# Eye-Head-Hand Coordination During visually guided Reaches in Head-Unrestrained Macaques.

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A THESIS SUBMITTED TO
THE FACULTY OF GRADUATE STUDIES
IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF
MASTER OF SCIENCE

Graduate Program in Biology

York University

Toronto, Ontario, Canada

March 2019

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# ***Abstract***

Non-human primates have been used extensively to study eye-head coordination and eye-hand coordination, but the combination —eye-head-hand coordination— has not been studied. Our goal was to determine if reaching influences eye-head coordination (and vice versa) in Rhesus macaques. Eye, head, and hand motion were recorded in two animals using search coil and touch screen technology, respectively. Animals were seated in a customized ‘chair’ which allowed unencumbered head motion and reaching in depth. In the reach condition, animals were trained to touch a central LED at waist level while maintaining central gaze and were then rewarded if they touched a target appearing at one of 15 locations in a 40° x 20° (visual angle) array. In other variants, initial hand or gaze position were varied in the horizontal plane. In similar control tasks, animals were rewarded for gaze accuracy in the absence of reach. In the *reach task*, animals made eye-head gaze shifts toward the target followed by reaches that were accompanied by prolonged head motion toward the target. This resulted in significantly larger velocities and final ranges of head position (and lower eye-in-head ranges) compared with the gaze control. Gaze shifts had shorter latencies, higher velocities, and were more precise, despite the lack of gaze reward. Initial hand position did not influence gaze, but initial gaze influenced reach latency. These results suggest that eye-head coordination is optimized for visually-guided reach, first by quickly and accurately placing gaze at the target to guide reach transport, and then by centering the eyes in the head, likely to improve depth vision during manual contact.

# ***Dedication***

*I dedicate this*

*thesis to my family.*

*Thank you for always supporting me and*

*giving me unconditional love.*

# ***Acknowledgements***

First and most importantly, I would like to thank Dr. John Douglas Crawford who gave me an extraordinary opportunity to conduct neurophysiology research in his laboratory and who has provided me with continued guidance and support throughout this project. Thank you for having confidence in me with this project and I will be forever grateful. Your compassion and dedication to research is an inspiration. It is more than I could ever dreamed of and I feel truly blessed to have an exemplary academic role model such as you.

Next, I would like to the thank all the members of Crawford lab for their excellent ideas, insightful conversations and great laughs. Thank you for always kindly answering all my questions and inquires.

I thank Dr. Xiaogang Yan for teaching me the proper procedure necessary for assisting in training the animals and always providing the technical support in lab and in office.

Along with him, I would like to thank Saihong Sun and Dr. Hongying Wang for their technical knowledge and support, without them, I would have trouble interpreting my data and deriving the quantitative measures. Dr. Hongying Wang who taught me the operational procedures in animals.

Crawlab lab accepted my lack of insight early on and shaped my growth throughout the journey. I could not have asked for a more positive environment to conduct my research.

I would especially like to thank my examining committee, Dr. Lauren Sergio, Dr. Nikolaus Troje and Dr. Denise Henriques who have taken the time to converse with me about research, for their helpful suggestions and feedback. I have received wonderful advice and challenging questions to fuel my fascinations within neuroscience.

Finally, I must thank my parents, Amarpreet Singh and Ravinder Kaur and my parent in-laws Pritpal Singh and Ranjit Kaur, my brother Rajjot Singh, and my partner and best friend, Jaspreet Singh for their immense love. They tolerate my uncertainties and provide nothing but encouragement that keeps me going toward the path of success.

# ***Contributions***

The candidate (Harbandhan Arora) was involved in all stages of the experimental work, such as experimental design, animal training, data collection and analysis, and the write-up of the manuscript presented in this thesis. This would have not been possible without the help of the co-authors:

Dr. Vishal Bharmauria helped in the analysis of the data and provided critical comments on the manuscript presented in this thesis.

Dr. Xiaogang Yan assisted with setting up the lab in order to conduct the experiments. Along with that, he helped with the training of the subjects, assisted with the surgery of the animals and early phases of data collection that is presented in this thesis.

Dr. Hongying Wang performed the surgeries required for each subject. And provided the technical support whenever it was required.

Saihong Sun contributed to the programming of the codes required for the analysis of the data collected in this experiment.

Dr. Veronica Nacher provided critical comments on the manuscript.

Lastly, Dr. John Douglas Crawford without whom none of this would be possible supervised this project and provided critical input and guidance into designing this experiment, analyzing the data, and write-up of the manuscript.

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# ***Chapter 1:***

# ***General Introduction***

## ***1.1 Introduction:***

On any given day, we become thirsty and need to grab a glass of water. Although we can carry out the action seamlessly, the discrete components that are involved in completing the task have been the aim of goal directed/action research. To accomplish this task, we initially begin with fixating our gaze on the water glass; followed by a rotation of our head. We finally move our arm towards the glass of water to grab it. This action requires intricate sensory and motor processes from the various brain areas, controlling the eyes, the head and the hand (arm). Reaching for an item involves three conditions: Firstly, position of the item with respect to the fovea, then eyeball with respect to the head, and the head with respect to the eye; secondly, information of arm position; and thirdly, coordination of eye, head and arm movements leading to movement of the gaze and arm towards the target. Behaviorally, dissecting the components of an action such as this one has been documented in humans but not as well documented in non-human primates, which is the ultimate goal of our project.

To make appropriate reach movement to the target, it is not enough to know the location of the target: knowledge of the initial eye and head position is also required. In addition, hand position is also required because the desired movement vector is defined as the difference between the initial and the final target reach position. The eye-hand coordination has a significant part in the advancement of human beings; however, we are just starting to treasure it. While trying to reach a glass of water, our brain uses visual feedback to guide the arm in right direction. This is shown by many studies (Van Donkelaar and Staub 2000; Helms Tillery et al. 1991; Prablanc et al. 1986; Rossetti et al. 1994) that motor tasks are completed at a higher quality with visual feedback. It is also shown that while looking straight at the target, subjects are less prone to reach the target without error, rather than looking right or left of it (Bock 1986; Van Donkelaar and Staub 2000; Johansson et al. 2001; Prablanc et al. 1979).

The efficiency of reaching for an item is not dependent on the relative timing between the motion of the eyes, the head and the arm, but individuals perform more precisely when their eyes are close to the item when reaching (Abrams et al. 1990; Bock 1986; Henriques et al. 1998). Individuals may reach an item precisely that they are glancing at because the brain has knowledge to both foveal signals and eye position signals to update spatial representation of the steady item. We tend to glance at things we reach to see them better and both the eyes and hand are eventually directed by the same retinal image.

(Snyder et al. 2002) showed that saccades are faster when accompanied with an arm movement towards either a visible target or remembered target in monkeys. Additionally, (Snyder et al. 2002) showed that reaction times were also shorter for the saccades made with an arm movement toward a target than when made without an arm movement. This suggests that motion of the hand can also impact movement of the eyes. A study by Stahl showed that the head moves more with the eyes for gaze shifts that are large (i.e. when the target is far from the fixation) but moves little for gaze shifts that are smaller (i.e. when the target is near fixation).

A lot of studies previously have been done on saccadic eye movements when the head is restrained in a variety of species such as humans, rhesus monkeys. To achieve large redirections in the line of sight the eyes and head can move together which is possible when the head is free (unrestrained). Eye-head coordination data were usually collected from movements guided along the horizontal direction (Barnes 1979; Bizzi et al. 1971; Phillips et al. 1995). Different patterns of eye-head coordination have been described based on relative onset of eye and head movements (Moschner and Zangemeister 1993). First, head movement occurs before eye movement onset, but the vestibule-ocular reflex holds the position of line of sight until the eyes start its movement. Second eye movement ends before the head starts to move. Third the head starts to move a little after the onset of the eye movement and then the eyes and head progress the movement together till the gaze end on the target. Therefore, to attain the required gaze shift the contribution of eye and head will vary according to the selection of eye-head coordination patterns stated above.

In our study, we provided head-unrestrained training from the beginning which yields more natural eye-head-hand coordination strategies that have not been recorded before. There are many studies on eye-hand and eye-head coordination in non-human primates but not so many studies are done on eye-head-hand coordination. This research gave an opportunity to compare the physiology of eye-head-hand coordination with human and provided an experimental model for the human in future neurobiophysics studies.

## ***1.2 Saccades***

Saccade is a quick, simultaneous movements of both eyes as the eye changes focus from one point to another within the visual field (Fig. 1).

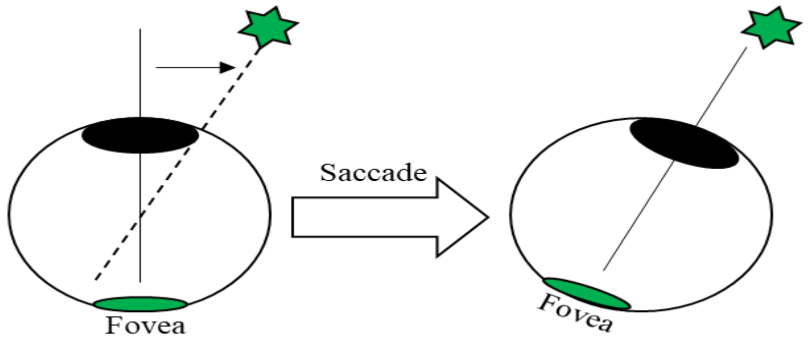

***Figure 1: What is saccade?*** *A saccade is made to bring an image in front of the fovea.*

The word was introduced by French ophthalmologist in 1880, as he experimented the eye movement while reading in silence by using a mirror on one side of the page to observe. He saw the succession of the discontinuous individual eye movements

### ***1.2.1 Behavioral***

Saccades are one of the fastest movements produced by the body. The eye movements of the monkey and not qualitatively different from those of man, monkeys also employ a combination of saccadic and smooth pursuit movements. The peak angular speed of the eye during a saccade reaches upto 900°/sec in humans and can reach 1000°/sec in monkeys (Fuchs 1967). The amplitude range of the saccade can vary from small movements made while reading a book to much larger movements made while looking outside the window. The reaction time for a saccade is usually measured around 200 msec (Fig. 2) (Fuchs 1967). During this 200 msec delay, the position of the target with respect to fovea is computed and the difference between the initial and intended position is converted into a motor command. This command helps the eyes to move in the correct direction and distance by activating the specific extraocular muscles. Saccades that are guided by both vision and proprioception tend to have smallest overshoot, comparatively, the saccades that are guided proprioceptively have largest overshoot (Ren et al. 2006).

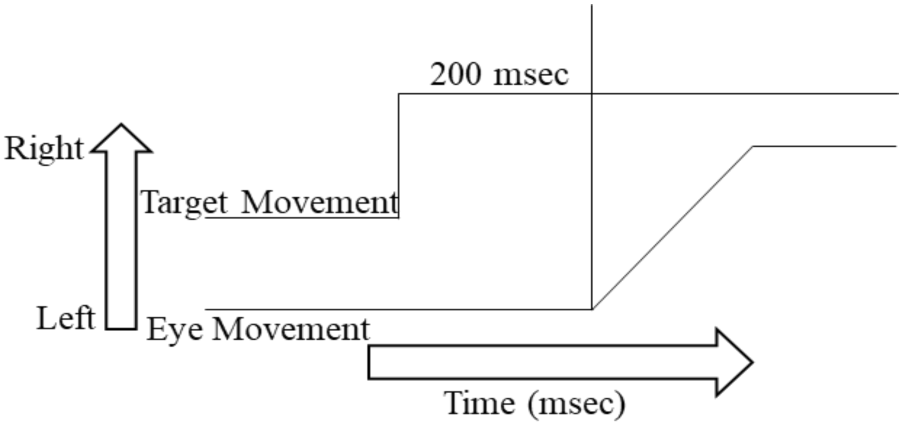

***Figure 2: The metrics of saccade eye movement.*** *When the target moves from left to right, the eye needs atleast 200 msec to start its movement towards the target (Fuchs, 1967).*

## ***1.2.2 Neurophysiology of Saccades***

Saccades are produced as a result of very complex combination of motor and visual system outcome. Visual system gets the information from the photoreceptors in the retina, which is then transformed into electrical signals and sent to lateral geniculate nucleus (LGN) via the optic chiasm. From the LGN the signal goes to primary visual cortex (V1) for further processing and moves to lateral intraparietal cortex (LIP). The signal moves from LIP directly to frontal eye field (FEF) and Superior Colliculus (SC). The electrical stimulation of LIP, FEF, SEF and SC have all shown to produce saccadic eye movements (Bruce et al. 1985; Klier et al. 2001; Martinez-Trujillo et al. 2003). The superior colliculus is a multilayered structure of the alternating grey and white layers found on the roof of midbrain. It has two functional layers: superficial and deep. The retinal ganglionic cells are projected onto the superficial layer to make a map of contralateral visual field. Visual information is further processed into a motor command in superior colliculus. This motor command after reaching paramedian pontine reticular formation (PPRF) is transferred into ocular motor pathways by interneurons present in this region. The burst neurons in PPRF get activated and produce horizontal saccades. For example, to make a leftward saccade, excitatory burst neurons in left PPRF will synapse onto a motor neuron and interneuron in the ipsilateral abducens nucleus, which activates the ipsilateral lateral rectus and contralateral medial rectus via the medial longitudinal fasciculus (MLF). Secondly, excitatory burst neurons also activate ipsilateral inhibitory burst neurons that are going to inhibit contralateral abducens nucleus to prevent the movement of the eyes toward the right side.

But how does the brain stop saccades when they are not needed? There is another set of pontine cells, omnipause cells that fire continuously when not performing a saccadic eye movement. These cells are located in the nucleus of the dorsal raphe. The function of these cells is to inhibit the contralateral burst neurons in the PPRF, and thus inhibit saccades. Figure 3 shows an overview of brain structures and their functional connectivity for the saccade and reach systems.

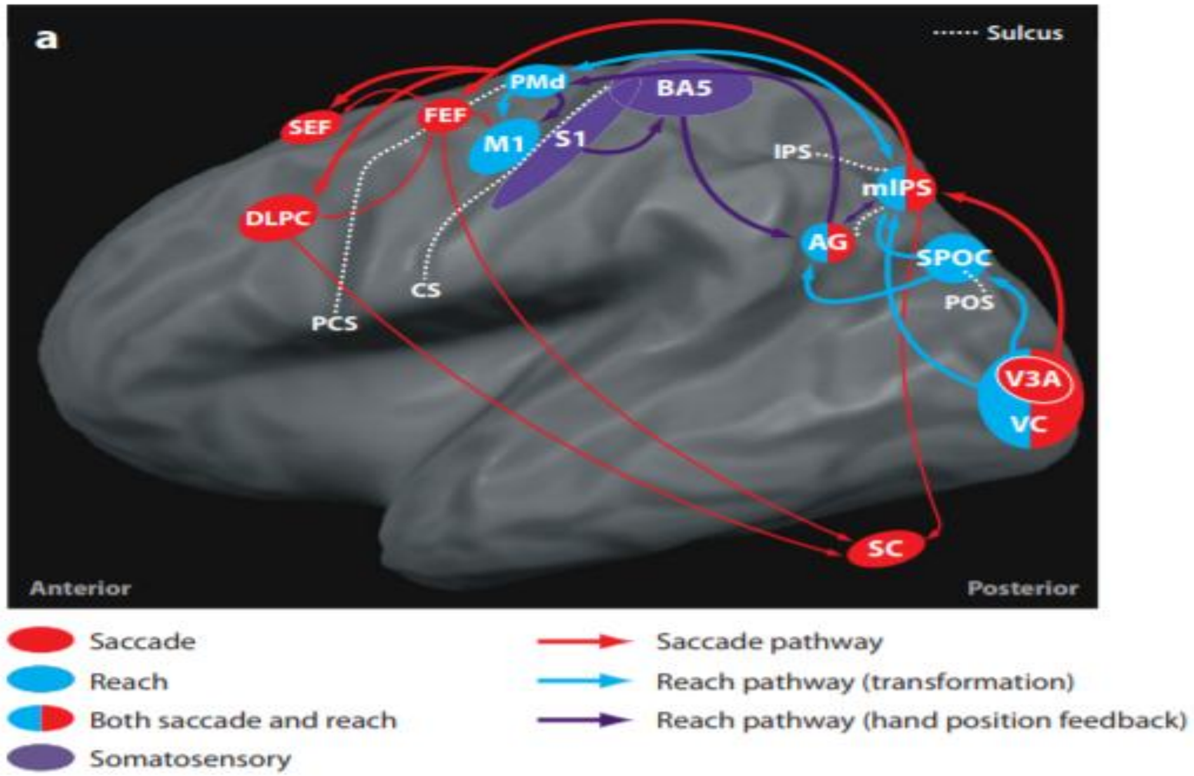

***Figure 3: Overview of visual brain areas and transformations.*** *Lateral view of the human brain showing the areas involved in processing visuomotor transformations and eye-hand coordination: visual cortex (VC), V3A, angular gyrus (AG), mIPS, mid-posterior intraparietal sulcus, and superior parieto-occipital sulcus (SPOC). Primary somatosensory area for arm movements (proprioception) (S1), Brodmann area 5 (BA5), primary motor cortex, dorsal premotor cortex (PMd), frontal eye fields (FEF), supplementary eye fields, dorso-lateral prefrontal cortex (DLPC), superior colliculus (SC), precentral sulcus (PCS), central sulcus (CS), intraparietal sulcus (IPS), parieto-occipital sulcus (POS). (Crawford et al. 2011)*

Saccades can be made voluntarily or involuntarily. Voluntary saccades are initiated by the frontal eye field (FEF) after receiving the signal from parietal eye areas and prefrontal cortex.

Examples of voluntarily made saccades are eye movements made in response to flashing or moving objects. In contrast, involuntarily made saccades are initiated by direct retinal input to superior colliculus (SC). Examples of involuntary saccades are the saccades made during rapid eye movement (REM) sleep and the fast phase of the optokinetic nystagmus.

## ***1.3 Eye-head coordination***

For large line of sight (gaze shifts), the eyes and head move together to accomplish these redirections. Gaze is the measurement of the eye position in the space, which is calculated by adding the eye position relative to the head and head position relative to space.

### ***1.3.1 Behavioral***

Usually we notice that the head moves after the initiation of the eye towards the target. An example trajectory of eye and head movement in vertical and horizontal dimension is shown from our experiment (Fig. 4). There is also a delay between the end of the eye movement and start of the head movement (Warabi 1977), during which the vestibular ocular reflex (VOR) stabilizes the gaze position and the image on the retina. Freedman (1997) showed that the head movements did not contribute to the change in gaze position during small gaze shifts (<20°) directed along the horizontal meridian. But for larger gaze shifts (25-90°), the head contribution to the gaze shift increased linearly with increasing gaze shift amplitude. The eye position in the orbits at the beginning of the gaze shift may also affect the relative timing of the eye and head movements (Fuller 1996; Volle and Guitton 1993). Head contribution increases with increased gaze amplitude (20-60°), peak eye velocity declined by > 200°/sec and head velocity increased by 100°/sec (Freedman and Sparks 1997a).

Monteon et al. 2012 show that moment-to-moment changes in visual cues can trigger different eye-head coordination strategies, as in their behavioral paradigm when monkeys "expected" to make a future gaze shift in the same direction, the current gaze shift was accompanied by a larger head movement. It is known that people are poorer at locating targets when their head rotates away from the body's midline (Biguer et al. 1984; McIntyre et al. 1997; Rossetti et al. 1994; Vercher et al. 1994)

With the development of 3-D recording techniques, neuroscientists can perform their experiments in more natural behavior where the monkeys' head is unrestrained and able to move freely (Battaglini et al. 2002; Crawford et al. 1999; Crawford and Guitton 1997; Li et al. 2017; Sajad et al. 2016)

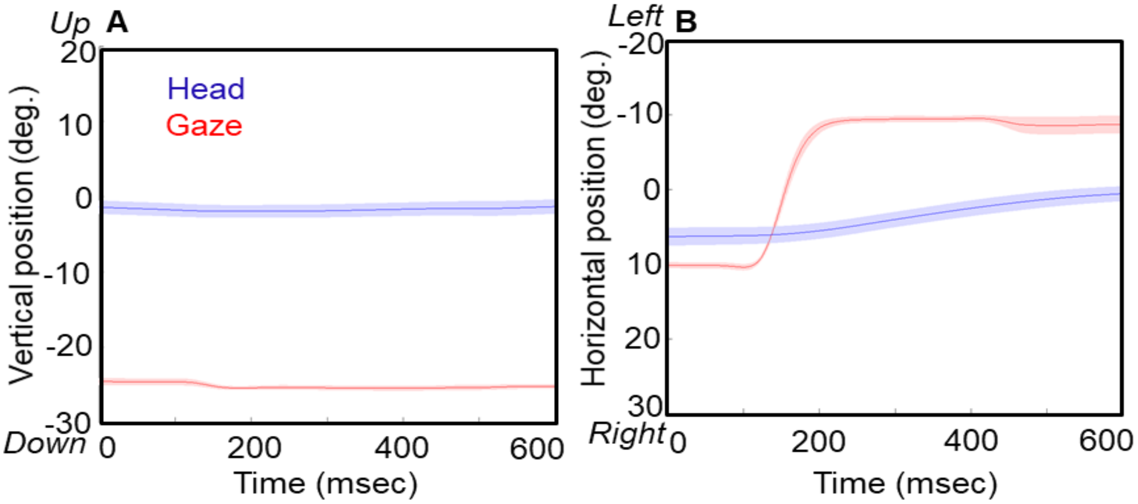

***Figure 4: Head free gaze trajectory.*** *A typical gaze shift showing the movement of eye and head in space in both vertical and horizontal dimension from our study.*

### ***1.3.2 Neurophysiology of head unrestrained gaze shifts***

As soon as we look at an image, the photoreceptors in the retina are stimulated and send an impulse to lateral geniculate nucleus, and from there moving onto lateral intraparietal nucleus (LIP). Electric stimulation of LIP produces saccades with no head movement (Constantin et al. 2007). The visual information from LIP is further transported to frontal eye field (FEF) and supplementary eye field (SEF) in frontal lobe, with addition to superior colliculus (SC). FEF, SEF, LIP and SC stimulation in macaques has shown to produce saccadic eye movement (Klier et al. 2001; Martinez-Trujillo et al. 2003). SEF and FEF stimulation is also associated with eye and head movements to produce gaze shifts in head-unrestrained rhesus monkeys (Martinez-Trujillo et al. 2003; Tu and Keating 2000). After the cortical areas, information is relayed to the superior colliculus in midbrain. From SC, the saccade motor command is transferred to brainstem structures (Gandhi and Katnani 2011). The anterior region of SC is shown to suppress saccades and maintain gaze position (Munoz and Wurtz 1993). Deeper layer of the remaining SC shows the gaze shifts combining normal eye and head trajectories (Freedman and Sparks 1997b; Klier et al. 2001; Sadeh et al. 2015; Walton et al. 2007). Neurons in SC have shown to fire up in anticipation of a saccade and are rapidly extinguished after saccade onset (Munoz and Wurtz 1995). Recently, unit recordings, electrical microstimulation and anatomical studies have shown that SC contains a gaze motor map, and proposed that the SC provides the brainstem pre-motor centers with a desired gaze displacement command (Guitton 1999; Sparks 1999). Neurons related to gaze from SC project to reticulo-spinal neurons (RSNs). From RSNs the projections are carried to the eye-related premotor neurons and to the spinal pre-cephalomotor neurons (Grantyn et al.  2004). Superior Colliculus is known as the significant middle ground between sensory and motor cortical centers. Brainstem reticular formation has different neuronal populations to represent the individual eye and head components in their respective coordinate frames (Pelisson and Guillaume 2009).

## ***1.4 Reach***

To reach is an essential everyday activity. The main use of the arm as an independent part of the body is for reaching toward objects.

### ***1.4.1 Behavioral***

Reaching is the result of a complex sensorimotor coordination. A study by (Roy et al. 2000) showed two similarities in the hand kinematics of monkey and man 1) pointing movements showed an asymmetry depending on the target location relative to the hand used; in particular, movements to an ipsilateral target look longer than those to a contralateral one. 2) Perturbation of target location decreased the magnitude of the velocity peak and increased the duration of pointing movements. These similarities indicate that the macaque monkeys are useful to understand hand kinematics.

The extent to reach an object of interest grows over a period of several months after birth. It is achieved by coordinated motions at the shoulder and elbow joints, which work together. These motions are result of the torques generated at each joint by the contraction of muscles.

Different muscles are used depending on the performance of the desired movement. For example, reaching forward involves the activation of anterior deltoid to acquire the protraction of shoulder joint along with the activation of biceps to prevent the extending forearm (Murphy et al. 1982; Soechting and Lacquaniti 1981). Humans and monkeys try to reach a target in a single movement that is almost equal to the distance that needs to be covered. This phenomenon develops gradually during infancy and it breaks down in patients with Parkinson’s disease. The initial reaching response of infants is composed of series of smaller movements that eventually grows into one single large movement in several months (von Hofsten and Lindhagen 1979). In Parkinson’s disease, the first movement component is too small, and a series of smaller movements are made again to reach the desired target (Flowers 1975). The accuracy to reach an aimed target is dependent on several factors firstly the initial point of the hand, secondly the distance between the hand and the target and lastly the position of the target. Most accurate movements are directed straight ahead, whereas least accurate are directed on either side, and slightly behind. Movements of the smaller distance are also more accurate.

Velocity profiles have been used to study reaching. When making a movement, acceleration occurs until a peak of 50% is reached after which deceleration occurs until contact between the target and effector is made (Bennett & Castiello, 1994).

### ***1.4.2 Neurophysiology***

Reaching involves areas V6A (SPOC in humans), the medial intraparietal (MIP) area (mIPS in humans) and the dorsal premotor cortex (PMd) (DeSouza et al. 2000; Fernandez-Ruiz et al. 2007; Filimon et al. 2009; Medendorp et al. 2003).V6A has been shown to be modulated by the direction of arm movements to visual or remembered targets (Battaglini et al. 2002; Fattori et al. 2001) and the arm and hand position in space (Galletti et al. 1997). Macaque  MIP were selectively modulated by the direction of hand movement and LIP encode a predictive representation of the stimulus movement (Eskandar and Assad 1999).

Furthermore, a study done in humans by (Vesia et al. 2010) using repetitive transcranial magnetic resolution (rTMS) of superior-parietal-occipital cortex (SPOC) resulted in deviation or reach end points and had no effects on saccade, but stimulation of midposterior intraparietal sulcus (mIPS) and angular gyrus (AG) increased end point variability for reaches and decreased saccade accuracy for contralateral targets. Therefore, suggesting that SPOC is encoding for reach goals, whereas, mIPS and AG have maps overlapping saccade and reaching.

The sensory information from primary premotor cortex (PPC) is transmitted to premotor cortex, which is divided into sub-regions called dorsal premotor cortex (PMd) and ventral premotor cortex (PMv). The PMd is involved in the planning of movements as it determines movement direction and trajectory (Cisek and Kalaska 2005; Hocherman and Wise 1991; Scott et al. 1997). Figure 3 shows an overview of brain structures and their functional connectivity for the saccade and reach systems.

Optic ataxia deficit usually occurs with peripheral vision suggesting that there are two anatomical substrates for reaching in 1) foveal vision and 2) extrafoveal vision. Keeping this in mind Clavagnier et al. (2007) performed a fMRI study in healthy subjects to determine the two systems. They demonstrated the existence of two systems: 1) reaching in central vision involves mIPS and the caudal part of PMd and 2) reaching in peripheral vision involves a more extensive network, including the parieto-occipital junction (Clavagnier et al. 2007) and caudal superior parietal lobule (SPL) (Granek et al. 2012).

The execution of movement depends on the activation of networks of neurons in the motor cortex and brainstem. Cortical motor areas and brainstem nuclei communicate directly with the local controls of the spinal cord which are known as descending pathway. The axons start from the primary motor cortex descending through the internal capsule to medulla where they cross over to the opposite side of the body and travel in a bundle known as the lateral corticospinal tract and project onto the ventral horn of the spinal cord. From the spinal cord, single nerve cells called motor neurons connect to the muscles. When the impulse travels down the axon to the muscle, a neurotransmitter is released at its ending. As the chemical impulse hits the muscle, the muscles fibers move against each other causing itself to become small and fat (contract). And the impulse from the motor neuron stops, the muscle fiber slides back to their original position (relax).

## ***1.5 Eye-hand coordination***

Eye-hand coordination is an important aspect of goal directed movement. Most of the activities that we perform in our everyday life use some degree of eye-hand coordination, such as writing or typing, playing sports (basketball, tennis) or as simple as inserting a credit card in a chip reader. What is eye-hand coordination? Eye-hand coordination is the ability of the vision system to coordinate the information received through the eyes to control, guide and direct the hands in the accomplishment of a given task.  For example, when we drive, we are constantly using eye-hand coordination because we must use the visual information to move our hands on the wheel, keeping the car in the middle of the lane and avoiding accidents.

Nonetheless, visual reaching is produced on the fact that a rudimentary eye-hand coordination is present in newborn (von Hofsten and Fazel-Zandy 1984).

### ***1.5.1 Behavioral***

Usually the eyes fixate on a target before the hands are used to engage in a movement, indicating that the eyes provide spatial information for the hands (Johansson et al. 2001). The duration that the eyes fixated on a target to be reached varies-it is observed that sometimes the eyes don’t move until the target is reached by the hand and the other times, the eyes seem to have moved to the other target of interest before the hand has even touched the target. The onset of electromyographic activity for the arm has been found to occur almost simultaneously with the start of (Biguer et al. 1982) or in advance of (Gribble et al. 2002) eye movements, suggesting that the nerve signals driving the eyes and hand may be derived concurrently.

The reaction times of the eyes and hands differ such that the saccade reaction time is shorter than the hand reaction time which could be due to the different inertial loads on different parts of the body (Biguer et al. 1982). Some studies have showed that the subjects perform more accurately when they have their eyes near the target when pointing (Henriques et al. 1998; Rossetti et al. 1994). Although they have also shown that the relative timing between the movement of the eyes and arm has no impact of the accuracy of reaching a target. Peak eye velocity is approximately 4% faster for the same saccade when the saccade is accompanied by a coordinated arm movement(Snyder et al. 2002). Saccades are also faster when the eye movement is accompanied with the arm movement (Snyder et al. 2002).

### ***1.5.2 Neurophysiology***

The neural control of the eye-hand coordination is complex as it involves every part of the central nervous system: the cerebral cortex, subcortical areas (such as cerebellum, basal ganglila and the brain stem), the spinal cord and the peripheral nervous system. Transformation of the peripheral visual information for reaching is believed to occur in parieto-occipital junction as found via fMRI (Gomi 2008). Figure 3 shows an overview of the brain areas involved for the visuomotor transformation for eye-hand coordination. A lot of studies are being conducted on parietal cortex in non- human primates, have found groups in parietal cortex related to movements of the eyes and hands. Lateral intraparietal area (LIP) to be the control of saccadic eye movement and parietal reach region (PRR) for the control of arm movements in macaque monkeys (Dean et al. 2011; Snyder et al. 1997). It has also been found that PPC helps to absorb visual feedback into on-going arm movements (Desmurget et al. 1999; Pisella et al. 2000). (Duhamel et al. 1992) states that the scenes we look at need to be stored in some way- either in a form that is independent of eye movement, or internally updated while making an eye movement. (Batista et al. 1999) demonstrated that the monkey parietal reach region (PRR)- an arm control center in the PPC- uses retinocentric receptive fields and a gaze-centered updating mechanism. This was also shown in psychophysics experiment done by (Henriques et al. 1998).

Numerous disorders and impairments have been found to disrupt the eye-hand coordination as a result of either damage to the brain itself, degeneration of brain due to disease or aging or an apparent inability to coordinate senses completely (Balint’s syndrome), optic ataxia or Parkinson’s disease.

## ***1.5 Eye-Head-Hand Coordination***

Comparatively, not much is known about the coordination between the eye-head and hand in non-human primates, but studies have been done in humans. To accomplish a straightforward task such as pointing a finger at a target involves a series of sensory and sensorimotor operations in order to elicit, the stimulation of the proper muscles and their synergistic control. Localization of the target with respect to the subject’s body is the starting point of the motor response. This will need knowledge of the head position with respect to the trunk, eye position with respect to the head, and finally the retinal position of the target (Biguer et al. 1982). A study done by (Carnahan and Marteniuk 1991) suggested that the behavior of the eye and head system can be altered by introducing arm movements, thus, contradicting the idea that eye, head and arm system is controlled by a single motor program. In their study, the eyes reached the target first, then finger and then the head, suggesting that movement termination patterns maybe a fundamental control variable. Reppert et al. 2018 also observed that eye moved first, then the arm and finally the head. Comparatively, previous studies have shown the eyes to reach the target first, followed by the head and lastly the finger (Biguer et al. 1982). Another study by Pelz 2001 proposed the idea that the coordination of the eye and head in gaze changes is usually the consequence of a synergistic linkage rather than an obligatory one. Another variable studied in eye-head-hand coordination lately is vigor (i.e., the speed with which the body part is moved (peak velocity) with respect to the population mean. Individuals who moved their head with high vigor also moved their arm with high vigor suggesting that arm and head vigor are tightly coupled. However, eye vigor did not correspond strongly with arm or head vigor (Reppert et al. 2018). Head movements appeared to be linked to the hand trajectories in our experiment. Usually, the eye, head and hand are in continuous motion during an ongoing behavior. This requires the coordination of these movements both in space and time. However, to this date we know relatively little about the nature of the coordination between the eye, head and hand.

## ***1.7 Aims and Hypothesis***

Non-human primates have been used extensively as animal models for human eye-head coordination and eye-hand coordination within a 2-D plane, but the more natural condition of eye-head-hand coordination during a 3-D reach has not been studied in monkeys. The objective of the study was to determine if reaching influences eye-head coordination, and vice versa, in the monkeys. In this study we looked at eye-hand coordination in head-unrestrained monkeys, which allowed the separation of the head and the body frames. We constructed a behavioral paradigm where animals were trained to either make a saccade towards the target or touch the target in complete darkness. Animals touched the target using the coordination strategy between eye and head of their choice. The animals were also trained on control task which was making eye-head gaze shifts towards the target without reaching. This gave us a chance to determine how the initial head, eye and hand position affect the relative timing and accuracy of the eye, hand and head movement when reaching for a target. This paradigm also gave an opportunity to analyze eye-head gaze shifts with and without hand movement. We analyzed the reaction time, velocity and accuracy of all the effectors. Gathering information from all the above-mentioned studies, our hypothesis is that all the factors (eye, head and hand) will influence the performance.

The following chapter describes the behavioral study I conducted in non-human primates. The objective of this study was to see if initial eye position has an effect on hand kinematics and behavior and to see if initial hand position has an effect on gaze kinematics and behavior.

In chapter 3, I explain the findings from the study presented here in view of the current ideology surrounding eye-head-hand coordination. Further, I describe possible mechanism that would explain eye-head-hand coordination during reaching. I also provide possible applications for the findings from this line of research within medicine. Lastly, I present future research avenues that are being pursued by another post-doc in the lab.

# ***Chapter 2:***

# ***Manuscript***

## 2.1 Title:

# Eye-Head-Hand Coordination During visually guided Reaches in Head-Unrestrained Macaques.

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**Keywords:** Eye-head-hand coordination, 3D reach, Head-unrestrained, Non-human primates, Saccadic eye movement.

## 2.2 Abstract:

Non-human primates have been used extensively to study eye-head coordination and eye-hand coordination, but the combination —eye-head-hand coordination— has not been studied. Our goal was to determine if reaching influences eye-head coordination (and vice versa) in Rhesus macaques. Eye, head, and hand motion were recorded in two animals using search coil and touch screen technology, respectively. Animals were seated in a customized ‘chair’ which allowed unencumbered head motion and reaching in depth. In the reach condition, animals were trained to touch a central LED at waist level while maintaining central gaze and were then rewarded if they touched a target appearing at one of 15 locations in a 40° x 20° (visual angle) array. In other variants, initial hand or gaze position were varied in the horizontal plane. In similar control tasks, animals were rewarded for gaze accuracy in the absence of reach. In the *reach task*, animals made eye-head gaze shifts toward the target followed by reaches that were accompanied by prolonged head motion toward the target. This resulted in significantly larger velocities and final ranges of head position (and lower eye-in-head ranges) compared with the gaze control. Gaze shifts had shorter latencies, higher velocities, and were more precise, despite the lack of gaze reward. Initial hand position did not influence gaze, but initial gaze influenced reach latency. These results suggest that eye-head coordination is optimized for visually-guided reach, first by quickly and accurately placing gaze at the target to guide reach transport, and then by centering the eyes in the head, likely to improve depth vision during manual contact.

**New and Noteworthy:**

Eye-head and eye-hand coordination have been studied in non-human primates, but not the combination of all three effectors. Here, we examined the timing and kinematics of eye-head-hand coordination in Rhesus macaques during a simple reach-to-touch task. Our most novel finding was that (compared to hand-restrained gaze shifts) reaching produced prolonged, increased head rotation toward the target, tending to center the binocular field of view on the target/hand.

## 2.3 Introduction:

Non-human primates have been used extensively as animal models for human eye-head coordination (Bizzi et al. 1971; Choi and Guitton 2006; Crawford et al. 1999; Freedman and Sparks 1997a; Quinet and Goffart 2007) and eye-hand coordination (Battaglia-Mayer A Genovesio A,et al. 2001; Dean et al. 2011; Hwang et al. 2014; Snyder et al. 2002), but in real-world circumstances, all three of these effectors (eye, head, and hand) are coordinated. A relatively small number of studies have examined eye-head-hand coordination in humans (Biguer et al. 1982; Blohm and Crawford 2007; Pelz et al. 2001; Reppert et al. 2018; Tao et al. 2018; Vercher et al. 1994), but to our knowledge no one has studied eye-head-hand coordination in the non-human primates. Animal models are particularly important for this topic, because most commonly available human neuroscience techniques (fMRI etc.) are incompatible with head motion, whereas head-unrestrained neurophysiological recordings have become relatively common in recent decades (Choi and Guitton 2006; Freedman and Sparks 1997b; Gandhi and Katnani 2011; Roy and Cullen 1998; Sadeh et al. 2015). Thus, a behavioral model of eye-head-hand coordination in monkeys could provide the basis for further neurophysiological studies of the corresponding neural mechanisms. The specific goal of the current study was to examine the influence of reach on head-unrestrained gaze kinematics, particularly the contribution of the head, and conversely the influence of gaze on reach behavior in rhesus macaques.

Behavioral studies of eye-*head* coordination during gaze shifts in macaques have primarily focused on 1) the relative timing of eye and head motion, 2) the relative contribution of head motion to the gaze shift, 3) amplitude-velocity relationships, and 4) three-dimensional kinematics (Crawford et al. 1999; Freedman 2008; Freedman and Sparks 1997a, 2000; Guitton 1992). Macaque gaze behavior has proven remarkably similar to human gaze behavior. The timing of eye and head motion during gaze shifts may depend on task variables (Collins and Barnes 1999; Fuller 1992; Stahl 2001), but typically a head-unrestrained gaze shift (i.e., rotation of the line of sight in space) begins with an eye-in-head saccade, accompanied by a slower, longer lasting head movement, and stabilization of gaze after the saccade by engaging the vestibulo-ocular reflex (Freedman and Sparks 1997a; Guitton 1992; Roy and Cullen 1998).

Head motion is sometimes measured as contribution to the gaze shift (the amount of head motion that occurs during the saccade) versus total head movement (lasting beyond the duration of the saccade) (Chen 2006; Freedman and Sparks 1997a; Monteon et al. 2010; Tu and Keating 2000). Typically, macaques (like humans) move their head more for larger gaze shifts (Freedman et al. 1997a), but the amount is task dependent. For example, if macaques are expected to keep gaze near center or if the head is already turned towards the target, the contribution of head will be less (Gandhi and Sparks 2001; Monteon et al. 2012). In contrast, if animals are cued to use a larger gaze range (Monteon et al. 2012), if the head is already turned away from the target (Freedman and Sparks 1997a; Gandhi and Sparks 2001), or if the contribution of the eye is physically limited ( Constantin 2004; Crawford and Guitton 1997), the head will contribute more motion for same sized gaze shifts. Further, head and gaze motion approximate a fixed amplitude-velocity relationship similar to that observed in the ‘main sequence’ of saccades (Freedman and Sparks 1997a). Finally, during eye-head gaze shifts, macaques employ various three-dimensional coordination strategies to maintain Listing's law of the eye and an analogous Donders' law of the head during interim fixations (Crawford et al. 1999; Monteon et al. 2010).

Studies of eye-*hand* coordination in macaques are somewhat less common than either studies of eye-head coordination in macaques or eye-hand coordination in the human. These can be grouped into studies where gaze fixation and hand motion were confined to a common two-dimensional plane (Dean et al. 2011; Pesaran et al. 2006; Snyder et al. 2002; Song and McPeek 2009; Vazquez et al. 2017), versus those where animals performed a three-dimensional reach in depth (Battaglia-Mayer A  Genovesio A, et al. 2001; Ferraina et al. 1997; Hawkins et al. 2013; Marconi B  Battaglia-Mayer A, et al. 2001; Marzocchi et al. 2008). Macaques will generally saccade in advance to capture the reach target (Pelz and Canosa 2001; Song and McPeek 2009). Reaches tend to decrease saccade latency and increase saccade velocity in both macaques and humans (Sailer et al. 2016; Snyder et al. 2002). Although macaques can be trained to decouple gaze fixation from reach direction (Hawkins et al. 2013), accuracy and temporal coupling are higher when animals are allowed to coordinate the eye and hand toward a common goal (Vazquez et al. 2017).  In general, the kinematic rules for eye-hand coordination in macaques are similar to those observed in the more frequently studied human eye-hand coordination system (Van Donkelaar and Staub 2000; Henriques et al. 1998; Prablanc et al. 1979). However, it is not known how well the macaque results translate directly to head-unrestrained reach behavior.

As noted above, we are not aware of any studies of eye-head-hand coordination in monkeys, but there are several in humans. Head orientation and eye-head-body geometry are accounted for in the sensorimotor transformations for eye-hand coordination (Blohm and Crawford 2007; Henriques et al. 2003; Henriques and Crawford 2002; Ren and Crawford 2009). The typical order of recruitment (at the behavioral level) appears to be eye, then head, then arm

(Biguer et al. 1982), whereas the order of termination has been reported to be gaze, then finger (on target) and lastly, head motion (Carnahan and Marteniuk 1991). Some authors have emphasized a common source model based on synchrony between eye, head, and reach commands, e.g., at the level of EMG and corrective response latencies (Biguer et al. 1982; Tao et al. 2018), whereas others have argued that the relative variability of eye, head and hand initiation contradicts control by a single motor program (Carnahan and Marteniuk 1991).

Reaching also appears to alter patterns of eye-head coordination (Carnahan and Marteniuk 1991). This study showed that when subjects pointed very fast with the finger, the head started to move before the eyes, whereas when subjects pointed slowly and accurately, the eyes started to move first, followed by the head and finger. However, when the subjects were told to point with only the eyes and head, eye movement occurred before the head, regardless of the speed accuracy instructions. It has been suggested that hand pointing accuracy does not depend on the relative timing of eye, head and hand movements (Vercher et al. 1994), but allowing the head to move appears to reduce pointing errors (Biguer et al. 1984). Finally, it was recently shown that during coordinated eye-head-hand reach movements, reach vigor (peak hand velocity for a given amplitude) was most tightly linked with the vigor of head rotations (Reppert et al. 2018). But again, it is not known how well these various results generalize to rhesus macaques.

In the current study, we investigated the influence of reach on gaze kinematics, and conversely gaze on reach behavior, in head-unrestrained rhesus macaques. We employed a behavioral paradigm where animals were rewarded for accurately reaching (in direction and depth), but importantly they were allowed to make head-unrestrained gaze shifts using the coordination strategy of their choice. We then compared this with the more standard task where animals were rewarded for making eye-head gaze shifts in the absence of a reach. The primary intent of this design was to explore the influence of reach on eye-head gaze kinematics, but we also examined the influence of reach (initial position, final position, timing) on gaze accuracy and timing, and the influence of initial gaze position on reach. Overall, our results confirm several of the multi-joint interactions between eye, head, and reach kinematics already reported in the literature, and importantly reveal an additional head-hand coordination strategy that may function to optimize vision for reach movements.

## *2.4 Methods:*

### 2.4.1 Animals and surgical procedures:

Data were collected from two female rhesus macaque monkeys (*Macaca mulatta, Animals W and O*). These animals weighed approximately 6 kg and 10 kg, respectively. Prior to the experiment, each animal underwent a surgery under general anesthesia (1.5% isoflurane following intramuscular injection of 10 mg/kg ketamine hydrochloride, 0.05 mg/kg atropine sulphate, and 0.5 mg/kg acepromazine). A stainless-steel head post was implanted onto the skull using a dental acrylic head cap, secured by using stainless steel cortex screws. The head post was only used to stabilize the head during preparation of the experiment i.e. while attaching the head coil and putting in the reward tube in place. During the experiments, a fluid dispenser and two orthogonal search coils were mounted on the head to provide 3D recordings of the head rotation relative to space. One Teflon coated stainless steel search coil (18 mm in diameter) was implanted in both animals subconjunctivally. A scleral coil was placed in one eye for 2D recordings of gaze orientation (horizontal and vertical) in space. Animals were given two weeks of recovery following the surgery with unrestricted food and fluid intake. Following this, animal fluid intake was controlled during working weekdays so that they received most of their fluids as rewards during training and/or performing experimental tasks. The animal's fluid and food intake, weight and health were monitored closely by the lab care staff and the university veterinarian. All surgical and experimental protocols were followed according to the Canadian Council for Animal Care guidelines on the use of laboratory animals and approved by the York University animal care committee.

### 2.4.2 Experimental setup and behavioral recordings:

The experimental setup, including a modified primate 'chair' (Fig. 5) and equipment for behavioral recordings and stimulus presentation, is shown in Fig. 6. During the experiments, animals were seated within a customized Crist primate chair (Crist instrument, MD, USA), placed so that the head was centered within three mutually orthogonal magnetic fields of 1 m distance in all directions (Fig. 6A). The primate chair was modified to allow free motion of the head (Crawford et al. 1999) and (for the current study) to allow both positioning of the initial hand position and unencumbered forward reaching movements. The modifications for head motion included a removable head restraint, removable top plates, and a security vest as described in our previous publications (Crawford et al. 1999; Klier et al. 2001, 2003). For this experiment, an aperture was added across the front of the chair to allow manual access to our full range of visual stimuli in both depth and direction. The width of the chair was also increased to provide free motion of the arm, whereas a shoulder collar was added to restrain the location of the right shoulder joint, and for enhanced security.  The upper body was prevented from rotating using an iron link chain that attached the primate jacket to the chair. In these experiments, only motion of the right hand was allowed; the left arm was restrained using an additional upper-arm

Velcro cuff. The cuff was put on the left upper arm which further connected to the chair with a thick cotton thread.

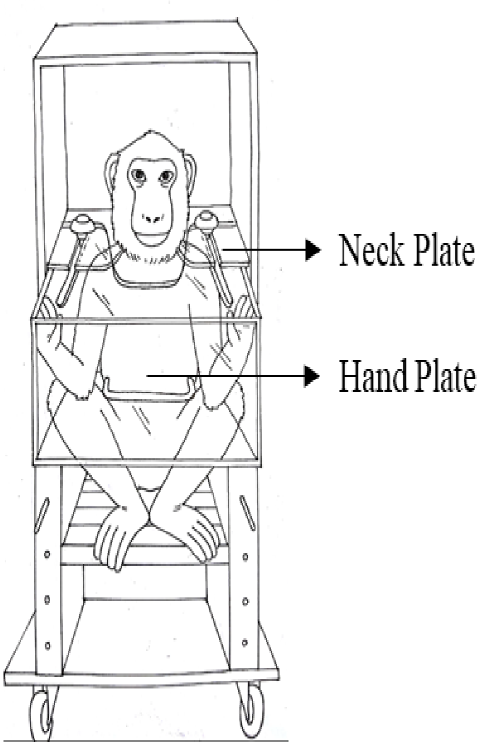


***Figure 5: Customized chair.*** *A sketch of our newly customized primate chair modified to allow the free movement of the hand and head in both direction and depth by removing the a) neck plate and b) hand plate.*

Visual stimuli were presented on a vertically mounted screen (OPTIR Touch 32” IR touch screen, Keytec) placed at 23cm distance ahead of the eye (Fig. 6B). This screen was surrounded by a frame equipped with vertical and horizontal infrared sensors in the plane of the gaze/reach stimuli. These sensors measured the central two-dimensional location of manual contact with an accuracy and precision of 1° radius. Initial hand position was controlled by training the animal to rest its hand on the LED bar attached to the chair at waist level (Fig. 6C), with the center LED 16 cm ahead and 28 cm below the right shoulder. A total of five LEDs were distributed horizontally along this bar at an average of 16 cm interval, at visual angles (from the eye) of (-19°,-64°), (0°,-64°), (19°,-64°), (34°,-64°) and (45°,-64°) in horizontal and vertical visual angle, respectively, where rightward positions are positive. This range was selected because animals were hesitant to move their right hand to the far left of their body. Correct positioning of the hand on the LED bar was measured using two strategies. First, we used infrared light to monitor the horizontal position of the hand, and second there was a vertical sensor above the LED bar, which detected whether the light was blocked by the animals' hand. Software codes for stimulus control and behavioral recordings were modified from our previous primate gaze control studies (e.g, Crawford et al. 1999; Li et al. 2017).

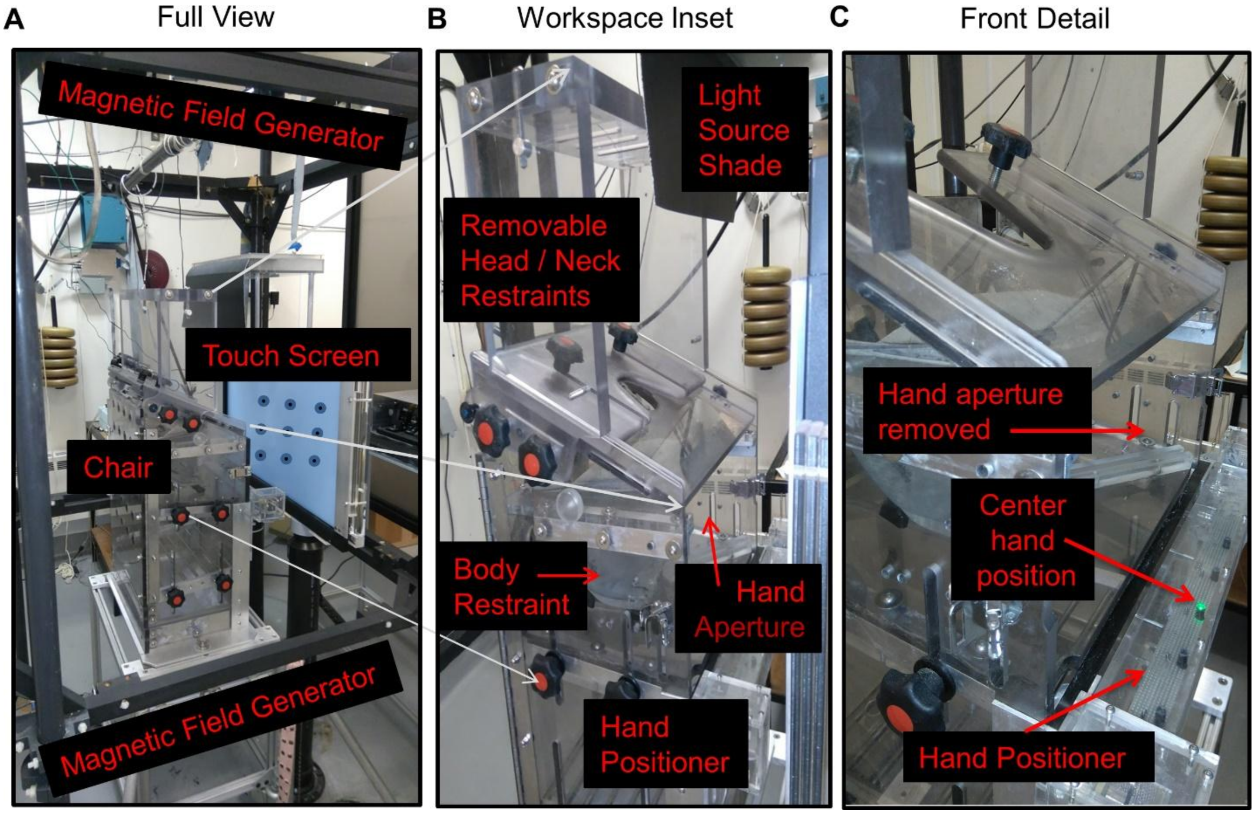


**Figure 6: Apparatus.** A: Full view. A modified primate '*Chair*' (Crist Instruments) was placed in the center of a *3D magnetic field generator* in front of a *Touch Screen*. B: (workspace inset) shows primate chair modifications provided to allow forward translation of the hand in both direction and depth and 3D rotation of the head motion by removing a hand aperture plate and *Head/Neck Restraints* during experiments. The *Hand Positioner* was composed of an LED bar placed at the waist level just in front of the hands. *Body restraint* was achieved by fitting jacket

around the torso of the animal and attached this to the inside the chair ( to prevent the spinning and escaping) and other obstacles were attached to the chair as required to reduce motion of the unused hand and other body parts. The Light Source Shade was simply a shade to remove reflections from the hand positioner LEDs. C: (Front-detail) shows a close-up of the front of the chair and the hand positioner. The illuminated green LED is the center hand position.

### 2.4.3 System Calibration:

Two separate calibrations were done to get precise search coil signals before each training or experimental session. Firstly, the 3D magnetic fields (three mutually orthogonal magnetic fields) were pre-calibrated before each experiment by rotating an external coil through each field direction and adjusting field strength in each direction to an equal maximum (Crawford et al. 1999; Li et al. 2017; Tweed and Vilis 1990). This was sufficient for computation quaternions from the 3D head coils. During experiments, the primate chair was positioned such that the head was at the center of three mutually orthogonal magnetic fields, and a reference position for the head was recorded while the animal looked straight ahead. To calibrate the 2D eye coil we then made the animals fixate each of the nine targets used in our main *Centrifugal* task (see next section) for one second.  The average data from two sequential runs of the paradigm were used by an on-line program that fit the eye coil signals to the correct physical locations of the stimuli (Monteon et al. 2010; Li et al. 2017). The touch screen apparatus was calibrated through the software which was provided by the manufacturer (Keytec).

### 2.4.4 Training and behavioral Paradigm:

Training and experiments were conducted in complete darkness to minimize extraneous stimuli and allocentric landmarks. Animals were rewarded with a drop of water for completing each trial correctly. Animals were first trained to perform the *Gaze Task,* i.e., the control task (Fig. 7A2). Training started with teaching animals to maintain their gaze at the central fixation point (red disc) for 1000 msec. They were further trained to make a saccade to the target (red cross) within 1000 msec. When the animal mastered fixating the center position and making a saccade towards a peripheral target, they were trained on the full *Gaze Task* (the control). Here the fixation dot was illuminated for 1000 msec and animals were required to maintain gaze fixation within a radius of 6° of this point for 400-800 msec (chosen randomly each trial) to avoid anticipation. At the end of the fixation period, the fixation point was extinguished, and simultaneously the target appeared at one of the fifteen positions (chosen randomly). Animals were required to a make saccade toward the target within a spatial window of 6°in the *Gaze Task*. The targets stayed on for 1000 msec and were 10° apart from each other in both directions, vertical and horizontal.

Moving on to the *Reach Task,* i.e., the experimental task (Fig. 7A1), animals were first trained to place their hand on an illuminated green LED at one of the five initial positions (starting with the shoulder-aligned LED, and later incorporating the more peripheral LEDs). Next, they were trained to touch a single target on the screen in front of them, chosen randomly from 15 different positions (Figure 7B1). When animals mastered placing their hand on the LED bar and touching the single target, they were trained on the full *Reach Task*. The animals started the task as they placed their hand on the LED (green) light for 700 msec. Then a central fixation (red circle) appeared on the screen for 1000 msec, and they were required to maintain their gaze at that point between 400-800 msec within the spatial window of 6°. As the fixation point disappeared, concurrently, the target appeared for 1000 msec. Animals were required to touch the target within the spatial window of 13° vertically and horizontally (typically they chose to place their fingers over the area where they saw a stimulus). Note that in the *Reach Task*, animals were not required to make a saccade towards the target in order to obtain a reward. In this way, they were allowed to choose their own gaze strategy while reaching. In both tasks, head motion was unencumbered and thus animals were free to use whatever eye-head coordination strategy they wanted to choose.

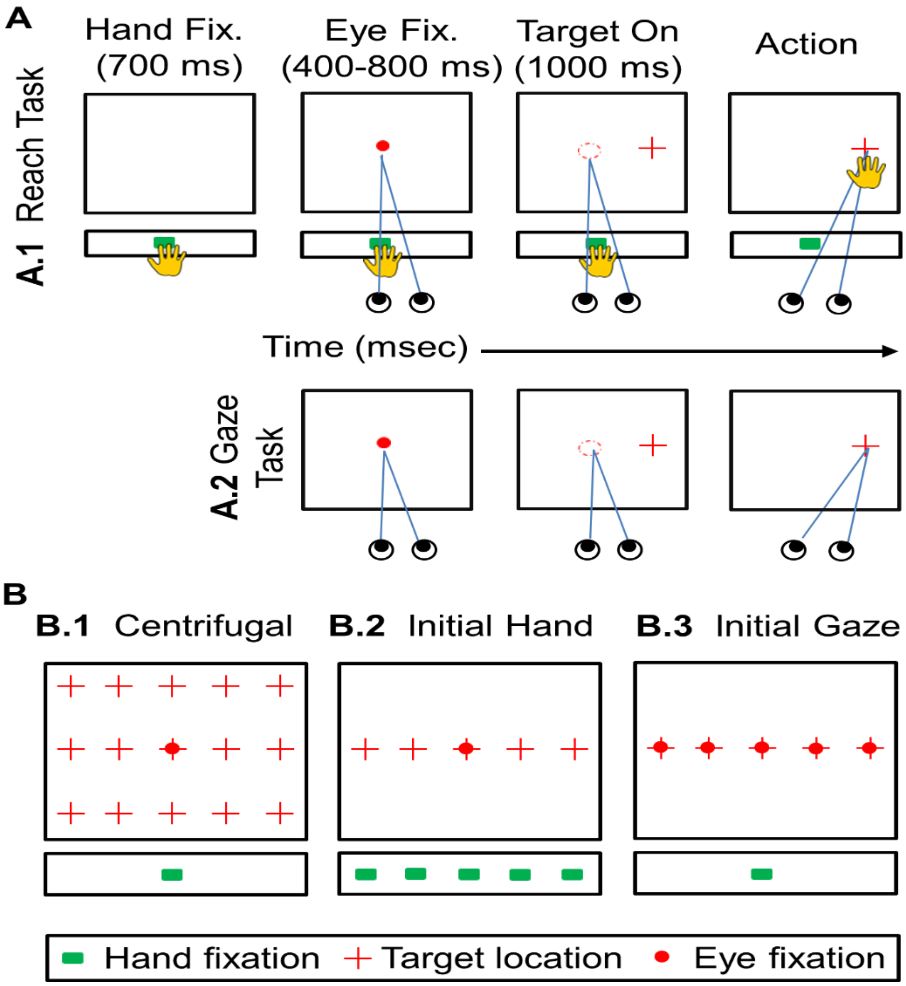


***Figure 7: Schematic illustration of the experimental paradigm.*** *A: Sequence of events in two major tasks. Colored symbols indicate the LED projected initial hand position (green square) /*

*laser projected fixation point (red circle) and target (red cross) for each trial; the room was otherwise dark. In A.1 (Reach Task) animals were required to touch the LED light (green square) on the LED bar at the waist level (for 700msec), and then maintain fixation (red circle) on touch screen infront of them for 400-800 msec. When the fixation light was extinguished, simultaneously, one of targets (red cross) on touch screen infront of them appear randomly, where animal is either required to touch it with unrestrained gaze (in Reach Task, A.1) or make a saccade towards it with reach restrained (in Gaze Task, A.2). B shows the three different spatial conditions that were studied. B.1 is the centrifugal task with one center eye fixation (red circle) and one center initial hand position (green square) were recorded with 15 different target locations (red cross) on the touch screen 10° apart from each other horizontally and vertically. B.2 is the initial hand task with five different variable hand locations (green square) and one central eye fixation (red circle) position with five different targets (red cross) 10° apart horizontally. B.3 is initial eye task with five different initial eye positions (red circle) and one central hand position (green square) with five different targets (red cross) 10° apart horizontally. Both Reach+gaze (A.1) and gaze-only (A.2) blocks were performed for each spatial condition.*

When animals completed the entire trial in both *Gaze Task* and *Reach Task* correctly, a water reward was provided for the correct trials. Trials were aborted when the animals either failed to make a saccade to the fixation point or target or they did not touch the target. When the animal was able to consistently complete entire trial without mistakes, training was complete. At this point, data collection commenced (using the preceding task parameters and both motor task variations), using the following three specific spatial condition configurations:

*Centrifugal Condition (Fig. 7B.1)*: Animals were required to reach (from the shoulder-aligned, waist-height hand LED) and/or gaze (from the eye-centered fixation light) toward one of the 15 targets in a 40° horizontal ×20° vertical (visual angle) array, with free movement of their eyes and head. Data were recorded for 8 weeks in animal W (resulting in 25 reach trials for each target and 25 gaze trials for each target) and 8 weeks in animal O (resulting in 25 reach trials for each target and 25 gaze trials for each target). In total we recorded 375 trials for *Reach Task* and 375 trials for *Gaze Task* in each animal, for a total (across both animals) of 1500 trials collected in this condition.

*Variable Initial Hand Position Condition (Fig. 7B.2)*: This was the same as the previous condition, except that the initial hand position was varied randomly between the five horizontally arrayed green LEDs (at waist height) and only 5 targets (the horizontal row at eye height) were used. Data were recorded for 15 weeks in animal W (resulting in 25 reach trials for each target and 25 gaze trials for each target) and 15 weeks in animal O (resulting in 25 reach for each target trials and 25 gaze trials for each target). We recorded 625 trials for *Reach Task* and 625 trials for *Gaze Task* in each animal, for a total of 2,500 trials collected in this condition.

*Variable Initial Gaze Position Condition (Fig. 7B.3):* This was similar to the previous condition, except that only the shoulder-aligned initial hand position was used, and instead the initial gaze position was varied between the 5 horizontal targets. Data was recorded for 12 weeks in animal W (resulting in 25 reach trials for each target and 25 gaze trials for each target) and 15 weeks in animal O (resulting in 25 reach trials for each target and 25 gaze trials for each target). In total we recorded 625 trials for *Reach Task* and 625 trials for *Gaze Task* in each animal, for a total of 2,500 trials in this condition. Thus, a grand total of 6500 trials were collected in all three tasks.

### 2.4.5 Data analysis:

Each animal's head was at the center of three mutually orthogonal magnetic fields, voltages from the coil were sampled at 1000 Hz, and data was digitized. This data was used to determine horizontal and vertical position signals of gaze (eye relative to space), head relative to space and eye relative to head. The two measures (eye and head) were calculated in visual coordinate system in degrees as stated previously in Crawford et al. 1999. Detailed measurement of initial hand position LEDs and final hand position according to the touch screen coordinates were used for further hand analysis in visual coordinate system. The visual angle of an object is a measure of the size of the object's image on the retina. The visual angle can be calculated as follows:

$$\tan(V)=S/D,$$

Where, V= visual angle

S=size of the image on the retina

D=distance between the eye and the object

Our apparatus allowed us to record the initial and final hand position as well as their timing. This allowed us to calculate mean hand speed, based on the overall length of the trajectory divided by (screen touch time – initial hand offset). This apparatus did not allow us to record hand positions or velocities during the reach movement.

Recorded trials were rejected if animals made a saccade or hand movement before a target stimulus appeared on the screen. Since animals were trained until they performed the task consistently, only a small number of trials (~5%) had to be eliminated. Only successful trials were included in analysis.

Experimental data were analyzed offline using custom scripts written in MATLAB 2016. The beginning of the gaze movement was marked when the velocity reached more than 50°/sec for 2 msec and end of the gaze movement was marked when the velocity reached less than 30°/sec for 2 msec for each rewarded trial. The gaze trajectory was determined for each trial and their endpoints were calculated. The timing of head movement onset was marked when the head velocity reached 20°/sec, and final head position was selected at the point in time when the animal touched the target (or the mean point in time after target onset in the *Gaze Task*). The 'arm onset' was marked as when the animal left the LED light and 'touch on the target' was marked as the end of the arm movement. Reaction time was measured from the onset of the target to the detected onset of the respective gaze, head and/or arm movement. Movement time was measured from the onset of gaze, head and/or arm movement to the completion of the gaze, head and/or arm movement.

To present endpoint distributions, 95% confidence ellipses were computed by averaging the orientation angles and major/minor axes of the individual subject ellipses. We also calculated the orientation angle to these ellipses to approximate the direction of greatest scatter of the reach and saccade distributions.

### 2.4.6 Statistical analysis:

We conducted several three-way ANOVAs (between factors: task condition and initial eye/hand position; repeated factor: target location) to test whether two task condition (gaze shift; reach), five different initial eye/ hand position (10° apart from each other horizontally), and fifteen/five target position (10° apart from each other in vertical and horizontal dimension) statistically affected reaction time, velocity and movement time. To compare scatter of endpoints across the two effectors for the eye and hand task to three conditions (centrifugal, hand variation and eye variation), the three-way ANOVA included the repeated factor, effector (eye, hand), as well as the initial eye/hand position and target location. We also performed unpaired t-test and Kolmogorov-Smirnov test to see whether the difference between the control (gaze shift) and the experiment (reach) were statistically significant for velocity and amplitude.  All statistical tests were conducted using the statistical package for social sciences (SPSS) and Microsoft Excel.

## ***2.5 Results:***

### 2.5.1 General Observations:

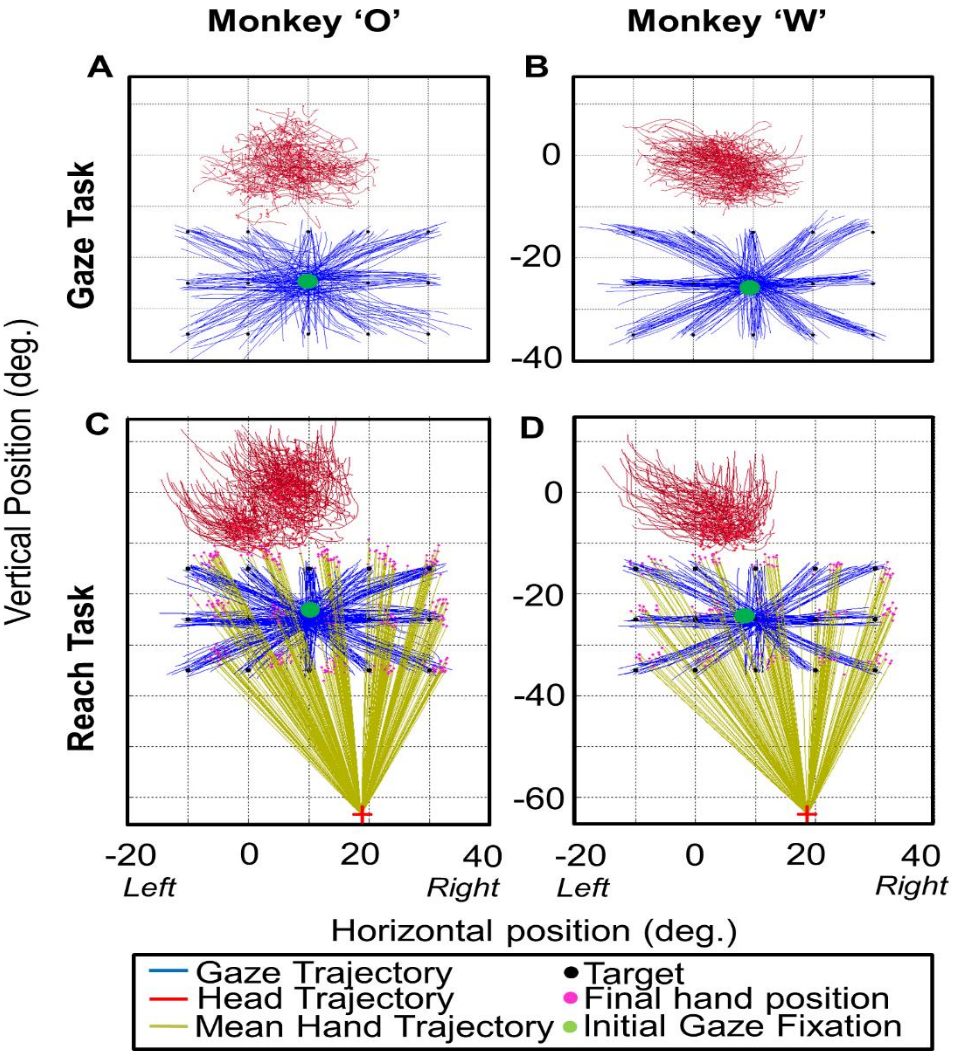


***Figure 8: Representative gaze, head, and hand trajectories:*** *Example 2-dimensional gaze (blue) and head (red) trajectories in the centrifugal gaze task (upper row A and B) and centrifugal reach task (lower row C and D) are shown for both animal O (left) and animal W (right). Trajectors are plotted from the time of initial gaze motion until the time of final hand contact on the touch screen. In the reach task the magenta dots show the reach endpoints for each target (black dots) and the initial hand position is shown by the red crosses. Complete gaze and head trajectories are provided, whereas the hand trajectories are only shown as vectors joining the initial and final hand positions (Light green lines). These data were taken from the centrifugal task, where the center green dot represents the initial eye fixation point for each trial. Comparing the gaze (control) task and reach+gaze (experimental) task, one can already notice that the head seems to move more during reaches, as shown in more detail in the following figures.*

Figure 8 provides typical two-dimensional trajectories of gaze (blue), head (red) and hand position for both animals in the *Gaze Task* (upper panels) and *Reach Task* (lower panels) in the *Centrifugal task* configuration. Data is provided in visual angles, projected onto the coordinates of the touch screen. The initial gaze fixation point is indicated by a green circle in each panel, centered at 25º down and 10º right in touch screen coordinates. Reaching always took much longer than gaze shifts, so data are plotted until the time of hand contact with the screen, or (in the case of the *Gaze task*) until the mean time of hand contact in the reach task for each animal. This convention was used throughout our analysis to compare eye-head kinematics in the presence or absence of reach on a similar time scale.

As expected in the control *Gaze task*, animals made centrifugal gaze shifts toward the targets (indicated by black dots). Since head positions corresponding to the central target were selected as reference orientations, the head range is centered approximately around zero, but this corresponds to our observation that animals generally faced forward with their eyes turned down toward the target. Similarly, in the *Reach task*, animals chose to make gaze shifts immediately toward the targets, followed (as we shall see) by reaches toward the same target, such that gaze and hand end points landed within a similar range. In both tasks, gaze shifts were accompanied by head movements in the general direction (as we shall see) of the gaze shifts. The first and most obvious observation we made was that the head appeared to move more in the reach task, especially in the vertical dimension.

The following sections quantify these and other details of the eye-head-hand coordination patterns, starting with the spatial aspects and then timing, and finally some spatiotemporal aspects. Since, the results from our three spatial task configurations (centrifugal, variable hand, variable eye) were qualitative and statistically similar, we present data from the *centrifugal* task, unless explicitly mentioned otherwise.

### 2.5.2 Spatial Analysis:

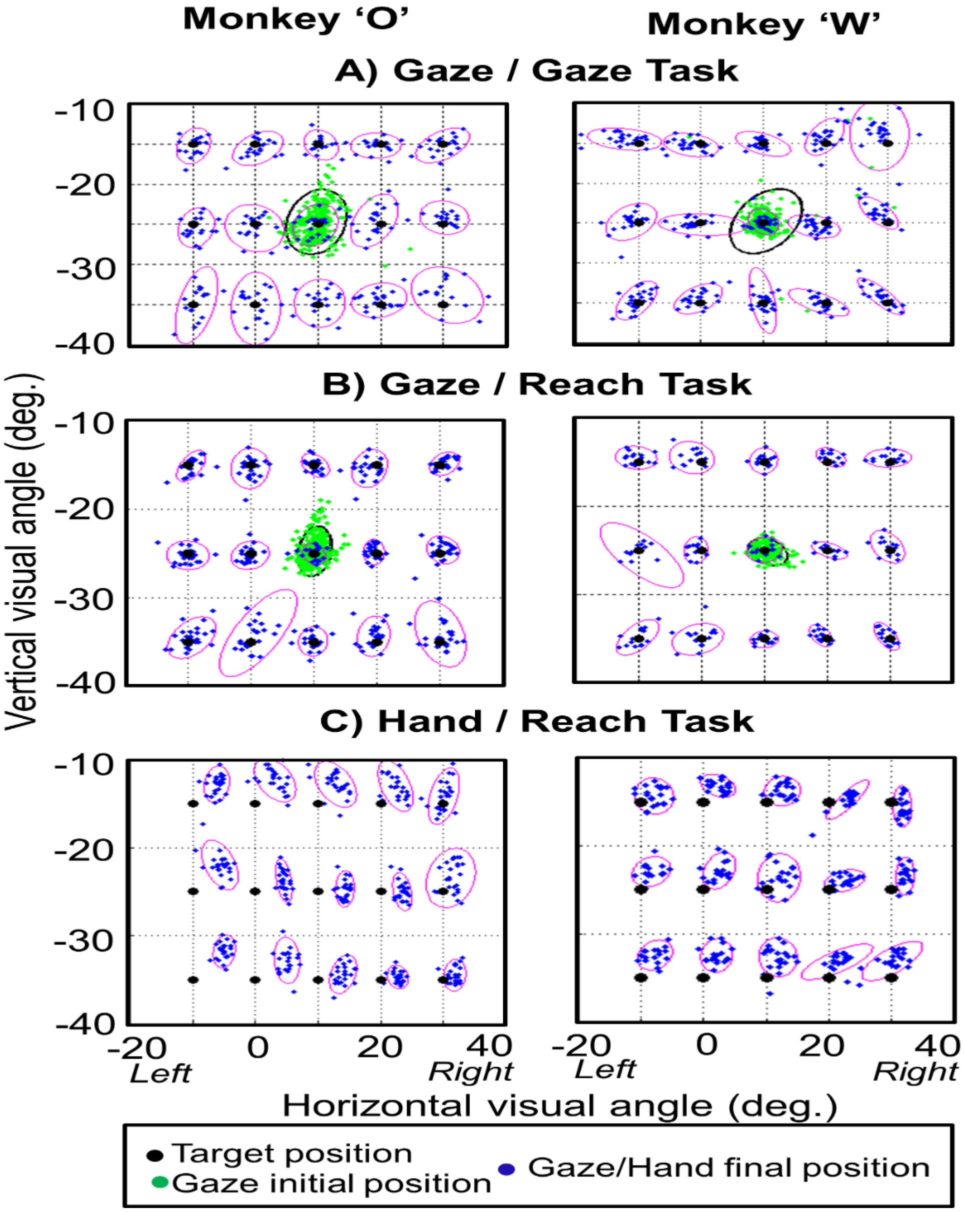


***Figure 9: 95% confidence ellipses for gaze and hand endpoints.*** *A: Gaze endpoints at the end of saccades in the Centrifugal Gaze task for both animals. B: Gaze endpoints at the end of saccades in the Centrifugal Reach task for both animals.C:Hand endpoints at the point of screen contact in the Reach task. The cluster of green dots shows the initial gaze position for each trial in both tasks. Black dots show target positions. Final gaze position was more precise in the*

*reach task (B), compared to the gaze task (A) (p = 0.043 , p = 0.017) for both animal W and animal O, respectively.*

Figure 9 shows the individual subjects' 95% confidence ellipses for the endpoints of gaze (upper two rows) and hand (lower row) in the *Gaze Task* (top row) and *Reach Task* (lower two rows) for each target in the centrifugal condition configuration. These ellipse fits were used as an overall measure of the scatter in final gaze, head or hand position. Even though saccades occurred before reaches (as documented in the next section), gaze was more precise (less variable) in the *Reach Task*. The mean ellipse area across all 15 targets was $32.7^{o2}$ (*Gaze Task*) vs. $23.4^{o2}$ (*Reach Task*) in animal O, and $19.7^{o2}$ (*Gaze Task*) vs. $15.3^{o2}$ (*Reach Task*) in animal W. The difference between the areas of the ellipses in *Reach Task* and *Gaze Task* was significant in both animals ( $p = 0.043$, $p = 0.017$; ANOVA test) in animal O and W, respectively. Thus, reach planning had an influence on gaze precision. However, there was no significant difference in accuracy (mean errors) between the two tasks ($p = 0.74$, $p = 0.82$; K-S Test). We did not find a correlation between reach and saccade end points within each target distribution ($r = -0.122$, $r = -0.27$; Pearson correlation test) for animal O and animal W, respectively. The scatter of reach endpoints was not significantly different between gaze endpoints in either animal ($p = 0.689$, $p = 0.330$; K-S Test). The same observations held in our other two spatial condition configurations.

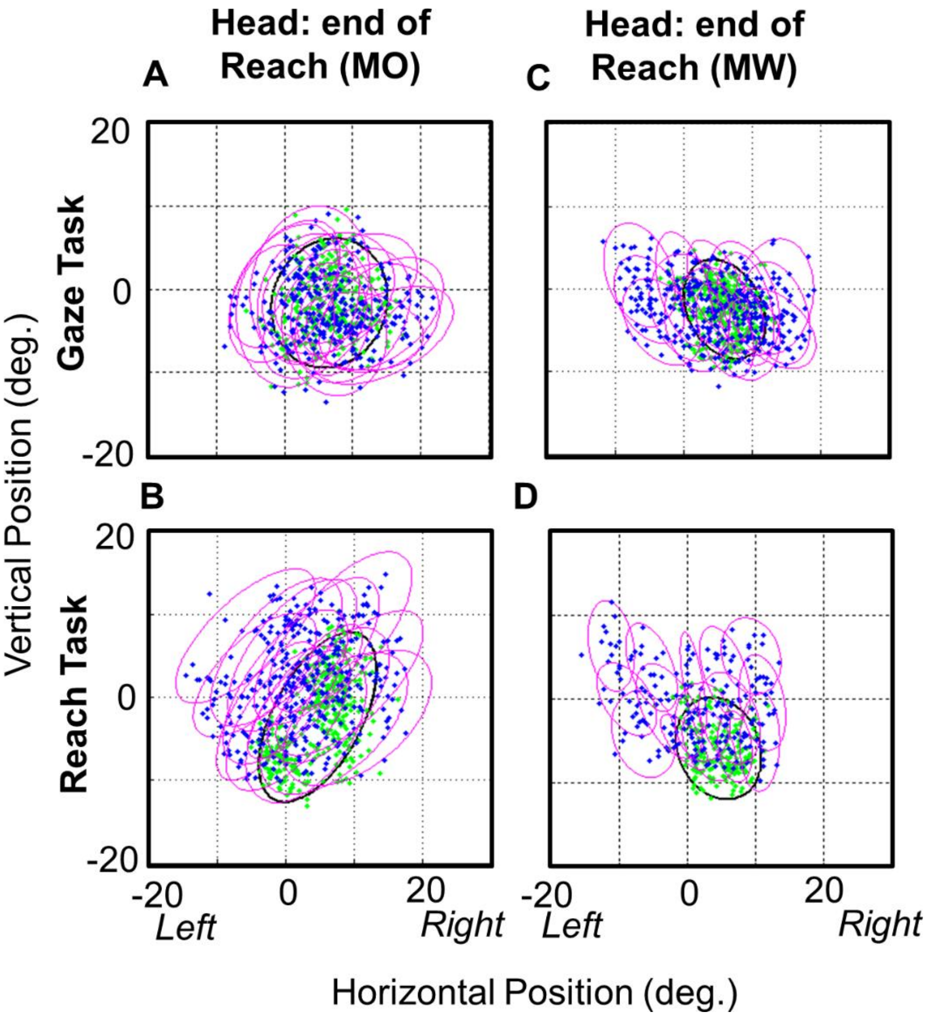


***Figure 10: 95% confidence ellipses for head endpoints.*** *The head endpoints are plotted at the time when the hand touches the target in the reach task (B and D), and at the equivalent average time in the gaze task (A and C) for each of the 15 targets in the centrifugal condition, and for both animals. The area of the ellipse fits to the head data were significantly less (across targets) than the area of the ellipses in the reach task ( $p = 1.31E\text{-}06$; $p = 0.0367$), stating that the head moves more in reach task.*

Figure 10 shows the 95% confidence ellipses for head endpoints (at the time of hand contact or mean equivalent) for each target in both animals in the *Gaze Task* (upper row) and *Reach task* (lower row). This results in two observations. First, the final head position scatter (i.e.

ellipse size) was larger in the reach task, especially in the vertical dimension. The area of the ellipses in the reach condition is significantly higher ($p$ = 1.31E-06, $p$ = 0.0367; K-S Test) in animal O and animal W, respectively. Second, there is greater separation between the ellipses for different targets in the reach task, suggeting that target position has more influence on final head position, presumably because the head is moving more in the direction of final gaze/target position.

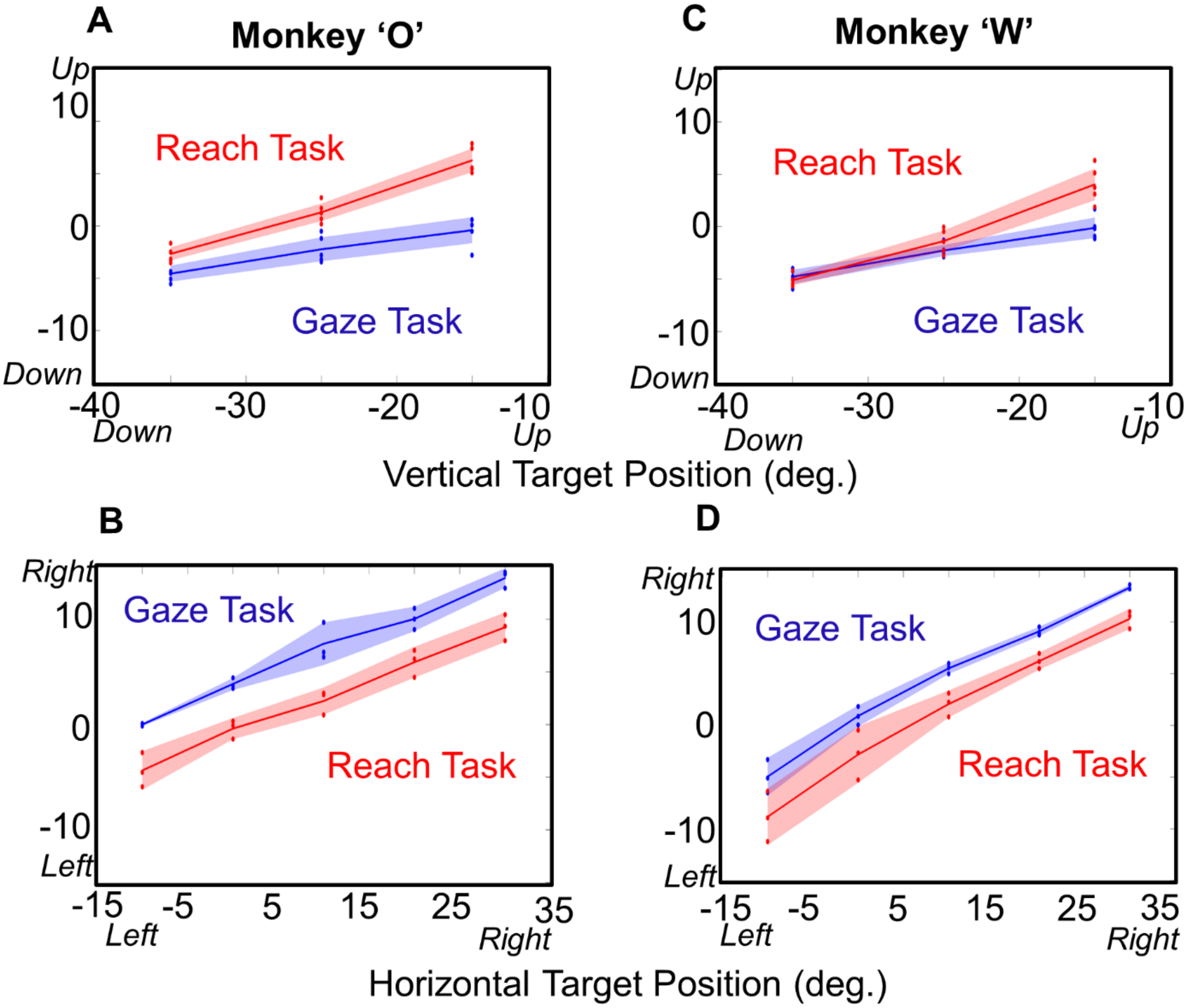


***Figure 11: Final head position as a function of target position,*** plotted separately for the vertical (A/C) and horizontal (B/D) directions from the centrifugal *Gaze Task* (blue) and *Reach*

*Task* (red) for animal W (left column) and animal O (right column). Each panel suggests a linear relationship between target position and final head position, where the slopes depend on both the direction of motion and the task (see text for slopes and statistics).

To test this assumption, we plotted final head position as a function of target position (Figure 11), separating this into vertical (left panels) and horizontal (right panels) components. This graph results in several observations: 1) the final head position depends on target position in both tasks and both dimenions, 2) in the Gaze task, the horizontal slope is steeper than the vertical slope, but 3) this is no longer true when the animal reaches. To quantify this, we did a one-way Anova test in each task. The gaze task showed a significant influence of target position on final head position in the vertical dimension (*p* = 8.71E-11, *slope* = 0.2077; *p* = 8.53E-11, *slope* = 0.2337; one-way ANOVA) but not in the horizontal direction (*p* = 0.58, *slope* = 0.3478; *p* = 0.47, *slope* = 0.4472; one-way ANOVA) in animals O and W, respectively. The reach task showed a significant influence of target position in both the vertical dimension ( *p* = 9.78E-11, *slope* = 0.4605; *p* = 9.45E-12, *slope* = 0.457; one-way ANOVA) and horizontal direction ( *p* = 0.03, *slope* = 0.3478; *p* = 0.027, *slope* = 0.473; one-way ANOVA) in monkeys O and W, respectively. Compared to the *Gaze Control*, the slope of the *Reach* relationship was significantly higher in the vertical dimension (p = 0.005; p = 0.01; K-S Test), but not in the horizontal dimension (*p* = 0.89; *p* = 0.136; K-S Test), in both animals O and W, respectively. We also noted that head positions for the *Gaze* data were biased to the right relative to the *Reach* data in both animals (or vice versa, since it depends which dataset is used as the reference).

From these results it follows that, since the head moved more overall in the reach task, and yet gaze was equally accurate, the overall distributions of final eye-in-head positions (not shown) must have a lower range. This was indeed the case as the slope of the eye-in-head as a function of target plot got significantly smaller in vertical direction for both animals ($p < 0.00001$; K-S test).

### 2.5.3 Relative Timing of Events:

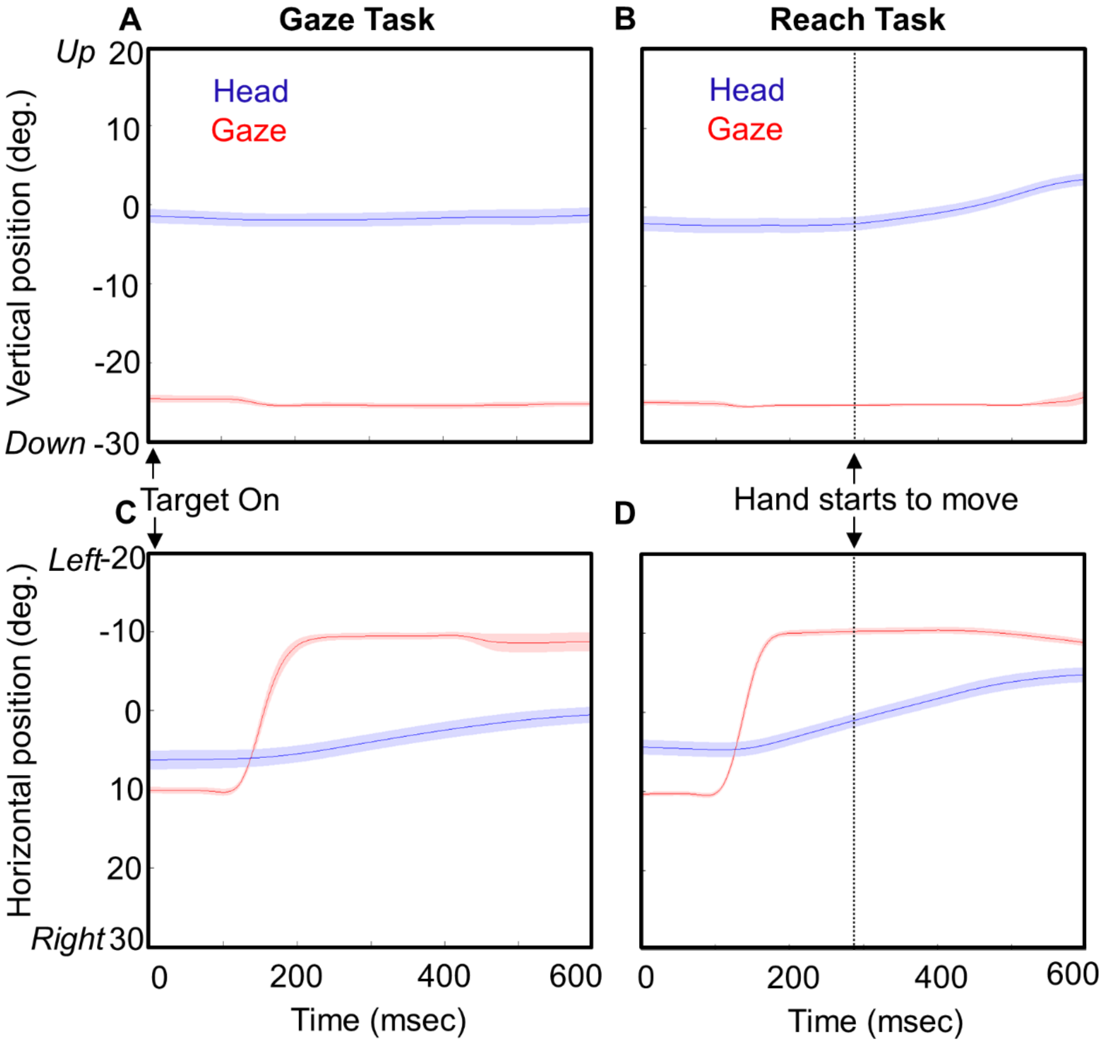


***Figure 12: Head and eye movement trajectories as a function of time.*** Averaged eye (red) and head (blue) movement trajectory (± 95% confidence intervals) are plotted in the horizontal (A/B) and vertical (C/D) dimensions in both the *Gaze Task* (left column) and *Reach Task* (right column). Black vertical lines show the time when the hand starts to move in the *Reach Task*. The end of trajectory marks the time when the animal touches the target in *Reach Task* and the

average equivalent time period in the *Gaze Task*. This example is taken from the centrifugal task when the target appears 20° to the left of the fixation point. The head starts to move with gaze in the main direction of the gaze shifts (horizontal), but only starts to move with the hand in the other dimension (vertical). The varibility in the head movement onset was weakly correlated with the reach onset time in vertical ($r = -0.06$ ;$r = -0.51$ ) and horizontal direction ($r = -0.1273$ ;$r =-0.42$ ).

Figure 12 shows the typical time course of the eye-head-hand coordination pattern that we observed. Vertical (upper row) and horizontal (lower row) components of gaze position (red) and head position (blue) are provided for 20 trials averaged across time toward the 20° leftward target in animal O, from the Gaze Task (left panels) and Reach task (right panels). The 'black vertical line' in each reach plot marks the onset of hand motion, and data plots are terminated at the end of hand motion (or the mean equivalent time in the Gaze task). The mean duration of hand movements across all centrifugal targets for animal O was 254.90 ± 36.12msec and for animal W was 276.65 ± 42.13msec.

Several features of coordinated eye-head movement difference between the reach and gaze conditions are observed by these movement trajectories. First, as reported previously (Snyder et al. 2002) there was a significant reduction in saccade reaction time in the reach task relative to the control in both animals ($p$ 0.0003 for animal O, $p = 0.0012$ for animal W; K-S Test). Second, gaze shifts were complete by the time the hand started moving, and gaze generally held its position until the hand made contact (meaning that the vestibule-ocular reflex was engaged). Third, it is evident that in both tasks, the head starts to move around the time of the gaze shift (at least along the main component of the gaze shift), but in our task most of the head motion occurs after the gaze shift. Head velocity peaked significantly later than gaze velocity both in the gaze task (Animal O: 233.2 ± 167.7º /sec, $p < 0.00001$; Animal W: 142.52 ± 140º /sec, $p$= 3.01E-31), and the Reach Task (Animal O: 300.6±164.04º /sec, $p < 0.00001$; Animal W:190.26 ±156.3º /sec, $p$ = 2.81E-43). Fourth, this late head motion is greater in the Reach task, particularly in the vertical dimension (as noted already). Further, in the vertical 'off axis' component of this example, the head only moves during the reach, and only starts moving at the onset of the reach movement.

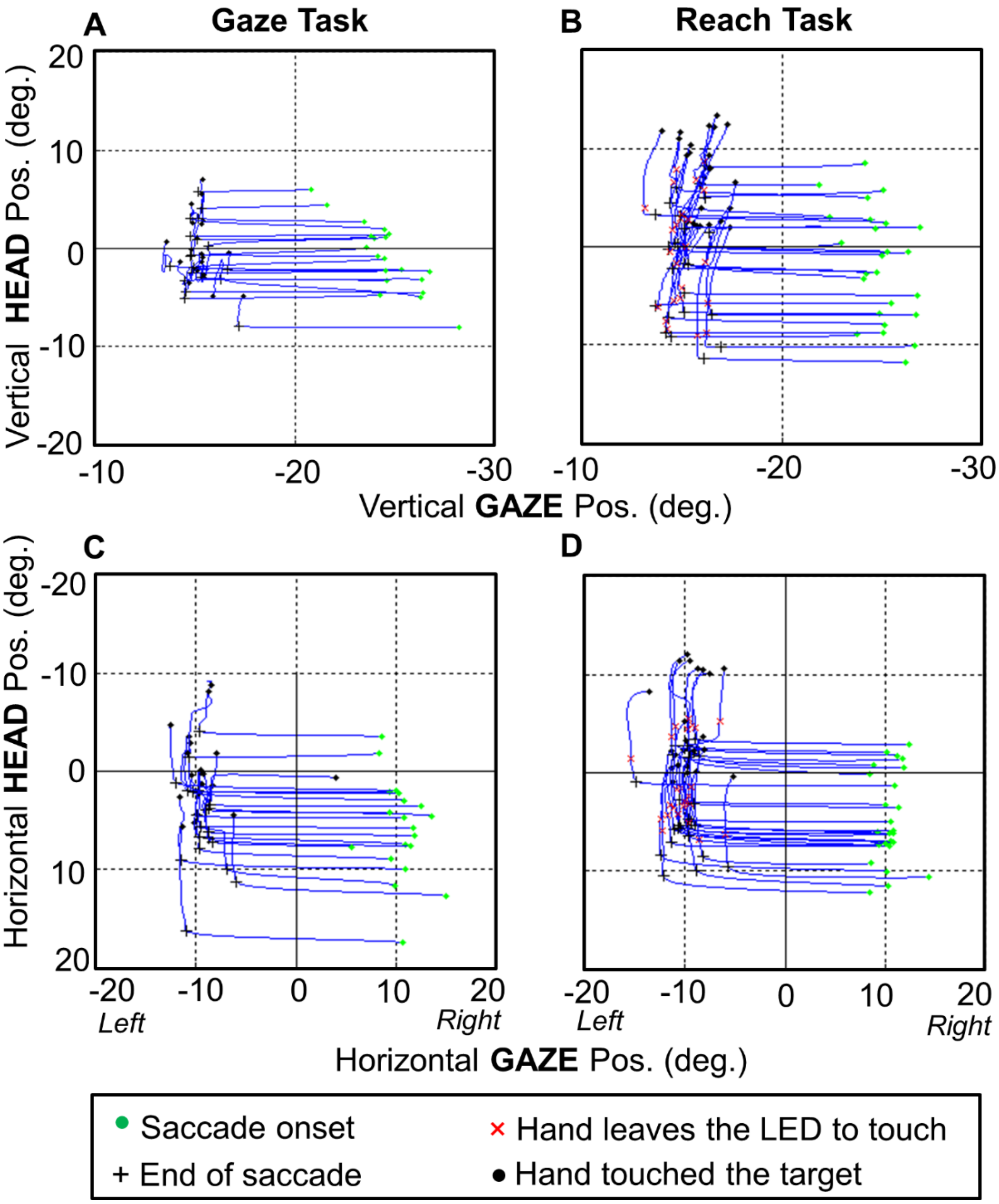


***Figure 13: Head trajectories as a function of gaze trajectories, coupled through time.*** The spatiotemporal coupling of head and gaze motion for one target (20 ° to the left of center) is shown both in the vertical dimension (A/B) and in horizontal dimension (C/D) in for both the *Gaze Task* (left column) and *Reach Task* (right column). Data are plotted from gaze onset until the hand contacts the target (or average equivalent in the *Gaze Task*). The green dots indicate the positions at the time of gaze onset, black crosses indicate positions at the end of the saccade (in both tasks), red symbols (x) indicate the time when the hand starts moving in the *Reach Task*, and black dots indciate the time when the target was touched for each trial. As in figure 7, the target was 20° to the left of the fixation point from animal O. This figure shows clearly how the majority of head motion occurred after the gaze shift, and coincided with the duration of hand movement.

Figure 13 illustrates the relative timing of eye-head-hand coordination using phase plots of head position (vertical axis) as a function of gaze position (horizontal axis). Here vertical components of a vertical gaze shift (upper row) and horizontal components of a horizontal gaze shift (lower row) are shown. Once again, we see a significant increase in head motion between the Gaze task (left panels) (20.74 ± 15.94, 23.32 ± 13.84) and the Reach task (right panels) (36.43 ± 14.44, 32.04 ± 13.84) in animal O and W, respectiely. The main point here is that in all plots, the saccade end point (+) occurs at the inflection between gaze and head motion, and more importantly, the duration of hand motion (x to ●) encompasses most of the head movement. Indeed, in the vertical component (where reach had the most influence) the reach start coincided very closely with the eye-head inflection point, more so than the horizontal component where the head began before the reach.

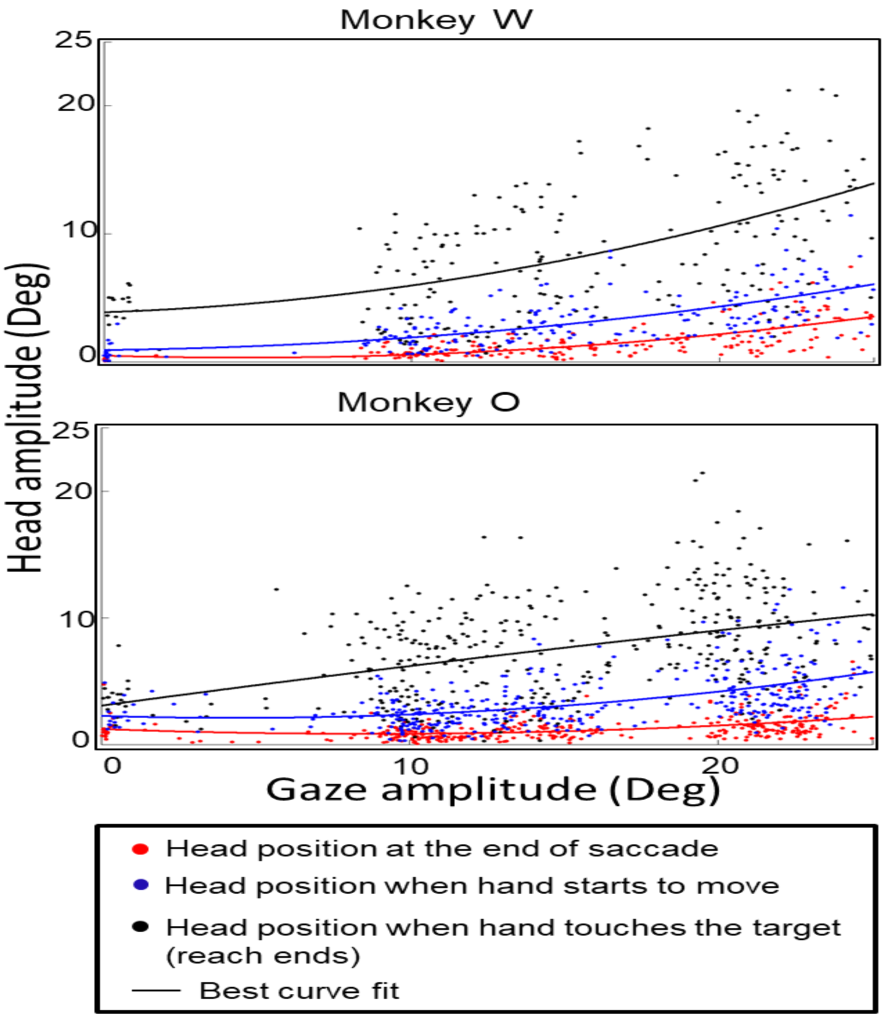


***Figure 14: Head amplitude as a function of gaze amplitude.*** *Head amplitude is shown at 3 different stages of each trial for the entire Centrifugal Reach dataset in both monkeys. Red dots indicate the data derived at end of saccades, blue dots indicate data derived when the hand starts to move, and black dots indicate data derived when the target is touched. The line in each color indicates its best fit. The head amplitude increase as a function of gaze amplitude in both animals. A small amount of the total motio occurs during saccades (red) and between saccades and reach onset (blue), but most occurs between reach onset and offset (black).*

Figure 14 summarizes these observations across our entire centrifugal reach dataset by plotting head amplitude as a function of gaze shift at three different task intervals (red points for head amplitude at end of saccades, blue points for head amplitude at the start of reach, and black points for head amplitude at the end of reach). This figure points toward several observations. First, as the distance of the eye movement increases, the head amplitude inceases as well in reach task. We see a significant positive correlation between the gaze shift and the head amplitude in reach task ($r = 0.4773$, $r = 0.6492$); ($p < 0.0001$; Pearson Correlation test) at the end of saccade, for animal O and animal W, respectively. Further, there is also significant positive correlation between the gaze shift and head amplitude in reach task ($r = 0.338$, $r = 0.5493$); ($p < 0.00001$; Pearson Correlation test) when the animal touches the target, for animal O and animal W, respectively.

Comparing the three different task intervals in Figure 14, one can see that most of the increased head motion occurs after the saccade, especially during the reach movement. A Kolmogorov-Smirnov test showed a significant difference ($p < 0.001$; K-S Test) in both animals between the red (saccade ends) blue (reach begins) and black (reach ends) points. Again the change in head amplitude at the time of touch (or equivalent) was significantly higher in the reach condition vs. controls (not shown) for both animals O ($p < 0.001$; K-S Test) and W ($p < 0.001$; K-S Test). The difference was more subtle at the end of the saccade but was still significant across all trials in both animals ($p < 0.001$; K-S Test). But as illustrated above (Figures 12 and 13), these patterns become more extreme in some situations, e.g., in horizontal gaze shifts where vertical position only moved during reach.

### 2.5.4 Velocity-Amplitude Relationships:

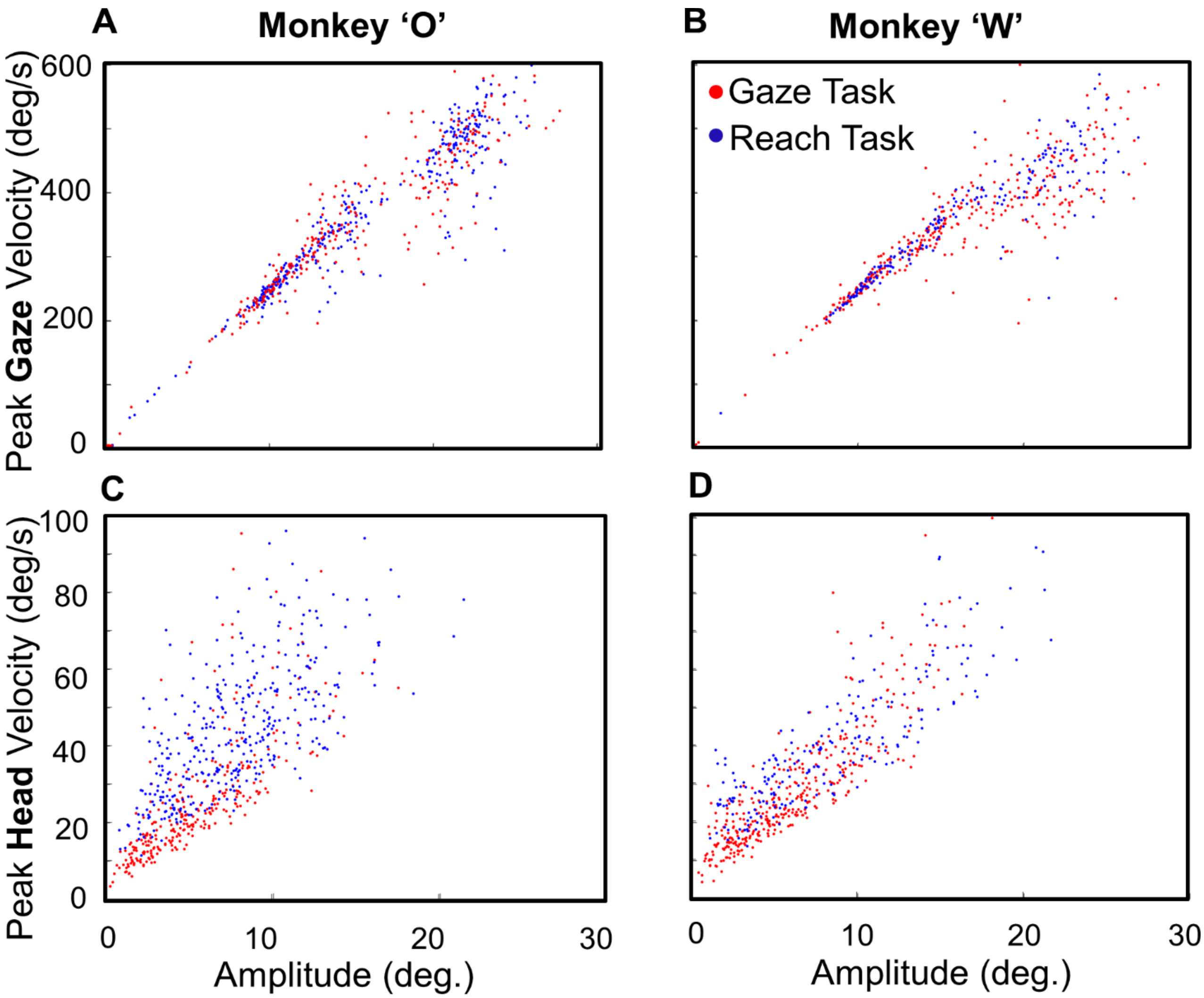


***Figure 15: Velocity-amplitude relationships for gaze and head motion.*** *A and B show the peak gaze velocity as the function of the gaze amplitude in the gaze task (red dots) vs. reach task (blue dots). These distributions were not significantly different in either animal (p = 0.43;p = 0.2; Kolmogorov-Smirvov Test). C and D show peak head velocity as a function of head amplitude in the gaze (red dot) vs. reach (blue dots) in both animals. Head velocity was significantly higher in the reach task for both animals (p = 2.38E-38;p = 8.21E-21; Kolmogorov-Smirnov Test).*

Figure 15 A/B plots peak gaze velocity as a function of gaze amplitude for the centrifugal condition, contrasting the control gaze data and experimental reach data for each animal. Peak eye velocity averaged across all 15 targets was higher in the reach task (346.96º/sec, 334.69º/sec) than the gaze task (341.07º/sec, 325.92º/sec) but their velocity-amplitude distributions were not significantly different in Kolmogorov-Smirnov tests ($p = 0.43$, $p = 0.202$; animals O and W respectively).

Likewise, figure 15 C/D plots peak head velocity as a function of head amplitude for the centrifugal task, contrasting the control gaze and experimental reach data for each animal. Averaged head velocity across all trials (combining all 15 targets) was 45.45º/sec and 40.65º/sec for reach task, compared with 26.16 º/sec and 25.27º/sec) in the gaze task for both animals O and W, respectively. In this case, the peak velocity-amplitude distributions were significantly higher when gaze was accompanied with an arm movement (Kolmogorov-Smirnov test : $p = 2.38E\text{-}38$, $p = 8.21E\text{-}21$ in animals O and W respectively), compared with the gaze control task. Target position had a significant effect on head velocity in reach and gaze task for both animals ($p < 0.001$; one-way ANOVA). Finally, we considered the recent that human reach velocity correlates better with head than gaze motion Reppert et al. (2018). Our set-up was not designed to measure peak hand velocity, but consistent with Reppert et al. (2018), we found a higher correlation between *mean* hand velocity (total amplitude/total duration) and peak head velocity ($r = 0.396$; $r = 0.487$; Pearson Correlation test) compared to peak gaze velocity ($r = 0.193$; $r = 0.196$; Pearson Correlation test) in both animals W and O respectively.

### 2.5.5 Influence of Initial Eye And Hand Position:

We repeated the analyses described above for our variable intial hand (Fig.7B.2) and variable initial gaze (Fig.7B.3) datasets, and found the same general results (summarized statistically in Table 1).

**Table 1**. **Statistical summary of differences in gaze parameters between the *Gaze Task* and *Reach Task* in the *Initial Gaze Position Condition*.**

| Behavioral Parameter | Animal | Gaze Task (mean±SD) | Reach Task (mean±SD) | Statistical Difference |
|---|---|---|---|---|
| Gaze Latency (ms) | W<br>O | 151.365±122.547<br>118.381±83.928 | 129.828±117.812<br>111.986±43.071 | **P = 0.00015**<br>**P = 0.033** |
| Gaze Velocity (deg/sec) | W<br>O | 246.569±158.906<br>343.533±182.027 | 270.381±184.561<br>359.578±237.177 | P = 0.092<br>P = 0.641 |
| Gaze Precision ($deg^2$) | W<br>O | 28.791±11.512<br>30.191±13.358 | 22.218±8.956<br>24.316±9.452 | **P = 0.015**<br>**P = 0.005** |
| Head Amplitude at End of Saccade (deg) | W<br>O | 1.654±2.186<br>0.967±0.934 | 1.851±2.104<br>1.399±1.653 | **P = 0.0028**<br>**P = 0.0047** |
| Head Amplitude at Time of target touch (deg) | W<br>O | 6.561±5.980<br>6.157±4.542 | 7.781±4.862<br>8.033±4.428 | **P = 0.0089**<br>**P = <0.00001** |
| Head Velocity (deg/sec) | W<br>O | 29.313±21.013<br>28.115±14.984 | 36.269±19.281<br>44.678±15.991 | **P = 0.00006**<br>**P = <0.00001** |

**Table 1**: Analysis performed for variable initial gaze position condition in control (gaze task) and experiment *(reach task*). The results were similar to centrifugal condition. The ‘head

amplitude at time of target touch' in gaze task, was taken at the mean time of touch calculated in reach task. The P-values arise from one-way ANOVA tests. Significant values are bolded.

Rather than repeat those confirmatory results at length, here we report additional analyses designed specifically to test the influence of intial gaze and hand position. A statistical summary of these results is provided in Table 2. Some of the significant interactions can be explained by known kinematic rules: for example, initial gaze position influenced gaze and head velocities (in the reach task), but this is expected simply because this altered the amplitudes of the movement for a given target, because head motion correlates with gaze motion, and overall the head moved more during reach. Likewise, *initial hand position* influenced hand speed by altering hand amplitude. In contrast, initial hand position had no influence on gaze or head kinematics or latencies (Table 2).

**Table 2. Statistical summary of the influence of *Initial Gaze Position Condition* and *Initial Hand Position Condition*.**

| | Animal | Gaze Reaction Time (ms) | Head Reaction Time (ms) | Hand Reaction Time (ms) | Gaze Speed (°/s) | Head Speed (°/s) | Hand Speed (°/s) |
|---|---|---|---|---|---|---|---|
| Initial Gaze Position (Gaze Task) | W<br>O | 0.276**<br>0.358** | 0.323*<br>0.939* | -<br>- | **< 0.001***<br>**< 0.001*** | 0.564*<br>0.231* | -<br>- |
| Initial Gaze Position (Reach Task) | W<br>O | **<0.00001****<br>**<0.00001**** | 0.327*<br>0.962* | **0.003***<br>**0.001*** | **0.0004***<br>**0.0008*** | **< 0.001***<br>**< 0.001*** | 0.126*<br>0.461* |
| Initial Hand Position (Reach Task) | W<br>O | 0.265**<br>0.415** | 0.711*<br>0.845* | 0.187*<br>0.306* | 0.671*<br>0.954* | 0.328*<br>0.136* | **0.0006***<br>**0.0015*** |

**Table 2**: Influence of Initial Gaze Position and Initial Hand Position on Gaze and Reach parameters. Top two rows show dependence of gaze and reach parameters on initial gaze position; bottom row shows their dependence on initial hand position. Cells show P values arising from one-way ANOVA tests. Significant values are bolded. *Indicates a test for a main effect in a 1-way ANOVA. ** Indicates a test for interaction in a two-way ANOVA.

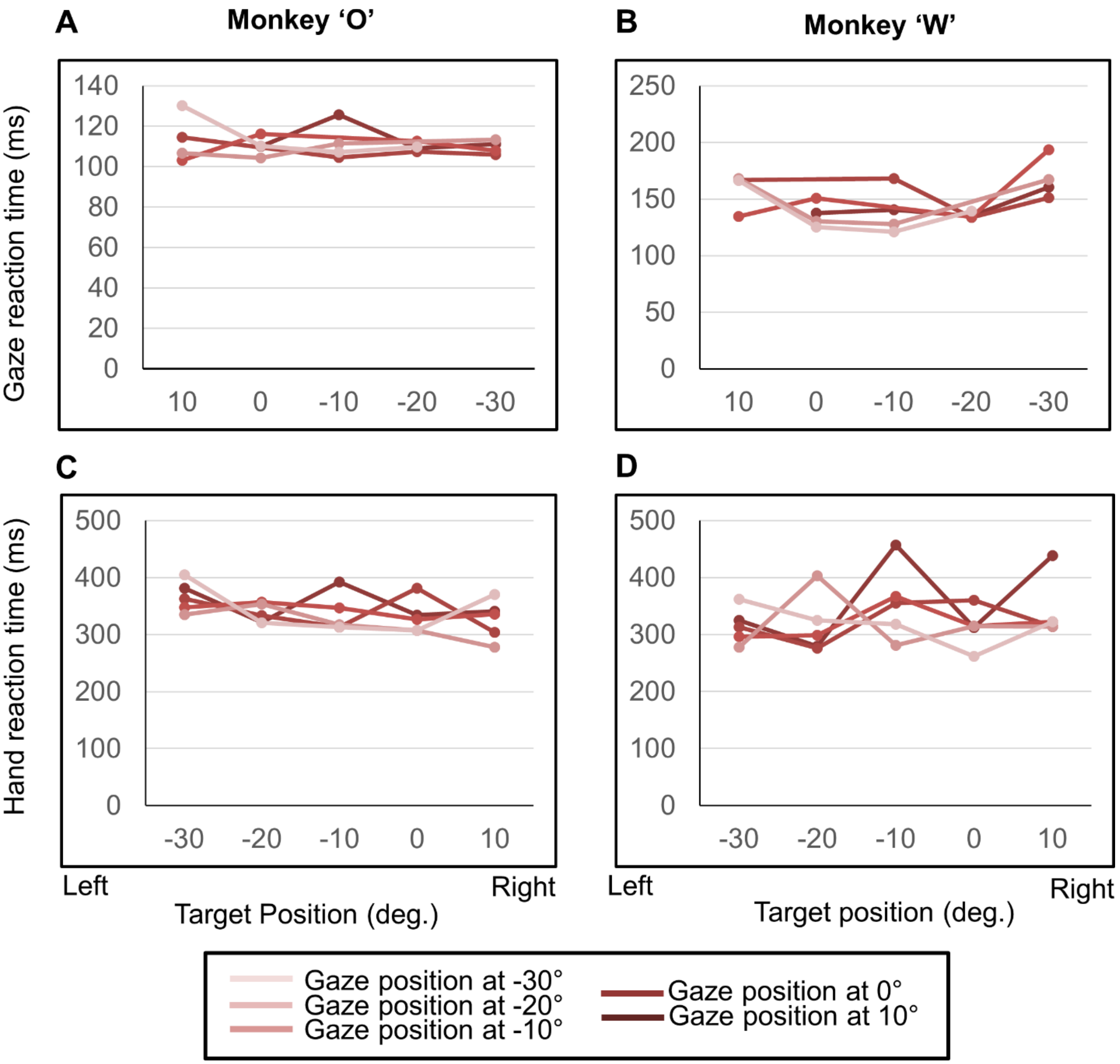


**Figure 16: Gaze and hand reaction times in the *Reach Task,* plotted as a function of target position.** Reaction times were calculated relative to fixation offset/target onset time. The top panels show mean gaze reaction times for each initial gaze location (color coded) and for both animals (A, B). The bottom panels show mean hand reaction times for each initial gaze position (color coded) and in both animals (C, D). The darker color represents the initial gaze position on the right and lighter color represents the initial gaze position on left, as shown in the key.

More interestingly, *Intial gaze position* influenced reaction time for both gaze and hand motion (Figure 16). Specifically, there was a significant interaction between the target and initial gaze position on the gaze reaction time in the reach condition, but not in the gaze, in both animals. Initial gaze position also had a significant influence on hand reaction time in both animal O and animal W. Taken together, these findings suggest that gaze position has an influence on both gaze and hand reaction time during reaches. Inspection of Figure 11 suggests a general trend (i.e, in some but not all cases) for reaction time to decrease for left fixation points right targets, possibly suggesting a right visual field advantage during reach.

## ***2.6 Discussion:***

We investigated the influence of reaching on gaze and head movement in rhesus Macaques and found several inter-relationships between these effectors. In our reach-for-reward task, animals typically initiated a saccade toward the target, followed by head movement in the same general direction, and lastly by an arm movement placing the hand towards the target. More importantly, we found that the head moved more in the reach task, in particular in the vertical dimension, and for the duration of the reach. We also observed that saccade accuracy increased, saccade latency decreased, and head velocity increased (for a given amplitude) when a reach movement accompanied the gaze shift. These observations suggest a considerable degree of coupling between eye, head, and reach control systems (Fig. 17), likely, as we shall argue, for the optimization of gaze kinematics for the visual control of reach.

### 2.6.1 Optimization of Gaze for Reaching:

Reaching had three main influences on gaze shifts in our animals. First, as reported previously in head-restrained human and monkey studies (Sailer et al. 2016; Snyder et al. 2002), reaches decreased saccade latency. Consistent with most human studies (Biguer et al. 1982; Carnahan and Marteniuk 1991), the recruitment order of our animals' movements was eye, head, and then hand. To some extent, this may be due to the relative excitation-contraction coupling times and inertia in these plants, but this cannot entirely account for the lag between initial eye/head motion and reach motion. This order appears to reflect an intentional strategy to foveate the target (which remained on for the duration of the hand movement) before the hand started moving. Second, as also reported in head unrestrained studies we found that hand motion altered the 'main sequence' of velocity-amplitude relations gaze shifts, i.e. providing higher velocities for the same amplitude gaze shift (Snyder et al. 2002). It has previously been reported that reaching increases eye-in-saccade velocities in humans and monkeys (Snyder et al. 2002). It has also been reported that hand velocity (and latency) tends to correlate with head velocity (and latency) (Smeets et al. 1996). Finally, reaches increased gaze accuracy, despite the absence of a gaze reward. Conversely, it has been reported that head movement increases gaze and reach accuracy (Guitton and Volle 1987). The net effect of these factors is that in our task, targets were foveated more rapidly and precisely before the reach even began.

Taken together, these factors suggest that, contrary to some suggestions (Vercher et al. 1994), visual gaze 'scouting ahead' is important for planning a reach movement (Bowman et al.

2009), presumably to help guide reach transport. In our simple task, gaze then remained fixed to the target until the reach was complete. A simple explanation for this is the potential advantage of foveal vision for aiming and guiding the hand movement. Consistent with this, hand pointing accuracy decreases when the target fixation was not stabilized before the target was extinguished in their experiment (Vercher et al. 1994). Finally, reaching and pointing is even more accurate when gaze aligns with the target in complete darkness (Bock 1986; Henriques et al. 1998; Henriques and Crawford 2000). This suggests the possibility that the internal sense of gaze direction can also be used to guide the hand (Bock 1986). Likewise, the influence of initial gaze position on both eye and hand latency in our reach task might be due to both simple visual factors (e.g., variable and distant peripheral retinal positions) and the increased computational load of accounting for noisy gaze position signals when transforming vision to reach commands (Blohm and Crawford 2007; Gauthier et al. 1990). In practice, it seems likely that both of these factors likely contribute to eye-hand coordination strategies, depending on visual conditions.

### 2.6.2 Eye-Head Coupling and Head Contribution:

Some studies have supported the notion that the early signals for gaze control in the cortex and superior colliculus primarily take the shape of an undifferentiated, eye-centered command for two-dimensional gaze direction, with default levels of 3-D eye-head coordination determined downstream (Freedman and Sparks 1997a; Klier et al. 2001, 2003; Sadeh et al. 2015; Sajad et al. 2016). However, this story becomes more complex when one considers both the various types of interaction between the eye and head, and their degree of independent control. Various studies have demonstrated both 2-D interactions between eye and head position (Freedman and Sparks 1997a; Gandhi and Sparks 2001; Tweed and Vilis 1990) and 3-D interactions (Crawford et al. 1999; Monteon et al. 2012; Tweed and Vilis 1990). As a result, most recent mechanistic models of eye-head coordination include signals for cross-talk between eye and head control (Daemi and Crawford 2015; Daye et al. 2014; Freedman and Sparks 1997a; Tweed and Vilis 1990). On the other hand, the high degree of context dependence of relative eye-head contribution that has been observed in various studies suggests the potential for independent control (Constantin 2004; Crawford and Guitton 1997; Freedman and Sparks 1997a; Gandhi and Sparks 2001; Kowler et al. 1992; Ron and Berthoz 1991). The current investigation is generally consistent with these previous studies of eye-head coordination studies in macaques but extends those to results eye-head-*hand* coordination, where the following new findings must also be considered.

### 2.6.3 Optimization of head motion for reach:

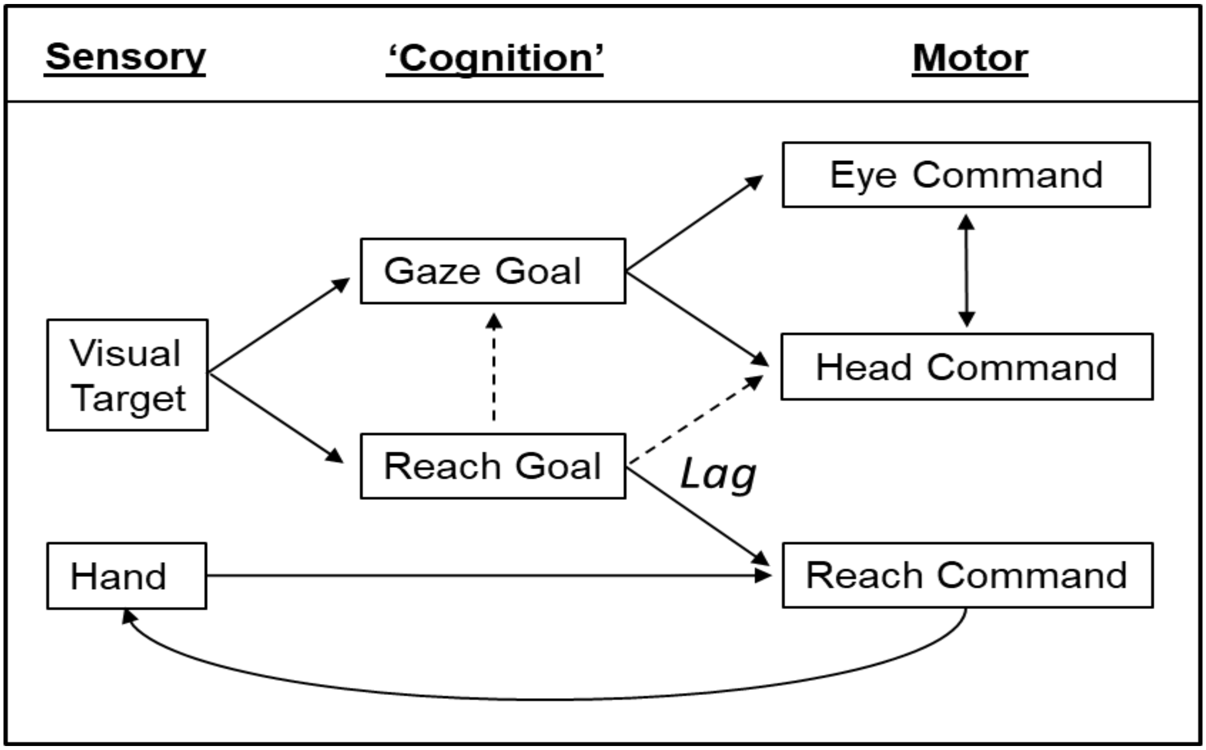
The current study suggests an additional drive for head motion in the presence of reach, in terms of peak amplitudes and velocities. This was already statistically significant during saccades (the head contribution to gaze) but was much more obvious during the prolonged head motion that accompanied subsequent reaches. This was particularly the case in the vertical dimension, but this might simply be because the head usually moves more horizontally than vertically in the absence of reach (Crawford and Guitton 1997; Goossens and Van Opstal 1997; Tweed et al. 1995). An increase in vertical head motion thus tends to equalize the horizontal and vertical components of head motion (Figure 11). There was also a constant bias in horizontal head position between the two tasks, but from our data it is unclear if this was due to the hand used (right in this case), and/or simply a postural adjustment resulting from opening the hand aperture.

In our dataset, the additional vertical head movement components appeared to accompany the timing of the reach rather than the saccade. To our knowledge, this additional head drive has not been reported previously. Reppert et al. (2018) briefly compared gaze kinematics with and without reach, but reported a *decrease* in head velocity during reaches, opposite to the increase we observed. This was not the focus of their paper, so it is unclear if our disparate results were due to the tasks or in the way we analyzed our data. It does not appear a species difference, because we have obtained similar preliminary results in the human (Al Tahan et al. 2018).

It would appear that the increased head drive in our study is more related to the reach goal than the reach vector, because in our data set the reach-related head movement was correlated to target position and was not modulated by initial hand position. Because the Vestibulo-ocular reflex stabilizes gaze position by rolling back the eye opposite to the head after saccades (Guitton 1992; Snyder and King 1992), this increased head motion must automatically center the eye in the head. To some extent this occurred in both of our tasks, but why would this be enhanced during reaches relative to ordinary gaze shifts? One possibility is that ordinary gaze shifts, beyond very close targets, are primarily concerned with re-directing gaze *direction*. In contrast, depth information becomes very important during three-dimensional reaches (as in our set-up), especially as the hand must decelerate and contact a specific depth in space. It has been shown that changes in eye orientation complicate depth vision (Blohm et al. 2008; Schreiber et al. 2001) and that depth vision is superior in the central oculomotor range. Therefore, it may be advantageous for the three-dimensional visuomotor transformation if increased head motion drives the eye toward the central range during reaches.

### **2.6.4 Possible Mechanisms**:

Figure 17 provides a simplified conceptual model for the main eye-head-hand interaction we observed in this study. Like most recent gaze-control models, the visual stimulus is used to derive an undifferentiated gaze goal, which then drives semi-independent control systems for the eye and head (the arrow between these indicates that they interact). However, to aim the hand in depth, the brain must compare 3-D estimates of initial hand position and target position to derive the desired movement vector (Sober and Sabes 2003). To indicate coordination between these systems, we have provided additional inputs (dashed arrows) from the reach goal command to both the gaze command (to explain our gaze latency, velocity, and accuracy results) and the longer lasting head command, to explain the hand-head linkages reported here and in Reppert et al. (2018). This cross talk could take the form of a relatively direct (and likely learned) neural connections, but if our visual hypothesis is correct, they might also be driven indirectly through



heightened visual attention to the reach target, and later the distance between the hand and target.

***Figure 17: Conceptual Model of Eye-Head-Hand Coordination**. Gaze goals in eye-centered coordinates are thought to drive both eye and head commands, which in turn influence each other during the gaze shift (Freedman 2008; Guitton et al. 1990). Reach Goals derived from the visual target are compared to hand position estimates derived from proprioception and vision of the hand to drive the reach command, and in turn influence the hand position (curved line) through internal feedback and actual motion (Bédard and Sanes 2009). This transformation appears to lag the eye-head command. The current study suggests the reach goal also influences gaze and head commands (dashed lines), either directly and/or through visual feedback.*

Note the lag introduced somewhere between the goal and in the commands of head and arm motion (Figure 17). This is added to account for the observation that in our dataset, most of the head (and reach) movement occurred after the gaze shift, with both ending at approximately the same time in the *Reach Task* (Figures 11, 12). Although some inertial lag is expected here relative to eye motion, it is not unusual in some *Gaze Tasks* for head motion to begin during the saccade during rapid gaze shifts (Freedman and Sparks 1997a; Guitton 1992; Roy and Cullen 1998). Likewise, mechanics alone may not account for the delay we observed between gaze motion and hand motion (205.1 msec in animal O and 174.26 msec in animal W), and even if it did, the system could chose to delay the gaze shift until the hand moves. Thus, this neuromuscular lag seems to be part of a deliberate strategy, again to 1) allow time for gaze to reach the target first so that foveal vision could be used to aim accurate reach movements, and then 2) to coordinate head and arm motion so that the head is position to optimize depth vision at the point of final contact (and in most real world tasks, manipulation of the object).

The possible neural substrates for gaze-hand coordination have been the topics of numerous reviews (Battaglia-Mayer A  Genovesio A, et al. 2001; Hwang et al. 2014; Marconi B Battaglia-Mayer A, et al. 2001). In contrast, very little is known about the higher-level control mechanisms for head motion. One possibility is that the hand-head influence might be implemented at the brainstem level. Although the superior colliculus is best known for its gaze signals (Freedman and Sparks 1997b; Munoz et al. 1991; Sadeh et al. 2015), it also shows head-related responses (Walton et al. 2007), and these responses become far more prominent when animals are cued to produce larger head movements (Monteon et al. 2012). The final ingredient to this mix is that the deep layers of the superior colliculus also show modulations with reach (Stuphorn et al. 2000; Werner 1993). It has been proposed that these modulations could mediate increases in eye velocity, and likewise, might mediate the reach-related changes in head motion described here. The cerebellum, which has been proposed to play a role in eye-hand coordination (Miall et al. 2001), might also be involved.

## ***2.7 Conclusion:***

Non-human primates have been used extensively as animal models for human eye-head and eye-hand coordination, but to our knowledge eye-head-hand coordination was not previously studied in monkeys.  Although we did not observe any influence of gaze parameters on reach in the current study, we did observe several instances of reach influencing gaze and eye-head coordination.  First, we observed that reaches improved gaze accuracy, and confirmed that they 'sped up' the gaze shift both in terms of latency and velocity.  Most interestingly, we observed an increased head motion in the direction of the gaze/reach target, coupled to the duration of the reach. This was accompanied by an increase in head velocity for a given head amplitude. As noted above, these adaptations may get the fovea rapidly on the target in order to aim reach transport and may optimize depth vision during the final contact phase of touch (which might be even more important during grasp). In general, these observations expand on the notion that the gaze system is the 'slave' to the reach system during eye-*head*-hand coordination (Crawford 1994), in the sense that it optimizes vision for successful reaching.

## ***2.8 Acknowledgments:***

This study was supported by Canadian Institutes for Health Research (CIHR) and Canada Research Chair (Tier 1) held by JDC. VB was supported by NSERC CREATE-IRTG fellowship and VISTA fellowship. HW and XY were supported by VISTA. The authors would like to thank Saihong Sun for programming codes for the analysis of the data and Dr. Veronica Nacher for critical comments on the manuscript.

## ***2.9 Disclosures:***

The authors declare no conflict of interest.

## ***2.10 Contributions:***

HKA trained the animals, did the experiments, collected and analyzed the data. VB contributed to the analysis of data and critical comments on the manuscript. XY helped with the training of the animals and technical support and assistance. SS made the programming codes for the analysis of the data. HW performed the surgeries and provided the technical support. JDC conceived the study and contributed to data analysis. HKA and JDC wrote the manuscript. All authors approved the final version of the manuscript.

# ***Chapter 3:***

# ***General Discussion and Conclusion***

## ***3.1 Overview of the study***

Visuomotor control mechanisms such as eye, head and hand systems are fundamental for our survival on the earth. The examples included in this eye-head and eye-hand coordination field are extensive from simply reaching for a cup of coffee to playing table tennis. Given its significance in our lives, it is finally triggering the scientists to study and understand this complex multi-movement systems which take place in our unconscious mind.

Non-human primates have been used extensively as animal models for human eye-head-hand coordination during gaze shifts (in a 2-D plane), but the more natural condition of eye-head-hand coordination during a 3-D reach has not been studied in monkeys. A large number of studies have looked into eye-head and eye-hand coordination in humans using functional magnetic resonance imaging, but eye-head-hand coordination is a new topic to observe even in humans. To our knowledge, no one has yet studied the coordination between eye-head and eye-hand in head-unrestrained non-human primates.

We performed experiments to examine the influence of hand on gaze and head movement, in addition, we also looked at the influence of eye on hand and head movement. While performing these experiments we also got a chance to observe the differences of head movement between gaze and reach conditions. Animals were seated in the ‘customized chair’ which allowed the head to move freely and allowed the hand to reach in every direction and depth while performing the experiments in dark room. Subjects were required to either make a saccade towards the target or touch the target. We observed many inter-relationships between the effectors. Compared to the previous studies, we also noted that the eye moved to the target first, followed by the head which was followed by the hand. Gaze shifts were completed by the time the hand started moving, and gaze kept its position until the hand touched target. It was seen that the head started moving, mostly after the gaze shift and before the hand started to move to touch the target. Therefore, the duration of hand motion encompasses most of the head movement. In the reach task, animals made eye-head gaze shifts toward the target and then touched the target with prolonged head motion, in comparison to gaze task.

The interesting finding was the large head movement when the saccade was accompanied by an arm movement, especially in vertical direction. We observed that the target position had an influence on the final head position in vertical and horizontal dimension, which was due to the head movement towards the direction of the target. Furthermore, when the eye movement was accompanied with an arm movement, the saccade reaction time was short, also been shown by Snyder et al. 2002.

There is a positive correlation between the gaze shift and head amplitude in reach and gaze task. Again, the head amplitude at the time of touch was comparatively higher in reach task than in gaze task. Head velocity peaked after the gaze velocity peaked in both reach and gaze task. In addition, we got noteworthy results for the head velocity which was also higher when the saccade was associated with an arm movement. Target position had a significant effect on head velocity in reach and gaze task. Hand speed showed a higher correlation with head velocity than gaze velocity. Additionally, we observed that the subjects were very accurate at looking towards the target with the motor movement of the arm. Hence, it shows that reach planning had an influence on gaze precision.

Further, we observed that initial eye position had an effect on reach latency but not on hand speed. Eye position also influenced head velocity in reach task but not in gaze task. Along with that, there was a significant interaction between target and eye position on eye reaction time in reach task but not in gaze task. Initial hand position showed no influence on eye reaction time, eye velocity and no influence on head reaction time, head velocity. Initial hand position only showed an influence on hand speed, but no effect on hand latency. Thus, initial eye position showed an effect on eye-head gaze kinematics, but initial hand position showed no effect on eye-head gaze kinematics.

## ***3.2 Possible Neural Mechanism:***

The coordination between the eye, head and hand is an important ability in both animals and humans. To achieve this, the brain needs to be able to perform complex sensory-motor transformations in the forward and inverse directions. To attain this communication, there could be two different pathways working simultaneously that bring eye, head and hand together to perform the reach. One pathway separately giving cues to the eye and head, and another pathway giving cues to hand and head. There is correlation between eye and hand as hand uses visual feedback to reach the target accurately. The FEF is implicated to pay a major role in the frontal area for saccade generator. This area sends signals to the brainstem nuclei (especially superior colliculus and saccade generator circuitry) that are critical to gaze movement. Low current stimulation of FEF generates the saccadic eye movement and eye-head coordinated gaze shifts (Monteon et al. 2010). There is a gradient of visual-to-motor responsiveness of pre-saccadic neurons: some neurons only respond to the visual stimulation of the retina (visual neurons), some contain both visual and motor responses (visuomotor neurons) and some only fire prior to or during saccade (motor neurons).With clear visual and motor functions of the FEF, this structure is implicated as one of the critical nodes for visuomotor transformations for gaze control. The superior colliculus located in the roof of brainstem is the most conserved structure in the visuomotor pathway. The superficial layer of SC contains neurons that are responsive to visual stimuli. Neurons in intermediate and deep layers of SC receive input from several cortical areas and are responsive to many modalities (Gandhi and Katnani 2011). SC transmit neurons for gaze (Sadeh et al. 2015) and for head movement (Monteon et al. 2012) through reticulo-spinal neurons. Superior colliculus is also shown to have neurons related to reach (Stuphorn et al. 2000; Werner 1993), therefore it could be a possibility that superior colliculus is the region where all the above mentioned effectors are communicating. These neurons further transmit to motor neurons in brainstem driving eye and head movement. The brainstem nuclei project these motor neurons to the eye and head (neck) muscles. The premotor cortex is known to be a site of visuo-somatosensory integration for the production of movement. Dorsal premotor cortex (PMd) is known to be involved in the planning and execution of reaching movements. The interneurons in PMd show increased firing rates than pyramidal neurons during both the planning and movement epochs (Kaufman et al. 2010). PMd uses a relative position code that specifies the differences in locations between all three variables (eye, hand and target). Such a relative position code may play an important role in coordinating hand and eye movements by computing their relative position (Pesaran et al. 2006). Therefore, suggesting the area where the instructions to the eye and hand are given. Whereas, ventral premotor area (PMv) an anatomical and physiological well differentiated area in premotor cortex supports both perceptual decisions and performance monitoring. A study suggested that PMv is involved in the use of recent and long term sensory memory to decide, execute and evaluate the outcomes of the subjects’ choices (Pardo-Vazquez et al. 2011).

## ***3.3 Clinical Implications***

Clinical implications of visuomotor coordination include patients suffering from optic ataxia, visual agnosia, alien hand syndrome, Parkinson's disease and stroke affecting the parietal lobes where the action or perception streams have been damaged. A neurologist, Dr. Rezso Balint coined the term Optic ataxia, as he was studying Balint's syndrome in 1909 (a disorder with three defining symptoms: psychic paralysis of gaze, spatial disorder of attention and optic ataxia). He believed optic ataxia was due to lack of coordination between visual input and motor outputs, and therefore the term *ataxia*, which is Greek for 'lack of order'. To further understand the pathophysiology and treatment options for these syndromes, we need to look at the brain in more detail. New animal studies are beginning to elucidate a finer grain of functional organization of PPC by neural recordings of the brain areas for reaching, grasping and eye movements. Studies using functional magnetic resonance imaging (fMRI), magnetoencephalography (MEG) and transcranial magnetic stimulation (TMS) are in more agreement with the animal findings of the functional localization.

Efforts by Andersen et al. 2014 and (Khan et al. 2005b, 2005a, 2007) have been made to understand the disease at the neural level. (Andersen et al. 2014) demonstrated that PRR was involved in reach-specific visuomotor pathways and reach goal disruption in PRR can be a neural basis of Optic ataxia. Along with (Khan et al. 2007), who observed that the target and the hand are compared at more than one level in the visuomotor pathway in multiple reference frames, and these comparisons are then integrated. Depending on the location of the damage within the PPC, these comparisons are disrupted, therefore causing inability to reach the aimed target. Inactivating the V6A area in non-human primates caused parietal weakness, reluctance to move, and specific deficits in reaching, wrist orientation and grasping (Battaglini et al. 2002). A patient with parietal lobe lesion manifested with 'magnetic misreaching', where her reach endpoints were determined by the place she was looking at, independent of the distance between target and fixation point (Carey et al. 1997).

These findings can further help the clinicians/scientists to help understand and treat these fearful disorders/diseases.

## ***3.4 Future Directions***

Finally, the next step in this line of research is to use electrophysiological techniques to record from posterior parietal cortex (PPC). Ultimately, the goal is to collect neuron data and decode the neural substrates of motor and visual representations for head-unrestrained reaching.

I trained the monkeys in the reach and gaze task for three different conditions (centrifugal, initial eye and initial hand) to collect the behavioral data, which provides the baseline for further neural data analysis. Another post-doc in our lab is recording neural data from two head-unrestrained monkeys performing reaches and gaze shifts in centrifugal condition from FEF, PMd, PMv areas. Previously, Ph.D students used an analytic technique involving statistical fits of different spatial model against neural response fields to show that visual response encode target direction and motor responses encoded planned gaze direction (both relative to initial eye orientation) in superior colliculus (SC) (Sadeh et al. 2015) and Frontal Eye Fields (FEF) (Sajad et al. 2015). Again, the analysis will be done with a similar methodology to investigate if a similar set of spatial codes are employed in these areas by the post-doc recording now-a-days. Preliminary analysis in PMv has shown an assortment of stimulus, gaze, pre-reach and reach related responses. A spatial fitting model analysis suggests that the visual response best encoded the target relative to the eye, whereas the gaze and hand onset responses showed a tendency towards coding the accompanying head motion in space coordinates. Further analysis will be able to describe the complete picture of the distribution of the eye, head and reach signals in the areas (PMv, PMd and FEF). I myself have moved to Seattle, Washington, and intend to continue pursuing my training in basic and clinical neurophysiology.

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