INFLUENCE OF A VISUAL LANDMARK SHIFT ON MEMORY-GUIDED REACHING IN THE MONKEY

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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

BIOLOGY
YORK UNIVERSITY
TORONTO, ONTARIO

NOVEMBER 2023

ABSTRACT

Reach and gaze data were collected from one female *Macaca mulatta* monkey (ML) trained to perform a memory-guided reaching task to determine the influence of allocentric cue shifts on reaching responses in the non-human primate. A landmark (4 ‘dots’ spaced 10° apart forming the corners of a virtual square) was presented at 1 of 15 locations on a touch screen. The landmark either reappeared at the same location (stable landmark condition) or shifted by 8° in one of 8 directions (landmark shift condition). ‘No-landmark’ controls were the same, but without the landmark. The presence of a stable landmark increased the accuracy of both gaze and touch responses and the precision of gaze. In the landmark shift condition, reaches shifted partially (mean = 29 %) with the landmark. Overall, these data suggest that the monkey is influenced by visual landmarks when reaching to remembered targets in a similar way as humans.

DEDICATION

To my friends and family, who have always given me unconditional love and support.

ACKNOWLEDGEMENTS

I would like to express my gratitude to my supervisor Dr. J Douglas Crawford for the opportunity to conduct this animal behaviour study. Thank you for welcoming me into your lab and encouraging me to present my work at various conferences. I appreciate your guidance and patience throughout this entire process. I am in awe of your achievements and seeing it happen in real time was inspiring. I have learned a lot from you and hope to continue to do so in my PhD.

Thank you to Dr. Hongying Wang who was there from the beginning and worked every day with me to train the animal. You taught me everything that I needed to know to successfully collect data. I would also like to thank the Vivaria staff.

I really appreciate the help with the data collection and analysis pipeline from Saihong Sun. You have helped me with every little thing and taught me a lot as I lacked experience in coding. I also appreciate Dr. Xiaogang Yan for being there for all the technical difficulties and helping to set up the task in the lab.

I would like to thank Dr. Jeffrey Schall for providing valuable feedback and asking challenging questions to encourage me to think deeper.

Thank you to all my lab members. Drs. Vishal Bharmauria and Verónica Nácher have been especially helpful and have always been so kind by giving me tons of advice.

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CHAPTER 1 GENERAL INTRODUCTION

In day-to-day life, we are constantly performing tasks that require us to reach towards objects. We can reach for an object by directing our gaze towards it or by using our memory and are able to do so accurately and easily without calculating our movements consciously. To do this, various sources of information, such as object locations, are taken in and further processed within a specific frame of reference, ultimately determining a mental spatial representation of the environment. Simons and Wang (1998) have illustrated that one can employ two types of reference frames, which are ways of representing the locations of objects in space (Figure 1). An egocentric frame of reference is defined by the axis of the navigator and encodes information about the location of objects in space relative to oneself (left-right, front-back, up-down) (Ruotolo et al., 2011). Egocentric reference frames can be internally updated to accommodate movement of an individual (Burgess et al., 2004). An allocentric frame of reference is defined by the axis of the navigator relative to an external reference point, and so the reference direction will not change. Allocentric spatial processing encodes information about the location of one object with respect to other objects within the environment (Ruotolo et al., 2011). Neuroimaging studies in humans suggest that reaching based on egocentric vs. allocentric cues activate different brain areas (Chen et al., 2014; Chen & Crawford, 2020) and that these cues might be integrated for action in the parietofrontal cortex (Chen et al., 2018), but the specific mechanisms are unknown.

In human reach studies, it has been shown that both types of information (egocentric and allocentric) are combined based on their relative reliabilities to create the best estimate of the goal location (Byrne & Crawford, 2010). A similar effect occurs in monkey gaze shifts (Li et al., 2017). This appears to involve specific cellular mechanisms in the prefrontal cortex (Bharmauria et al., 2020, 2021). However, these results have not been replicated in the monkey reach system. The purpose of the current study was to replicate the behavioral results of egocentric-allocentric weighting in the monkey reach system, as a potential experimental model for studying the underlying cellular mechanisms. To do this, we subtly shifted a landmark in a cue-conflict reaching task. The reach response will tell us if the monkey is using the landmark as a cue for reaching and if so, how much this landmark is weighted. We also looked at the effect of a stable landmark and compared the reach responses in this condition to the no landmark and landmark shift conditions.

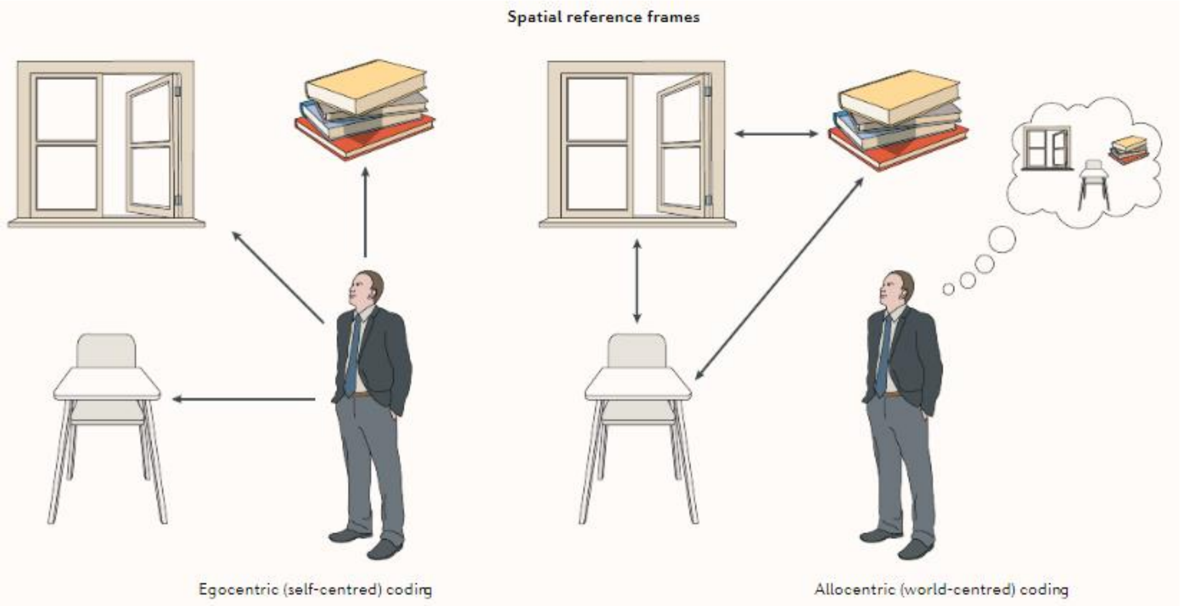

Figure 1. Egocentric and allocentric spatial processing. Egocentric reference frames encode information about the location of objects in space relative to oneself. Allocentric reference frames encode information about the location of one object with respect to other objects within the environment. Adapted from “Spatial navigation deficits — overlooked cognitive marker for preclinical Alzheimer disease?”, by Coughlan, G., Laczó, J., Hort, J. et al. Spatial navigation deficits — overlooked cognitive marker for preclinical Alzheimer disease?. Nat Rev Neurol 14, 496–506 (2018). https://doi.org/10.1038/s41582-018-0031-x

1.1 The Dorsal and Ventral Visual Streams

The two streams hypothesis is a well-known model regarding the processing of vision (Alipour et al., 2022) and is closely associated with the notions of egocentric versus allocentric visual processing (Goodale & Milner, 1992; Goodale & Murphy, 2000). The hypothesis states that visual information travels from the occipital lobe to two different streams (Figure 2). It was proposed that the visual areas are organized hierarchically into two cortical visual pathways: the dorsal pathway and the ventral pathway (Ungerleider & Mishkin, 1982). The dorsal stream runs from the primary visual cortex to the posterior parietal cortex (Goodale & Milner, 1992). It was first proposed to be the “where pathway” as it specializes in locating where an object is (Mishkin et al., 1983). The dorsal stream is also known as the “how pathway” as it is involved in visually guided motor behaviour (Goodale & Milner, 1992). The dorsal stream is also thought to encode spatial information in an egocentric frame of reference and uses short-term memory for real-time movements as egocentric representations degrade over a delay of several seconds and can start as quickly as < 500ms (Chen et al., 2011; Westwood et al., 2001). The ventral stream, also known as the “what pathway”, runs from the primary visual cortex to the inferior occipito-temporal cortex (Goodale et al., 2004; Milner & Goodale, 2008). It is involved in the visual identification of objects and uses our long-term memory (Alipour et al., 2022). Moreover, the ventral stream is thought to encode spatial information in an allocentric frame of reference and is used for memory-guided movements as allocentric representations remain relatively stable after a delay of several seconds (Chen et al., 2011).

Human neuroimaging studies have confirmed that dorsal versus ventral stream areas are activated when humans remember reach goals in egocentric versus allocentric coordinates (Chen et al., 2014, 2018; Chen & Crawford, 2020). While this study found overlapping regions of cortical activity during the egocentric and allocentric task, they found areas that were involved in encoding a specific reference frame (Chen et al., 2014). Their egocentric task elicited higher activation in the parietofrontal cortex (premotor cortex, medial intraparietal sulcus, and superior parieto-occipital cortex), and the allocentric task elicited higher activation in the early visual cortex (lingual gyrus, calcarine, and cuneus) during the delay phase when only target location was specified (Chen et al., 2014). They also found that the superior occipital gyrus and the inferior occipital gyrus exhibited egocentric directional selectivity (target location relative to gaze), while the inferior temporal gyrus and inferior occipital gyrus were found to exhibit allocentric directional selectivity (target relative to a visual landmark).

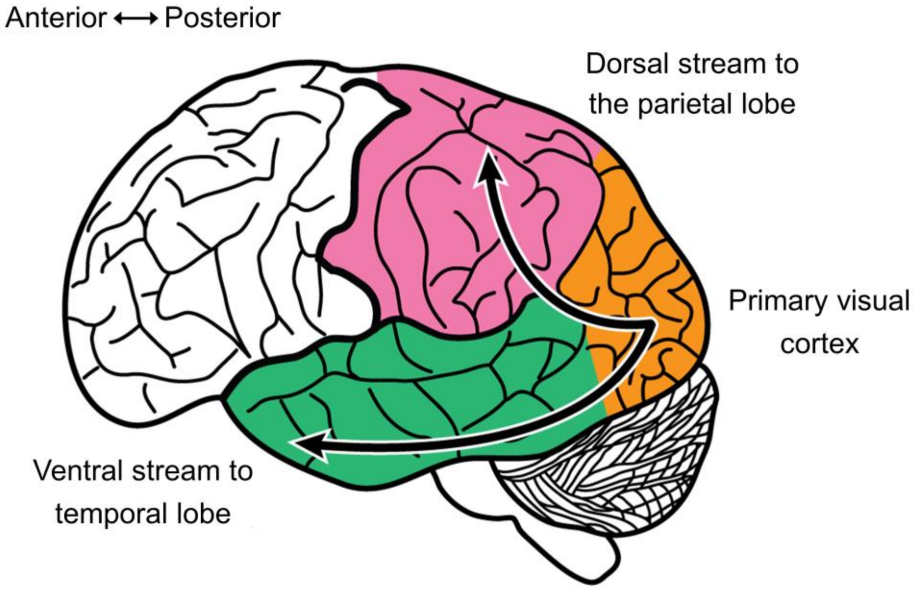

Figure 2. The dorsal and ventral streams. Information is processed in the primary visual cortex and travels through the dorsal stream and the ventral stream. The dorsal stream runs from the primary visual cortex to the posterior parietal cortex (Lu & Fiehler, 2020). It is known as the “where pathway” and “how pathway”. The ventral stream, also known as the “what pathway”, runs from the primary visual cortex to the inferior occipito-temporal cortex (Lu & Fiehler, 2020). Adapted from Henley, C. (2021). *Vision: Central Processing*. https://openbooks.lib.msu.edu/neuroscience/chapter/vision-central-processing/

1.2 The Frontal Parietal Cortex Reach Networks in the Primate

Many areas of the cerebral cortex are involved in the execution and planning of a voluntary movement. The parietofrontal pathways are a cortical network that allows these areas to communicate with each other to accurately execute a movement (Figure 3). The parietal cortex takes information from the external environment and one’s own body that is used for planning and guidance of movement. The posterior parietal cortex (PPC) is viewed as an important area for sensory-motor integration and higher-level cognitive functions related to action, such as forming early plans for movement, also known as intention (Andersen & Buneo, 2002). The PPC has been found to be more active during movement preparation compared with the reaching movement (Beurze et al., 2007). The superior parietal lobule (SPL) is involved in early reach planning and online reach monitoring (Hawkins et al., 2013). A large proportion of cells in this area exhibits directional tuning. Neurons deeper in the SPL were strongly modulated during target presentation and during the reaching movement. The intraparietal sulcus (IPS) and parietal-occipital sulcus (POs) were found to be modulated during anticipation, target presentation, and during the reaching movement (Hawkins et al., 2013). The parietal reach region (PRR) which includes the medial intraparietal area (MIP), area 7a, and the dorsal part of the parieto-occipital area, were strongly activated when planning an arm movement (Snyder et al., 1997). The MIP was found to have the highest number of neurons that coded reach and these neurons were found to code the direction of the movement (Eskandar & Assad, 1999). MIP neurons respond to stimuli within reaching distance and respond to pure visual information or to both visual and somatosensory information (Matelli & Luppino, 2001).

The frontal lobe areas involved in this reach network are the premotor cortex (PMC) and the primary motor cortex (M1). The PMC is involved in higher-order processes of response selection and movement planning (Scott et al., 1997). It is an important area for selecting and preparing visually guided movements (Crammond & Kalaska, 1996). An anterior-to-posterior gradient can be seen with reach or hand-only responses in the caudal parts of the dorsal premotor cortex (PMd) (Filimon, 2010). The PMC has shown increased fMRI activity in macaques during visually guided arm movements (Premereur et al., 2015). The majority of neurons in this area are directionally tuned and show maximal responses when reaching towards the preferred direction (Kettner et al., 1996; Scott et al., 1997). In addition, neurons in this area are sensitive to changes in arm orientation during reaching movements and during stable arm postures (Scott et al., 1997). It is activated by forelimb reaching to both visual and memorized targets, with some regions preferentially activated by reaching toward a visual target and some towards a memorized target (Gregoriou et al., 2005).

Finally, the primary motor cortex contains neurons that are activated mainly during execution while the premotor and parietal cortices contain neurons that are activated during planning (Kandel et al., 2014). The M1 receives converging information from many cortical and subcortical regions and provides information to the descending corticospinal tract and alpha-motoneurons (Scott, 2003). M1 is strongly activated during visually guided hand movements and has been found to encode intrinsic parameters of movement such as muscle force, joint torques, and angles (Caminiti et al., 1990, 1991; Scott & Kalaska, 1997) and extrinsic parameters such as the direction and speed of limb movement (Caminiti et al., 1990, 1991; Crammond & Kalaska, 1996; Georgopoulos et al., 1982; Kalaska et al., 1989). All the mentioned cortical areas communicate with each other through reciprocal projections and can integrate different types of information to form the motor plan.

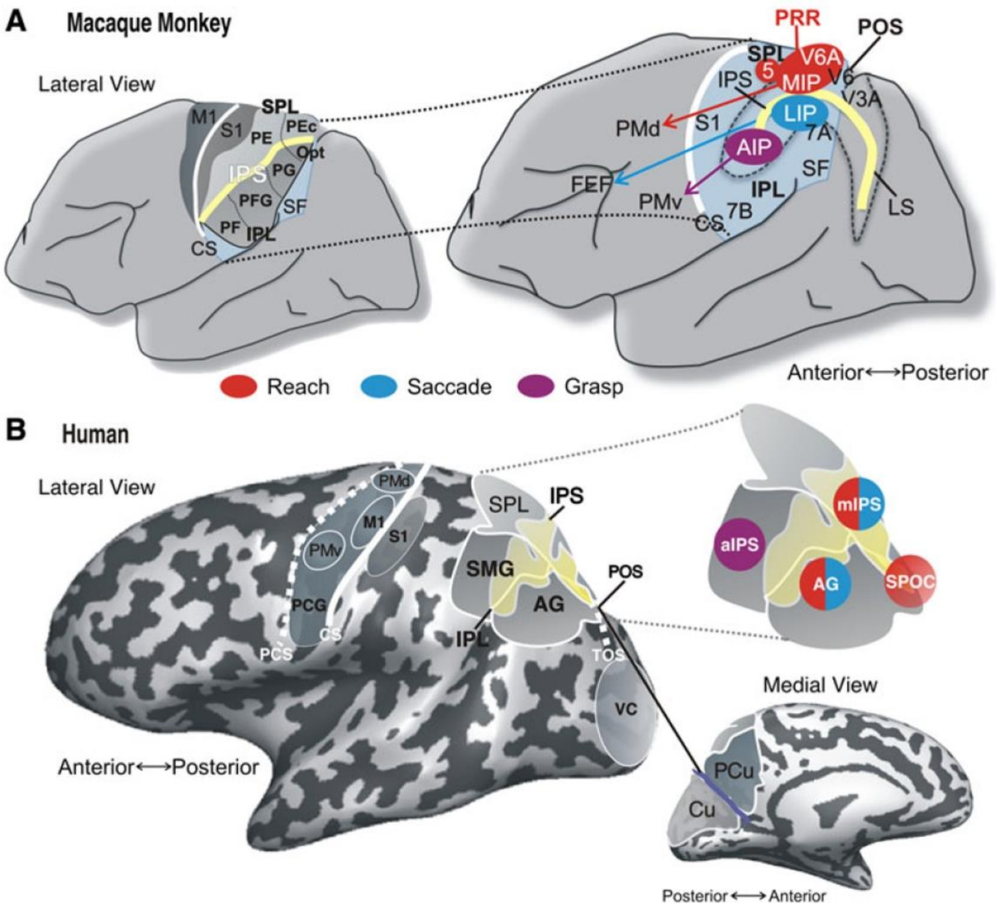

Figure 3. Comparison of the macaque monkey and the human parietal lobes. The MIP (medial intraparietal area) and V6a in the monkey and mid-posterior IPS (intraparietal sulcus), AG (angular gyrus), and SPOC (superior parieto-occipital cortex) in the human are responsible for reach. Adapted from Vesia, M., & Crawford, J. D. (2012). Specialization of reach function in human posterior parietal cortex. Experimental Brain Research, 221(1), 1–18. https://doi.org/10.1007/s00221-012-3158-9

Reach areas of the brain have been found to have eye, head, hand, shoulder, and body-centered coding but are likely to make use of mixed representations. The parietofrontal reach system seems to be primarily dominated by egocentric coding schemes. For example, visual stimuli for reach activate eye-centered codes in the parietal cortex (Beurze et al., 2010; Fernandez-Ruiz et al., 2007; Medendorp & Crawford, 2002; Pesaran et al., 2006) whereas the M1 neural codes for movement tend to be body-centered and the premotor cortex shows a mixture of eye-centered and body-centered codes (Batista et al., 1999; Bernier & Grafton, 2010; Caminiti et al., 1990; Graziano et al., 1997). It is noteworthy that even when reach targets are defined in allocentric coordinates, once an action is planned and executed, the typical parietofrontal network is activated in neuroimaging experiments (Chen et al., 2014, 2018; Chen & Crawford, 2020). Other neuroimaging experiments suggest that allocentric codes are integrated into this network within the parietal and premotor cortex (Chen et al. 2018). However, these experiments could only reveal functional anatomy, they could not reveal specific cellular mechanisms.

1.3 Eye-Hand Coordination

Typically, saccadic eye movements precede goal-directed hand movements and are much shorter and quicker (Arora et al., 2019; Bekkering et al., 1994, 1995; Biguer et al., 1982; Prablanc et al., 1979). An eye movement is needed for guiding a limb to the target and thus goal-directed hand movements are more accurate when the visual target stimulus is gazed at in a dark and lit environment (Henriques et al., 1998, 2003; Henriques & Crawford, 2000; Neggers & Bekkering, 1999, 2000; Prablanc et al., 1979). These eye movements are made to targets in order to use the high foveal receptor density on the retina and when targets are not fixated, pointing accuracy decreases (Neggers & Bekkering, 2000; Prablanc et al., 1979; Vercher et al., 1994). It seems that during the phase of the movement where the moving hand is decelerating (from peak velocity to the end of the movement), visual stability could be a prerequisite for pointing (Neggers & Bekkering, 2000). It has been suggested that a saccade might enforce the hand to wait for the saccade to be completed to obtain foveal information about the target before executing the movement (Neggers & Bekkering, 1999; Prablanc et al., 1979). Thus, only peripheral target information is used to execute a saccade and foveal visual information is used to produce a hand movement. In addition to the influence of the final gaze position, the initial gaze position was found to decrease both gaze and hand latency, potentially due to visual field advantages. In monkeys, there was a right visual field advantage when the animal used their right hand, but the opposite was found in humans showing an advantage of the contralateral side (Arora et al., 2019; Woods et al., 2015).

In addition to a saccade guiding the movement, gaze has been found to follow the target intended by the arm movement and is unable to fixate on a new target before the hand has reached the initial target (Neggers & Bekkering, 2002; Rand & Stelmach, 2010). This is known as ‘gaze anchoring’, where the central nervous system (CNS) enforces ocular fixation of a pointing target or inhibits a second saccade away from a pointing target until the pointing is completed (Neggers & Bekkering, 2001). This mechanism would ensure that there is a stable visual target representation for the arm movement. This is also seen in the dark when the moving arm cannot be seen meaning that the visual signal related to the moving arm is not driving this mechanism (Neggers & Bekkering, 2001). Rather, it may be an efferent signal related to motor control or an afferent proprioceptive signal that carries information on the dynamic status of the arm. It has also been found that when a reach movement accompanies the gaze shift, there was an increased saccade accuracy and a decreased saccade latency (Arora et al., 2019; Snyder et al., 2002). However, when forcing the eyes and the arm to move in opposite directions, there was an increased saccade latency and high peak gaze velocity (Gorbet & Sergio, 2009). In addition, they found that the hand paths were more curved possibly due to the disruption of control processes that typically form straight hand paths. When in the presence of multiple targets, the eye and arm usually move to the same target, possibly due to the CNS enforcing a co-alignment of the ocular and manual motor systems (Gielen et al., 1984; Neggers & Bekkering, 2002).

When reaching to remembered target locations, gaze is not used in the same way (Flanagan et al., 2008). Gaze behaviour was found to be erratic with some trials having coordinated gaze and hand movement and a majority of trials having minute gaze movements that stayed near the initial fixation. This may be due to gaze accuracy not being ensured via visual feedback of the remembered target (Flanagan et al., 2008). During free gaze, this study found that participants' pen markings tended to undershoot the most eccentric targets and overshoot the least eccentric targets. There was no reliable correlation observed between the absolute pen marking error and gaze fixation error. The maximum coefficients of correlation between pen and gaze were greater for visible targets than remembered targets. When gaze was maintained at the central fixation, pen marking accuracy did not differ from free gaze conditions. This means that pointing accuracy to remembered targets did not depend on gaze landing position. In addition, when marking the remembered target with gaze fixation, the error was significantly lower than when marking with a pen. Thus, the large gaze errors found in this study during pointing with free gaze were not due to the inability of the oculomotor system to access stored information about the target locations (Flanagan et al., 2008).

Similarly, gaze marking also tended to undershoot the most eccentric target locations and overshoot the least eccentric targets. This may suggest that similar memory representations were used when marking the target with the hand and gaze. In an object manipulation task, differences can be seen when performing the task in light versus dark. In the light, gaze fixations were always directed to the hand and the target (Johansson et al., 2001). However, in the dark, gaze fixations were broadly scattered and were rarely directed at the landmarks (Flanagan et al., 2008).

1.4 Weighting Egocentric Vs. Allocentric Cues for Reach

Humans can be instructed to reach based on either egocentric or allocentric (landmark-centered) cues, but in most cases, we probably rely on both types of cues (Byrne & Crawford, 2010; Fiehler et al., 2014; Li et al., 2017; Lu & Fiehler, 2020). In this situation, the presence of an allocentric landmark reduces the variability of pointing direction (Byrne et al., 2010). This suggests that there must be some way that the brain weighs between such cues. One factor that is likely to influence the weighting and use of these cues is their relative reliability (Byrne & Crawford, 2010). The less reliable a cue is the lower we tend to weigh this cue. Studies have shown this effect in action as subjects' responses have increased variability when the cue is less reliable (Byrne & Crawford, 2010; Knill, 2007). Estimated reliability may also be influenced by heuristics based on experiences. For example, spatial information derived from stable cues might have a higher weight than those that are unstable, even if they are equally reliable on average. Many studies have shown that humans perform better in spatial memory tasks when the cue does not change locations (Burgess et al., 2004; Byrne & Crawford, 2010; Fiehler et al. 2014).

The Bayesian model is a statistical model that uses prior knowledge to explain the integration of cues. This model describes the probability of an event based on prior experience that is related to this event and the likelihood of a certain outcome. It says that we combine the probability distributions from priors and the likelihood which gives us the posterior probability that can be constantly updated based on new information. In terms of cue integration, we would combine the probability distributions from two information sources (e.g., egocentric and allocentric cues) to find where the two sources of information overlap. The Bayesian model states that the brain can optimally integrate information while also taking into account the uncertainty of the information. Therefore, if we are uncertain about one cue, we will lean towards the more certain/reliable cue. Lastly, the maximum likelihood estimation (MLE) model is used to estimate the value of the parameters of a probability distribution that maximizes the probability of observing the data from a given dataset. It can predict how multiple stimulus estimates with different reliabilities combine in a statistically optimal fashion (Byrne & Crawford, 2010).

1.5 Cue-conflict Studies in Humans

Byrne and Crawford (2010) were the first to use the MLE to predict and describe the weighting of egocentric and allocentric cues for reach by creating a conflict between these cues. Their MLE model relied on both cue reliability and the stability heuristic. The stability parameter affected the weighting of the cues by modulating the influence of the actual reliability. It artificially decreases the reliability estimate for allocentric information when landmarks are unstable. They used the model to simulate and predict the results of a reach-to-touch paradigm. In one condition of the paradigm, a spatial conflict between egocentrically and allocentrically defined target locations is induced by shifting the allocentric cue (landmark) during the memory delay. In the other two conditions, the stability of visual landmarks (adding a vibration to them) or the actual reliability of the egocentric cue (varying total gaze movement amplitude during the memory delay) were varied. The allocentric weight (AW) can then be calculated from the results. Each response was transformed by translating, rotating, and scaling its position vector so that the original target (T) is at the origin of the new coordinate system (0,0) (Figure 4). The allocentric location (T') would be at the (1,0) location. To calculate AW, the projection of TR onto TT' (d) was divided by the magnitude of TT' (D). The AW would be zero if a subject was using only egocentric information and one if the subject was using only allocentric information. In the cue-conflict condition, they found that the mean reaching response always shifted away from the original target location toward the allocentrically defined target location. The overall average weighting was 60% egocentric and 40% allocentric. This indicated that the subjects were using both egocentric and allocentric cues at different degrees, but this does now tell us how these factors are weighted. To test this, the overall gaze trajectory length was differed to change the egocentric cue reliability and only egocentric information was available. It was found that reaching endpoints were more variable after large gaze shifts than small gaze shifts. The overall reaching variance was also greater for large gaze shifts. However, there was no significant difference between small and large gaze shifts in terms of allocentric weight. This study then varied the vibration amplitude of the allocentric cue. An unstable landmark would be less useful, and the subject would place less weight on it. They found that landmarks with a small vibration amplitude had a greater effect on reaching endpoints than landmarks with a large vibration. These results indicate that both extrinsic cue stability and reliability are important for determining cue weighting in memory-guided reaching.

Reach studies conducted on humans have tried to determine the weighting of allocentric and egocentric cues. When landmarks are available, the brain seems to combine gaze-dependent egocentric representations with gaze-independent allocentric information to guide immediate and delayed reach movements (Schütz et al., 2013). Schütz et al. (2013) have demonstrated the use of both of these cues by showing that reaching errors fell between patterns of purely egocentric coding and allocentric coding. However, this study did not identify the weighting of these cues. More recently Fiehler and colleagues have used this approach to investigate various factors that modulate this weighting in real-world conditions. A real-time reaching task study found that subjects weighted allocentric cues around 23% (Lu & Fiehler, 2020). Reach response errors have been shown to be significantly influenced by gaze direction (egocentric cue) regardless if there are landmarks (allocentric cue) present (Schütz et al., 2013). This effect is present in both memory-guided and real-time reaching. Similar behaviour was observed during a reaching task in a naturalistic visual scene. The results of this study showed that reaching movements were largely affected by allocentric shifts (Lu & Fiehler, 2020). The more the allocentric cue shifted, the larger the effect it had on the reach response. This effect was additionally shown to be stronger in memory-guided reaching than in real-time reaching. Furthermore, Fiehler et al. (2014) found that the higher the number of allocentric cues that were shifted in a scene, the more it influenced reach responses. These studies demonstrate that egocentric and allocentric cue integration is highly flexible and the results were consistent with the Bayesian model.

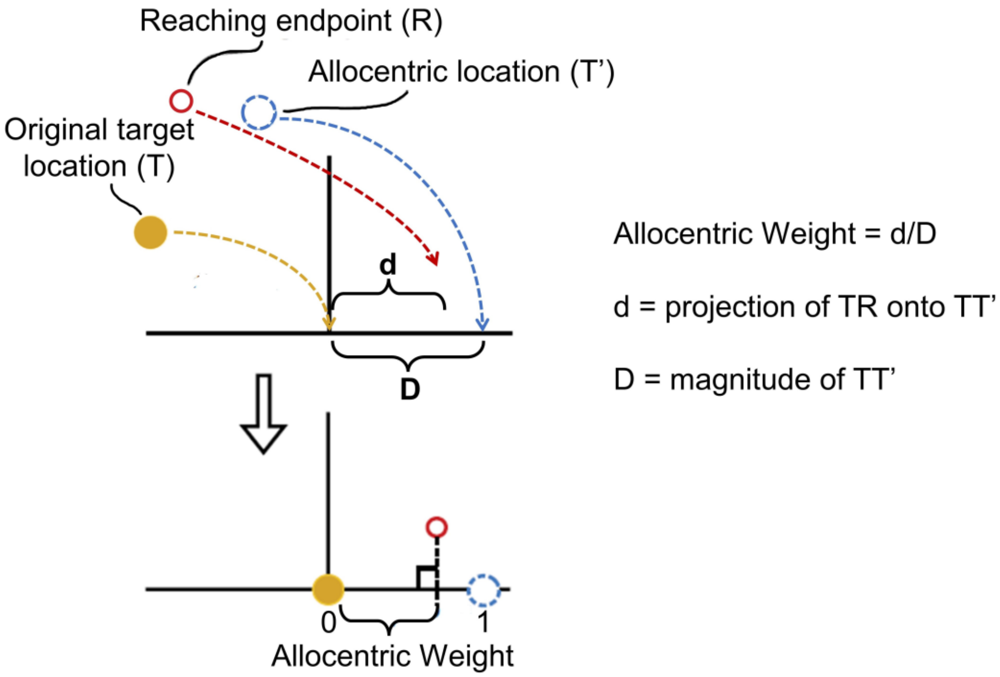

Figure 4. Allocentric weight transformation procedure. Each reaching endpoint (small red circle) was transformed by translating, rotating, and scaling its position vector so the original target (solid yellow circle) would be at the origin of the new coordinate system. The allocentric location (dashed blue circle) would be transformed to be at (1, 0) location. Adapted from Byrne, P. A., & Crawford, J. D. (2010). Cue reliability and a landmark stability heuristic determine relative weighting between egocentric and allocentric visual information in memory-guided reach. *Journal of Neurophysiology*, *103*(6), Article 6. https://doi.org/10.1152/jn.01008.2009

1.6 Cue-conflict Studies in Monkeys

In addition to research in humans, research in non-human primates has also given us fundamental knowledge about the human brain due to the similarities between the two species. Similar to reach studies in humans, the presence of an allocentric cue reduced the variability of gaze responses in monkeys and also shifted the response in the direction of the cue (Li et al., 2017). The allocentric weight increased when the allocentric cue was positioned closer to the initial fixation location. This may be because the landmark becomes of higher relevance to the task and so the landmark shift was more likely to be perceived as apparent motion (Li et al., 2017). In addition, the allocentric weight increased when the landmark shifted away from the original target location and when the landmark shifted away from the initial fixation location. Ultimately, the weighting of the allocentric cue was found to be around 25% and the egocentric to be 75% for gaze in monkeys.

Based on these results, neurophysiology studies have investigated how allocentric information is integrated into egocentric motor commands for goal-directed actions (Bharmauria et al., 2020, 2021). Adopting the same cue-conflict gaze task as Li et al., (2017), a model-fitting analysis approach was used to examine if, when, and how the frontal eye field (FEF) contributes to the integration of egocentric and allocentric cues for eye movements (Bharmauria et al., 2020). The FEF was found to play an important role in integrating allocentric information into the egocentric gaze code. In another study, Bharmauria et al. (2021) used a model-fitting analysis approach to investigate if, when, and how egocentric and allocentric information is integrated in the supplementary eye fields (SEF). These studies show that the allocentric cue shift can be detected in the memory and motor activity of FEF and SEF neurons. In addition, data collected from these neurophysiological studies and previous human studies are used to propose a neural circuit model. This neural circuit explains the path allocentric and egocentric cues travel when being integrated in the frontal cortex.

1.7 Specific Questions and Hypotheses

So far, the behavioural influence of allocentric cues has been studied in the human reach system and the neural influence has been studied in the monkey gaze system. Although important frontal and parietal reach area equivalents have been found in monkeys, this influence has not been studied in the monkey reach system. For that reason, the current study investigated mechanisms of egocentric and allocentric visual integration during reaching movements in monkeys. This study examined how allocentric cue shifts affect reaching responses in non-human primates and how eye-hand coupling compares to Arora et al. (2019) and between our different conditions. We conducted a memory-guided reach experiment which include both egocentric and allocentric (landmark) cues on one female rhesus macaque monkey (*Macaca mulatta*). Behavioural data was collected to investigate the effect of allocentric cue reliability during reaching tasks by surreptitiously shifting the allocentric cue during the memory interval between seeing the target and reaching. We hypothesized that (1) the stable landmark will increase the accuracy and precision of gaze and reach responses. (2) If the gaze is used to guide the hand, then their final position should correlation relative to the landmark. We also hypothesized that (3) like human reach and monkey gaze responses, reaches will deviate in the direction of the allocentric cue shift, and (4) there will be an increase of allocentric cue shift influence when the landmark is located closer to the fixation gaze point and (5) when the landmark shifts away from the gaze fixation point.

CHAPTER 2 THE INFLUENCE OF A VISUAL LANDMARK SHIFT ON MEMORY-GUIDED REACHING IN THE MONKEY

2.0 Abstract

The brain uses various sources of visual information, including both egocentric cues (e.g., object location relative to the eye) and allocentric (e.g., object location relative to other visual landmarks) to aim movements. It has been shown that humans optimally weigh egocentric and allocentric (landmark) cues when pointing (Bryne & Crawford 2010) but it is not known if monkeys do this. The main purpose of this study was to determine the influence of allocentric cue shifts on reaching responses in non-human primates. To do this, reach and gaze data were collected from one female *Macaca mulatta* monkey (ML) trained to perform a memory-guided reaching task. The hand was initially placed at 1 of 3 varying locations of a waist-level LED bar while the gaze fixated centrally. A landmark (4 'dots' spaced 10° apart forming the corners of a virtual square) was then presented at 1 of 15 locations on a touch screen after a delay. A visual target then appeared transiently at a variable location within or outside this virtual square, followed by a visual mask. After the mask, the landmark either reappeared at the same location (stable landmark condition) or shifted by 8 degrees in one of 8 directions (landmark shift condition). The fixation light then extinguished, signaling a reach to the target. 'No-landmark' controls were the same, but without the landmark. Compared to gaze responses, reach had lower variance and decreased reaching error. The presence of a stable landmark increased the accuracy of both gaze and touch responses and the precision of gaze. It also decreased the reaction time for both gaze and touch. In the landmark shift condition, reaches shifted partially (mean = 29%) with the landmark. We

found the gaze responses to shift (mean = 38%) with the landmark too. Overall, this data suggests that the monkey was influenced by visual landmarks when reaching to remembered targets in a similar way as humans.

2.1 Introduction

Numerous types of information, such as an object's location, are taken in and further processed within a specific frame of reference. Simons and Wang (1998) have illustrated the presence of two types of reference frames, which are ways of representing the locations of objects in space. An egocentric frame of reference is defined by the axis of the navigator and encodes information about the location of objects in space relative to oneself (left-right, front-back, up-down) (Ruotolo et al., 2011). The dorsal stream is also thought to encode spatial information in an egocentric frame of reference and uses short-term memory for real-time movements as egocentric representations degrade over a delay of several seconds (Chen et al., 2011) An allocentric frame of reference is defined by the axis of the navigator relative to a reference point, and so the reference direction will not change. The ventral stream is thought to encode spatial information in an allocentric frame of reference and is used for memory-guided movements (Chen et al., 2011). The two streams have been studied extensively but the division between the two frames of reference and visual streams and where and how egocentric and allocentric information is processed within the brain is still unclear.

Studies in humans have shown that egocentric and allocentric cue integration is highly flexible and that both types of information are combined based on their relative reliabilities (Byrne & Crawford, 2010). Several studies have found that the presence of an allocentric cue improves the accuracy and the precision of reach responses, but shifting of the allocentric cue caused individuals to reach towards the direction of the shift and away from the original target location (Byrne & Crawford, 2010; Fiehler et al., 2014; Lu & Fiehler, 2020). Studies in monkeys also show the effect an allocentric landmark has on gaze responses. Similar to reach studies in humans, the presence of an allocentric cue reduced the variability of gaze responses in monkeys and also shifted the response in the direction of the cue (Li et al., 2017). In addition, neurophysiology studies have shown that the allocentric cue shift can be detected in the memory and motor activity of FEF and SEF neurons (Bharmauria et al., 2020, 2021)

The current study has collected behavioural data from one female rhesus macaque monkey (*Macaca mulatta*) to investigate the effect of an allocentric cue shift during a reaching task. We hypothesized that (1) the stable landmark will increase the accuracy and precision of gaze and reach responses. (2) If the gaze is used to guide the hand, then their final position should correlation relative to the landmark. We also hypothesized that (3) like human reach and monkey gaze responses, reaches will deviate in the direction of the allocentric cue shift, and (4) there will be an increase of allocentric cue shift influence when the landmark is located closer to the fixation gaze point and (5) when the landmark shifts away from the gaze fixation point.

2.2 Methods

2.2a Animals and Surgical Procedures

Data was collected from one female rhesus macaque monkey (*Macaca mulatta*). The animal weighed around 7kg at the time of the study. The animal underwent several surgeries before the experiment, some described previously (Arora et al., 2019). Under general anesthesia (1.5% isoflurane following intramuscular injection of 10 mg/kg ketamine hydrochloride, 0.05 mg/kg atropine sulfate, and 0.5 mg/kg acepromazine) a steel head post was implanted onto the skull using an acrylic head cap secured by screws. One Teflon-coated search coil was implanted in both eyes subconjunctivally and a scleral coil was placed in the eye to record horizontal and vertical 2D eye orientation. The animal then rested for two weeks after surgery to recover. During data collection, fluid intake was controlled as the animal received fluid as a reward for correct trials. All of the surgical and experimental protocols were done according to the Canadian Council for Animal Care guidelines. The use of laboratory animals was reviewed and approved by the York University animal care committee.

2.2b Experimental Setup and Behavioural Recordings

The experimental setup was similar to the one used by Aurora et al. (2019) (Figure 5). During the experiment, the animal was seated in a customized Crist primate chair that allows for free motion of the head and forward reaching movements. The animal wore a removable head restraint, removable top plates, a security vest, and a shoulder collar. Additional restrictions included a chain that attached the animal's vest to the chair and an upper arm Velcro cuff connected to the chair that restrains the left arm. The animal was trained to rest its hand on an LED bar attached to the chair at waist level. The center of the LED was 16 cm ahead and 28cm below the right shoulder. The three LEDs we used are at (-19 °, -64 °), (19 °, -64 °), and (45 °, -64 °) in the horizontal and vertical visual angles, respectively. We used infrared light to monitor the horizontal position of the hand, and a vertical sensor above the LED bar, which detected whether the light was blocked by the animals' hand. Visual stimuli were displayed using a laser projector that projected onto a touch screen that was 23 cm distance ahead of the eye. A frame surrounded the screen and measured the central 2D manual contact using vertical and horizontal infrared sensors.

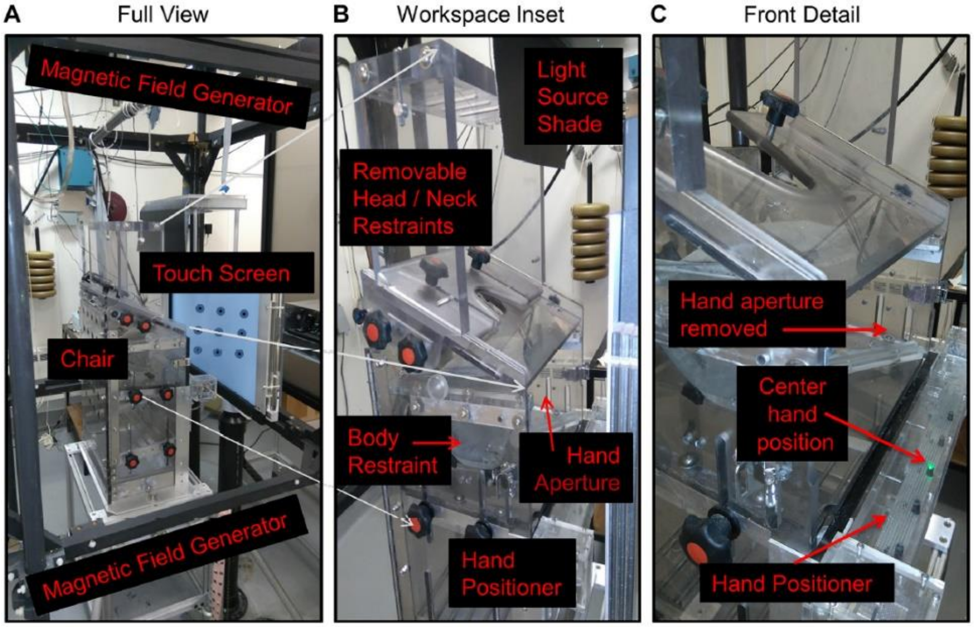

Figure 5. Laboratory setup. (A) A touch screen will be placed in front of the customized Crist primate chair. (B) The removable head/neck restraints will be removed during the experiment to allow for movement of the head. The body restraint was a jacket attached to the inside of the primate chair. This will secure the monkey's body position. Removing the hand aperture will allow movement of the hand. (C) The hand positioner was composed of the LED bar positioned at waist level and in front of the hands. The green LED light will indicate the center hand position. Adapted from "Eye-head-hand coordination during visually guided reaches in head-unrestrained macaques", by Arora, H. K., Bharmauria, V., Yan, X., Sun, S., Wang, H., & Crawford, J. D., 2020, *Journal of Neurophysiology*, *122*(5), 1946–1961. Copyright 2019 by the American Physiological Society.

The steel head post was used to stabilize the animal's head during setup. The head coil, 2D eye coil, reward tube, and fluid dispenser were attached to the head cap.

Two calibrations were done before the experiment. The 2D magnetic fields were precalibrated by rotating an external coil through each field direction and adjusting field strength in each direction to an equal maximum (Arora et al., 2019). The second calibration required the animal to fixate on each of the nine targets displayed on the screen for 1s.

2.2c Behavioural Paradigm

The experiment was conducted in complete darkness to eliminate other stimuli. All visual stimuli were presented in red, with the target stimulus having the highest intensity. The egocentric cue was a dot at the center of the screen where the monkey will fixate their gaze towards during each trial (Figure 6). The allocentric cue, known as the landmark, was four identical dots positioned at the vertices of a square with a 10^{o} edge length. The landmark was located at 15 different locations within a 50^{o} by 30^{o} rectangle (Figure 6). The target was a dot located at a random location within a 5^{o} diameter circle at the center of the landmark. We also included “catch trials” where the targets were located outside of the landmark to ensure the animal was reaching towards the target rather than the center of the landmark.

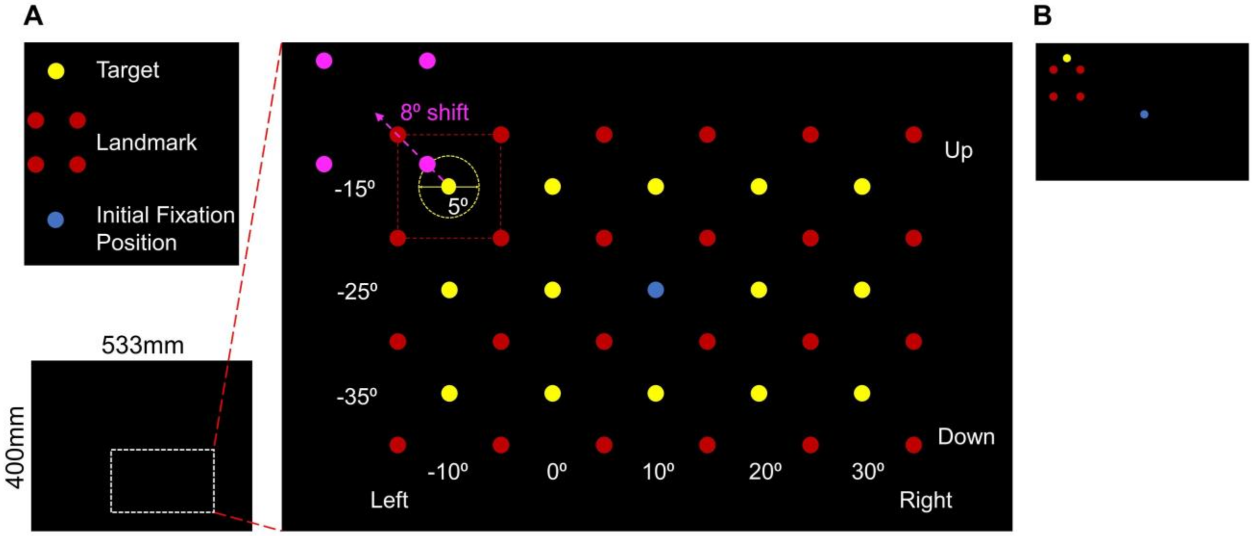

Figure 6. (A) Possible locations of the target and landmark. This figure shows the fifteen locations where the target and landmark will appear during each trial. The corresponding target will be located within a 5° diameter circle at the center of the landmark (B) An example of a “catch trial” where the target is located outside of the landmark.

The experiment consisted of 3 conditions: one with no landmark (1), one with a stable landmark (2), and a cue-conflict condition with a landmark shift (3) (Figure 7). A trial began when the monkey fixated its hand on the LED bar for 700 ms. The fixation dot appeared for 300 ms to allow the animal to fixate its gaze at a controlled location for each trial. In conditions two and three, the landmark and a fixation dot appeared for 500 ms. The target flashed for 100 ms, followed by a 300 ms delay displaying only the central fixation dot and landmark. A bright LED mask that faded to black near the edges the covered the entire screen for 200ms. The mask concealed the apparent motion of the landmark and prevented the monkey from shifting its attention to the landmark. It also prevented the influence of any aftereffects caused by the illumination of the target and landmark and ensured the monkey responded based on their memory rather than the afterimage of the target (Chen et al., 2014). The landmark and fixation dot appeared again for 600 ms, but in the cue-conflict condition, the landmark shifted by 8° in one of eight directions (up, down, left, right, and diagonally). Finally, the monkey had 2000 ms to respond by reaching and touching the screen where they thought the target was relative to the landmark, similar to Byrne and Crawford (2010). They received a reward when they touched within a 5.2 cm radius circle touch window. This window was large enough to include both the original target location and the newly shifted target location. The same was shown in the no landmark condition except in the absence of a landmark. The initial gaze fixation in the no landmark condition was also 500 ms longer. During this 500 ms, the landmark was displayed in the stable and landmark shift conditions.

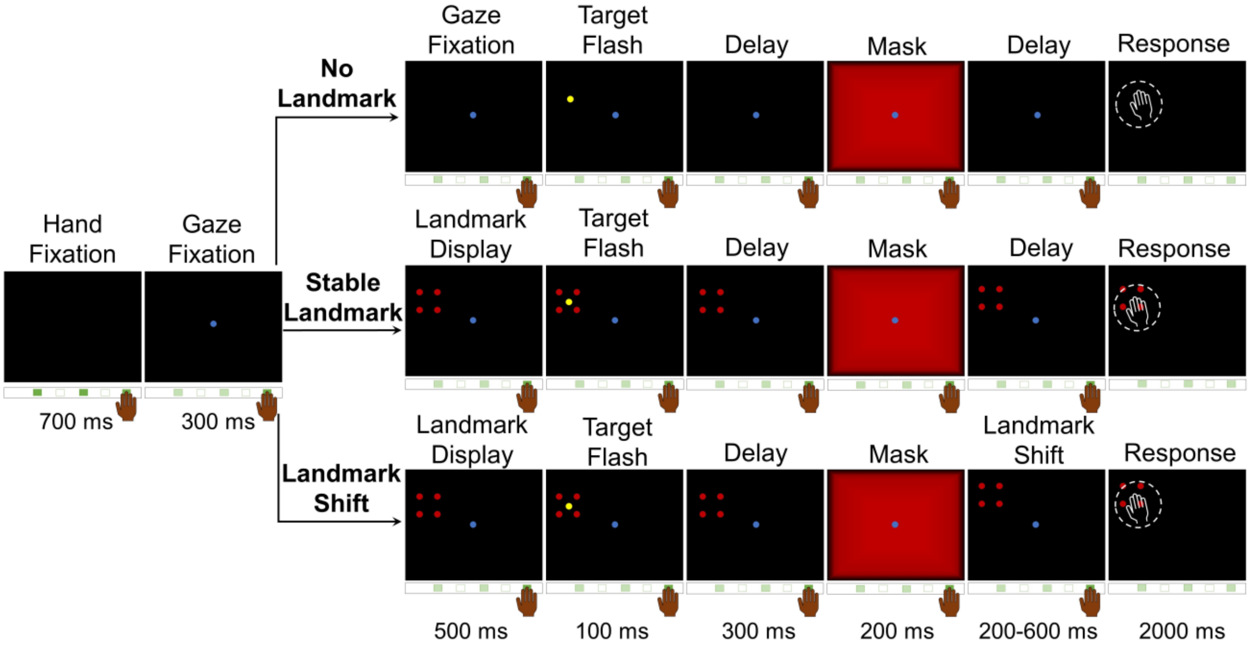

Figure 7. Experimental paradigm and timing. The figure shows the time course and visual information shown to the monkey during the no landmark condition, stable landmark condition, and landmark shift condition. The blue dot is the gaze fixation dot, the yellow is the target, and the four red dots represent the landmark.

2.2d Data Analysis

The voltages from the head and eye coil were sampled at 1000 Hz, digitized, and converted into 2D angles of the eye and head in space. Experimental data were analyzed using MATLAB and the beginning and end of each saccade were marked manually.

To isolate the influence of the landmark shift from systematic reach errors, we subtracted the mean reach error (stable landmark condition) from the reach data in the landmark shift condition. This correction was performed for each of the 15 targets. We conducted several One-Way ANOVAs and unpaired and paired t-tests to test if the task condition, initial hand position, target location, and landmark shift direction statistically affected reach accuracy, reaction time, reach variance, or allocentric weight. All statistical tests were conducted using a combination of MATLAB, Prism 5, and Microsoft Excel.

2.3 Results

2.3a Timing

Gaze onset time was measured as the time from when the fixation dot turned off to the time when the gaze velocity exceeded 50 degrees/s. Figure 8 shows the horizontal gaze trajectory from -250ms before the go signal for the target (10, -15) in the no landmark condition. Gaze reaction time was 100.62 ± 1.95 ms (Mean ± SEM) for the landmark shift condition and 103.17 ± 2.70 ms for the stable landmark condition. These reaction times were significantly shorter than the no landmark condition (148.21 ± 2.52ms; One-way ANOVA, $F(2,4371) = 133.35$, $P < 0.0001$), but not significantly different from each other (two-tailed unpaired t-test, $t(2914) = 0.78$, $P = 0.4381$). In most trials, gaze shifts were complete by the time the hand started to move. The gaze landing times were 137.61

±1.88 ms (landmark shift), 138.94 ± 2.58 ms (stable landmark), and 210.04 ± 2.10 ms (no landmark). The landmark shift and stable landmark conditions were significantly different from the no landmark condition (One-way ANOVA, F(2,5823) = 268.16, $P < 0.0001$), but not significantly different from each other (two-tailed unpaired t-test, t(4183) = 0.42, P = 0.6718).

When looking at the hand onset time, the time from when the gaze fixation dot turns off to when the animal's hand leaves the LED bar (i.e., reaction time), the reaction time for the stable landmark was 158.85 ± 2.10 ms. This was significantly shorter than the no landmark condition (198.51 ± 2.22 ms) and the landmark shift condition (196.84 ± 1.44 ms) (One-way ANOVA, F(2,5823) = 129.38, $P < 0.0001$). The no landmark and landmark shift conditions were not significantly different from each other (two-tailed unpaired t-test, t(4267) = 0.68, P = 0.5109). The mean duration of hand movement was 252.29 ± 7.24 ms (no landmark), 252.64 ± 5.57 ms (stable landmark), and 309.23 ± 5.90 ms (landmark shift). The no landmark and stable landmark conditions were significantly shorter than the landmark shift condition (One-way ANOVA, F(2,5823) = 29.62, $P < 0.0001$) but not significantly different from each other (two-tailed unpaired t-test, t(3196) = 0.04, P = 0.9691).

Completion time was measured from when the gaze fixation dot turned off to when the animal touched the screen. The mean completion time for the stable landmark condition was the lowest at 411.50 ± 5.96 ms by a significant amount (One-way ANOVA, F(2,5823) = 54.47, $P <0.0001$). The no landmark condition had a mean completion time of 450.80 ± 7.64 ms which was significantly shorter than the landmark shift condition with a mean completion time of 506.10 ± 6.03 ms (two-tailed unpaired t-test, t(4267) = 5.68, P < 0.0001).

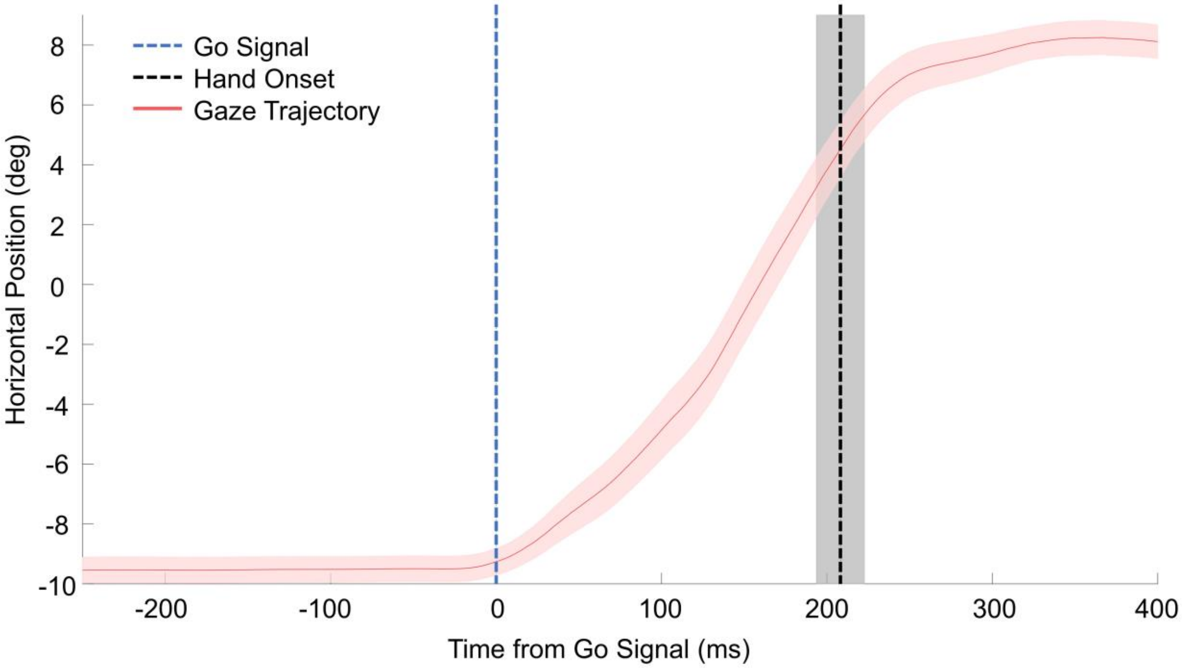

Figure 8. Gaze movement trajectory as a function of time. Averaged eye movement trajectory (± 95% confidence intervals) are plotted in the horizontal dimensions for one target (10, -15) in the no landmark condition (n = 71). Time 0 ms is when the home fixation turns off, signaling the animal to go.

Using a MATLAB code, the head, gaze, and hand positions of the animal were plotted for each of the conditions. Figure 9 shows example gaze trajectories (blue), vectors from initial to final hand position (orange), head position at gaze landing (red), and target positions (black), for each of our three experimental conditions. The data is provided in visual angles projected onto the coordinates of the touch screen. The animal can be seen making centrifugal gaze shifts toward the targets in each of the three conditions, although there was a general tendency to overshoot in the upward direction.

Hand trajectories started from three initial positions and generally converged toward the target array (only rewarded movements are shown).

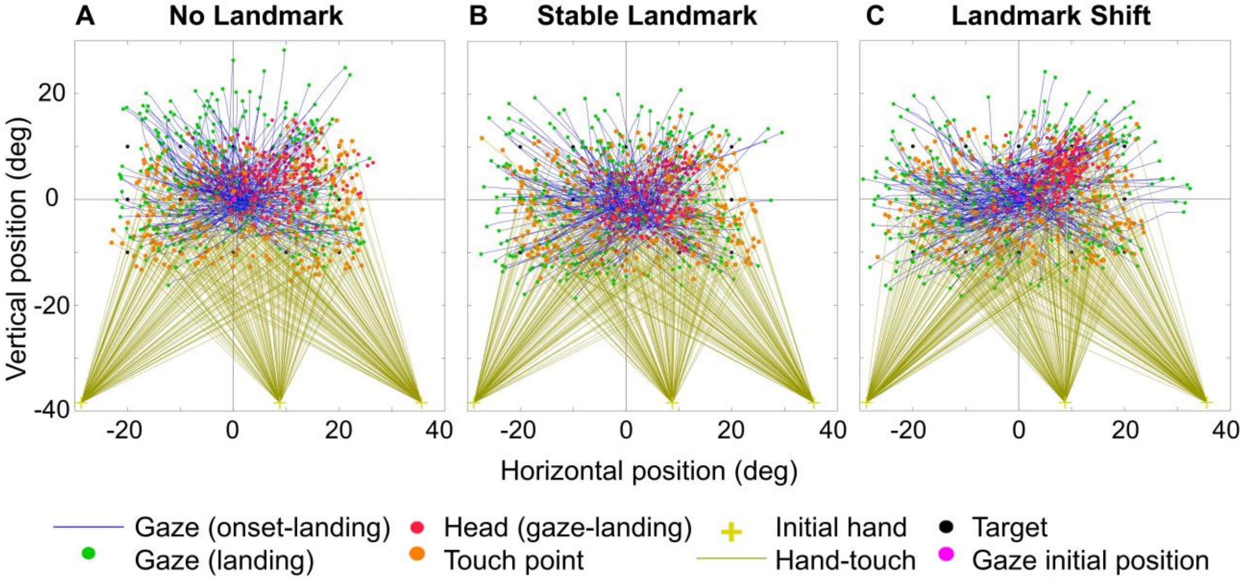

Figure 9. Gaze, head and touch endpoints, and 2-D gaze trajectories. Trajectories are plotted from the time of initial gaze motion to the end of the saccade. Complete gaze trajectories are provided, whereas the hand trajectories are only shown as vectors joining the initial and final hand positions.

Overall, the mean horizontal reach error (between the endpoint and target) was the lowest for the stable landmark condition (3.06° ± 0.05). The no landmark condition error was 3.38°± 0.06 (Mean ± SEM), and 3.66° ± 0.05 for the landmark shift condition. There was a significant increase in reach error found between each of the conditions (One-way ANOVA, F(2,5823) = 33.33, P < 0.0001). The mean vertical reach error for the no landmark condition was 3.17° ± 0.05, 3.28° ± 0.05 for the stable landmark condition, and 3.99° ± 0.06 for the landmark shift condition. The vertical mean error was significantly higher in the landmark shift condition (One-way ANOVA, F(2,5822) = 135.75, P <0.0001) but not significantly different between the no landmark and stable landmark conditions (two-tailed unpaired t-test, t(3196) = 1.57, P = 0.1155). The raw error includes both endogenous error and errors caused by the landmark shift in the landmark shift condition and so this may have caused the higher reach error in the landmark shift condition. The increase in error for the landmark shift condition may be due to the landmark shifting the reach response in each of the directions of the landmark shift. Also, the difference in reach accuracy between the no landmark condition and the stable landmark condition may be due to the presence of the allocentric cue, making the animal's reach response more accurate.

The horizontal and vertical locations of the target were also taken into account when looking at the reach error. For all three conditions, the error was the highest for the left-most targets and lowest for the right-most targets and this difference in error was significantly different (No landmark: One-way ANOVA, F(4,4725) = 122.26, P < 0.0001, Stable landmark: One-way ANOVA, F(4,14032) = 29.66, P < 0.0001, Landmark shift: One-way ANOVA, F(4,7302) = 86.03, P < 0.0001). The reach errors increased gradually as the targets moved toward the left side of the touch screen. There was a significant difference between each of the horizontal target positions in the stable landmark conditions. In both the no landmark and landmark shift conditions, 2/5 horizontal target positions were significantly different from each other. There was no significant difference in reach error when the targets differed in their vertical positions (No landmark: One-way ANOVA, F(2,4727) = 0.60, P = 0.5495; Stable landmark: One-way ANOVA, F(2,13484) = 0.37, P = 0.6941; Landmark shift: One-way ANOVA, F(2, 7304) = 0.81, P = 0.4452).

2.3b Gaze and Reach Accuracy Versus Precision

To separately quantify the accuracy and precision of these movements, we fitted 95% confidence ellipses to the endpoint distributions around each target. For this analysis, we only used the targets that fell within the four-landmark array. Figure 10 shows the gaze (left column) and touch (2nd, 3rd columns) endpoints (15 per target), along with the 95% confidence ellipses fit to these data. The rows separate the three conditions by row (no landmark, stable landmark, landmark shift) with space coordinates used in the first two columns and hand touch also shown in landmark coordinates (i.e., relative to the center of the four initial landmark cues) in the right column. (Note these were not present in the no-landmark condition, so we used the same spatial location for comparison). The individual endpoints for the initial gaze position are shown as green dots for gaze/hand end positions as blue dots. One can see that most of the data points are contained within the ellipses, and the touch data mostly falls within the landmark array (right column).

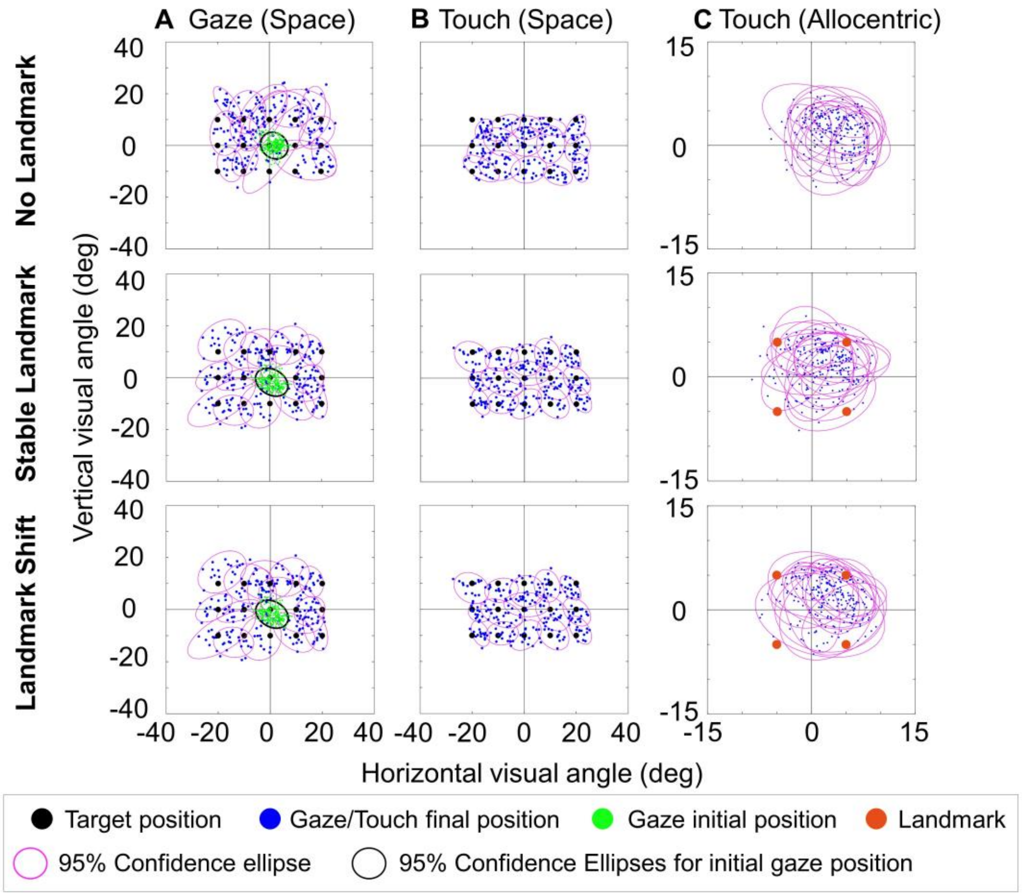

Figure 10. 95% confidence ellipses for data collected in one session. (A) gaze endpoints at the end of saccades in each condition (B) touch endpoints at the point of screen contact. (C) touch endpoints at the point of screen contact in allocentric coordinates.

Figure 11 shows the 95% confidence ellipses fit to all of the gaze and touch endpoints collected in this experiment, plotted using the same conventions as Figure 10 but without the original data points. The centers of these ellipses provided a measure of accuracy whereas the areas provided a measure of precision (with larger areas signifying more variable error). The mean distances of the gaze ellipse centers from the corresponding targets were 3.02 ± 0.27 degrees (Mean ± SEM) (stable landmark), 4.29 ± 0.49 degrees (no landmark), and 4.43 ± 0.29 degrees (landmark shift). The distance is significantly shorter in the stable landmark condition (One-way ANOVA, F(2,42) = 4.68, P = 0.0146). There was no significant difference between the no landmark and landmark shift conditions (two-tailed paired t-test, t(14) = 0.40, P = 0.6967). The mean gaze ellipse area across all 15 targets for gaze was 276.67 ± 25.23$^{\circ 2}$ in the stable landmark condition, 423.97 ± 33.81 $^{\circ 2}$ in the shifted landmark condition, and 429.97 ± 52.82$^{\circ 2}$ in the no landmark condition. There was a significant decrease of the ellipse area in the stable landmark condition (One-way ANOVA, F(2,42) = 4.95, P = 0.0117) but no difference between the no landmark and landmark shift conditions (two-tailed paired t-test, t(14) = 0.15, P = 0.8827).

The mean distances of the touch ellipse centers from the corresponding targets were 2.65 ± 0.23 degrees (stable landmark) 2.90 ± 0.25 degrees (landmark shift), and 3.29 ± 0.32 degrees (no landmark). There was only a slight difference between the stable landmark and the no landmark condition (two-tailed paired t-test, t(14) = 2.47, P = 0.0268), but they were not different from the landmark shift condition (No landmark: two-tailed paired t-test, t(14) = 1.20, P = 0.2496, Stable landmark: two-tailed paired t-test, t(14) = 1.28, P = 0.2225). The mean ellipse area across all 15 targets for touch was 122.97 ± 5.45$^{\circ 2}$ (stable landmark), 129.58 ± 8.57$^{\circ 2}$ (no landmark), and 151.50 ± 7.65$^{\circ 2}$ (landmark shift). There was a significant difference between the ellipse areas between the stable landmark and landmark shift conditions (two-tailed unpaired t-test, t(14) = 6.24, P < 0.0001) and the no landmark and landmark shift conditions (two-tailed paired t-test, t(14) = 4.91, P = 0.0002).

Finally, the mean distances of the touch ellipse centers from the target were significantly shorter than the gaze in the landmark shift condition (two-tailed paired t-test, t(14) = 4.90 P = 0.0002). However, no difference was seen in the stable landmark (two-tailed paired t-test, t(14) = 0.95, P = 0.3599) and no landmark (two-tailed paired t-test, t(14) = 1.46, P = 0.1659) conditions. The areas of the gaze ellipses were significantly larger than the touch ellipses in all three conditions (No landmark: two-tailed paired t-test, t(14) = 6.41, P < 0.0001, Stable landmark: two-tailed paired t-test, t(14) = 6.70, P < 0.0001, Landmark shift: two-tailed paired t-test, t(14) = 8.59, P = 0.0001).

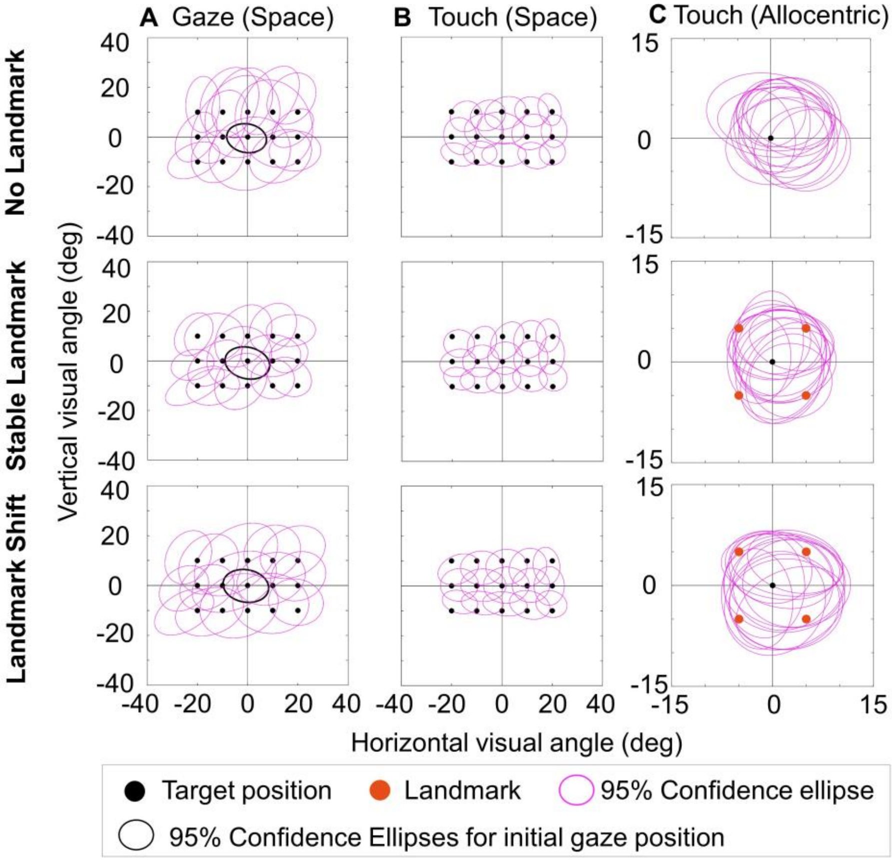

Figure 11. 95% confidence ellipses for the complete data set. (A) gaze endpoints at the end of saccades in each condition (B) touch endpoints at the point of screen contact. (C) touch endpoints at the point of screen contact in allocentric coordinates.

Finally, we examined if the angles of the main axis of the ellipses were influenced by the initial position, i.e., as one would expect if they were elongated in the direction away from the initial position. This was done using data collected from the no landmark condition as this eliminates any effect of the allocentric cue. We found no significant influence of initial hand position on the touch ellipse angle as they were not significantly different from each other (One-way ANOVA, F(2,42) = 1.62, P = 0.2095) (Supplementary Figure 1). We found no significant correlation between the expected angle of the ellipse to the data we collected for each of the hand positions. We then tested the correlation between the expected angle of the ellipse for both gaze and reach to our results for each condition. The only significant correlation we found was between the expected angle of the main axis of gaze ellipses and our data in the stable landmark condition (Pearson r = 0.6288, P = 0.0120). In addition, we found no significant correlation between the angle of the gaze ellipse and the touch ellipse. There was no significant difference between the angles of the gaze ellipses (One-way ANOVA, F(2,42) = 0.47, P = 0.6261) in each condition and between the angles of the touch ellipses (One-way ANOVA, F(2,42) = 0.46, P = 0.6377) in each condition.

Lastly, we tested if the shift directions affected the accuracy and precision of touch responses by analyzing the distance from the center of the ellipse to the target and the area of the ellipse (Supplementary Figure 2). A landmark shift toward the upper left direction had the highest accuracy and was significantly more accurate than three other shift directions (Upper right: two-tailed paired t-test, t(14) = 4.08, P = 0.0011, Right: two-tailed paired t-test, t(14) = 3.58, P = 0.0030, Lower right: two-tailed paired t-test, t(28) = 3.32, P = 0.0025). A landmark shift toward the bottom left direction had significantly higher accuracy than a shift toward the upper right (two-tailed paired t-test, t(14) = 2.90, P = 0.0117), and the right (two-tailed paired t-test, t(14) = 3.17, P = 0.0069). We found no significant difference between the area of the ellipses for any of the shift directions meaning there was no difference in variance of the touch responses (One-way ANOVA, F(8,126) = 5.08, P = 0.6261).

2.3c Influence of Target vs. Landmark Position

Figure 12 shows the correlation of gaze in space (left column), hand touch in space (middle column), and hand in landmark coordinates (right column) against horizontal target position in our three conditions. Gaze correlations in space were the highest in the stable landmark condition (Pearson r = 0.9299, P < 0.0001). The gaze correlation in the shifted landmark condition was slightly higher (Pearson r 0.9220, P <0.0001) than in the no landmark condition (Pearson r = 0.9192, P < 0.0001). Hand correlations were higher in all three conditions. The no landmark condition had the highest correlation (Pearson r = 0.9673, P <0.0001), the stable landmark had a slightly lower correlation (Pearson r = 0.9663, P < 0.0001), and the lowest was in the landmark shift condition (Pearson r = 0.9547, P < 0.0001). Similar trends were found for vertical positions.

To ensure that hand position was modulated by target position and not simply aiming for the center of the landmarks, we checked if there was a correlation between hand position and target positions in landmark coordinates (Figure 12C). The horizontal touch to target correlation was the highest in the no landmark condition (Pearson r =0.3576, P < 0.0001), intermediate in the landmark shift condition (Pearson r = 0.1120, P < 0.0001) and lowest in the stable landmark condition (Pearson r =0.0938, P = 0.0002), and Similar trends were found for the vertical correlations. It was the highest in the no landmark condition (Pearson r = 0.2505, P < 0.0001), lowest in the stable landmark condition (Pearson r = 0.0906, P = 0.0003), and intermediate in the landmark shift condition (Pearson r = 0.1463, P < 0.0001). One reason these correlations might be low was simply because of the very small range, relative to noise, in this coordinate system. When we included outlier targets located outside of the landmark array in the stable landmark condition, the correlation between touch and target increased to 0.8154 (Pearson r, P < 0.0001) and 0.8341 (Pearson r, P = 0.0014) in the horizontal and vertical dimensions respectfully. These correlations were both significant showing that hand position was indeed modulated by target position, and not just landmark position.

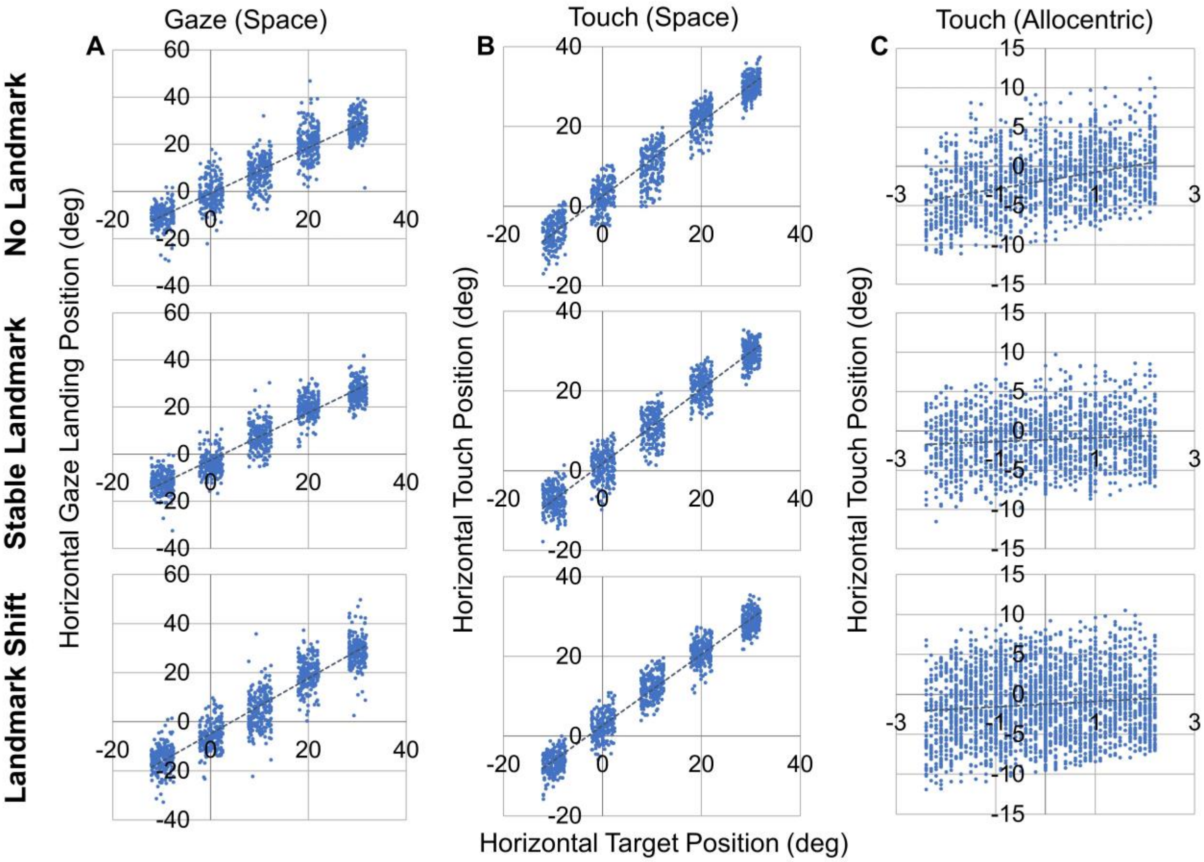

Figure 12. Correlation of hand and gaze position to target position. Shown in the horizontal dimension. (A) Correlation of gaze landing to target position in space. (B) Correlation of hand touch to target position in space. (C) Correlation of hand touch to target position in landmark coordinates.

2.3d Gaze-Hand Coordination

As noted in the introduction, our animals showed a very tight coupling between gaze, and hand position in a similar task without a memory delay or landmarks (Arora et al.). The previous analysis suggests that this coupling was not as strong, primarily due to reduced accuracy in gaze position, in the current task. To examine this directly we correlated horizontal/vertical gaze position as a function of hand position (Figure 13).

The gaze-to-hand touch correlation was the highest in the no landmark condition (Pearson $r = 0.9253$, $P < 0.0001$), intermediate in the landmark shift condition (Pearson $r = 0.9142$, $P < 0.0001$), and lowest in the stable landmark condition (Pearson $r = 0.9046$, $P < 0.0001$) for the horizontal dimension. For the vertical dimension, the no landmark had the highest correlation again (Pearson $r = 0.8250$, $P < 0.0001$), intermediate in the stable landmark condition (Pearson $r = 0.8061$, $P < 0.0001$) and lowest in the landmark shift condition (Pearson $r = 0.7696$, $P < 0.0001$). In landmark coordinates, there was a lower correlation between gaze and touch in the no landmark condition (Horizontal: Pearson $r = 0.3876$, $P < 0.0001$; Vertical: Pearson $r = 0.2881$, $P < 0.0001$). The stable landmark condition had a low correlation in the vertical dimension (Pearson $r = 0.1796$, $P < 0.0001$). The landmark shift condition had a low and negative correlation in the horizontal dimension (Pearson $r = -0.005854$, $P = 0.0027$). However, there was no significant correlation between the gaze and touch response in the horizontal for the stable landmark condition (Horizontal: Pearson $r = 0.0046$, $P = 0.8548$) and vertical dimension for the landmark shift conditions Vertical: Pearson $r = 0.0070$, $P = 0.7211$)**.**

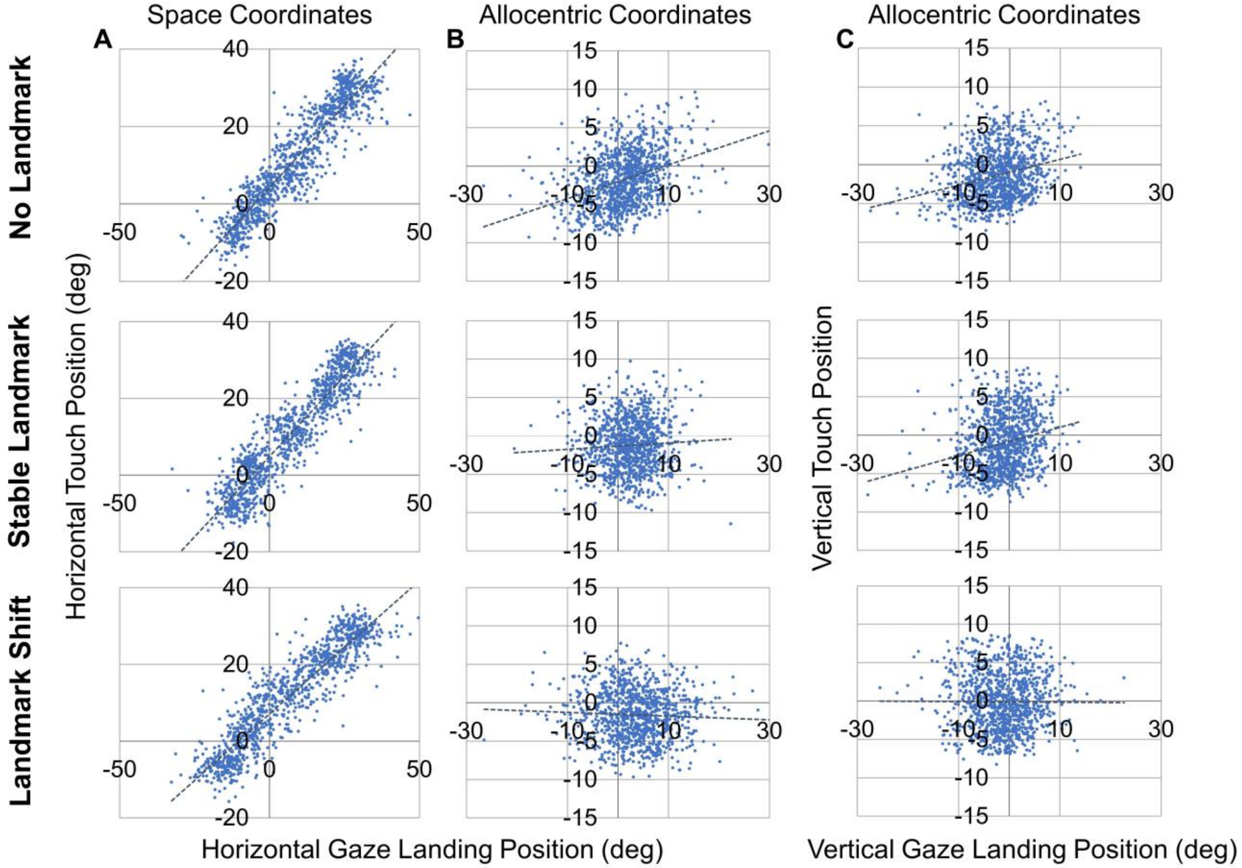

Figure 13 Correlation of hand touch position to gaze landing position. (A) Correlation of horizontal hand touch to gaze position in space. (B) Correlation of vertical hand touch to gaze position in space. (C) Correlation of horizontal hand touch to gaze position in landmark coordinates.

2.3e Allocentric Weight

We have already observed that the landmark shift condition reduced gaze and reach accuracy relative to the original target/landmark positions. Here we examined if this influence is spatially specific to the direction of the shift, i.e. did gaze / reach endpoints shift in the same direction? To test this, we calculated the allocentric weight (AW) parameter used in previous studies (Byrne & Crawford, 2010; Li et al., 2017). First, the mean touch error for each target in the stable landmark condition was subtracted from each touch response for the same target in the landmark shift condition to account for systematic biases in the monkey's reach behaviour. Then we rotated the remaining errors into a coordinate system where the shift direction was to the right (Figure 14a). Figure 14b shows the distribution of errors for gaze endpoints in this coordinate system. The gaze AW (mean = 0.38, median = 0.39) was found to be significantly shifted toward T' (Wilcoxon Signed Rank Test, P <0.0001). Figure 14c shows the distribution of the touch AW (mean = 0.29, median = 0.34) and it significantly shifted toward T' (Wilcoxon Signed Rank Test, P < 0.0001), indicating the influence of the shifted landmark on reaching endpoints.

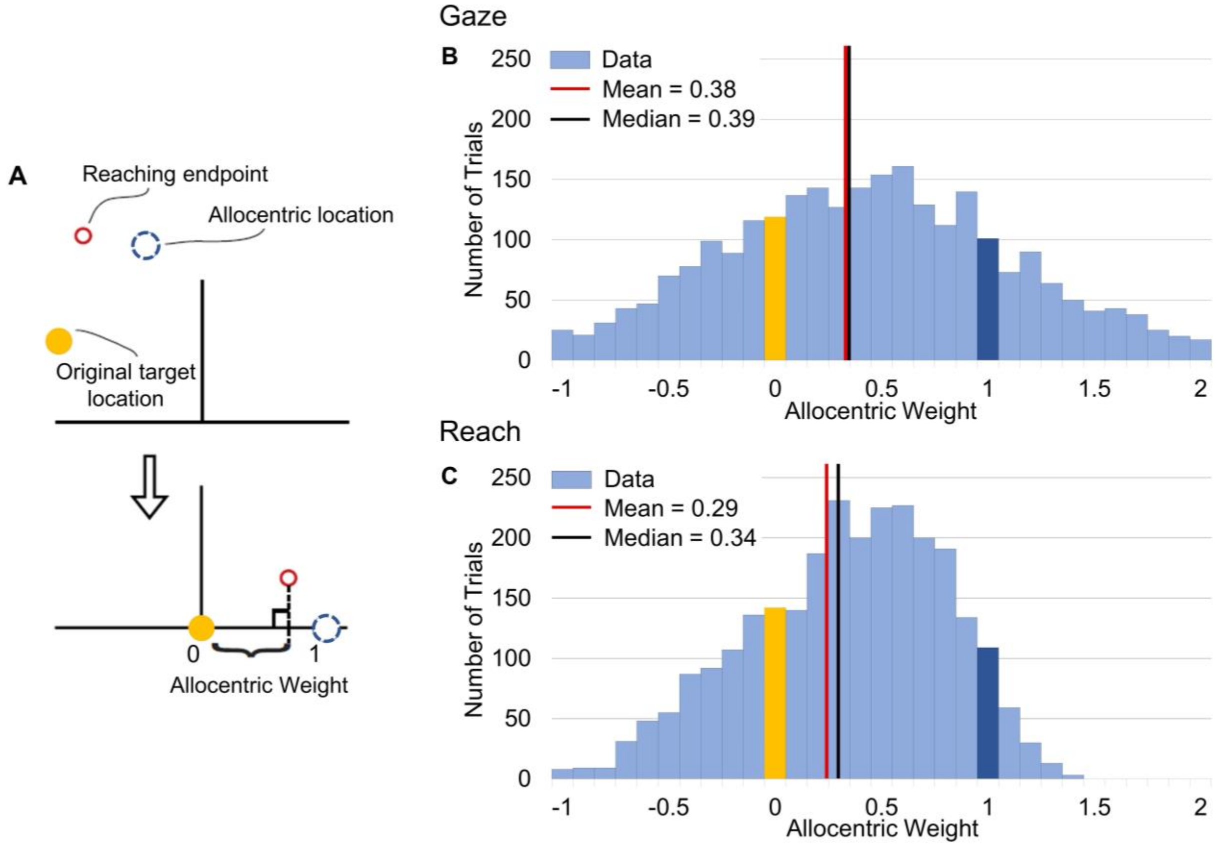

Figure 14. Distribution of allocentric weights. (A) Coordinate system where the shift direction was to the right. (B) Histogram showing the distribution of allocentric weights for touch plotted against the number of trials (Y axis) collapsed across all sessions. (C) Histogram showing the distribution of allocentric weights for gaze plotted against the number of trials (Y axis) collapsed across all sessions.

We then examined if the value of the reach AW depended on other parameters such as the direction of the shift or distance from the gaze position (Li et al. 2017). The AW when the landmark shifted away from the initial gaze position is 0.27 and increased slightly when the landmark shifted toward the initial gaze position (AW= 0.28) (Figure 15). The AW was the highest when the landmark shift is neutral (shift is perpendicular to the away and toward landmark shift direction) at 0.316. However, the difference in AW due to landmark shift direction was not significant (One Way ANOVA, F(2,1457) = 1.25, P = 0.2875).

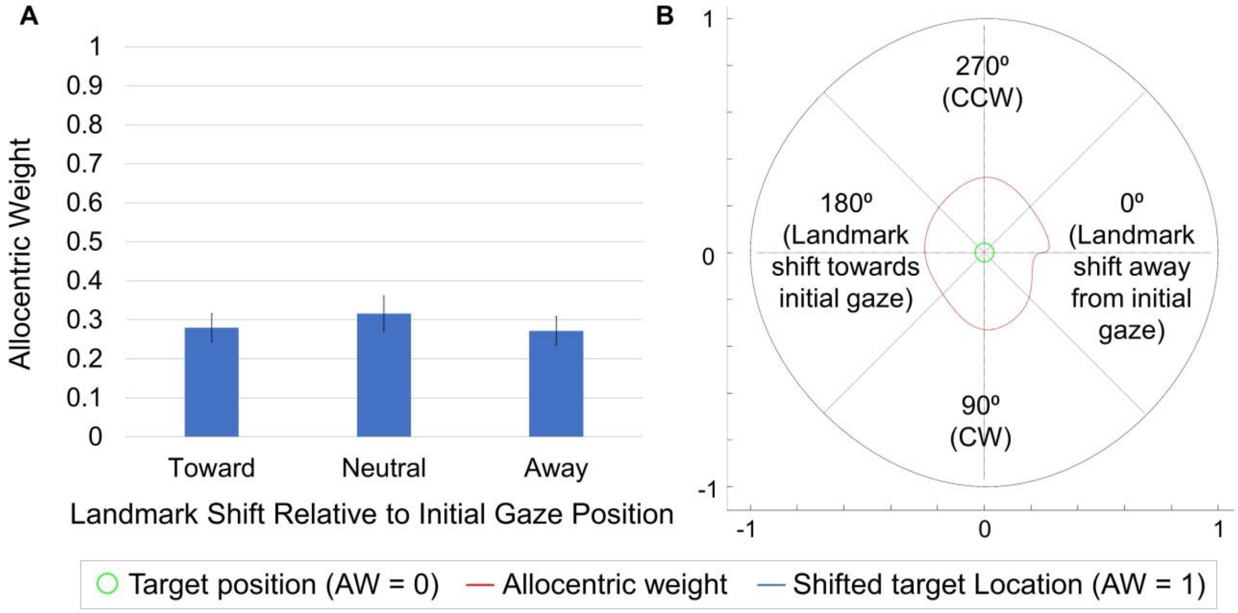

Figure 15. Influence of landmark shift direction relative to initial gaze position on AW. (A) Comparison of the mean AW (y-axis) between landmarks that shift towards, away, or perpendicular (neutral) from the initial gaze position (X-axis). (B) Overall allocentric weight sorted by landmark shift direction.

We analyzed if the distance between the landmark position and the initial gaze position affected the AW. The landmarks included were the ones in the same row or the same column as the initial gaze position. They are then divided into 2 groups: horizontal and vertical. There was a significant increase for both the horizontal (One Way ANOVA, F(2,908) = 4.97, P = 0.0071) and vertical groups (two-tailed unpaired t-test, t(531) = 3.16, P = 0.0017) when the landmark was located closer to the initial gaze position (Figure 16). However, there was no significant difference between the 0 degree and 20-degree groups (two-tailed unpaired t-test, t(732) = 0.83, P = 0.4052).

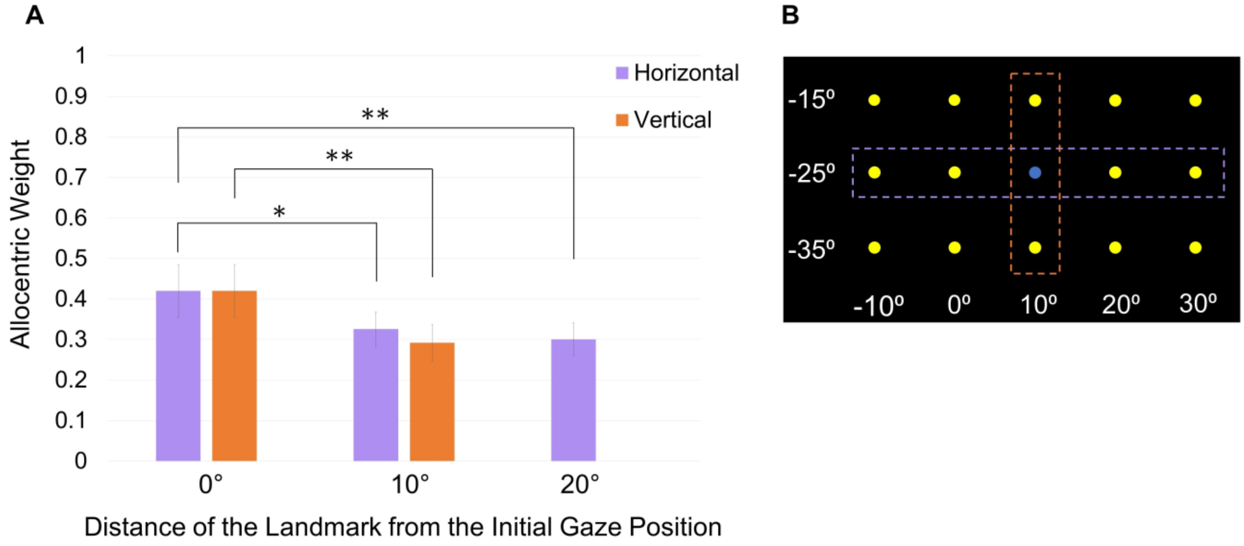

Figure 16. Influence of initial landmark position relative to initial gaze position on AW. (A) Comparison of the mean AW (Y axis) between landmarks divided into their horizontal and vertical positions located closer or further from the initial gaze position (X-axis). (B) Positions of the horizontal and vertical landmarks used in this analysis.

2.4 Discussion

The main purpose of this study was to analyze the effect of an allocentric cue, and a surreptitious shift on this cue, on reaching behaviour in monkeys. Gaze onset, hand onset, and completion times were all the shortest in the stable landmark condition. The mean horizontal reach error was significantly lower in the stable landmark condition compared to the no landmark condition. The horizontal reach error was also affected by the location of the target. The reach errors increased gradually as the targets moved toward the left side of the touch screen. Gaze accuracy was the highest in the stable landmark condition and both the gaze and touch variance were significantly lower in this condition. We also found a difference in correlations between gaze-target, hand touch-target, and gaze-hand touch. The gaze-to-target correlation was significantly higher in the stable landmark condition, while the hand touch-to-target and gaze-to-hand touch correlation was the highest in the no landmark condition. There was no correlation between gaze-to-hand touch in allocentric coordinates.

As predicted, in the cue-conflict landmark shift condition we found that reaches deviated in the direction of the allocentric cue shift. The influence of this allocentric cue also known as allocentric weight was found to be 29%. There was a significant increase in AW when the landmark was located closer to the initial gaze position in both the vertical and horizontal dimensions. The shift direction of the landmark did not significantly change the AW. While the gaze response was not restricted or rewarded, the gaze was still affected by the landmark shift. The gaze AW was larger than the reach AW at 38%. These observations show that an allocentric cue shift affected monkey reach like human reach and monkey gaze responses, and a stable landmark is a reliable cue for reach. I will discuss each of these points in detail, beginning with the basic behavior observed in our control (no-landmark) task.

2.4a Reaching in the Absence of Visual Landmarks

In our control (no landmark) task the animal was provided with no visual cues except for the visual fixation point (which turned off just before the reach) and the target (which turned off well before the gaze and reach movements). This condition allowed us to set a baseline for studying landmark influence and to describe some basic aspects of eye-hand coordination, as follows.

To interact with objects in the environment, we need to make a coordinated combination of eye and reaching movements. When pointing with the arm or reaching towards a target, a saccadic eye movement is made to this position shortly before which is also what we found in our study (Arora et al., 2019; Brouwer & Knill, 2007; Neggers & Bekkering, 2000; Song & McPeek, 2009). We found that the gaze onset times were on average 50.30 ms before the hand onset time. This was slightly shorter but similar to other studies that found the movement of the hand to start 60-100 ms (Angel et al., 1970; Prablanc et al., 1979) and 50-100 ms (Snyder et al., 2002) after the eye movement initiation. This 100 ms is a classical delay between the contraction of the agonist arm muscles and resulting limb movement (Biguer et al., 1982). However, another study found the onset of the hand movement to be 19-32 ms after (Rand & Stelmach, 2010). Our gaze onset and hand onset times were significantly longer in the no landmark condition than in the stable landmark condition. Compared to previous studies, the gaze onset time was only slightly later than Arora et al., (2019) and slightly earlier than Brouwer and Spering (2022). Saccades accompanied by reaching or arm movements were found to be faster faster (Arora et al., 2019; Snyder et al., 2002). Our hand onset time was similar to what Brouwer and Spering (2022) found and about 150 ms shorter than what Biguer et al., (1982) found in humans, and about 170 ms shorter than what Rogal et al., (1985) found in monkeys. This difference may be due to differences in the task, such as memory-guided vs visually-guided. Memory-guided saccades and saccades made in the dark are generally slower and more variable than visually guided saccades (Becker & Fuchs, 1969; Flanagan et al., 2008; Sharpe et al., 1975; Snyder et al., 2002). Similar to other studies, gaze shifts were always complete by the time the hand started to move but were the slowest in the no landmark condition (Arora et al., 2019; Brouwer & Knill, 2007). The mean duration of the hand movement was the shortest in this condition but was not significantly shorter than the stable landmark condition and was very similar to what was found by Arora et al., (2019).

Reaches were more accurate and precise than gaze as shown by the mean distance of the 95% confidence ellipse centers from the corresponding targets and the area of the ellipses. The difference in accuracy between reach and gaze however was not significantly different. Both the reach and gaze responses were less accurate and precise than in the stable landmark condition, but the touch precision was not significantly worse. When performing the same task with and without a delay, the error was significantly larger when there was a delay (Obhi & Goodale, 2005). Due to our task being a memory task, the reaching accuracy may have been affected as accuracy decreases when the target fixation is not stabilized (Vercher et al., 1994). In addition, pointing to a memorized peripheral target is less precise than to a target that is fixated on (Sheth & Shimojo, 2004). In our study, the monkey had to fixate at the home fixation when the target flashed, therefore most of the targets would appear in the periphery possibly affecting the precision.

The gaze has been found to be anchored to the reaching goal while people are reaching (Neggers & Bekkering, 2000). It is suggested that gaze is used to guide the reaching movement (Henriques et al., 1998; Henriques & Crawford, 2000; Neggers & Bekkering, 1999, 2000; Prablanc et al., 1979). Both our gaze and the reach responses were highly correlated to the target. The gaze-to-target correlation was the lowest in the no landmark condition, while the hand-to-target correlation was the highest. Compared to the gaze-target and hand-to-target correlations, the gaze-to-hand correlation was slightly lower. The lower gaze-to-hand correlation in this condition may have caused slight errors in reaching responses as goal-directed hand movements are more accurate when the visual target stimulus is gazed at (Henriques et al., 1998, 2003; Henriques & Crawford, 2000; Neggers & Bekkering, 1999, 2000; Prablanc et al., 1979). It was found that the gaze is less locked to the target and hand position after a memory delay compared to a visually guided reach task (Arora et al., 2019). When reaching to remembered target locations, gaze behaviour was found to be erratic with some trials having coordinated gaze and hand movement and a majority of trials having minute gaze movements that stayed near the initial fixation (Flanagan et al., 2008). In addition, in the light, gaze fixations were always directed to the grasp and the target (Johansson et al., 2001). However, in the dark, gaze fixations were broadly scattered and were rarely directed at the landmarks (Flanagan et al., 2008). Compared to a reaching task done in a lit environment, our gaze or reach-to-target correlations may be lower due to this reason.

2.4b Influence of a Stable Landmark

As remembered target location information is old and possibly not correct anymore in a changing world, the world is used as an external memory (Brouwer & Knill, 2007). Even when the world hasn’t changed, memory is expected to be more uncertain than the current visual information provided. Eye movements and remapping of information to a more stable reference frame can introduce noise and so visual information such as a landmark can be a reliable cue. Since our target was only presented for 100 ms, the spatial information about the landmark can be used quickly to help estimate and encode the target location (Obhi & Goodale, 2005).

In the stable landmark condition, there was a significant decrease in reaction time for both gaze and reach compared to the no landmark condition. This may be due to the presence of the landmark allowing the animal to make a quicker response as they know the target is somewhere in the center of the landmark. Ohbi and Goodale (2005) did not find a significant effect of the landmark on their reach reaction time, but this may be due to the participant not being able to view the target scene during the delay. Chen et al., (2011) found reduced reaction time in their short-delay allocentric task compared to their egocentric task. However, they concluded that this reduction was not due to the landmark as there was no difference in reaction time with longer delays. Lu and Fiehler (2020) found that their memory-guided delay condition had a faster reaction time and hand movement duration than both their memory-guided no-delay and online conditions. This may be due to the subject having more time to process information and plan their reach before the go signal. However, in Krigolson and Heath's (2004) study, they found the reaction time to be longer in the delay condition. They also found that the hand movement duration was longer in the presence of a landmark, while we found no significant difference between our no landmark and stable landmark conditions. The reaction times of tasks with landmarks did not increase significantly while the reaction time from the no landmark task suffered when increasing the delay time (Chen et al., 2011). Compared to the no landmark condition, the gaze onset to hand onset time difference was only slightly longer at 55.68 ms, and similar to but in the lower range of what previous studies have found (Angel et al., 1970; Prablanc et al., 1979; Snyder et al., 2002). The gaze shifts in this condition were also on average always complete by the time the hand started to move.

The presence of allocentric landmarks has been found to improve the accuracy and precision of reach and gaze (Krigolson et al., 2007; Krigolson & Heath, 2004; Li et al., 2017; Obhi & Goodale, 2005; Schütz et al., 2013b). Results from our study also show increased accuracy and precision in reach and gaze behaviour in the presence of a stable landmark. Only the difference in touch precision was not significantly different than the no landmark condition. The mean distance of the gaze 95% confidence ellipse centers from the targets and the area of the ellipses significantly decreased in the presence of a stable landmark. The mean distance of the touch 95% confidence ellipse centers from the target also significantly decreased. These results were consistent with what Li et al., (2017) found for gaze. The information provided by landmarks may be used to improve the accuracy of the estimation of the target location (Obhi & Goodale, 2005). In addition, the landmark may have increased the stability of the representation of the target during the delay period, when the memory of the target location is decaying. We also found a significant correlation between the expected angle of the main axis of gaze ellipses and our data in the stable landmark condition. When comparing target locations, there was an increase in reach accuracy for the targets located closer to the right end in the presence of a stable landmark. This effect may be due to the animal reaching with its right hand as reaching towards ipsilateral targets has been found to have greater endpoint accuracy (Carey et al., 1996).

The correlation between gaze and target was the highest in this condition and the hand-to-target correlation was only slightly lower than in the no landmark condition. The gaze-to-touch correlation was also only slightly lower than in the no landmark condition. When we calculated the correlation in landmark coordinates, there was no correlation between the gaze and touch in the horizontal dimensions.

2.4c Influence of the Landmark Shift

It has been determined that humans and non-human primates use a combination of egocentric and allocentric cues to accurately complete a motor command. Individuals can reach to remembered targets accurately by relying on either egocentric or allocentric cues (Byrne & Crawford, 2010). In this study, we have shown the egocentric versus allocentric weighting and the effects of an allocentric cue shift on a monkey’s reach response.

The gaze reaction time and gaze landing time in the landmark shift condition were significantly shorter than the no landmark condition but not different from the stable landmark condition. The hand reaction time was significantly longer than the stable landmark. In addition, compared to the no landmark and stable landmark conditions, the hand movement duration time and the completion time were significantly longer. The time from the gaze onset to the hand onset time was the longest at 95.89 ms, This is similar to but in the higher range of what previous studies have found (Angel et al., 1970; Prablanc et al., 1979; Snyder et al., 2002). Similar to the other two conditions, the gaze landing was also on average always complete by the time the hand started to move.

When looking at the distance of the ellipse centers from the corresponding targets to measure accuracy and the area of the ellipses to measure precision. We found no difference in the accuracy and precision of gaze endpoints, and accuracy of touch responses when compared to the no landmark condition. There was a decrease in the precision of touch responses in the presence of a landmark shift compared to the no landmark condition. The gaze and reach responses were both less accurate and precise than in the stable landmark condition. The touch accuracy however did not decrease by a significant amount. The decrease in accuracy and precision found could be due to the landmark shift causing the responses to deviate in the direction of the landmark shift and away from the original target location. We also included the responses from 8 different landmark shift directions which would have deviated reach and gaze responses in 8 different directions.

Human reach behaviour tends to be biased towards nearby landmarks in memory-guided tasks causing the reach to deviate in the direction of the landmark shift. In our study, we found the influence of the allocentric landmark, allocentric weight, to be about 29% for reach which is similar to previous human reach and monkey gaze studies (Byrne

& Crawford, 2010; Li et al., 2017). The allocentric weight in human studies was found to be higher and can be due to the memory delay period being longer (Balitsky Thompson & Henriques, 2010; Byrne & Crawford, 2010; Fiehler et al., 2014; Lu & Fiehler, 2020; Sheth & Shimojo, 2004). A longer delay period can lead to increased decay of egocentric information and favor the use of allocentric information (Li et al., 2017). Random body twitches, drifts in eye position, or body movements can occur during the delay and can increase the noise in the intrinsic egocentric system (Sheth & Shimojo, 2004). The influence of an allocentric landmark has also been found in large-scale and dynamic environments using virtual reality and naturalistic scenes (Karimpur et al., 2020; Lu & Fiehler, 2020). We found the influence of the landmark shift on reach responses to be larger when the landmark was located closer to the initial fixation position in both the horizontal and vertical dimensions. This effect was also found when monkeys performed a saccade task and may be due to allocentric landmarks having increased salience and relevance when they are closer to the attended fixation point (Li et al., 2017).

We predicted that gaze would also be affected by the landmark shift as the gaze and touch/reach responses were highly correlated. In addition, previous studies have shown that the gaze follows the target intended by the arm movement (S. F. W. Neggers & Bekkering, 2001, 2002; Rand & Stelmach, 2010). We indeed found that gaze responses were affected by the landmark shift even though we did not restrict or reward for correct gaze landing. We found the gaze allocentric weight to be 38%.

2.4d Possible Neural Mechanisms

At the neurophysiological level, both the FEF and SEF are involved in the integration of allocentric and egocentric visual cues for gaze (Bharmauria et al., 2020, 2021). In the presence of a landmark, FEF visual and motor responses were dominated by eye-centered egocentric codes. However, there was a partial shift towards landmark-centered coordinates in the visuomotor neurons and then later in the motor neurons (Bharmauria et al., 2020). The SEF was also dominated by the same egocentric codes in the presence of a visual landmark (Bharmauria et al., 2021). There was a shift in the motor neurons after the landmark shift and another one before a saccade. The landmark shift may be first assessed in the SEF preparatory activity and then relayed to the FEF. Allocentric and egocentric signals become integrated in the SEF visuomotor neurons and then are relayed to the FEF motor neurons for complete integration.

We suspect a similar transformation in the reach system where the visuomotor neurons and the motor neurons go from egocentric to allocentric reference frames in the reach areas of the brain, such as areas in the posterior parietal cortex and the frontal cortex. Also, we expect to see eye-centered reference frames and possible head and shoulder-centered reference frames. Reach related neurons do not encode information within a pure sensory or motor reference frame, but rather combine them into a mixed representation (Burnod et al., 1999). Movements are always represented in multiple reference frames and it is the statistical reliability of these reference frames that determines their relative weighting (McGuire & Sabes, 2009). Reach areas of the brain have been found to have eye, hand, limb, shoulder, body-centered coding, and a mix of these.

FMRI and neurophysiology studies have shown areas of the frontal cortex and parietal cortex represent target locations in a mix of coordinate frames. The parietal reach region (PRR) of the posterior parietal cortex (PPC) displayed neural activity that was consistent with an eye-centered coding of reach targets (Batista et al., 1999; Buneo et al., 2002). They suggested that due to eye movements being planned in eye coordinates, the use of the same coordinates for reaching may facilitate eye-hand coordination. The medial intraparietal area (MIP) encodes the target in eye-centered coordinates (Pesaran et al., 2006). Area 5 of PPC was found to encode the target location in both eye and hand-centered coordinates (Buneo et al., 2002).

The premotor cortex has been found to show a mixture of eye and body-centered encoding (Bernier & Grafton, 2010). The dorsal premotor cortex (PMd) activity during reach planning was influenced by the target location relative to the eyes and arm (Batista et al., 1999). The neurons in the PMd have reach-related activity and encode the relative position of the target, hand, and eye (Pesaran et al., 2006). This relative position code may help coordinate hand and eye movements. PMd activity during reach planning was influenced by the target location relative to the eyes and limbs (Batista et al., 1999). Neurons in the PMd have also been found to encode information using limb-centered and shoulder-centered coordinates (Batista et al., 2007; Caminiti et al., 1991). The premotor cortex and the PPC were found to display target location in body-centered coordinates for both humans and monkeys (Beurze et al., 2010; Cisek & Kalaska, 2002; Pesaran et al., 2006). The PPC and PMd displayed neuronal activity that was modulated by the hand relative to the gaze position and represented the target location in eye-centered coordinates (Beurze et al., 2010). These areas have access to both a gaze-centered target and a gaze-centered hand representation and are likely to be involved in the integration of these two types of information (Beurze et al., 2010). The primary motor cortex has been found to code hand trajectory within a coordinate system centered on the shoulder joint (Caminiti et al., 1990). Movement in M1 at the single-cell level was found to be centered on the hand. The M1 cells were then involved in transforming this extrinsic representation to an intrinsic shoulder-centered coordinate (Caminiti et al., 1990, 1991). The activity of M1 cells during a reaching movement can be best described by a body or limb-centered coordinate system (Caminiti et al., 1990, 1991; Scott et al., 1997)

Target locations coded in eye-centered reference frames are thought to be transformed into head, body, or mixed reference frames before the motor commands are computed (Andersen et al., 1993; Chen et al., 2011). Allocentric representations of the target location must eventually be transformed into egocentric commands for reach and the visual-motor systems seem to do so at the first possible opportunity (Chen et al., 2011). This would allow the system to be ready to react faster in real-world situations. Allocentric representations could enter the PPC, specifically the PRR, from the visual cortex, such as area V4 or area V6A, or area TEO (inferior temporal cortical area) and converge into the egocentric representation (Batista et al., 1999; Caminiti et al., 1999; Chen et al., 2011; Distler et al., 1993; Ungerleider et al., 2008). Object-based allocentric representation might also initially form in the ventral visual stream and then transferred to the parietofrontal loop via the posterior parietal regions for visuomotor control (Byrne & Crawford, 2010). Information may then be sent to the dorsocaudal premotor cortex, which has direct access to the primary motor cortex (Caminiti et al., 1999). The reference frame transformation for reaching is thought to take place within the frontal-parietal cortex reach network. Chen et al. (2018) identified the right posterior Precuneus (medial posterior parietal cortex), right pre-supplementary area (frontal cortex), and bilateral dorsal premotor cortex (frontal cortex) as likely candidate areas specific for allocentric to egocentric transformations for reaches in humans.

2.4e Conclusions

The cue-conflict memory-guided task we used in this study shows the use of both egocentric and allocentric reference frames when reaching in the monkey. We have shown the effects a stable landmark and a shifted landmark can have on the reach response.

Overall, this data suggests that monkeys show similar behavior to humans in this paradigm, and thus provide a good experimental model for investigation of the physiological mechanisms. This opens up the possibility of using neurophysiological techniques to investigate the mechanisms of egocentric and allocentric visual integration. Event-related fMRI paradigm studies have found that the brain transforms allocentric codes to egocentric commands for action at the first opportunity possible (Chen et al., 2011, 2018). Chen et al. (2018) identified the right posterior Precuneus (located in the medial posterior parietal cortex), right pre-supplementary area (located in the frontal cortex), and bilateral dorsal premotor cortex (located in the frontal cortex) as likely candidate areas specific for allocentric to egocentric transformations for reaches. The PMd and the PPC were found to have access to both a gaze-centered target and a gaze-centered hand representation and are likely to be involved in the integration of these two types of information (Beurze et al., 2010). These four areas may be potential targets for neurophysiological studies when investigating the mechanisms for egocentric and allocentric visual integration. In particular, we can use techniques developed by Bharmauria et al. (2020) to study the effect of the allocentric cue shift on neurons in the monkey reach system. Studying mechanisms for the use of egocentric and allocentric information and visual integration can aid in the diagnosis of conditions that cause topographical disorientation. In addition, single-cell recordings can contribute to the improvement of brain-machine interfaces (BMIs) and allow users to better manipulate their physical environment.

CHAPTER 3 GENERAL DISCUSSION

3.0 Discussion

In this chapter, I will discuss how our results have contributed to research about egocentric and allocentric frames of reference during reaching. I will then discuss the limitations, implications of this study, and future directions.

3.1 Summary and Scientific Implications

Our results have revealed that like human reach and monkey gaze, monkey reach responses also deviate in the direction of the allocentric cue shift. We found the influence of the allocentric landmark, allocentric weight, to be about 29% for reaches and 38% for gaze. The influence of the landmark shift on reach responses were larger when the landmark was located closer to the initial fixation position in both the horizontal and vertical dimensions. We did not find the landmark shift direction relative to the initial gaze position to have any effect on the allocentric weight. The stable allocentric cue in our study increased reach accuracy and decreased reach reaction times. The cue also increased gaze accuracy and precision, and decreased gaze reaction times even though gaze responses were not rewarded. The eye, hand, and target were all highly correlated in each condition. The stable landmark increased the correlation between the gaze and target but had a lower target-hand and gaze-hand correlation compared to the no landmark condition. We did not find the gaze and hand positions to be correlated in landmark coordinates meaning that gaze was not used to guide the hand.

These results did support our hypotheses, which were based on results from human reach and monkey gaze studies of egocentric versus allocentric frames of reference. The influence of the landmark shift direction on allocentric weight however was not present in our study. We also did not find the gaze to guide the hand in our study. These results contribute to what has already been found about egocentric and allocentric weighting. The cue-conflict memory-guided task we used in this study showed the use of both egocentric and allocentric reference frames when reaching in monkeys. It provides a good experimental model for the investigation of the physiological mechanisms. We can use neurophysiological techniques to investigate the mechanisms of egocentric and allocentric visual integration, such as when and where in the brain these two types of information are integrated. Defining the reference frame displayed by neurons while performing or preparing a reach allows us to understand how the brain encodes object location and processes spatial orientation strategies to interact with objects in peripersonal space (Piserchia et al., 2017).

3.2 Limitations

The limitations in our study are very similar to the ones mentioned by Li et al., (2017). To train monkey behaviour, we could not simply ask them to perform the task as we could do with human participants. We provided a reward after a correct behaviour and had to make sure we were not forcing the animal to fully rely on either allocentric or egocentric cues. We had to choose a reward window large enough to include both the original and shifted targets. This larger window prevented us from training the animal to do a purely egocentric and a purely allocentric task that was done by Bryne and

Crawford (2010). We may have also underestimated the amount of allocentric weighting by conducting a visually impoverished task that has a single simple landmark. Fiehler et al. (2014) found that allocentric weight increased with the number of task-relevant objects that were shifted. A monkey's natural habitat would contain more complex landmarks and could play a stronger role in nature thus increasing the allocentric weight.

Initially, we thought that our landmark would allow the animal to aim for the center of the landmark instead of the target and still get rewarded. To ensure that the animal knew to aim for the target, we included outlier targets located outside of the landmark array in the stable landmark condition. This showed that hand position was indeed modulated by target position and not just landmark position. In addition, while the gaze could accurately be tracked with the 2D eye coil system, the reach responses were recorded using the touch screen. The touch screen recorded the first point of contact of the monkey's hand. The monkey in our study used their entire hand to touch the target and so the recorded point of contact may not be their intended response. While we tried to eliminate anticipation by adding a variable delay in the task, the monkey was still able to anticipate to some degree. During some trials, they would start the saccade away from the initial gaze fixation dot and still get rewarded as they stayed within the gaze fixation window.

Lastly, it is difficult to conclude whether the results we found are true or if we were unable to see a significant result in some tests as we only have one monkey. A small sample size is prone to error including both false negatives (insufficient statistical power) and false positives (biased sample). Effects that we found may be significant or may be unique to the monkey in this study and so it may not be reliable and reproducible.

3.3 Practical Implications

One's ability to navigate through an environment is essential for survival and used in everyday life. In our daily life, allocentric cues are everywhere in everything we do. The use of maps, compasses, and other tools has been developed to help travel through a given environment. The sun is a well-known reliable allocentric cue/landmark that people use. The sun allows us to use compass directions (north, south, east, and west) which are an example of an allocentric frame of reference. These directions do not change and are advantageous when navigating a new environment. Another example is when you are reading words off the computer screen. As you are scrolling down the page, it is easy to lose track of which line you just read as all of the words have shifted up. The borders of the computer screen or the position of your cursor (if kept in the same position) can be reliable cues for where your eyes should go next.

Athletes also use allocentric cues in sports. A soccer player would have to know where the goalkeeper is relative to the goalpost and where the ball is relative to his foot to decide how to position the foot to make contact with the ball and which direction to kick to score the goal. Golf players may not be able to see the hole when they are so far away and so they would use allocentric cues such as a tree that they know is in the direction of or close to the hole. If you are just relying on egocentric information, it is easy to turn your body and forget which direction the hole is in. Knowing how far you are in relation to the tree you are using as a landmark is also useful in helping you decide how hard you want to putt the ball.

3.4 Clinical Implications

Different medical conditions can affect a person's ability to use egocentric and allocentric frames of reference. Patient CF was found to have topographical disorientation meaning she could not navigate the environment in daily life. However, her object-location memory was affected only when her viewpoint was shifted (N. Burgess et al., 2006). This meant that she could not locate objects relative to the environment (allocentric) but could do so when relative to the perceived viewpoint (egocentric). Early Alzheimer's disease is suspected, but the cause of this is unknown as progressive neurodegeneration takes time to become visible using structural imaging. Topographical disorientation can also be caused by stroke and normal aging (Demeyere & Gillebert, 2019; Lithfous et al., 2014). The specific brain areas that are involved in remembering allocentric information to guide reaching have been investigated by Chen et al. (2014). However, how these brain areas process allocentric information and how they contribute to the control of actions is unknown. Answering these question may help understand why patient CF's allocentric spatial memory is impaired. Also knowing the difference between normal age-related cognitive decline in spatial memory and abnormal decline may be used to help diagnose individuals, such as those with early stages of Alzheimer's disease (Lithfous et al., 2014).

Studying mechanisms for the use of egocentric and allocentric information and visual integration can aid in the improvement of BMIs. BMIs are controlled by the production of specific patterns of neural activity. Therefore, investigating the activity of neurons and the modulation and interaction between different reach areas during the use of both egocentric and allocentric in our reach task may allow users to have more accurate reaching movements with their device.

3.5 Future Directions

The next step is to successfully train a second monkey to perform the task and different conditions in this study. This would allow us to see if the results we found are also seen in the second monkey or if it is unique to the first monkey. New or different findings may lead us to ask different questions and conduct further research.

We have shown that both types of information (egocentric and allocentric) are used in our reaching task. We found the weighting to be 71% egocentric and 29% allocentric, however, these results do not tell us when and where this information is processed and integrated in the brain. Our cue-conflict task can be used to test if certain areas of the brain are involved in the integration process. We can use a model-fitting analysis approach developed by Bharmauria et al. (2020) to examine if, when, and how areas such as the PMd contribute to the integration of egocentric and allocentric cues for reaching movements. Studies have shown that the allocentric cue shift can be detected in the memory and motor activity of FEF and SEF visuomotor and motor neurons (Bharmauria et al., 2020, 2021). They found a partial shift towards landmark-centered coordinates from eye-centered coordinates in the neurons. When the coordinate system shift occurs during the task in different brain areas can tell us how the information flows. Therefore, we should also be able to see this in reach areas involved in the integration of egocentric and allocentric information during our reaching task. In addition, data collected from neurophysiological studies and previous human studies can be used to propose a neural circuit model for reach. This neural circuit explains the path allocentric and egocentric cues travel when being integrated in the brain, possibly the frontal cortex.

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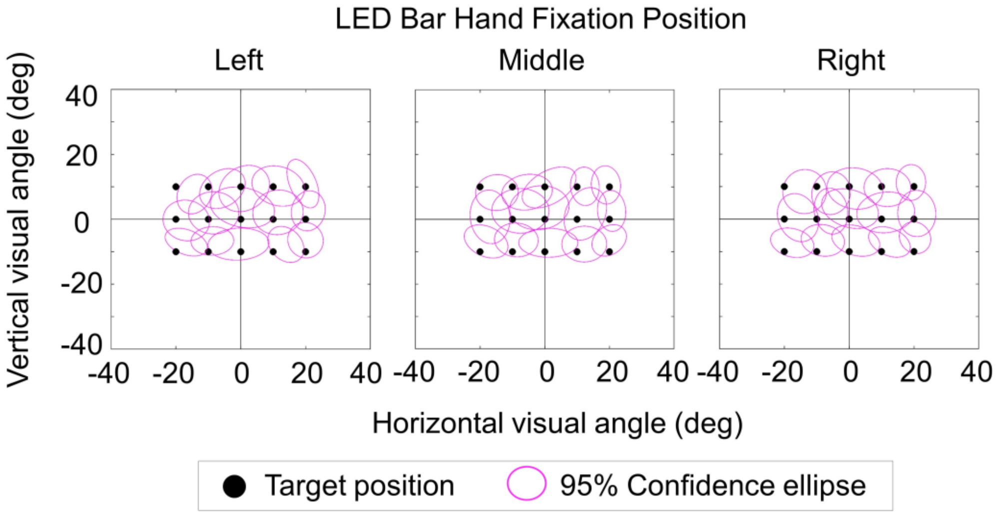
APPENDICES

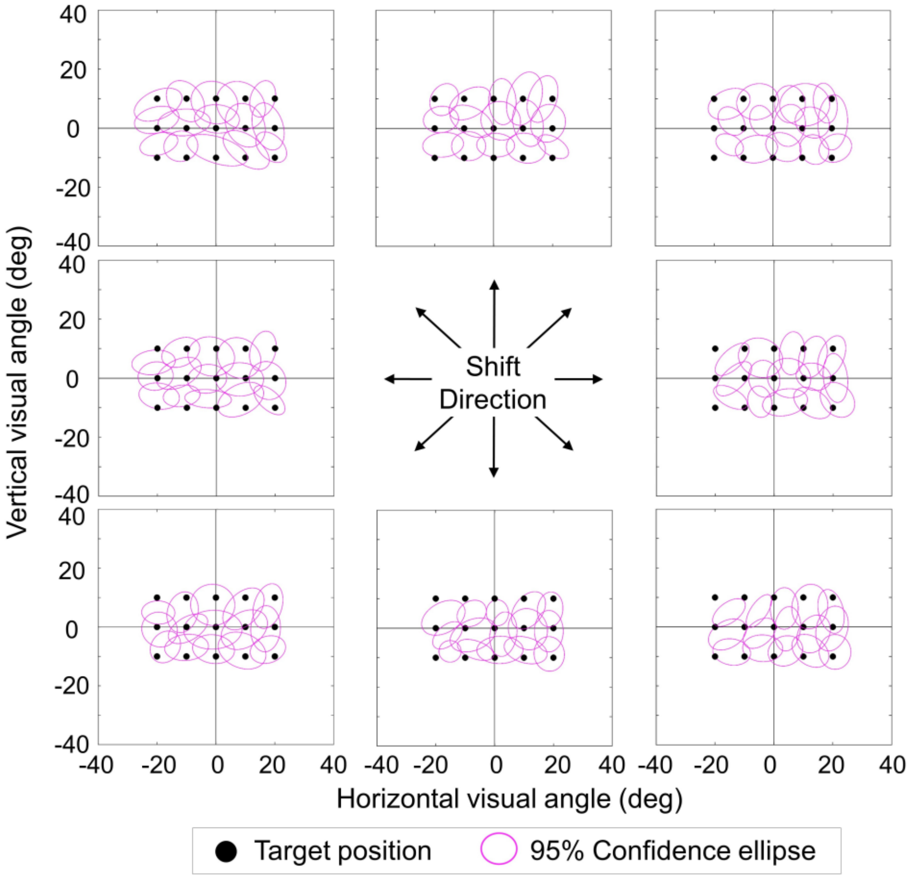
Appendix A: Author Contributions

I contributed to the project design, data analysis, and data interpretation and I wrote the paper. Dr. Crawford contributed to the project design, data interpretation, and editorial comments.

Appendix B: Supplementary Figures



Supplementary Figure 1. Influence of different hand fixation positions on 95% confidence ellipses for touch. Data from the no landmark condition was separated into three initial hand fixation positions.



Supplementary Figure 2. Influence of different landmark shift directions on 95% confidence ellipses for touch. Data from the landmark shift condition was separated into the eight shift directions.