. To establish the role of PMd in the reference frame transformation for visually-guided reaching, the first key question is whether or not PMd neurons encode the location of reach goals relative to gaze (as do the neurons in posterior parietal cortex which presumably provide a dominant input). Despite the apparent simplicity of this question, and nearly two decades of research on it (Boussaoud et al., 1998), the extent to which PMd neurons are sensitive to target locations relative to the direction of gaze remains unclear.

There is uniform agreement that PMd neurons are tuned to the location of the reach target relative to the hand (Wise et al., 1997; Caminiti et al., 1991; Boussaoud et al., 1998; Cisek and Kalaska, 2002a; Pesaran et al., 2006; Batista et al., 2007) (See [Methods](#) for definitions of terminology.) It is debated whether PMd neurons are tuned to the location of the reach target relative to the retina (or, equivalently, the direction of gaze), and that is the issue we address here. Two studies (Pesaran et al., 2006; Batista et al., 2007) reported that PMd neurons are sensitive to the target’s location relative to the direction of gaze. An earlier study (Cisek and Kalaska, 2002a) reported a more modest influence of the direction

of gaze in PMd. Before that [Boussaoud et al. \(1998\)](#) reported a sensitivity to gaze direction in PMd. Note that there are important interpretational differences among these four studies (see [Discussion](#)), but the key issue here is that three are consistent with the view that PMd neurons are sensitive to the reach target’s location relative to gaze, and one paper suggests that this sensitivity is quite modest. Given that three studies from different labs (six monkeys and about 500 neurons altogether) support the view that gaze tuning is present, and one study (one monkey, 73 neurons) supports the view that gaze tuning is weak, it would seem that the issue was resolved based on a preponderance of evidence.

Important methodological differences exist among all of these studies, but perhaps the key one is that in all three studies in which gaze sensitivity is reported, animals were trained to fixate, and fixation was required while reaches were planned. In the study where gaze sensitivity was reported to be modest, gaze was unconstrained, and gaze training had never been performed. We sought to resolve this debate by recapitulating the methods of [Batista et al. \(2007\)](#) as closely as possible, with the exception of allowing gaze to be unconstrained, as did [Cisek and Kalaska \(2002a\)](#).

To our surprise, we found that PMd neurons are almost completely insensitive to the location of the reach target relative to the direction of gaze. This contradicts the findings of [Batista et al. \(2007\)](#), [Pesaran et al. \(2006\)](#), and [Boussaoud et al. \(1998\)](#). It is consistent with the findings of [Cisek and Kalaska \(2002a\)](#). However, our analyses indicate that the tuning to gaze direction in PMd is actually weaker than they concluded, to the extent that we do not even consider the description of the tuning as modest to be warranted.

The logic of our study proceeds as follows. Animals performed delayed memory-guided reaches. Their eye position was not constrained in any way. We found that 90% of neurons were tuned to the reach target’s location relative to the hand during the delay period preceding the reach. This finding is consistent with all other studies of PMd. Our first-pass analysis showed that 86% of neurons were tuned to the target’s location relative to the direction of gaze. For this analysis, we identified two main variables: 1) the firing rates during eye fixations in the delay period, and 2) the set of locations found by subtracting fixation positions from target location. Then we checked for tuning by regressing the firing rates with the set of locations.

However, we believe this constitutes an overestimate of the tuning of the target relative to the eyes. The reason for this is because we observed that the animals' gaze behaviors did not uniformly sample the workspace and were dependent on the task geometry. Imagine if an animal always looked directly at his hand. If a neuron was in actuality tuned only for the target's location relative to the hand, it would still appear to be tuned for the target's location relative to the eyes, because of this coupling between hand and eye position. In fact, it is precisely to break this coupling that animals are trained to fixate in reference frame studies. However, as [Cisek and Kalaska \(2002a\)](#) suggested, this training may actually induce a sensitivity to eye position. Our analyses support their argument. Through simulations and statistical analyses, we show here that nearly all apparent target-eye tuning in PMd is an artifact of the natural non-uniformity of the animals' gaze behavior in this task. We conclude that in animals not trained to fixate, target-eye tuning is virtually nonexistent in PMd.

3.2 METHODS

3.2.1 Terminology

Clear terminology is especially important in reference frame studies. A neuron is said to be tuned to the location of a target relative to the hand if the firing rate (measured in action potentials per second) of the neuron depends on the location of the target relative to the hand. Such tuning might indicate that the neuron encodes target locations in a hand-centered reference frame, but that is a stronger statement. Tuning to the target's location relative to the hand may indicate that the neuron is using some mixed reference frame, such as a relative position coding scheme ([Pesaran et al., 2006](#)). For the purposes of this study, we focused our analyses on two reference frames: target location relative to the hand (TH; target-hand) and target location relative to the eyes (TE; target-eye)([Figure 3.1b](#)).

"Eye sensitivity" or "gaze sensitivity" are terms that have been used while observing changes in neural firing when the direction of gaze is shifted. However, they are overloaded terms. The underlying cause of this change in neural firing might be two different things.

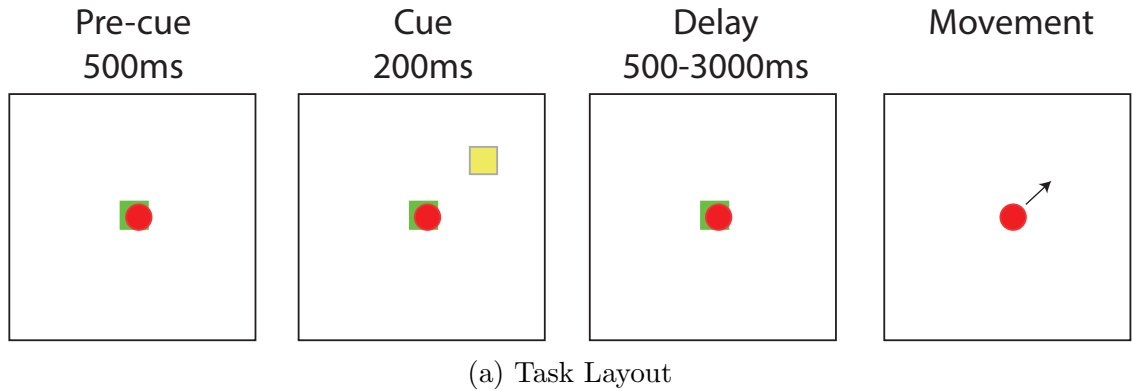


Figure 3.1: Task Layout and Reference Frame Definitions. (A) Diagram of the experimental task. Hand position was represented on a monitor by a red circle. Trials were initiated by touching a central start target. A reach target appeared at one of eight possible locations. After a variable delay period, the monkey was instructed to reach to the remembered target location. (B) We investigated two reference frames: target location relative to the hand (TH) and target location relative to the eyes (TE). Behavioral data was taken and target positions were realigned to be defined in relation to either the hand (right) or the eyes (left).

First, it may be that neurons are sensitive to the location of the target on the retina (that is, in visual coordinates.) It is important to note that our definition of a TE reference frame is one that is anchored to the retina (retinocentric). It may also mean that neurons are sensitive to the position of the eyes in the orbits. Those sensitivities may combine in a multiplicative manner (Andersen and Mountcastle, 1983; Pouget and Sejnowski, 1997), additive manner, or in some other way. For this reason, we refrain from describing a cell as having eye/gaze "sensitivity". Instead, we describe tuning in terms of a goal-effector pair. The goal is what the cell is encoding and the effector is what the response profile is anchored to. For example, a cell tuned in a target-eye reference frame would show modulation in response to changes of the location of the target relative to the position of gaze.

3.2.2 Behavioral Task

Data collection occurred while monkeys performed a center-out reaching task in a virtual reality environment. Monkeys were seated in a primate chair; head-fixed with a modified halo system (Davis et al., 2009) with the non-reaching arm restrained. Hand movements made by the reaching arm were represented on a monitor by the position of a circular cursor. The monkey was unable to see his actual hand during the task.

Each trial was initiated by the monkey acquiring and holding his hand position within a central green square (14x14 mm), termed the start target (Figure 3.1a). After a 500ms pre-cue period, a yellow square (14x14 mm), termed the reach target, appeared in the monkey's periphery. Reach targets could appear at one of eight possible locations chosen pseudorandomly. The reach target only remained visible for a period of 200ms. Monkey I performed a version of this task where all targets were visible for the entirety of the trial and shown in gray. A variable delay period (Monkey L: 500-2000ms, Monkey I: 1000-3000ms) followed where the monkey had to continue to withhold any arm movement. The end of the delay period was signaled by the removal of the start target. This go cue instructed the monkey to make an arm movement to the remembered position of the reach target. The monkeys received a water reward after successfully arriving at the target and holding for 350ms.

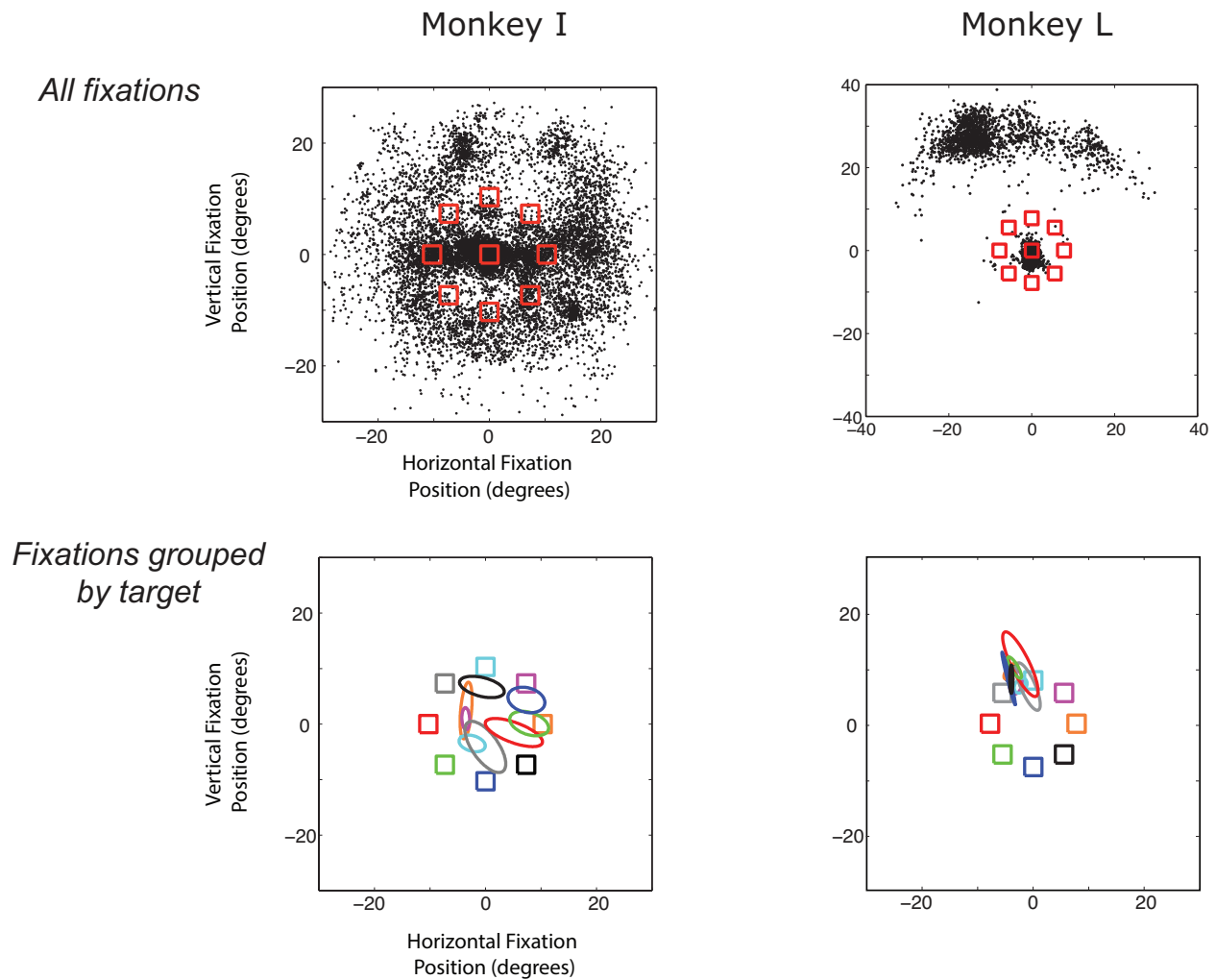


Figure 3.2: Gaze behavior of both animals. *Top*: All fixations made by Monkey I and Monkey L. Each dot is a single fixation (dwell time ≥ 150 ms) recorded during the delay period of a trial. Red squares are the locations of reach targets. *Bottom*: Gaze behavior influenced by target. Ellipses represent the covariance of the average fixation position for all experimental sessions. Squares are target location and color coded to match a corresponding ellipse.

3.2.3 Data analysis

All data was analyzed offline with custom software using MATLAB (MathWorks). Neural spiking that occurred during fixations and within the delay period of each successful trial were used in our analysis. Spikes that occurred within the first 150ms of the delay period were removed from analysis to insure any neural transients from the visual target cue subsided. Fixations were identified as periods of ≥ 150 ms during which eye movement speed did not exceed 20% of the local peak speed. Firing rates were calculated for each fixation episode using a window that starts 50ms after the end of a saccade and goes on until the beginning of the next saccade.

The relationship between target position and firing rate under each reference frame was examined using planar regression analysis. Horizontal and vertical components of target position were regressed against firing rate for each neuron. Target position was defined relative to hand or eye position, depending on the reference frame being analyzed. Two regressions were performed for each neuron using the same firing rate data: one for target locations centered on the hand (TH) and another for target locations centered on the eyes (TE). Each regression analysis produced a coefficient of determination (R^2), used to quantify the goodness of fit. Significance of the regressions was determined using an F-test ($p < 0.05$).

Confidence intervals for the R^2 values were estimated using a bootstrap method. For each cell, N firing rates were randomly sampled (with replacement) from the N experimentally determined firing rates. Target locations were not shuffled. A new R^2 value was calculated using these firing rates. Ten thousand iterations were performed and 95% of the bootstrap-determined values were used to define the confidence interval, indicating the range within which the R^2 would have fallen 95% of the time.

We also tested how well each reference frame explains a neuron's firing rate variance after accounting for the influence of the other reference frame. To do this we used partial regression analysis. Target position was regressed against firing rate and the firing rate residuals of the best-fit plane were calculated. Those residuals were put through a second regression using target position data from another reference frame, where a partial R^2 value was calculated. Confidence intervals were estimated for the partial R^2 values as well.

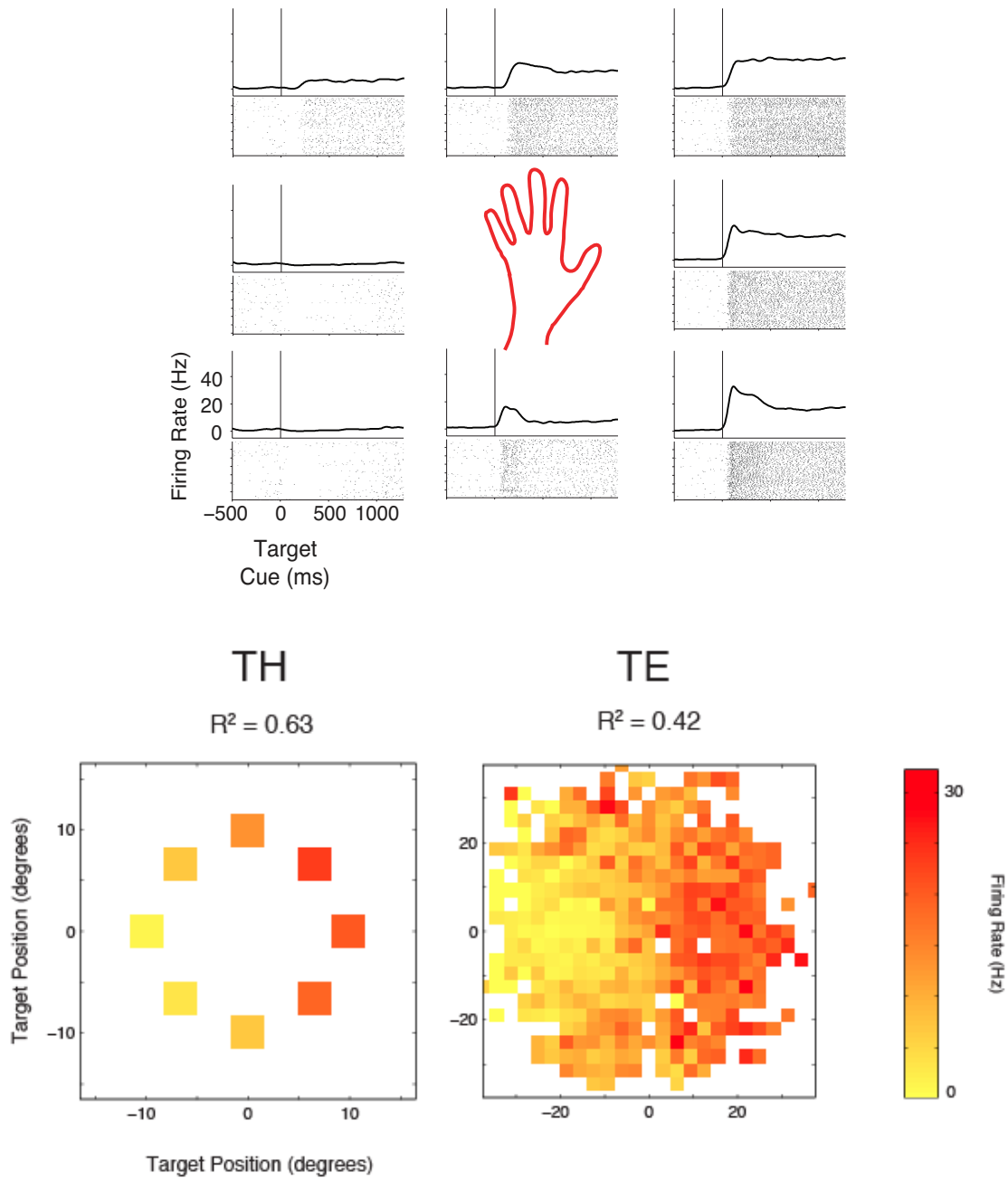


Figure 3.3: Tuning within a representative PMd neuron. *Top*: Eight peristimulus time histograms (PSTH) grouped by target direction. Spike rasters are aligned to the time of target cue. Spikes that occurred 500ms before and 1300ms after target cue are shown and averaged across all trials. *Bottom*: Firing rates were binned and averaged across the workspace. R^2 values were calculated from the planar regression of firing rates and target position. Left: Target position centered on the hand. Right: Target position centered on the eye.

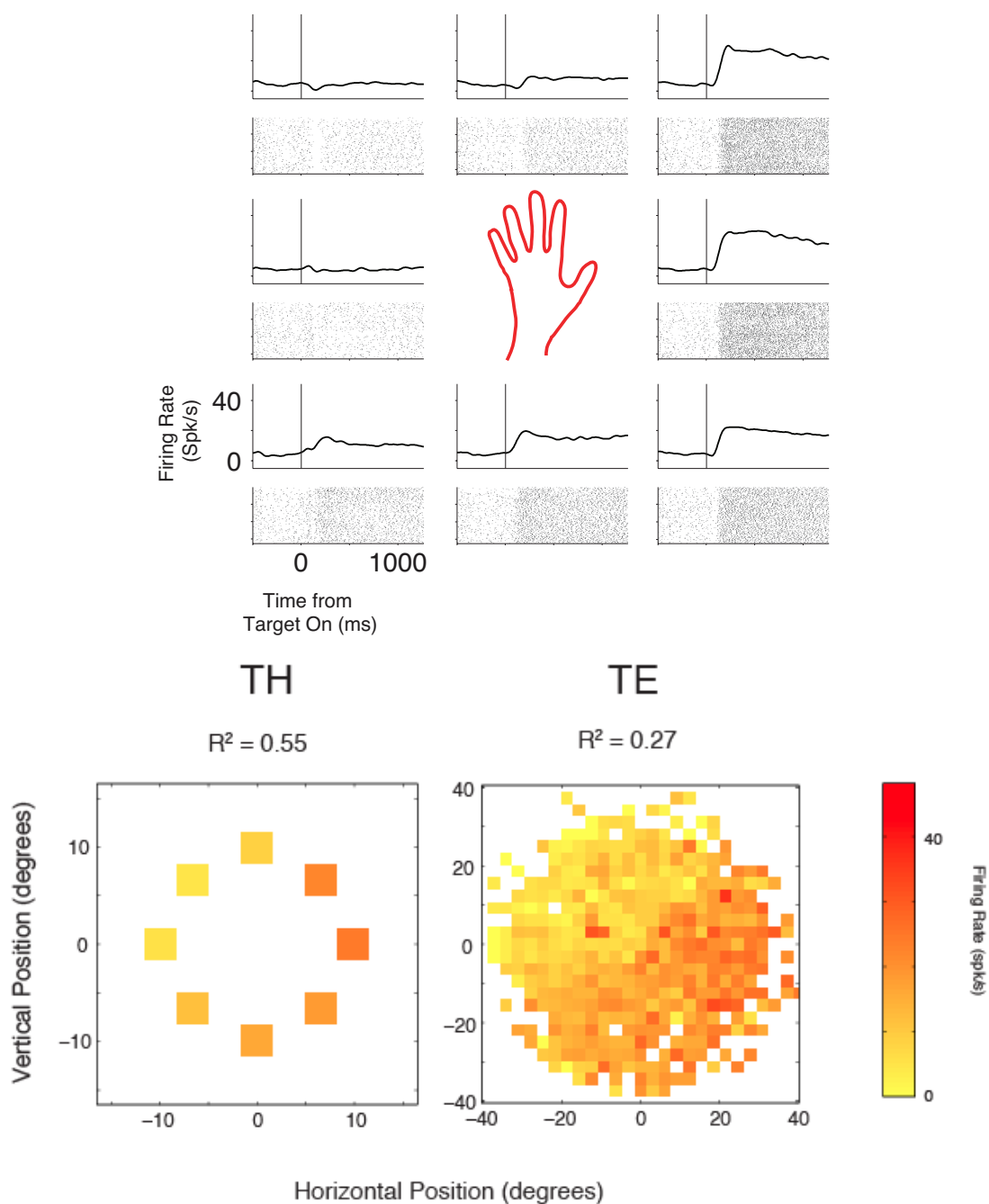


Figure 3.4: Best example of a neuron with greater TH tuning. This cell showed the largest difference between TH and TE R^2 values and had a larger TH R^2 than TE. Same configuration as [Figure 3.3](#).

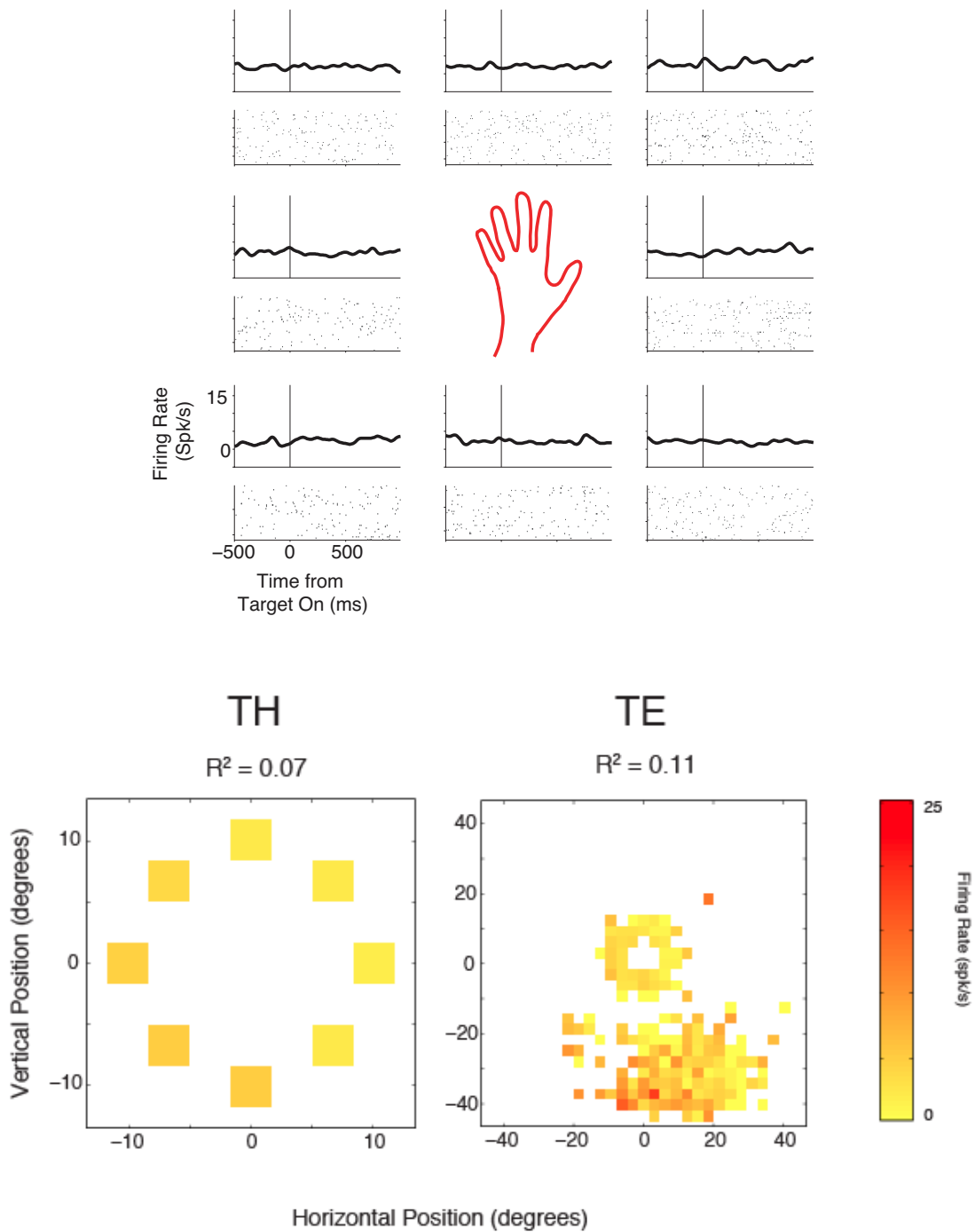


Figure 3.5: Best example of a neuron with greater TE tuning. This cell showed the largest difference between TH and TE R^2 values and had a larger TE R^2 than TH. Same configuration as [Figure 3.3](#).

Each animal showed behavioral idiosyncrasies that could bias our reference frame analyses. In order to investigate the effect of unconstrained gaze behavior on our results, we built simulated neurons with known tuning properties. Each of the n simulated neurons was built using a linear firing rate model:

$$FR_{i,j} = b_{0i} + b_{xi} * x_j + b_{yi} * y_j + \varepsilon_{i,j} \quad (3.1)$$

where b_{0i} , b_{xi} , and b_{yi} are the coefficients taken from the planar regression analysis of neuron i , x_j and y_j represent the horizontal and vertical components, respectively, of the target location during fixation j . Target locations were either defined relative to hand position (TH) or eye position (TE). In this way, we were able to explicitly build cells that are only tuned to the location of the target relative to the hand (TH-only) or the eyes (TE-only). We did this by only using target position relative to the hand in the firing rate model for the TH-only cells and only using target position relative to the eyes in the firing rate model for the TE-only cells. Noise (ε) was drawn from a zero-mean normal distribution whose variance was set equal to the standard deviation of the regression residuals. Each simulated neuron was run through the same planar regression analysis as the real neurons.

3.3 RESULTS

We recorded from 447 cells in the dorsal aspect of the premotor cortex (PMd) of two Rhesus monkeys while they performed a delayed center-out reaching task. The gaze behaviors of both monkeys were recorded, but were not constrained by the conditions of the task. On electrodes where neurons were found, there were, on average, 1.2 and 1.3 well-isolated neurons per electrode per experimental session for monkeys L and I, respectively. One-hundred and seventy-one (171) of these neurons came from Monkey L (43 per session on average), and 276 were from Monkey I (55 per session on average). We did not attempt to track individual neurons over days, nor did we attempt to verify that neurons recorded on different days were distinct. Additional recording sessions with each monkey allow us to verify that the properties we observed were stable over time.

First, we present a conventional analysis of tuning in PMd. It suggests that neurons in PMd are moderately sensitive to the location of the target relative to the eyes. We then provide two further analyses (simulations and partial regressions; see [Methods](#)) which show that apparent target-eye tuning is in fact spurious.

3.3.1 Gaze behavior

Eye position was recorded throughout each trial for both animals. Gaze behavior was not constrained by the demands of the task. Only those fixations made within the delay period were analyzed. Each monkey made 2 fixations during the delay period on average with a dwell time of 330ms. When we examined the areas that our monkeys tended to look, we observed very idiosyncratic gaze behavior ([Figure 3.2](#)). Monkey L tended to look well above the workspace during his trials. In fact, his fixations extended beyond the top of the monitor. We could not find any salient stimulus that would cause him to look in that area. While trials were executed in a dark and quiet room, we cannot claim to have sealed out all light and sound. It is worth noting that the monkey studied by [Cisek and Kalaska \(2002a\)](#) also had a strong tendency to look at a specific visual feature. Monkey I fixated much more uniformly within the workspace. However, when we conditioned his fixations based on target location we noticed that he had a strong tendency to look away from the cued reach target. For example, if a rightward target was cued, he would look toward the left side of the workspace. We performed a bootstrap analysis on his gaze behavior by randomly assigning eye positions to target locations. Then we found the average eye position for each target location and calculated the average pairwise distance between them. The distance between eye position and target location in our experimentally observed data was significantly different from the randomized case.

3.3.2 Tuning in PMd

[Figure 3.3](#) shows the activity of a representative PMd neuron from our population. This cell shows no activation before reach target information is revealed, but a burst of activity at the time of the target cue and sustained activation during the delay period. This cell

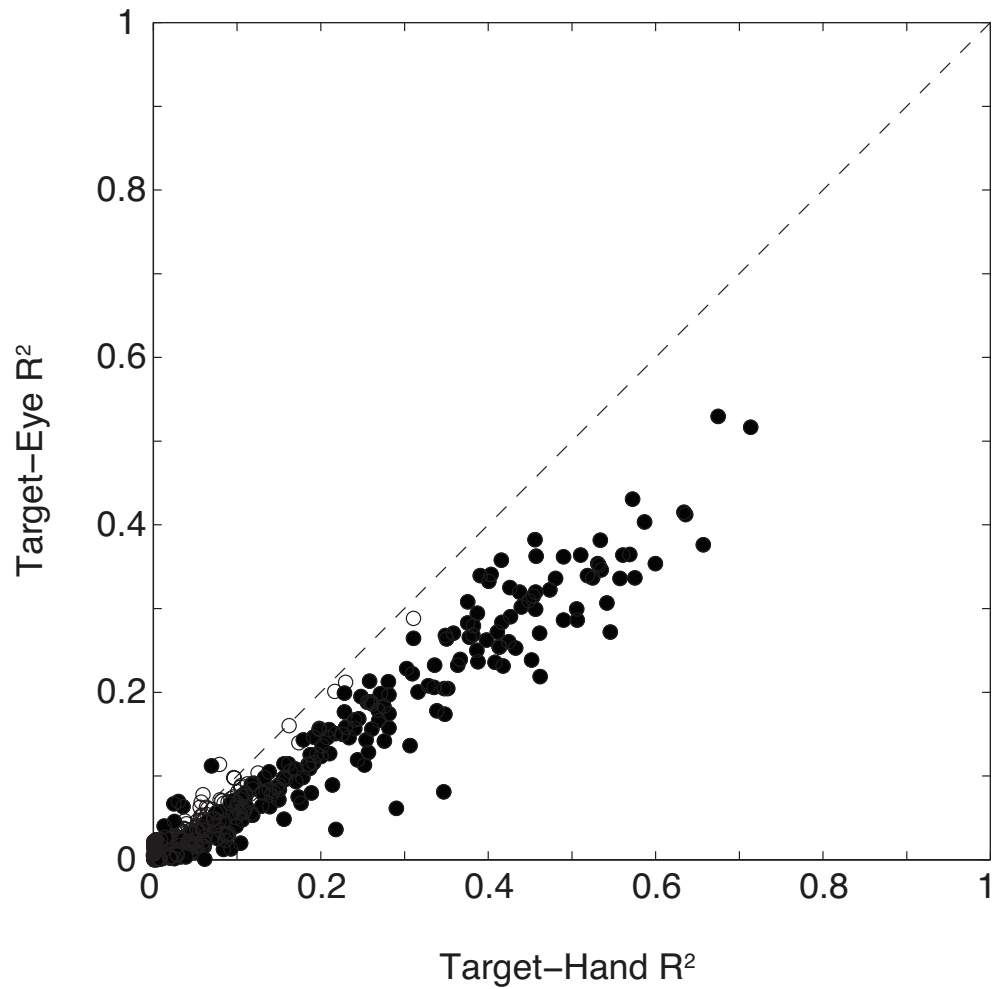


Figure 3.6: Comparing TH and TE regression R^2 . Each point is a neuron from our two monkeys. Neurons strongly influenced by the location of target relative to the hand lie below the diagonal. Neurons more influenced by the location of target relative to the eyes are above the diagonal. Filled points are cells with confidence intervals that do not cross the unity diagonal.

was significantly tuned to the direction of the target and showed the largest modulation for reaches to the right side of the workspace. [Figure 3.4](#) and [Figure 3.5](#) show the best examples of TH and TE cells from our population, respectively. These are cells that showed the largest difference between TH and TE R^2 values, where the best TH cell had a larger TH R^2 than TE and the best TE cell had a larger TE R^2 than TH.

Neural activity for each neuron was fit to a planar regression. Response heatmaps for one cell are shown in [Figure 3.3](#). Cell discharge due to changes in the hand-centered location of the target is strong ($R^2 = 0.63$). When we realign the firing rate data to the eye-centered location of the target, we see strong tuning as well ($R^2 = 0.42$), however not as strong as in the TH reference frame. Across the neural population, we see a similar pattern. In [Figure 3.6](#), we directly compare the influence on firing rate of changing target location within a TH versus a TE reference frame. Neurons that are more influenced by changes to target location relative to the hand lie below the diagonal and may encode reach goals in a TH reference frame. Those cells shown above the diagonal are more influenced by target location relative to the eyes and may encode reach goals in a TE reference frame. Filled points indicate neurons whose confidence intervals do not cross the diagonal. The vast majority of the cells (83%) showed a significant regression in both the TH and TE reference frames. However, 52% lie confidently below the diagonal, while only 4% confidently lie above the diagonal (filled points). As such, our cells seem to encode reach goals in a TH reference frame. Note that this does not ignore the clear presence of TE tuning. These results are in accord with [Cisek and Kalaska \(2002a\)](#) in that they indicate the presence of cells in PMd that encode target location relative to the eyes, but show the strength of the tuning to be moderate.

3.3.3 Target-eye tuning is spurious

The problem we face with our analysis methods is that gaze behavior that does not uniformly sample the workspace will introduce apparent TE tuning even if none exists. Let us imagine recording from a hypothetical PMd neuron whose firing is exclusively influenced by the location of a target relative to the hand. Let us also imagine that the monkey chooses to look directly at his hand while planning the reach. If we looked for TE tuning in that cell,

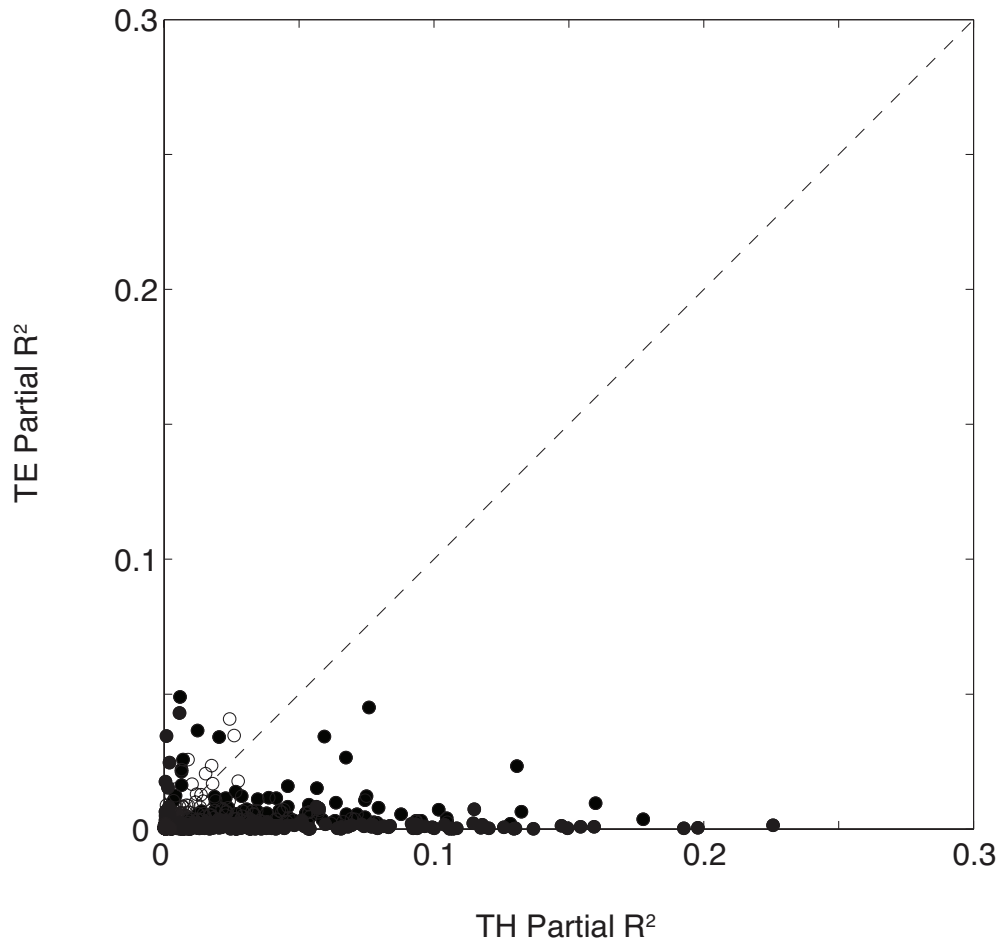


Figure 3.7: Partial Regression R^2 . PMd neurons had a partial regression applied to them. Data was regressed against target-hand position and the residuals regressed against target-eye position (TE Partial R^2) The reverse was also performed: data was regressed against target-eye position and the residuals regressed against target-hand position (TH Partial R^2). Cells below the diagonal are strongly influenced in the TH reference frame. Those above the diagonal are strongly influenced in the TE reference frame. Filled points are cells with confidence intervals that do not cross the diagonal.

not only would we surely find it, but it would look identical to the TH tuning we observed. In fact, any non-uniformity in the monkeys' gaze behaviors may introduce some artifactual TE tuning.

We used a partial regression approach to compare how much firing rate variance was uniquely explained by the location of the target relative to the hand and relative to the eyes. We did this by performing a planar regression on neural activity against the location of target relative to the hand. This is exactly the same procedure shown in [Figure 3.3](#). The residuals from this calculation were taken and another planar regression was performed on the previous residuals against the location of target relative to the eyes. In doing this, we are able to quantify how much influence target-eye position has on neural activity that cannot be attributed to the influence from target-hand position. What we find is that after accounting for the variance already explained in a TH reference frame, TE tuning is small. This is the case across our population of neurons ([Figure 3.7](#)). We performed the complementary analysis for comparison: regress our data against target-eye position and then regress the residuals against target-hand position. Thirty-six percent of cells from both monkeys were still significantly tuned in the TE reference frame after the partial regression analysis, while 76% were still significantly tuned in the TH reference frame. Close to half (42%) of the neurons that had significant tuning in the TE reference frame in our initial analysis lost that tuning once TH tuning was accounted for using the partial regression.

From the partial regression analysis, we found that eye position explained very little residual variance in our data. Could the particular gaze behavior our monkeys demonstrated, when coupled purely with TH tuning, explain the magnitude of the apparent TE tuning? To test this, we created simulated neurons. For each neuron in our population, we built a model neuron with a matching R^2 , but whose tuning was entirely dependent on the target's location relative to the hand. By construction, the firing rate of these cells did not depend on the target's location relative to the eyes. We sampled from these tuning functions using the actual gaze behavior demonstrated by the monkeys. Then, we computed the TE tuning for that model neuron. The response heatmaps in [Figure 3.8](#) show one of our cells in this analysis. Not only do we see strong TE tuning for our model neuron ($R^2 = 0.43$), but the tuning is nearly identical to the real neuron.

In fact, all of our model neurons were similarly tuned to the location of the target relative to the eyes as their real neuron counterparts (Figure 3.9, top row). The effect here is striking. Points fall near the unity diagonal, which means for almost every neuron, the measured TE tuning is just as strong as the TE tuning computed from a model neuron which only has TH tuning. What this tells us is the TE tuning we observed can be explained simply as the product of the non-uniformities in the monkeys’ gaze behaviors combined with the TH tuning these neurons are known to possess. We then created a set of uniformly distributed fixations and sampled from our model neurons using this synthetic gaze behavior. Target-eye tuning all but disappeared in this case (Figure 3.9, middle row). When we consider the complementary model – simulate neurons whose firing rate is explained only by the location of target relative to the eyes – the TH tuning of those simulated cells is less than the TH tuning measured in the real data (Figure 3.9, bottom row). In this way, TH tuning cannot be explained as an artifact of true TE tuning.

3.3.4 Is there any eye tuning in PMd?

We examined the hand-centered and eye-centered tuning curves of every neuron in our population. We saw no cells for which we felt the TE tuning was demonstrably strong by visual inspection. We used the population analyses described above to pre-select a small group of neurons which were particularly likely to exhibit meaningful TE tuning – the cells above the unity diagonal in the analyses depicted in Figure 3.6 and Figure 3.7 for all experiment sessions. Figure 3.10 shows the most convincing example of TE tuning we found in our entire population. This cell is weakly tuned in a TE reference frame when we use a standard and partial regression (R^2 : 0.11, partial R^2 : 0.04). We believe this cell provides a powerful illustration that TE tuning is virtually absent in PMd in animals not trained to fixate.

3.3.5 Tuning for eye position

The analyses so far have not examined any effect of the position of the eyes in the head (that is, EH tuning). Eye position tuning is well known to activate neurons, in a multiplicative ”gain field” sense (Andersen and Mountcastle, 1983; Pouget et al., 2002) in which the firing

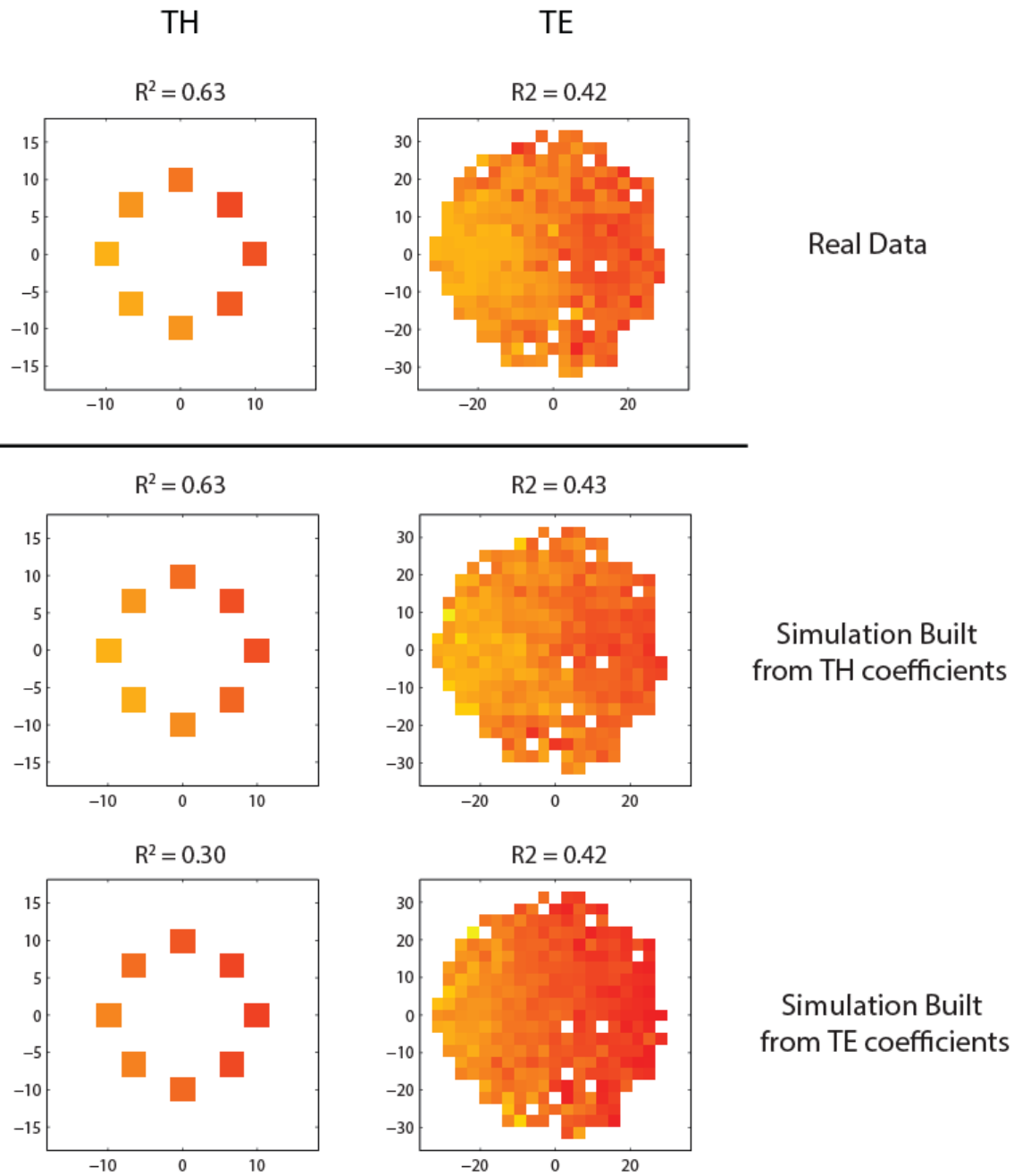


Figure 3.8: Tuning in a simulated neuron. Neurons were simulated using TH-tuned and TE-tuned linear firing rate models. *Top:* Tuning properties in TH and TE reference frames taken from real neural data. *Middle:* Tuning properties of simulated neuron built to only have TH tuning. *Bottom:* Tuning properties of simulated neuron built to only have TE tuning.

rate for a target relative to the retina is multiplied (up to a saturation) by the position of the eyes in the head. Eye position tuning can also be additive and affect neural tuning even in the presence of a target. Eye-head tuning is particularly relevant here because that is the main type of tuning that [Cisek and Kalaska \(2002a\)](#) examined. We considered the possibility that EH tuning is present in PMd in either an additive or gain-modulation sense.

To examine EH tuning in an additive sense, we considered the pre-cue epoch. If the direction of gaze activates PMd neurons regardless of the presence of a target, then tuning to direction of gaze should be evident in this epoch. We performed planar regressions on data from the pre-cue epoch and calculated the R^2 values and regression slopes for all neurons in all sessions for both monkeys. During the pre-cue epoch, EH R^2 values and regression slopes were very low across the population (median $R^2 = 0.008$, median slope = 0.12 Hz/degree). This was comparable to what ([Cisek and Kalaska, 2002a](#)) saw in their pre-cue epoch.

The traditional form of eye-position gain-modulation is an enhancement of target-eye tuning ([Andersen and Mountcastle, 1983](#)). Since TE tuning was all but absent from our population, we could not examine an EH gain effect on it. Instead, we considered the possibility that EH tuning affected TH tuning. To do this, for each neuron, we identified the target location that evoked the largest firing rate. We built a linear regression between firing rate and eye position for that target location only. Thirty-two percent of our neurons showed significant tuning to eye position during reaches to the neuron’s preferred direction, but the influence on firing rate was small (median slope = 0.11 Hz/°). In this way, we found that EH tuning was present but weak in the population.

3.4 DISCUSSION

We addressed the prospect of the dorsal premotor cortex (PMd) as an area where visual-motor reference frame transformations are completed. We investigated this question by looking into the extent that eye-centered tuning is present in PMd. Multi-unit neural activity was recorded from two monkeys while they performed delayed center-out reaches. Their gaze behavior was unconstrained during the task and they had never been trained to perform

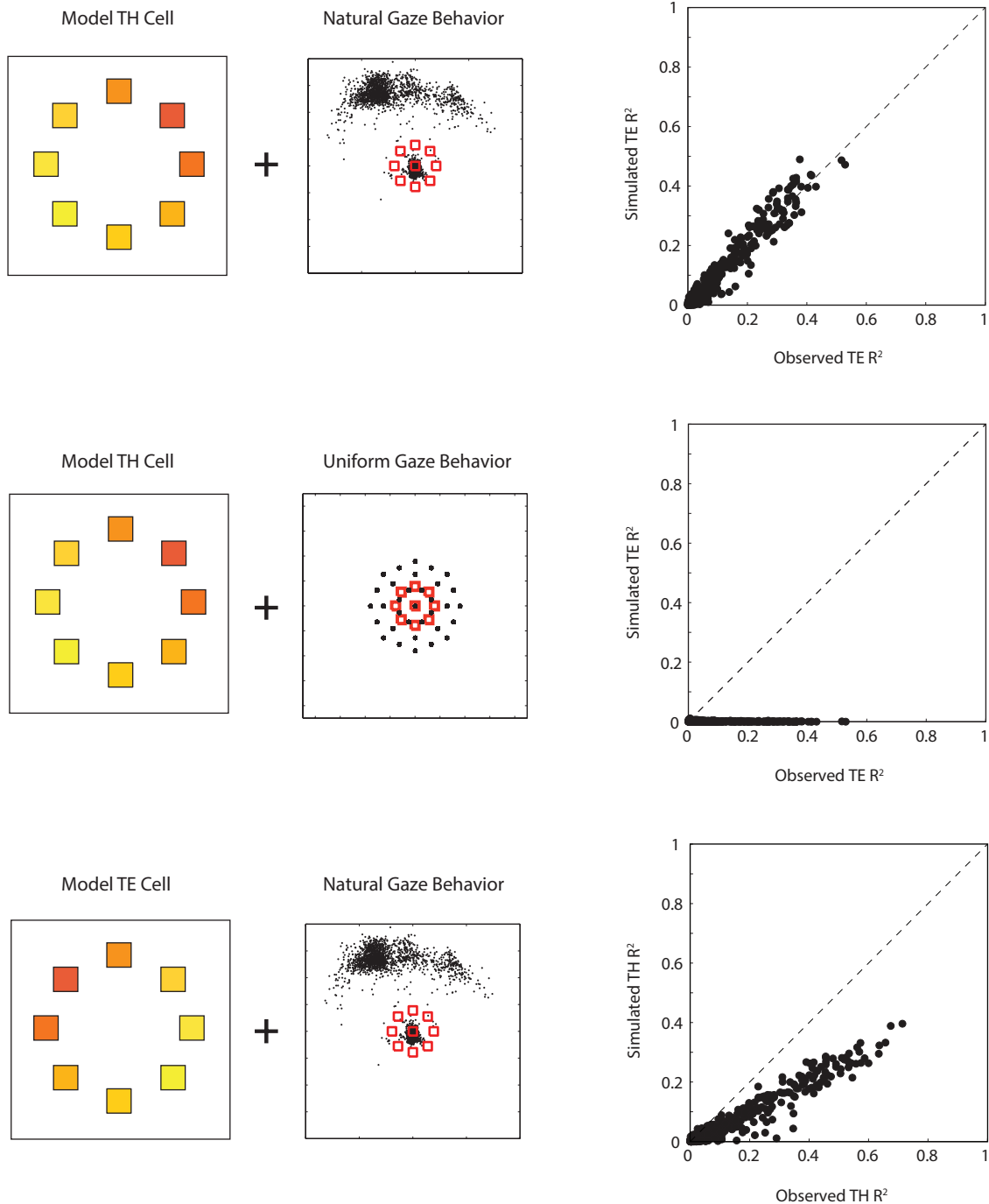


Figure 3.9: Comparing tuning in real and simulated neurons. *Top*: Model neurons built to only have tuning in a TH reference frame show strong TE tuning, similar to what we observed in our real neurons. *Middle*: The same model neurons lose their TE tuning when we sampled from them using a synthetic uniform gaze pattern. *Bottom*: Model neurons built to only have tuning in a TE reference frame do not show strong TH tuning.

instructed fixations. Using planar regression analysis, we found that cells in PMd appeared to show tuning to the location of a target relative to the eyes. Eighty-six percent of our cells were significantly tuned to this reference frame (F-test, $p < 0.05$). However, while the presence of tuning in this reference frame were clear, we concluded that the strength of this tuning was moderate. Only 4% of our cells had a coefficient of determination (R^2) that was significantly larger within a target-eye reference frame than a target-hand reference frame (95% confidence level).

Further analysis into our data uncovered biases in our results due to the monkeys' natural behaviors. Monkeys were permitted to look anywhere in the workspace while performing their task and often made multiple fixations. However, the animals never uniformly sampled the workspace, causing our regression analysis to overestimate the amount of target-eye tuning we observed. Monkey L consistently looked well above the workspace during the task and Monkey I looked in the opposite direction of the cued target, showcasing behavior that was highly dependent on the location of the target. To properly account for this, we built simulated neurons modeled using the spiking properties of our actual cells. Cells were built to have a tuning function that was only dependent on the location of the target relative to the hand. Sampling from these model cells using our monkeys' non-uniform gaze behavior showed strong target-eye tuning. Performing the reverse analysis, building model cells only tuned to the location of the target relative to the eyes, showed much weaker target-hand tuning. This showed us that the target-eye tuning we observed could be explained as a product of the non-uniform gaze behavior our monkeys showed and the target-hand tuning that PMd neurons are known to possess.

Our planar regression analysis was then modified in order to account for correlations between behavior and target. We used partial regressions to calculate the amount of firing rate variance that could be explained in a target-eye reference frame after removing the variance already explained in a target-hand reference frame. In essence, we wanted to ask if the neural variance unexplained by the location of the target relative to the hand is instead a product of the location of the target in an eye-centered frame. After removing the variance explained by a target-hand reference frame, 36% of our cells were significantly tuned to the target-eye reference frame, but only 3% had a TE R^2 value that was significantly larger than

the TH R^2 value. Of those cells with significant eye-centered regressions, we found none that had PSTHs that were convincing examples of eye-centered tuning. My work directly supports the conclusions of [Cisek and Kalaska \(2002a\)](#) and adds weight to the claim that fixation training and/or fixation instruction may have an effect on neural tuning.

We recognize that the visual-motor system is not static within our task epochs. The signals that encode target position may develop and vary over time throughout the delay period. Our analyses did not explicitly investigate the temporal dynamics of our data by looking for potential eye or hand signal variation across time. For example, cells may express stronger eye-centered tuning during fixations that occur early on in the delay period than during fixations that occur closer to reach execution. In addition, because eye position was unconstrained, it is possible that saccade plans contributed to the signals we recorded ([Pesaran et al., 2010](#)).

3.4.1 Concluding thoughts on reference frame transformations

Visually-guided reaching requires a diversity of neural computations, such as target selection ([Cisek and Kalaska, 2002b](#)), hand path optimization ([Todorov and Jordan, 2002](#); [Scott, 2004](#); [Churchland et al., 2006](#)), and a sensory-to-motor coordinate frame transformation. Of all of these processes, it seemed reasonable to believe that the latter would be the most experimentally tractable ([Kalaska and Crammond, 1992](#)). However, despite three decades of research ([Andersen and Mountcastle, 1983](#)), the neural mechanisms of reference frame transformations have remained elusive. Questions have been easy to ask, but troublingly elusive to answer. The explanation for this apparent discrepancy might be somewhat paradoxical: Reference frame transformations may actually be a simple process for the brain to perform, which may mean that their neural mechanisms are difficult to locate and isolate. In theory, a reference frame transformation can be achieved via a simple linear transformation, easily implemented through a single stage of feedforward synaptic connectivity ([Salinas and Abbott, 1995](#); [Pouget and Sejnowski, 1997](#); [Zipser and Andersen, 1988](#)). Because it is so simple, perhaps no specialized neural machinery need be devoted to the process. The brain may be able to perform reference frame transformations rapidly and flexibly, and perhaps in

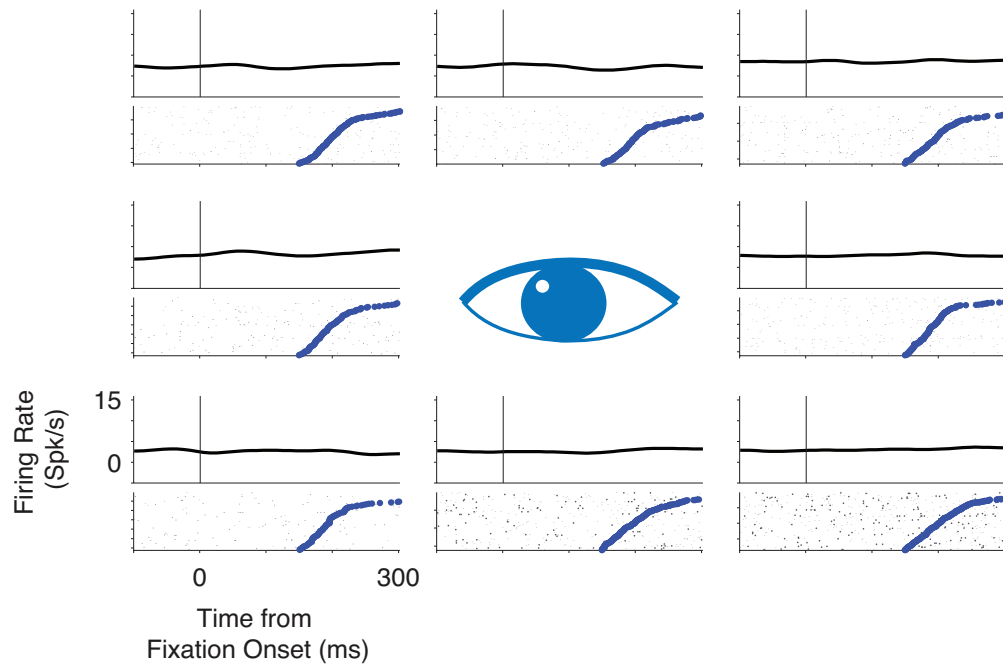


Figure 3.10: Best example of TE cell. Eight peristimulus time histograms (PSTH) grouped by target direction centered on the position of the eyes. Spike rasters are aligned to the time of fixation onset. Spikes that occurred 100ms before and 300ms after fixation began are shown and averaged across all trials. Blue points on the spike rasters are the time that each fixation ended. Only spikes during a fixation were averaged.

tandem with more intricate neural computations. This means that the neural underpinning of reference frame transformations may be particularly hard to isolate and reveal. We speculate that reference frame transformations are flexible (we can reach accurately regardless of where the hand and eyes begin) and that their neural mechanisms probably accompany other processes related to reaching, such as target and movement selection (to minimize effort or maximize rewards), anticipation of outcomes, such as the reward, and learning ([Cisek and Kalaska, 2010](#)). If this is true, then the deceptively simple phenomenon of a reference frame transformation might be rather difficult to isolate and observe in the presence of other more intricate neural processes.

4.0 SECONDARY ANALYSES

The following chapter details several additional analyses that were performed on PMd data in [Chapter 3](#). These analyses were outside the scope of our study or yielded ambiguous results.

4.1 GAUSSIAN MEANS

The linear relationship between reach goal location and firing rate is well established in premotor and primary motor cortex literature ([Georgopoulos et al., 1982](#); [Caminiti et al., 1991](#)). As such, we chose to use a two-dimensional plane to model the relationship between target position and neural firing rate. However, sensory processing studies have long observed that tuning in visual areas are well modeled using a unimodal firing distribution ([Soodak, 1986](#)). Therefore, we developed an analysis method that would allow us to look for eye position modulation in PMd using a Gaussian distribution model. The following analysis was performed with the help of Jeffrey Chiou.

We took data from one session in Monkey I. Each trial was placed into one of eight groups based on the location of the target for that trial. Those trials where the monkey was instructed to reach to Target 1 were grouped together, reaches to Target 2 were grouped together, and so forth. The lack of target variability in each group eliminated any influence of target location on firing rate. [Figure 4.1](#) contains eight heatmaps that show the firing rates from one PMd neuron as eye position changes across the workspace. Again, data is separated by cued target location. We can see a difference in firing rates based on target location; heatmap intensity is strongest when the target is cued at 215° and weakest at 45° .

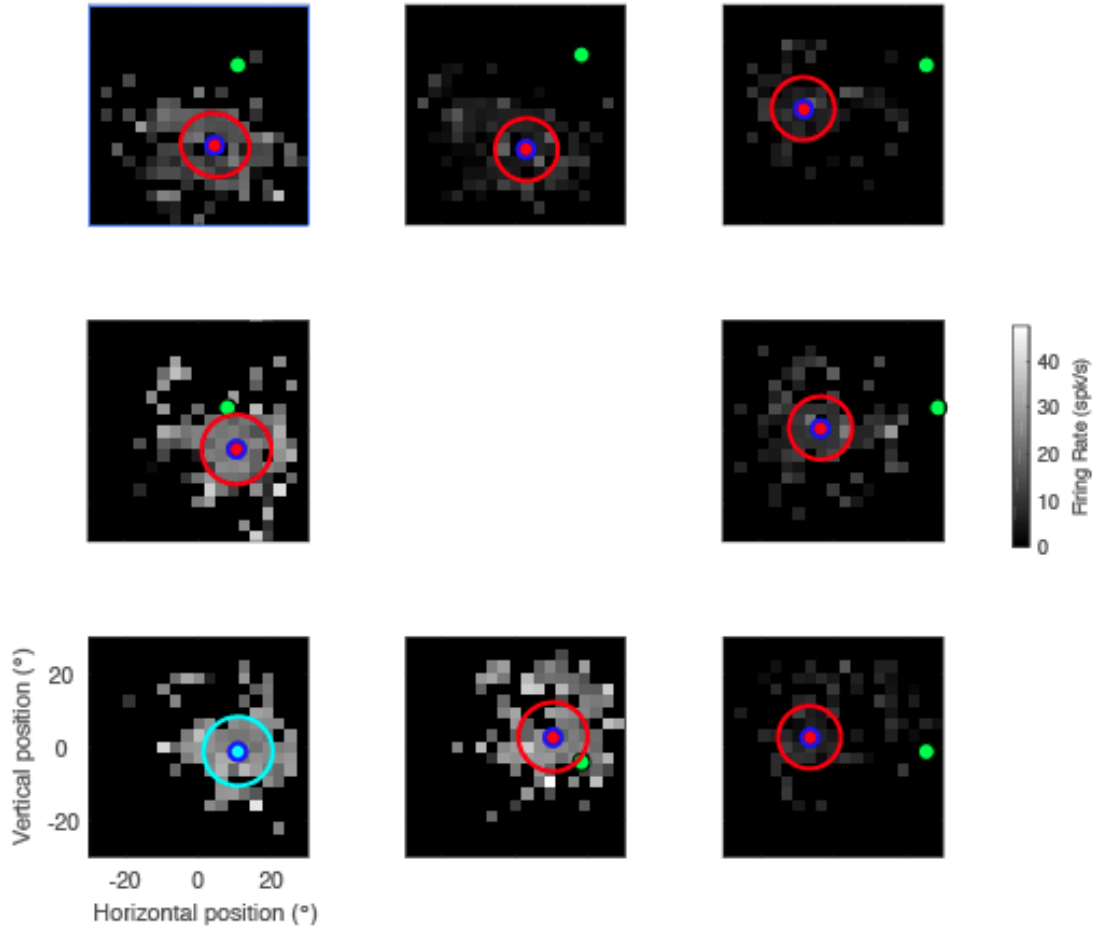


Figure 4.1: Target-conditioned Gaussian fits. Heatmaps were created from trials separated by target location. Gaussian distribution was fit over each heatmap. A "best-fit" Gaussian was selected (blue ellipse) and each of the other distributions were re-fit and constrained using the covariance of the best-fit distribution. The green point represents the expected location of the distribution means in a target-eye reference frame.

We then attempted to fit a two-dimensional Gaussian distribution to each heatmap in order to quantify the likelihood of eye-related tuning in our cells. First, a separate Gaussian distribution was fit to each of the eight heatmaps. The fit with the highest peak was used as the best-fit distribution. Each of the other seven distributions were re-fit and constrained using the covariance of the best-fit distribution. In [Figure 4.1](#), the blue ellipse in the bottom-left plot represents the mean and covariance of the best-fit distribution for this cell. The re-fit distributions are shown in red on the other plots, with the red point representing the mean and the ellipses representing the covariance. If the distribution means in each heatmap are all in the same location, that would show evidence for tuning in an eye-hand reference frame. However, what we see is that the distribution means are in completely different locations in each plot, making it unlikely that this cell’s tuning is tied to changes in eye position.

There is also no evidence in this analysis that tuning is well explained using a target-eye reference frame. In the best-fit condition, we anchored the mean of the distribution (blue point) to the location of the target. Each of the other plots contain a green point that represents the expected location of the distribution mean in a target-eye reference frame. Our analysis showed no evidence that the distribution means were anchored to the target.

While this analysis supports the conclusions drawn in [Chapter 3](#), these results may be biased due to a lack of data. We know that our animals had gaze behaviors that did not uniformly sample the workspace and conditioning our data based on target location further clustered the data into discrete areas. The accuracy of our best-fit distribution suffers when there is not enough data to properly fit. We tested the efficacy of our fitting algorithm by using a single Gaussian distribution split into nine high-resolution heatmaps. We found that our algorithm fits distributions reasonably well and can handle distributions where the mean lies outside of the workspace ([Figure 4.2](#)). Ideally, the ellipse border (black line) should connect across all the plots. Our data is of much lower resolution than this example, so actual fitting accuracy was not ideal.

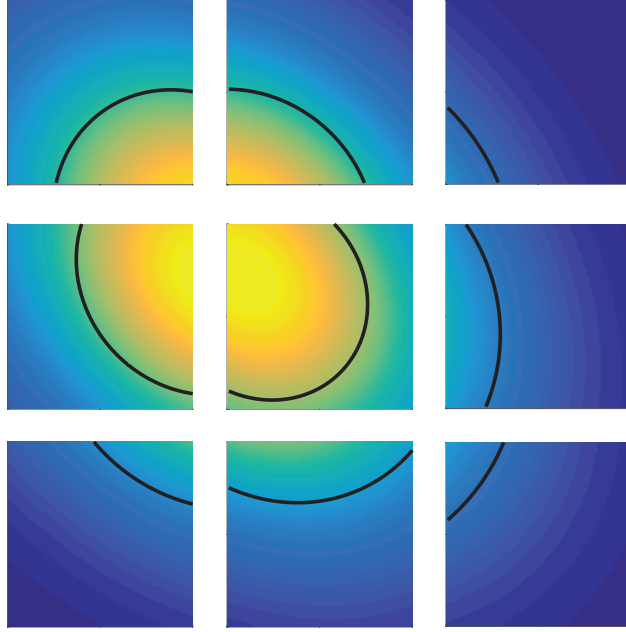
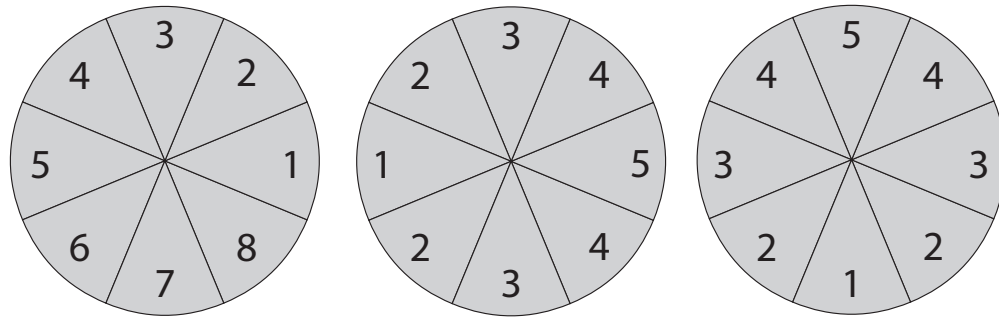


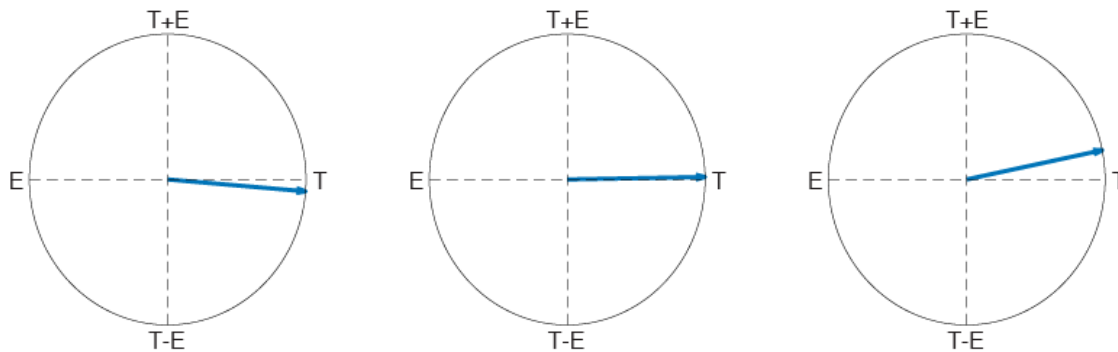
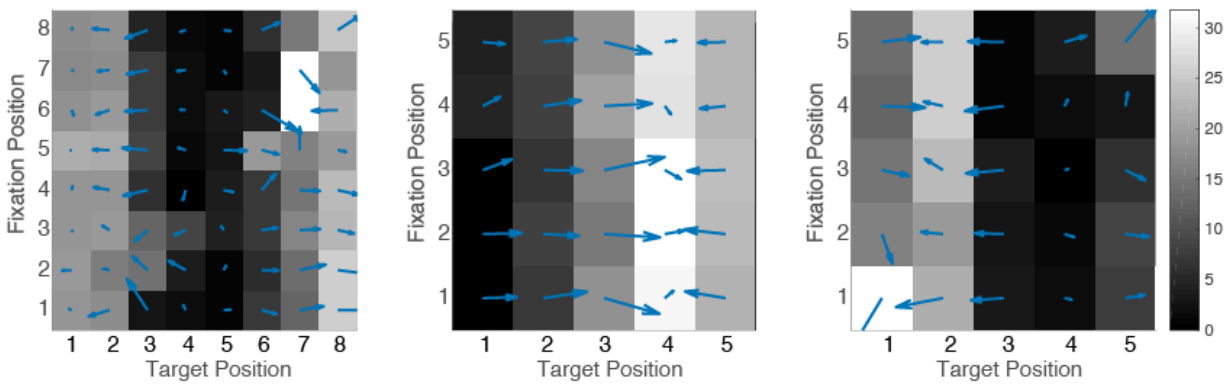
Figure 4.2: Re-fit using an ideal Gaussian distribution. The result of our re-fit algorithm on a single Gaussian distribution split into nine high-resolution heatmaps.

4.2 SINGULAR VALUE DECOMPOSITION AND GRADIENT ANALYSIS

The methodology we employed in [Chapter 3](#) was based on the studies of [Cisek and Kalaska \(2002a\)](#) and [Batista et al. \(2007\)](#). The advantage here was that we could make a direct comparison between our results and those reported in those two papers. Another study we attempted to compare our results to was [Pesaran et al. \(2006\)](#), which also investigated the presence of eye-centered reference frames in PMd. They found PMd cells that used an encoding scheme that incorporated the relative positions of the hand, eyes, and reach target. What this tells us is that, in their cells, neural tuning during a reaching task was best explained using the combined location of these three effectors. This section details our attempt to analyze our data using the methods of [Pesaran et al. \(2006\)](#) in order to provide a direct comparison with their results. The following analysis was implemented with the help of Jeffrey Chiou.



(a) Converting a circular workspace into a response matrix for SVD



(b) Gradient orientation for PMd neuron

Figure 4.3: Singular value decomposition (SVD). A) Our circular array of targets were converted into 8x8 or 5x5 matrices to facilitate SVD analysis. B) Response gradient and orientation analysis on a representative PMd neuron.

Our task design made it very difficult to perform this analysis. The task paradigm used by [Pesaran et al. \(2006\)](#) aligned the positions of the target, eye, and hand into rows and required that each of these effectors remain fixed within the a trial. This allowed them to easily translate their spatial workspace into a response matrix. In our experiment, we arranged targets in a circle around a constant hand position and allowed the monkeys to freely look around the workspace. We attempted to get around this by sectioning our workspace into angular wedges. Target and eye positions were labeled based on each of the three illustrations shown in [Figure 4.3a](#). Response matrices were filled using this assignment protocol.

$$A = USV^T \tag{4.1}$$

We took our data and built response matrices that contained firing rates during different combinations of eye and target positions. Then, using singular value decomposition (SVD), we factorized each response matrix into three matrices – two orthogonal matrices (left and right singular vectors) and a diagonal matrix (singular values) – that were used to characterize the tuning components of our PMd neurons (equation 4.1). Matrix A is the response matrix, U and V^T are orthogonal matrices that contain the left and right singular vectors, respectively, and S is the diagonal matrix that contains the singular values. In this way, gradient analysis is similar to cross-correlation, but more sensitive. If the value of the first singular value was high relative to the other singular values (as determined by a t-test compared to randomized trial conditions), then we considered eye and target to be separable. Then, we determined the orientation of the response field using a gradient analysis. The orientation quantified how much the cell’s response shifted in response to a change in eye and target position. The two-dimensional gradient of the response matrix was estimated using the MATLAB gradient function. After which, the angles of each gradient vector were doubled in order to account for symmetric response fields and vector summation was executed.

[Figure 4.3b](#) shows the gradient analysis performed on one example cell. This cell has a response gradient orientation shows the most change in response to target position. We could not properly quantify the orientations we observed because of a lack of uniformly sampled

data. The SVD analysis could not be performed because of missing data in our response matrices. Even when matrices did not have missing data, the non-uniform distribution of fixations results in the construction of some responses from very few data points.

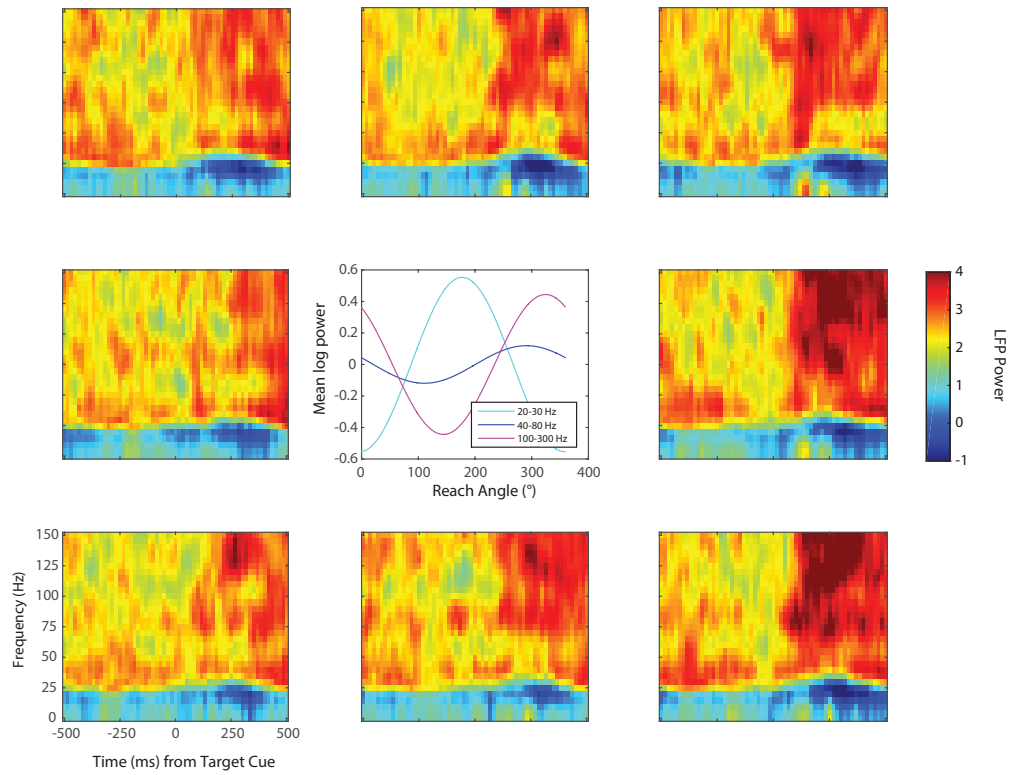


Figure 4.4: LFP spectrograms. Power spectral density is aligned to time of target cue onset and organized by target direction. Tuning curves show directional preference in 20-30Hz (LFP_L), 40-80Hz (LFP_M), and 100-300Hz (LFP_H) frequency ranges.

4.3 LOCAL FIELD POTENTIALS IN PMD

The following analysis was performed by Ryan Williamson.

All of the analyses I reported on in [Chapter 3](#) utilized multi-unit activity recorded using microelectrode arrays. Using this data, we concluded that PMd cells are only tuned to the position of a target relative to the hand in animals not trained to fixate. Visual information about the position of the target seemed to be absent at this stage of the visual-motor pathway. We thought it would also be useful to look at local field potentials (LFP). Several studies that have investigated neural tuning properties in motor cortex have found that LFP signals can reliably be used to decode hand position, stimulus direction, or velocity information ([Mehring et al., 2003](#); [Rickert et al., 2005](#); [Heldman et al., 2006](#); [Zhuang et al., 2010](#); [Bansal et al., 2011](#); [Flint et al., 2012](#); [Perel et al., 2015](#)).

Simultaneous multi-unit and LFP recordings were made in Monkey I while performing a reaching task. Raw voltage traces were filtered using an interpolation filter at 60 and 180 Hz. Local field potentials were obtained by applying a power spectral density (PSD) estimation algorithm to the filtered signal. The PSD was calculated for a frequency range of 0-300 Hz with a step size of 30ms and overlap of 100ms using BCI2000 Project. To obtain values for assessing LFP directional tuning, the estimated PSD power was averaged within three frequency ranges in each trial, resulting in 3 different mean LFP values. All data was assessed during 150-1150ms after the initial target presentation (Delay). Average LFP power was calculated by averaging the LFP values obtained from PSD estimation within the Delay time interval for the following frequency ranges: 20-30 Hz (LFP_L), 40-80 Hz (LFP_M), and 100-300 Hz (LFP_H). Tuning was then calculated for each frequency range by performing a regression on the average LFP power against target direction.

[Figure 4.4](#) shows eight LFP spectrograms from a representative channel from our array. Each spectrogram is using data from the delay period separated by target location. Directional tuning curves are in the center; each curve for a frequency range. What we notice in this channel is that the LFP power increases in the LFP_H band (100-300Hz) after target cue, but decreases in the LFP_L band (20-30Hz). When we took the estimated PSD within every fixation period and ran it through a planar regression, we found very little influence from

changes in target location relative to the hand (median $R^2 < 10^{-3}$ for all frequency ranges) and target location relative to the eyes (median R^2 : $LFP_L = 0.0046$, $LFP_M = 0.0020$, $LFP_H = 0.0012$). Figure 4.5 shows the data from every frequency range. LFP signals during fixations seemed to poorly represent target location in both reference frames, although the data was better fit to target location relative to the eyes than to the hand.

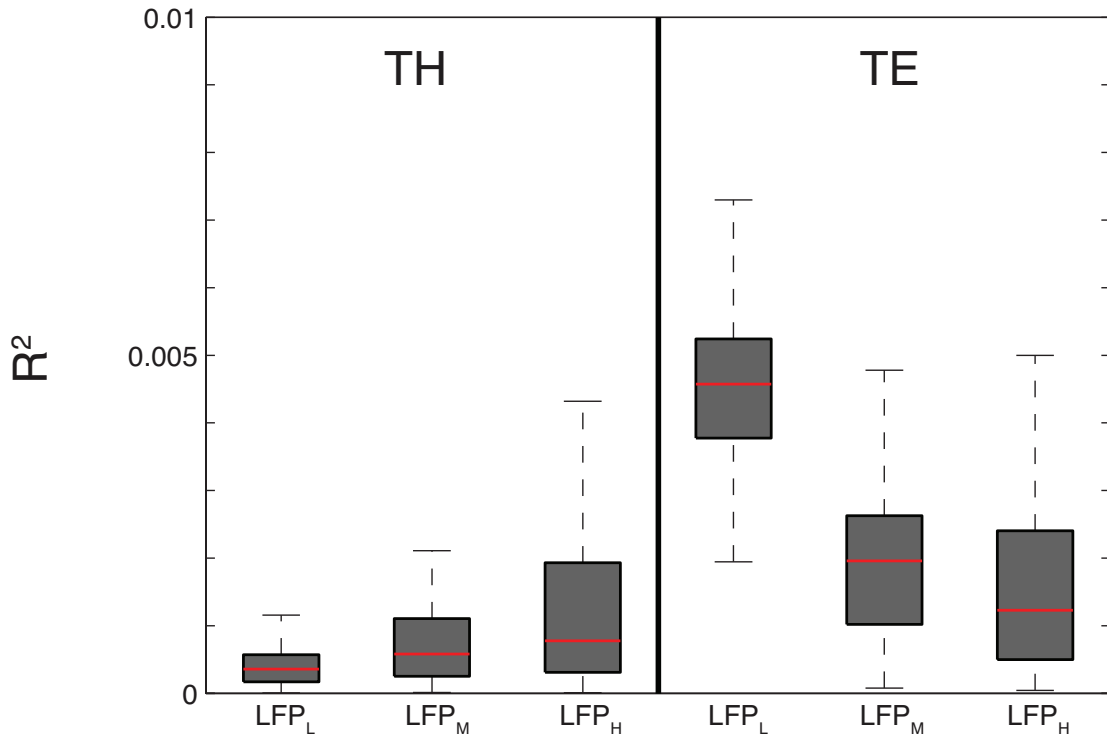


Figure 4.5: LFP TH and TE tuning R^2 . Power spectral density was estimated as each frequency range and averaged for every fixation. Data was fit to a planar regression using target location relative to the hand and to the eyes. Box plots show the 25th and 75th percentile of R^2 values. Red line is median value.

5.0 CONCLUSIONS AND FUTURE DIRECTIONS

5.1 SUMMARY

The theme of this dissertation is focused around how the visual-motor pathway transforms visually salient information from striate and extrastriate areas into reach-related signals to be used by the motor cortex, as well as where in cortex this transformation is completed. Eye-hand coordination has been studied in monkeys ([Georgopoulos et al., 1982](#); [Mountcastle et al., 1975](#); [Colby et al., 1988](#); [Colby, 1998](#); [Caminiti et al., 1991](#); [Wise et al., 1997](#); [Boussaoud et al., 1998](#); [Batista et al., 1999, 2007](#); [Iriki et al., 1996](#); [He et al., 1993](#); [Tanné et al., 1995](#); [Cisek and Kalaska, 2002a,b, 2010](#); [Wallis and Miller, 2003](#); [Pesaran et al., 2006](#)) and humans ([Bower et al., 1970](#); [Carlton, 1981](#); [Mather and Fisk, 1985](#); [Neggers and Bekkering, 2002](#); [Henriques et al., 1998](#); [Medendorp and Crawford, 2002](#); [Pouget et al., 2002](#); [Sober and Sabes, 2005](#); [Sorrento and Henriques, 2008](#)) for over 40 years and we have yet to truly understand the mechanisms that allow for this process to occur.

Here we report that PMd neurons carry virtually no representation of the location of a target in visual coordinates. We arrived at this conclusion after a series of analyses. First, we applied a conventional regression analysis. That did reveal apparent, although moderate, tuning for target location in visual coordinates. But then through simulations and a partial regression, we found that target-eye tuning is all but absent in our recordings from two animals; its appearance in our initial analyses was probably a spurious artifact of regularities in the animals' gaze behavior which makes it difficult to disassociate the effects of target-eye tuning from target-hand tuning.

5.2 THOUGHTS ON INTERPRETATIONAL CAVEATS WITH PHYSIOLOGY DATA

Much of neurophysiology is not just about how data is analyzed, but how it is not analyzed. We often miss important and interesting results by virtue of not looking for them. Here, we note that our initial analyses into the reference frames employed by PMd found ourselves with evidence to support the findings of [Pesaran et al. \(2006\)](#) and [Batista et al. \(2007\)](#). A majority of our neurons showed significant modulation from changes in reach target location in an eye-centered reference frame. It was not until we noticed the glaringly nonuniform gaze behavior of our monkeys that we pursued additional analyses to control for the sampling bias in their respective behaviors. In doing so, our data revealed more to the story that was sitting just under the surface.

5.3 FUTURE DIRECTIONS FOR REFERENCE FRAME STUDIES

The visual-motor system is responsible for our ability to perform eye-hand coordinated movements – an important aspect of daily life. However, the mechanisms that enable the brain to transform motor goals from visual coordinates ([Batista et al., 1999](#)) to a limb-centered action plan ([Georgopoulos et al., 1982](#); [Caminiti et al., 1991](#)) are not well understood. Here I discuss potential directions for reference frame studies focusing on PMd and its role in visually-guided reaching.

5.3.1 Flexibility and plasticity of PMd reference frames

It is possible that learning a reaching task that enforces instructed fixations causes development of eye-related modulation in PMd that is permanent and pliable based on context. Choosing behavioral tasks that will be maximally informative is an important part of neurophysiology studies. Electrophysiology and behavioral neuroscience paradigms are designed to isolate relevant behavior. Systematic changes in experimental conditions are then used to

alter that behavior in order to study the properties in the brain responsible for or effected by the behavior. Studies that have investigated visual tuning in dorsal premotor cortex (PMd) have utilized different tasks to collect their data. One of the major differences between our visual-motor task and some of the previous reference frame studies (Boussaoud et al., 1998; Pesaran et al., 2006; Batista et al., 2007) is that we did not require our monkeys to constrain their gaze behavior in order to succeed at the task. Our monkeys were free to look anywhere they wanted through the entirety of the trial (Figure 3.2). When we analyzed the data from our trials, we did not find cells that reliably encoded target location in eye-centered coordinates. Our results were similar to Cisek and Kalaska (2002a), who also employed a free-gaze reach task. However, those studies that found cells with strong eye-related reach tuning implemented task constraints on their animals' gaze behavior. Is it possible that experimental conditions relevant to the task, and thus relevant to reward acquisition, may cause eye-centered tuning to develop or become enhance? This is ultimately a question about the flexibility of PMd reference frames.

It would seem possible that requiring fixation and making it explicitly relevant to the task may induce or enhance a sensitivity to that sensory modality. In Boussaoud et al. (1998), Pesaran et al. (2006), and Batista et al. (2007), animals were required to fixate at instructed stimuli. A failure to maintain this action would result in a failure of the trial, making gaze behavior highly relevant for the success of the reach. We know that PMd is capable of learning arbitrary associations between nonspatial cues and reach goals, as well as being capable of making perceptual movement decisions (Wallis and Miller, 2003). Those associations are learned due to the significance of the sensory information to the success of the task. Dorsal premotor cortex, faced with the requirement to direct an accurate and precise movement to an object in the visual periphery, may adapt eye-centered tuning properties to guarantee a correct reach plan.

Similarly, PMd may choose to encode reach goals using stimuli and effectors that are most stable within the task. In our paradigm, monkeys made several fixations throughout the workspace. These fixations had no effect on the success or failure of a trial, but caused the visual field to shift all relevant stimuli every time a saccade was made. When trying to encode a reach goal, it would seem inefficient and computationally taxing to use an

effector that causes your frame of reference to shift often. In fact, there is evidence that sensory integration while planning a reach is driven by the computational demands of the task. [Sober and Sabes \(2005\)](#) found that the relative weighting of vision and proprioception depends on the sensory modality of the target and the information content of the visual feedback. Neural tuning observed in [Pesaran et al. \(2006\)](#) and [Batista et al. \(2007\)](#) were taken from cells with the ability to utilize stable representations of the reach goal relative to the eyes.

A future study could test this by recording from cells in PMd while an animal performs two different reaching task paradigms. One task would be similar to the task we implemented in [Chapter 3](#): during each trial, the monkey will only be instructed on where to initiate the reach from (starting hand position) and where the reach goal is (reach target location). The hand and target positions should both be independently varied. During this task, there should be no constraints on gaze behavior, but eye position should be recorded through the entire trial. The second task would be identical to the first, with the exception of an additional stimuli to instruct the monkey's eye position. Require the monkey to maintain fixation at all times in the reach task and vary fixation position along the same dimension as the hand position. If the requirement to perform instructed fixations has an effect on PMd target encoding, then it should be apparent when analyzing the data between these two tasks.

It is also important to not only consider the behavioral conditions of these paradigms on a trial-by-trial basis, but the long-term effects of learning ([Lomo, 1966](#)). We track behavior and record from neurons only after our monkeys are able to reliably perform our visual-motor task with a high success rate. In fact, many neurophysiology studies overtrain their animals on a specific task. This approach helps to minimize behavioral variability that may affect the data being recorded. However, this technique also ignores the effect of learning. In order for the monkeys in [Boussaoud et al. \(1998\)](#), [Pesaran et al. \(2006\)](#), and [Batista et al. \(2007\)](#) to accurately perform their tasks, they had to be taught to associate the fixation stimuli as locations where their visual field must be centered. Does this type of training have an effect on reference frames in PMd?

Conditional visual-motor learning occurs when a person or animal associates a visual stimulus with a response in a learned motor repertoire. Previous studies have looked at conditional visual-motor learning in PMd (Mitz et al., 1991) and concluded that in addition to its speciality for motor planning, it has a specific role in the movement selection on the basis of arbitrary visual-motor associations. Lesions in dorsal premotor and ventral prefrontal cortices show very severe deficits in conditional visual-motor learning (De Toni and Tonchia, 2001; Eliassen et al., 2003), while any involvement of the parietal cortex in conditional visual-motor learning has yet to be found (Rushworth et al., 1997; Pisella et al., 2000). It may be the case that PMd's involvement in abstract visual-motor learning produces learning effects in low-level aspects of visual-motor reaching as well.

A future study could test this by recording from a population of PMd cells simultaneously from a microelectrode array in a naive monkey who has only been trained to perform a simple reaching task without any restrictions on his eye behavior (pre-training data). After collecting neural data from that task, the monkey would be trained to perform the same reaching task, but with enforced fixation. The microelectrode array would enable stable collection of spiking data through the monkey's entire process of learning (training data). Once the monkey can reliably perform the enforced fixation task, collect data using the original free-gaze task (post-training data). Using the same task before and after training allows you to make direct comparisons between the two periods. It can be surmised that any differences in neural tuning between the pre-training and post-training data will be due to the behavioral training that occurred. It is important to note that even though pre- and post-training data will be recorded under the same experimental conditions (free-gaze task), the monkey's gaze behavior could change after training. At that point, it would be important to account for those changes in behavior.

5.3.2 Functional differences within premotor cortex

My proposed longitudinal study into the effects of fixation training should also be adapted to other premotor areas. Premotor cortex is separated into several subregions that include dorsal premotor cortex (PMd), ventral premotor cortex (PMv), and pre-PMd (rostral to

PMd; [Picard and Strick, 2001](#)). Important functional differences between these areas exist and, in an effort to better understand their role in visual-motor transformations, comparing brain areas in the same animals and under the same experimental conditions is necessary. PMv activity is closely related to the perception of a motor performance ([Schwartz et al., 2004](#); [Hoshi and Tanji, 2007](#)). The activity within pre-PMd exhibits fixation and saccade responses ([Bon and Lucchetti, 1992](#)), while activity within PMd retains the more classical view of movement-related modulation. It is possible that pre-PMd and PMv develop a more drastic increase of eye-related modulation after training than PMd, due to the more pronounced visual and oculomotor signals present in these areas ([Fujii et al., 2000](#); [Schwartz et al., 2004](#)). On the contrary, PMd may show a stronger change in eye position signals because of its role in sensory-motor mappings ([Weinrich and Wise, 1982](#); [Mitz et al., 1991](#)).

5.3.3 PMd as a Jack of all Trades

Much of this chapter has been spent discussing the claim that dorsal premotor cortex (PMd) develops eye-centered tuning in response to training and task instruction. The results from [Boussaoud et al. \(1998\)](#), [Cisek and Kalaska \(2002a\)](#), [Pesaran et al. \(2006\)](#), [Batista et al. \(2007\)](#), and my own work make a compelling argument for this theory. Naturally, if this turns out to be true, it brings into question what other tuning properties may be learned. It may be that many of the findings in the published literature are an artifact of training, and specifically, rewarded behaviors.

When provided with incomplete information about a future action plan, PMd modulates in a manner that encodes the information available at the time. [Cisek and Kalaska \(2002b\)](#) found that when given two reach targets, PMd neurons will encode both motor plans. Monkeys were given two visual cues that informed them of their potential reach targets. While in this period, signals in PMd represented both targets simultaneously. Following a delay period, they were given another cue to instruct them on which of the previous two targets they were to reach to. Once this information was received, cells in PMd disregarded the signal to the rejected target and the signal encoding the chosen target remained. [Riehle and Requin \(1989\)](#) found that when given incomplete information about a motor instruction,

PMd encodes the partial information it receives. Monkeys were instructed on either the direction or amplitude of an upcoming reach. Once the monkey was instructed to reach, the remaining information about the reach location was given. These two reports show that PMd modulates in response to incomplete goal information when the full reach instruction is forthcoming.

There is evidence that PMd is active during any goal-directed movement, not simply arm movements. [Cisek et al. \(2003\)](#) showed PMd cells that had similar tuning for reaches using either the ipsilateral or contralateral arm. Not only were cells tuned for both limbs, but preferred directions of these cells were not significantly different. PMd is capable of encoding a reach plan in an effector-independent way. In addition, several studies have shown saccade-related responses throughout premotor cortex ([Bon and Lucchetti, 1992](#); [Fujii et al., 2000](#); [Lebedev and Wise, 2001](#); [Ohbayashi et al., 2003](#); [Pesaran et al., 2010](#)). Similar to their findings for reach targets, [Pesaran et al. \(2010\)](#) found a relative position code being used by PMd neurons that combines the positions of gaze, the hand, and a saccade goal. While monkeys performed a center-out saccade task, cells in PMd showed sustained preparatory activity that was significantly above their baseline level and directional tuning to the location of the saccade goal. This tuning to saccade goal was shown to be stronger in their PMd cells than in parietal reach region (PRR). Then, using a position-coding task ([Pesaran et al. 2010](#), Fig. 1), they found that changes in eye position, hand position, and saccade goal location caused robust neural modulation. While saccades are often directed toward a reach goal before movement, these results are interesting in that saccade modulation is present even when a reach is not planned. This points to the strong possibility that PMd adapts tuning to the effector that enables the successful completion of a trained action.

PMd is also active when anticipating an action done by another party. [Cisek and Kalaska \(2004\)](#) found that cells in PMd show task-related modulation during observation of a well-learned motor task. Monkeys were trained to do a center-out task and then made to watch an unseen actor perform the task. PMd neurons showed task-related activity that began before the onset of movement and was comparable to activation seen when performing the task. In order to make sure the monkeys were paying attention to the task when they were instructed to observe, they were given juice rewards when the actor completed a trial correctly. Even

when the actor delayed their reach, to simulate a slow reaction time, PMd cells stayed active in a manner that was related to the anticipation of a correct reach, not the dynamics of the movement cursor. It seems likely that the expected reward associated with this motor task is playing a large role in driving the activity of these PMd neurons.

Even so, there are plenty of reasons to view PMd as an area primed for reaching. Cells in PMd display activity that mirrors what we see in primary motor cortex (M1), a convincingly motor area (Weinrich and Wise, 1982; He et al., 1993; Caminiti et al., 1991). Intracortical microstimulation in PMd causes forelimb or body movements (Fujii et al., 2000). Inactivation and lesioning of PMd causes directional motor errors associated with improper understanding of abstract instructional cues (Kurata and Hoffman, 1994; Passingham, 1988). However, the most powerful studies moving forward will be those that compare neural responses in different brain areas in the same animal, or those that test hypotheses for which the potential impact of training is irrelevant.

APPENDIX

OUTREACH AND TEACHING

During my graduate career, I balanced my time in the laboratory with science outreach and advocacy. I have a very strong passion for education and mentorship. Positive mentors and role models have had a huge impact on my own success. I feel a deep responsibility to give back to students at all stages of their academic journey.

A.1 DIVERSITY ADVOCACY

When I first arrived at the University of Pittsburgh, I immediately leapt at the chance to help recruit and retain underrepresented minority (URM) students. The stats were very clear: In 2013, URM students accounted for 4% of total PhD candidates (16) and 3% of total Masters students (16) in the Swanson School of Engineering, while nationally they accounted for 11% of all graduate students in Engineering ([NSF, 2013](#)). As a person from an underrepresented group, I wanted to do whatever I could to move that needle up.

I began by traveling on recruitment visits to my alma mater, the University of Maryland Baltimore County. I was originally recruited by the University of Pittsburgh through one of these visits while I was an undergraduate student, so I was very familiar with how effective it could be. I typically traveled with Dr. Harvey Borovetz (former Department Chair and current Professor in Bioengineering) and Dr. Sylvanus Wosu (Associate Dean for Diversity and Associate Professor in Mechanical Engineering & Materials Science). During these visits,

I would get the opportunity to speak to undergraduate students about my experience at the University of Pittsburgh, my thoughts on graduate school, and advice on how to be a strong doctoral program applicant. I have also recruited for the university at the National Society of Black Engineers (NSBE) conference.

I also began to get involved with campus organizations at the University of Pittsburgh that allowed me to work on diversity advocacy. I served as the Graduate Liaison for the local chapter of NSBE. My time on the executive board allowed me to organize an event where I gave a presentation on the realities of graduate school and important strategies that can prepare prospective students to pursue an advanced degree. It was a great experience to be able to give insight and encouragement to URM undergraduate students. However, I increasingly felt the absence of an organization that specifically catered to URM graduate students in the Swanson School of Engineering. Organizations like NSBE, the Society of Women Engineers (SWE), and Society of Hispanic Professional Engineers (SHPE) are doing a fantastic job of providing a community for undergraduate URM students in engineering disciplines at University of Pittsburgh. The only graduate level organization at the University of Pittsburgh catering to URM students is the Graduate Women in Engineering Network (GWEN).

Hall (1999) wrote that "the availability of ethnic and cultural organizations, and the "critical mass" of African American students, helped to reduce the isolation and alienation generally found on predominantly White campuses." To address this issue, I formed the Engineering Diversity Graduate Students Association (EDGSA), the first student organization at the Swanson School of Engineering that catered specifically to URM graduate students. The organization was formed under the advisement of Dr. Sylvanus Wosu. I served as the President of the organization for 3 years. In that time, I worked to improve recruitment and retention of URM graduate students at the university through a concerted effort to establish the EDGSA as a community for URM students. Since its inception, we have organized several social and professional development events for our members, including a panel discussion with local STEM professionals, a mental health seminar, and a mixer with engineering faculty. As President, I also testified in front of the School of Engineering Diversity Committee and the Board of Visitors. I am proud of to be leaving a lasting legacy of diversity advocacy on the University of Pittsburgh campus.

A.2 SCIENCE COMMUNICATION OUTREACH

I participated in numerous outreach opportunities through the EDGSA and the local chapter of the Biomedical Engineering Society (BMES). I have given presentations to middle and high school students at the University of Pittsburgh, Carnegie Science Center, North Hill Middle School, and Hill House Passport Academy Charter School. In most of these events, I spoke about the interesting work going on in the field of Bioengineering and explained my specific research. Lots of children are interested in the sciences, but for one reason or another can become discouraged from it or lose interest. Presenting at events like these was a really great way for me to ignite the imaginations of these kids and talk to them about some of the cutting edge science going on. It also helped me to learn how to distill my research into a way that general audiences can understand and find exciting. It was always exhilarating to see kids intently paying attention to me talk about my research. My positive experience with these outreach opportunities led me to begin volunteering at the Carnegie Science Center in their Demonstration Theaters department doing live science demos for general audiences.

A.3 SUMMER ENGINEERING ACADEMY

For two summers, I was a lead instructor with the Pitt EXCEL Program's Summer Engineering Academy. The Pitt EXCEL Program is an undergraduate diversity program committed to the recruitment, retention, and graduation of academically excellent engineering undergraduates, particularly individuals from groups historically underrepresented in the field. The Summer Engineering Academy's main goal is to help students make the adjustment to the demands of college life and prepare them for the rigors of an engineering curriculum. Each course that I taught lasted 2 weeks. The first was Engineering Problem Solving and the second was Pre-Calculus. In both courses, I set up my own lesson plans, homework assignments, and exams, as well as graded all of the assignments myself. It was very challenging, especially the Pre-Calculus class. I had to quickly learn how to develop lesson plans and teach in a way that I did not get to do as a teaching assistant.

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