Effect of Allocentric Landmarks on Primate Gaze Behaviour in a Cue Conflict Task

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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

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JUNE 2016

ABSTRACT

The brain can remember the location of a peripheral target relative to self (egocentric) or to an external landmark (allocentric). The relative reliabilities of egocentric and allocentric coding had been examined in reach, but it was never explored in the gaze control system. In this study, we utilized a cue conflict task to create a dissociation between egocentric and allocentric information to assess the effect of allocentric cues on gaze behaviour in two macaque monkeys. The results showed that the monkey gaze behaviour is a combination of both reference frames depending on the reliability of the allocentric cue. We also found that the allocentric cue was significantly more reliable when it is located closer to the fixation point, and when the cue shifts further away from the fixation point or the original target. Our findings suggest that the influence of allocentric cues on gaze behaviour depends on various gaze parameters.

DEDICATION

I dedicate this
thesis to my family.
Thank you for your love.

ACKNOWLEDGEMENTS

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INTRODUCTION

There are five fundamental senses that an individual can use to interact with their surroundings: hearing, smell, taste, touch, and vision. Information is collected through these senses and transformed into behaviour. Different species have evolved to depend on each of these five senses distinctly based on their niche in their habitat. For example, canines possess a keen sense of smell to aid in stalking prey, however, their vision acuity is poorer in comparison. On the other hand, humans have evolved to rely on the visual system in comparison to all other senses. In order to rely on the visual system, higher order organisms such as humans and nonhuman primates (NPH) have developed a highly specialized region in the center of the retina that is responsible for visual acuity called the fovea (Ross, 2000). The fovea is packed with photoreceptors facilitating acute colour vision and high-resolution perception of objects in the direction of gaze, where as the rest of the retina is less sensitive to colour and contrast. It is impossible to develop a fovea-like acuity throughout the retina because the cortical surface area required to process all the visual information would exceed convenient skull size (Williams and Coletta, 1986). Consequently, when eccentricity increases and objects are further away from the fovea, visual acuity deteriorates. To maximize visual acuity, the visual system has developed a coping mechanism in the form of ballistic eye movements, known as saccades, towards interesting objects in the immediate environment.

Saccade Behaviour

Saccades can be both voluntary and automatic, occurring three times per second on average when viewing a natural scene (Rayner 1998). Saccades are driven by sensory signals known as retinal error, which is the difference between the retinal location of the target and the fovea (Figure 1). Each saccade aims to bring the retinal image of the target in line with the fovea. Contrary to the goal, the visual system is suppressed during a saccade and no new visual information is acquired (Matin 1974; Uttal and Smith 1968; Volkmann 1986). Fortunately, visual information before and after each saccade fills in the gaps to form a continuous representation of the world (Brooks et al., 1981; Campbell and Wurtz, 1979), rather than a sequence of snapshots interleaved with incomprehensible blurs. To minimize these periods of suppression, saccades occur at ballistic speeds. Consequently, saccade durations are limited to 20-200 ms in humans (Zangemeister and Stark, 1982). Saccades alone can compensate for objects positioned within a 20º eccentricity (Tomlinson and Bahra, 1986).
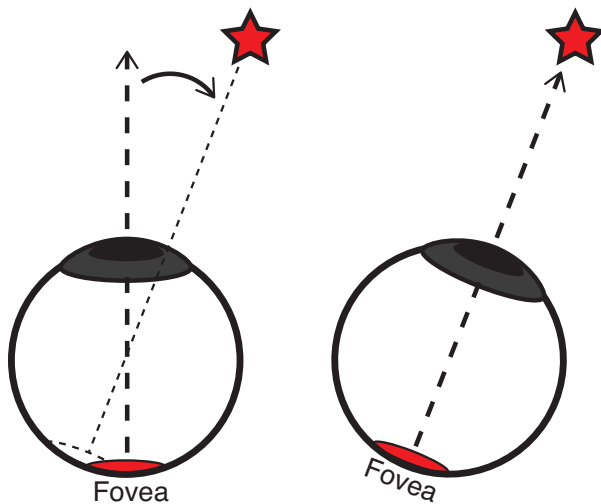
Figure 1. Saccadic eye movement. A saccade brings the image of the object (red star) into the fovea.

Gaze Behaviour

For larger eccentricities, re-fixation of the fovea involves coordinated movements of the head and body, in addition to saccades (Guitton and Volle, 1987; Guitton, 1992; Norton and Stark, 1971; Radau et al., 1994). These movements are called gaze shifts. Gaze is the measurement of eye position using space as a frame of reference (eye in space), calculated by combining eye position relative to head position (eye in head, describes a saccade) and head position relative to space (head in space). The visible world consists of 360º of viewing potential, but less than 180º is available in the primate visual field. Therefore, gaze shifts are required to visualize targets outside of this range. In a typical gaze shift (Figure 2), the eye initiates a saccade before the head movement because it needs to overcome a lower moment of inertia. After a brief delay, the head turns in the same direction. There is also a delay between the end of the saccade and head movement (Warabi, 1977), during which the vestibular ocular reflex (VOR) stabilizes the gaze position and the image on the retina by interpreting sensory signals from the vestibular system to generate eye movements in the direction opposite to head movement (Simpson and Graf, 1985).

In the past, nonhuman primate electrophysiology studies have focused on 2-dimensional saccadic, eye in head, behaviour by conducting experiments while the monkeys' head is secured in a constant position. A major limitation in these types of experiments is that their results may not accurately reflect natural behaviour. In the wild, monkeys do not simply utilize saccades to survey their environment. Head, shoulder, and body all actively participate in producing three dimensional gaze shifts.

With the advancement of 3-dimensional recording techniques, researchers have begun to consider protocols where the monkeys' head is unrestrained and able to move freely (Crawford and Guitton, 1997; Crawford et al., 1999).

Head-Free Gaze Trajectory
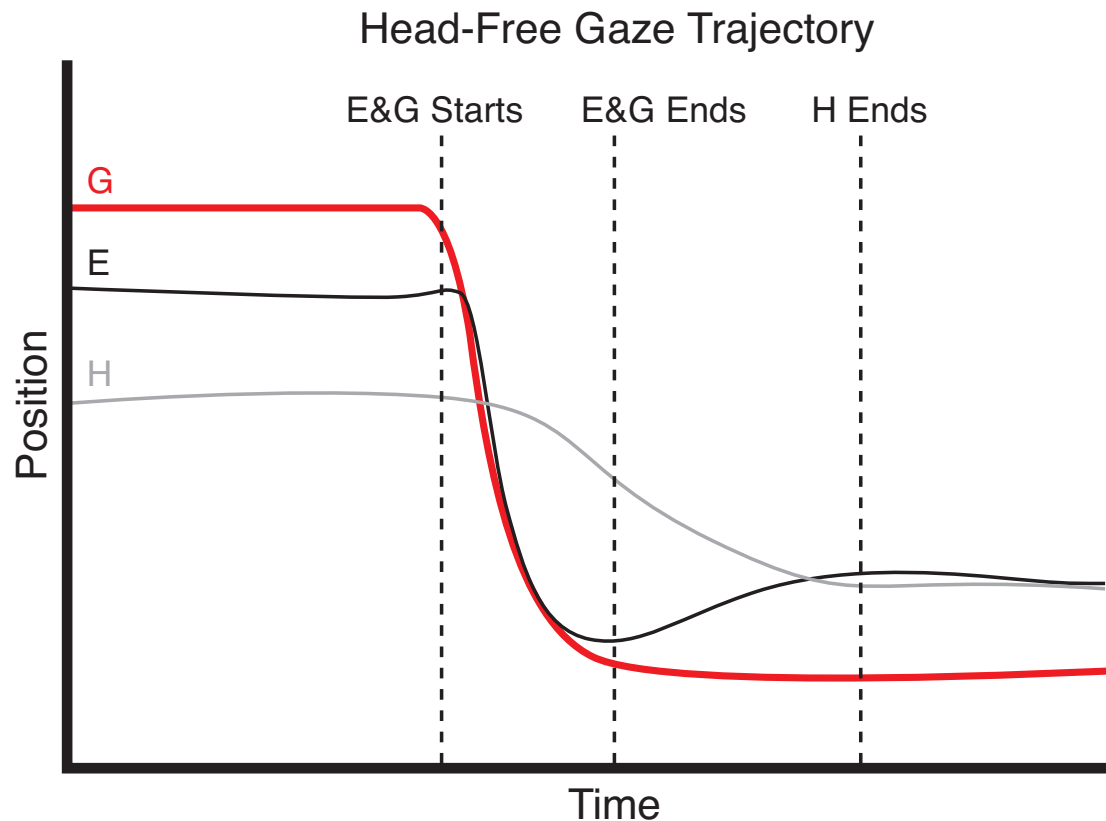
Figure 2. Head-free gaze trajectory. A typical gaze shift using the position of eye (E), head (H), and gaze (G) in space.

Neural Substrates of the Gaze System

When visual information is coded by the photoreceptors in the retina, they are transformed into electrical signals and conducted to the lateral geniculate nucleus (LGN) via the optic chiasm. Then, the LGN projects to the primary visual cortex (V1) for initial processing before moving dorsally towards the lateral intraparietal cortex

(LIP). The LIP has been associated with elevated activity in response to visual stimuli before spatially guided saccadic eye movements (Andersen et al., 1987; Goldberg et al., 1990). Note that electric stimulation of LIP produces saccades with no head movement (Constantin et al., 2007). The LIP sends direct inputs to the frontal (FEF) and supplementary (SEF) eye fields in the frontal cortex, and the superior colliculus (SC) in the brainstem. Electrical stimulation of the LIP, FEF, SEF, and SC had all been shown to generate saccadic eye movements (Bruce et al., 1985; Klier et al., 2001; Martinez-Trujillo et al., 2003; Robinson, 1972; Robinson and Fuchs, 1969; Schiller and Stryker, 1972).

Cortical Mechanisms

The FEF and SEF work in concert to organize gaze shifts, and they share similar patterns of connectivity (Krauzlis, 2004; Shook et al. 1999), both direct and indirect, with brainstem oculomotor structures including the SC. The FEF is a dorsolateral frontal cortex structure associated with the generation of saccades to known target locations (Gaymard et al., 1998). In addition, FEF stimulation in the head-unrestraint condition yielded eye-head gaze shifts (Chen, 2006; Knight and Fuchs, 2007; Tu and Keating, 2000). The SEF, located on the dorsomedial frontal cortex, coordinates eye and head movements to produce gaze shifts in head-unrestrained monkeys (Martinez-Trujillo et al., 2003). All of the aforementioned cortical gaze control areas project to the SC.

Brainstem Mechanisms

The SC is located on the dorsal area of the midbrain where it produces and relays the saccade motor command to other brainstem structures (Gandhi and Katnani, 2011; Sparks, 1986; Wurtz and Albano, 1980). Electrical stimulation of the anterior region of the SC suppresses saccades and maintains gaze position (Munoz et al., 1993; Munoz and Wurtz, 1995b; Munoz and Istvan, 1998). Remainder of the SC integrates sensory information and plays a role in target selection using a multilayer topographical map of visual space (Horowitz and Newsome, 1999; McPeak and Keller, 2002; Schiller and Koerner, 1971): the superficial layer is a retinotopic map similar to V1 (Sparks 1986), and the deep layer receives projections from higher order cortical gaze structures. Deep layer electrical stimulation results in gaze shifts combining normal eye and head trajectories (Freedman and Sparks, 1997; Klier et al., 2001; Klier et al., 2003). Neurons in the SC fire relative to a place coding system, where the direction and magnitude of the final saccade is dependent on the topographic location of the neuron rather than its firing rate (Freedman and Sparks, 1997). Therefore, the SC encodes targets relative to an eye-centered frame of reference (Klier et al., 2001). Neurons in the SC ramp up their firing rate in anticipation of a saccade and are rapidly extinguished after saccade onset (Munoz and Wurtz, 1995a).

Goal Directed Action

Real life scenarios are guided by goal directed actions, which are mediated by feedforward movement plans. Feedback is not always available because movement speeds exceed a certain limit (Carlton, 1981; Keele and Posner, 1968; Zelaznik et al. 1983) or because the target is no longer visible (Blohm and Crawford, 2007). Imagine a golfer hits the ball into the tall grass of the rough–the desired target (ball) is no longer visuble. In these situations, the brain must encode an internal spatial representation of the last visible target location to be used in a feedforward fashion to guide the movement (Ariff et al., 2002; Flanagan et al., 2001; Robinson 1981). The remembered spatial representation of the target location is passed through an inverse internal model and transformed into an effector command that dictates the output movement (Figure 3). An efference copy of the subsequent saccade or reach updates the position and movement signals for the internal model to minimize movement error.
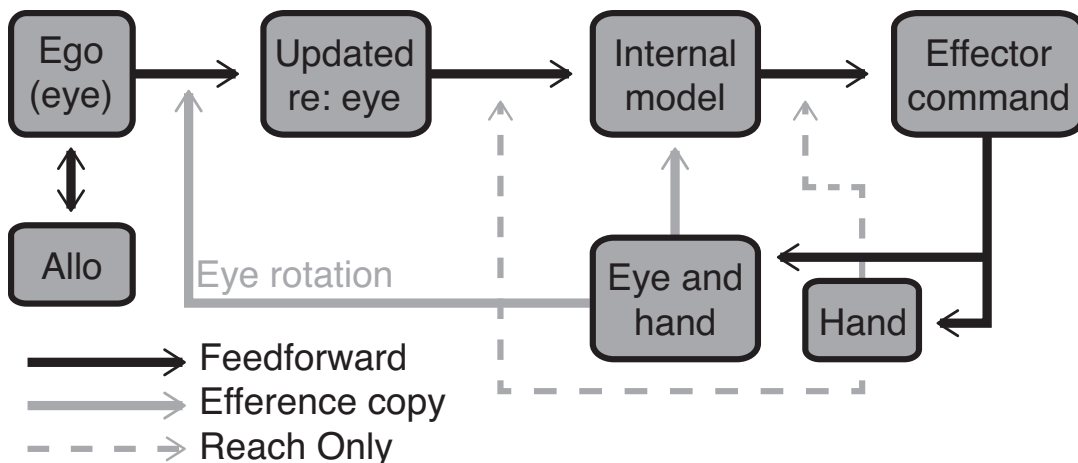
Figure 3. Transformation of visual representation into a motor command. Egocentric and allocentric frames of reference are weighted to generate the spatial representation of the target.

Frames of Reference

There are at least two ways in which the visual system can encode a frame of reference, which is a representation of the location of peripheral targets in visual space: relative to a part of the observer (egocentric coordinates) or to an external landmark or stimuli (allocentric coordinates) (Vogeley and Fink, 2003). Returning to the analogy of the golf ball, the golfer has two ways to locate the ball. First, he may rely on egocentric information: the last location where the ball was visible (registered on his retina, relative to his direction of gaze, head, and body orientation). Alternatively, he may rely on allocentric information: the ball was last visible 10 m to the right of a tree, a stable landmark. However, how could the brain process the same visual information (where the ball was last visible) in two distinct ways?

The two-streams hypothesis is a model of visual processing, which argues that humans possess two unique visual systems (Goodale and Milner, 1992; Milner and Goodale, 2008; Schenk, 2006). Both streams originate from the early visual areas (area V1). The dorsal ("where") stream projects to the posterior parietal cortex and processes the spatial location of the object relative to the viewer (egocentric) and guides gaze behaviour. On the other hand, the ventral ("what") stream projects to the infero-temporal cortex and perceives the form and shape of the object, and recognizes an object or the relative formation of a group of objects (allocentric). This hypothesis proposes a model where the dorsal action system maintains an updated spatial representation of a target in an egocentric frame of reference for an upcoming goal-directed action. If allocentric information were to influence motor behaviour, it must

be transformed from the ventral (perception system) to the dorsal stream and into the action system (Chen et al., 2011). The ventral stream mechanisms retain spatial information for a longer period of time relative to the dorsal stream (Carrozzo et al., 2002; Lemay et al., 2004; McIntyre et al., 1998). Therefore, egocentric cues quickly fade and the brain is more reliant on allocentric cues when memory delays increase (Glover and Dixon, 2004; Goodale and Haffenden, 1998; Obhi and Goodale, 2005).

Egocentric information is always available to healthy subjects and many studies have shown that saccades and reach towards remembered targets are reasonably accurate using exclusively egocentric cues (Batista et al., 1999; Blohm and Crawford, 2007; Buneo et al., 2002; Crawford et al., 2004). When viewing a natural environment, allocentric landmarks are frequently available and improve the accuracy and precision of movements towards a remembered target location (Krigolson and Heath, 2004; Krigolson et al., 2007; Obhi and Goodale, 2005; Thaler and Goodale, 2011). When both reference frames are available, the brain combines their information (Battaglia-Mayer et al., 2003; Diedrichsen et al., 2004; Sheth and Shimojo, 2004) based on their relative reliabilities (Byrne and Crawford, 2010; Fiehler et al., 2014; Thompson and Henriques, 2010).

Allocentric Coding

The relative influence of egocentric versus allocentric frames of reference has been examined primarily in reach models. A wide range of variables have been shown to influence these interactions, such as age (Hanisch et al., 2001; Lemay et al.,

2004), memory delay (Carrozzo et al., 2002; Chen et al., 2011; Glover and Dixon, 2004; Hay and Redon, 2006; Obhi and Goodale, 2005), context (Neely et al., 2008), task demands (Bridgeman et al., 1997), size of the allocentric cue (Inoue et al., 2015; Uchimura and Kitazawa, 2013), location of the cue relative to reach direction (de Grave et al., 2004), and perceived stability of the cue (Byrne and Crawford, 2010; Byrne et al., 2010).

In contrast to reach models described above, relatively little is known about how the gaze control system utilizes the egocentric and allocentric frames of reference. In particular, to our knowledge, the influence of a landmark that is independent of the saccade target has not been studied.

CURRENT STUDY

In summary, the influence of allocentric cues has been examined extensively in various reach models. However, its influence in the gaze control system has not been systematically explored. A recent study by Byrne and Crawford (2010) revealed that cue stability and gaze shift amplitude correlate significantly with allocentric landmark reliability in a human reach paradigm. In order to study how neurons in the gaze control system encode an allocentric cue, first we need to show that monkey behaviour is also influenced by allocentric landmarks. If this is true, then we can determine which gaze parameters affect the reliability of an allocentric landmark.

The objective behind this study will be to assess whether allocentric landmarks influence gaze behaviour. We designed a paradigm to dissociate the egocentric and allocentric reference frames and accurately measure the dominance of each frame with respect to a variety of gaze parameters. We will compare and contrast our findings with the literature in reach models. Ultimately, the aim is to apply electrophysiological techniques to nonhuman primates to identify the relevant neuromechanisms underlying the application and maintenance of egocentric and allocentric information for goal-directed action (both reach and gaze).

Using a large-scale allocentric landmark in the cue conflict task, we will directly test the hypotheses that:

1) The presence of an allocentric landmark will improve precision and accuracy of gaze shifts towards remembered target locations.

2) Gaze endpoints will be biased towards the nearest landmark.

3) An internal weighing process will combine egocentric and allocentric information making a gaze shift to remembered targets locations. The weighting of either reference frame is dependent on gaze parameters such as the initial fixation position and direction of: target, landmark, landmark shift, and gaze shift.

MATERIALS AND METHODS

Surgical Preparation

Data were collected from two female rhesus macaque monkeys (*Macaca mulatta*, M1 and M2). Both animals were 10 years of age and weighed approximately 6 kg at the time of study. Each monkey was prepared for experiments by undergoing a surgery described previously (Crawford et al., 1999; Klier et al., 2001; Klier et al., 2003) under general anaesthesia (1.5% isoflurane following intramuscular injection of 10 mg/kg ketamine hydrochloride, 0.05 mg/kg atropine sulphate, and 0.5 mg/kg acepromazine). A stainless steel head post was attached to the skull using a dental acrylic head cap anchored using 13 stainless steel cortex screws. One Teflon coated stainless steel search coil (18mm in diameter) was implanted subconjunctivally to record 2D eye position. The monkeys were allowed two weeks of recovery following the surgery with unrestricted food and fluid intake. The animal care staff and university veterinarians closely monitored the monkeys' intake, weight, and health. All surgical and experimental protocols were consistent with the Canadian Council for Animal Care guidelines on the use of laboratory animals and were approved by the York University Animal Care Committee.

Experimental Apparatus

Visual displays were generated using MATLAB (The MathWorks, Natwick, MA), and displayed on a 2 m by 1.5 m screen 0.81 m in front of the animal, using a

projector (WT600 DLP Projector, NEC). Custom software was used to control the behavioural paradigms, send data to a Plexon data acquisition system, and deliver reward to the monkeys. Eye positions were monitored using the magnetic search coil technique (Fuchs and Robinson, 1966), where subconjunctival eye coils were placed in a magnetic field, and the voltage generated in the coils based on horizontal and vertical eye position was recorded. During experiments, two orthogonal coils were secured in a plastic base and attached to the head cap to record 3D head position. The monkeys were trained to sit in a custom chair (Crist Instruments Inc., Maryland, USA) designed to allow unrestrained head movement inside a 1 m^3 magnetic field generator (Crawford et al., 1999). Fluid rewards for correct behavior were delivered via a 'juice tube' mounted onto the head implant. Head unrestrained recordings were used because they represent the more natural situation, whereas any restraint on eye or head motion can result in adapted neural strategies (Crawford and Guitton, 1997; Martinez-Trujillo et al., 2003).

Calibration

Before each training and experimental session, two distinct calibrations were completed to ensure accurate search coil signals. First, the magnetic fields were pre-calibrated and assessed by rotating an external coil through each field and adjusting gains until the output signal was equal to one at each maximum point (Crawford et al., 1999; Tweed et al., 1990). Then, each monkey performed a calibration paradigm

inside the magnetic field, to correct for any deviation in the surgically implanted eye coils from the forward position and to determine the reference position of eye in space. This calibration paradigm required the monkey to make sequential saccades to nine targets and maintaining fixation on each target for 1 s. The targets were presented at -30º, 0º, and +30º along each of the X and Y axes, forming a 3 by 3 grid centered at (0, 0). Calibration started from the central fixation point (0, 0), and then continued from the top left (-30, 30) to the bottom right (30, -30). When the monkey successfully maintained fixation on a target for 1 s, it was rewarded 2 drops of water. Reference position of eye in space was derived using the average data from two consecutive runs of the calibration paradigm.

Training and Behavioural Paradigm

　　To prepare animals for the experimental task (Figure 4) we trained animals on a series of successive approximations using standard fixation, saccade, and memory-guided saccade paradigms (Hikosaka and Wurtz, 1983). This proceeded until animals maintained fixation within 5º of a visual target for 1500 ms before saccading to previously presented target. At that point, additional visual features (Figure 4, described below) were slowly introduced (by increasing their contrast) until animals consistently performed the experimental task for several hundred trials per day. During experimental trials with the 'shift' condition described below, the spatial

reward window for final gaze position was increased to 10º so that animals were rewarded whether they were influenced by the landmark or not.

Figure 4 illustrates the main experimental tasks that were used to test the influence of allocentric landmarks on gaze behaviour. Animals began each trial by maintaining fixation on the central fixation spot (red circle with diameter of 0.5º). After 500 ms of fixation, a target (white circle with diameter of 0.5º) was presented for 100 ms in one of eight radial locations forming a square (-20º, 0º, +20º horizontal vs. 20º, 0º, +20º vertical from center). An allocentric landmark (two intersecting lines, one horizontal and one vertical, spanning the visual field) appeared simultaneously and remained visible for the remainder of the trial. The intersection point of these lines was located at one of four oblique directions 11º from the target. After a 100 ms delay period, a grid-like mask (white grid lines separated by 2° visual angle) was shown for 100 ms, such as to occlude any current or future landmark. When the mask was removed the allocentric landmark re-appeared, and after a variable delay (300-700ms) the fixation point extinguished, signalling the animal to saccade toward the remembered saccade target location within 400ms, and then fixate for another 400ms to obtain a reward.

In the 'no shift' condition, the landmark reappeared in the same location, whereas in the 'shift' condition, the allocentric landmark was displaced by 8° in one of eight radial directions. One 'no shift' control was provided for each initial target/landmark combination, and both conditions were randomly interspersed. In an

additional experiment (not shown) the influence of a stable landmark was assessed by interspersing cued 'no shift' trials with 'control' trials where the landmark was completely absent, but otherwise identical.
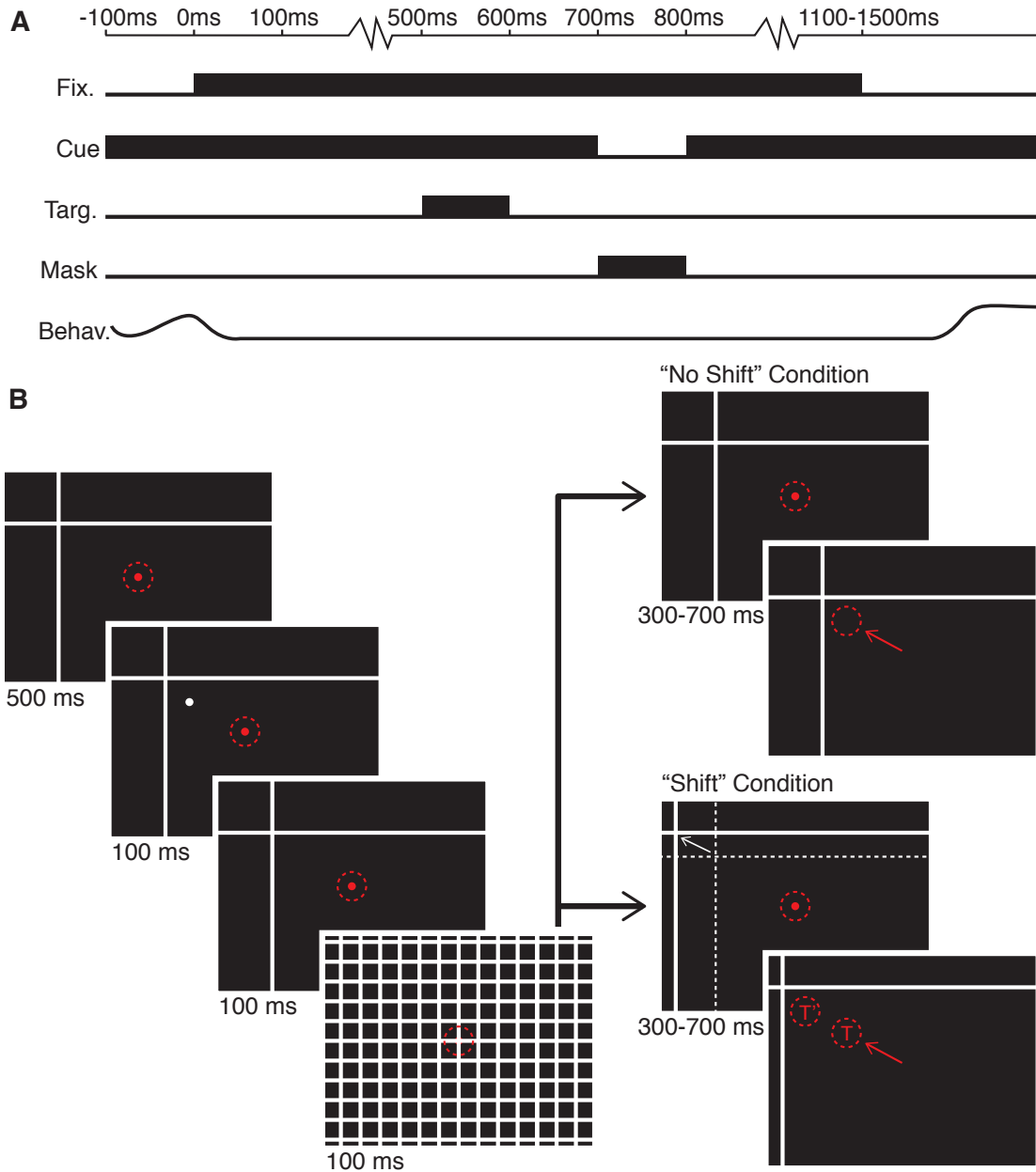

Figure 4. Cue conflict task. A) Time course for the cue conflict task. B) The dotted circles represent the eye position at each interval, and the arrows indicate gaze shifts. The red dot represents the fixation

point, the white dot represents the target, and the white crosses represent the allocentric landmark that spans the range of the screen. The red arrows represent a head-unrestrained gaze shift towards the remembered location of the target.

Data Analysis

Raw coil signals were digitized at a sampling rate of 1000 Hz and converted into 2-D angles of the eye and head in space. Specifically, these were the components of the 2-D vector orthogonal to the forward magnetic field and current gaze/head pointing direction, scaled by the magnitude of this rotation. Experimental data were analyzed offline using custom scripts written in MATLAB. The beginning and end of each rewarded saccade was marked manually using a visual display. Anticipatory (reaction time <100 ms) and multi-step saccades were excluded from analysis. Trials where a saccade was made during the fixation interval were also excluded. The gaze trajectory was determined for each trial and their endpoints were calculated.

When assessing the influence of the allocentric landmark on gaze endpoints, we compared both the accuracy (mean distance from target) and precision (variance per target) of gaze endpoints in each condition. To isolate the influence of the landmark or landmark shift from general errors, we subtracted the mean gaze error for the 'no cue' control from the 'no shift' data, and the mean 'no shift' error from the 'shift' data, respectively. This correction was performed separately for each of the eight targets and for each recording session. To quantify the influence of a stable landmark in the 'no shift' condition we defined the landmark position as the intersection point of the two landmark lines, because it is the sum of the minimum

vectors from the target to both lines and a highly salient visual feature. Landmark influence (LI, Figure 5A) was calculated using the target location (T), landmark intersection location (L), and gaze endpoint (G). **TG** was projected onto **TL** (d), and then divided by the magnitude of **TL** (D). The output can be 0, indicating no landmark influence, or it can be positive or negative, indicating a bias towards or away from the landmark, respectively.

Likewise, for the shift condition, reliance of gaze on the allocentric landmark was established by calculating the allocentric weight (AW, Figure 5B) from the original target location (T), shifted target location (T'), and gaze endpoint (G). If gaze coding was exclusively egocentric, the monkey would ignore the landmark altogether and simply saccade to T. On the other hand, if allocentric coding dominated, the monkey would encode the vector between T and L then apply this vector to the shifted landmark (L') and saccade to the virtual location of T'. To calculate AW, the projection of **TG** onto **TT'** (d) was divided by the magnitude of **TT'** (D). The outputs were values between 0 and 1 where the absolute gaze coding is egocentric or allocentric, respectively. These weights (LI and AW) were categorized across combinations of different gaze parameters such as target, landmark, shift, and gaze directions and their means were compared using one-tailed Welch's t-tests, factorial analysis of variance, and post hoc analysis using the Bonferroni correction. Statistical analyses were computed using a combination of MATLAB, SPSS, and Microsoft Excel.
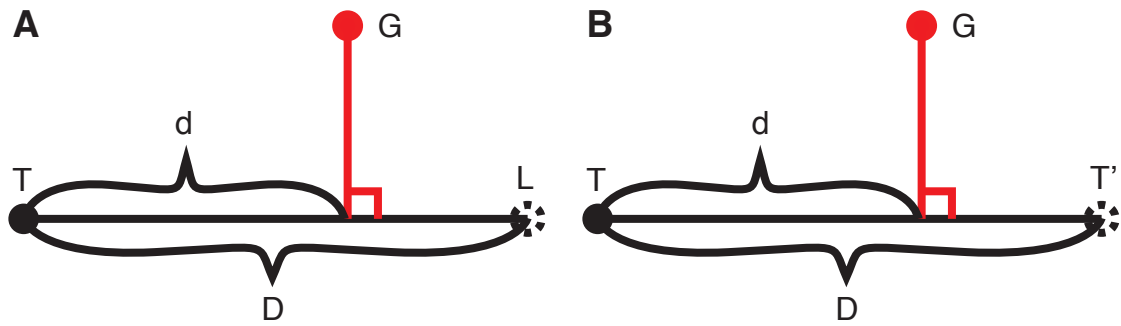
Figure 5. Calculating landmark influence and allocentric weight. A) Landmark influence (LI) is calculated using the target location (T), landmark location (L), and gaze endpoint (G). The projection of **TG** onto **TL** (d) was dividing by **TC** (D). **LI = d/D**. B) Allocentric weight (AW) is calculated using the original target location (T), shifted target location (T'), and gaze endpoint (G). The projection of **TG** onto **TT'** (d) was dividing by **TT'** (D). **AW = d/D**.

RESULTS

Various iterations of the cue conflict task were run while training M1. Different combinations of target, landmark, and shift were tested to maximize the rate of success while controlling for confounding factors. After finalizing the cue conflict task, both monkeys were trained until they were able to successfully complete memory guided gaze shifts to remembered target locations in all conditions. M1 was less motivated by the water reward in comparison to M2, completing an average of 300 trials per session, while M2 was capable of completing an average of 1200 trials per session. Sessions with less than 150 successful trials were excluded to guarantee that the monkey performed all the different combinations of conditions. The data shown in this experiment were collected over a two-month period for M1, and a two-week period for M2.

Allocentric Landmark Influence on Gaze Endpoint

First we were interested in the effect of the large-scale allocentric landmarks on gaze behaviour towards a stable remembered target. Data were collected on consecutive days until we collected a total of 1394 trials for M1 and 1555 trials for M2, where the landmark was available in 50% of the trials. The monkeys' gaze endpoints in cued 'no shift' and no cue 'control' conditions were analyzed. When the allocentric landmark was available, we found a significant decrease in gaze endpoint variability (M1: $F = 1.42$, $p < 0.01$; M2: $F = 2.78$, $p < 0.01$). We also saw a trend of

improved gaze accuracy with the presence of an allocentric landmark; however, this did not reach significance (M1: $p = 0.06$; M2: $p = 0.24$).

Subsequently, we calculated landmark influence (LI) using gaze trajectories extracted from the raw data (Figure 6). First, we collected gaze trajectories from the 'no cue' control condition, and found the mean gaze endpoint for each target location (Figure 6A). To account for systematic biases in the monkeys' gaze behaviour, we determined the mean gaze errors, which are the vectors between each target location and the corresponding 'no cue' mean gaze endpoint location (Figure 6B). Mean gaze endpoints in the cued 'no shift' condition were calculated (Figure 6C), then corrected by extracting the mean gaze error for the corresponding target (Figure 6D). We performed this correction for each individual recording session. Each trial in the "shift" condition was then normalized for landmark direction in order to calculate their LI (Figure 5A).

If the monkeys were not influenced by the landmark, LI would equal to 0, but if the gaze endpoints were biased towards or away from the landmark, LI would be positive or negative, respectively. Figure 7 shows histograms of LI distribution, we categorized the LI of each monkey into 40 bins, each with a size of 0.05. All in all, there was a significant bias towards the landmark ($p < 0.01$), with a mean LI of 0.14 in M1 and 0.17 in M2 (where 0 = target location and 1 = landmark location).

Furthermore, we also analyzed whether the distance between the allocentric landmark position and the initial gaze position affected LI. The results are shown in

Figure 4. We separated trials into three groups based on landmark eccentricity relative to the initial gaze position. We found that LI increases as the landmark eccentricity decreases. This effect was significant for M1 ($p < 0.01$, Figure 8A), but not for M2 ($p = 0.26$, Figure 8C).
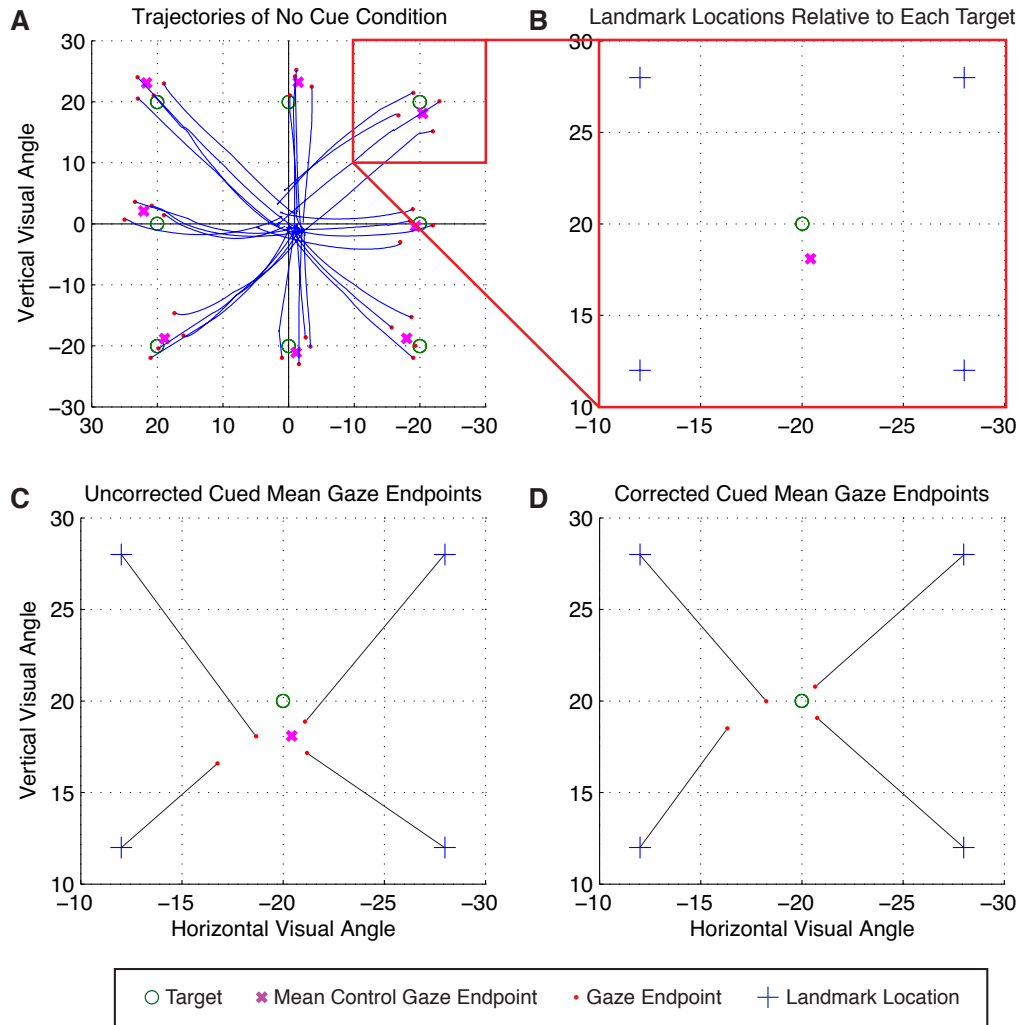
Figure 6. Converting raw data to landmark influence, sample session. A) Gaze trajectories in the 'no cue' control condition are shown in blue. Target locations are represented using dark green circles. Mean gaze endpoints, magenta crosses, are calculated for each target location. B) Close up of the upper right target in Figure 6A. Landmark locations are represented using blue crosses. C) Uncorrected mean gaze endpoints for each allocentric landmark in the cued 'no shift' condition are shown in red. Black lines connect gaze endpoints to their corresponding landmarks. D) Corrected mean gaze endpoints for the 'no shift' condition.
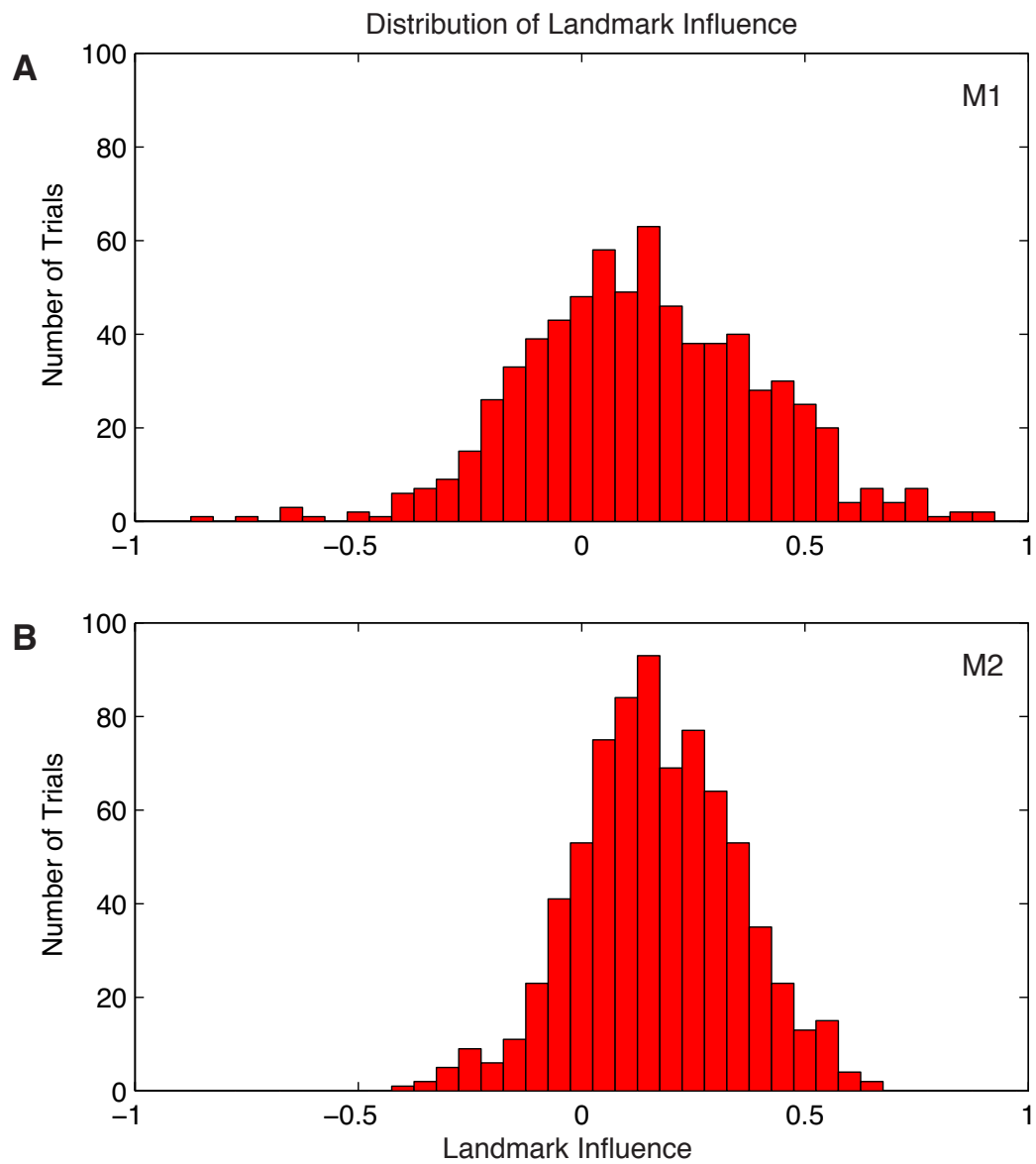
Figure 7. Distribution of landmark influence. A) Histogram showing the distribution of landmark influence for M1 (X axis) plotted against the number of trials in each bin (Y axis). B) Histogram showing the distribution of landmark influence for M2.
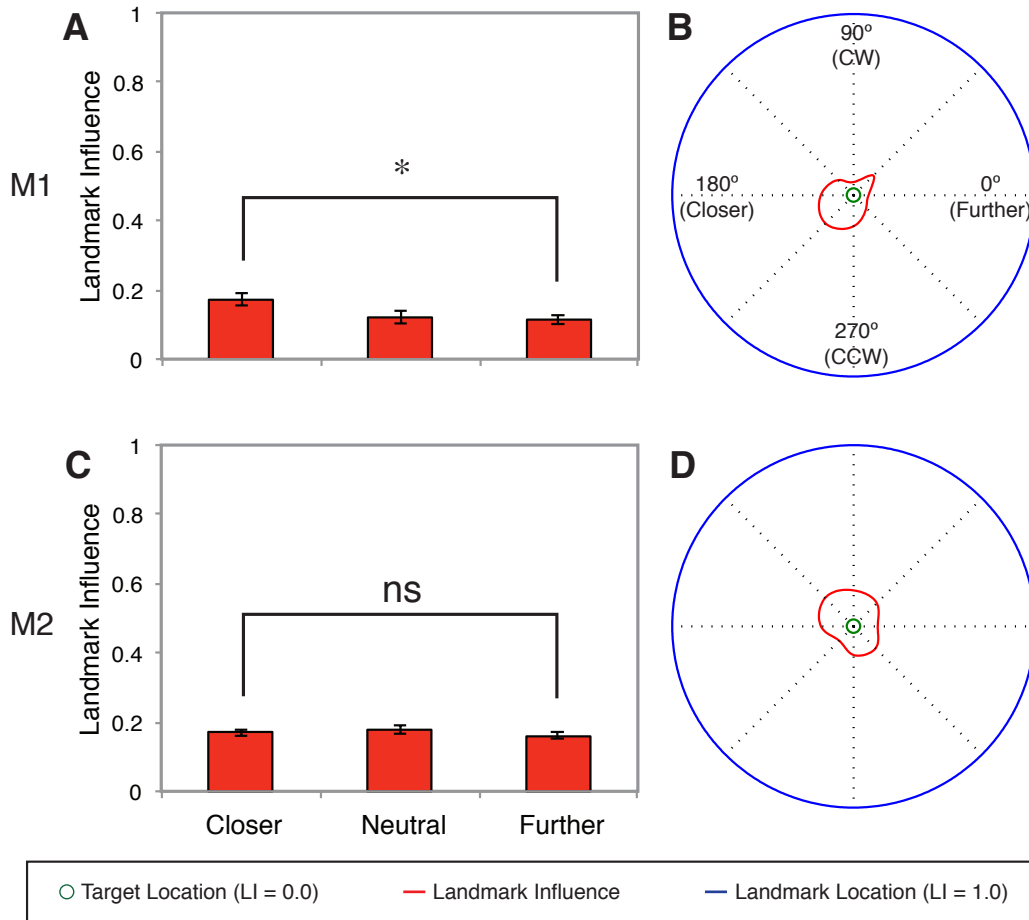
Figure 8. How distance between the allocentric landmark position and the initial gaze position affects landmark influence. A) Comparison of the mean LI (Y axis) between allocentric landmarks positioned closer or further from the initial gaze position (X axis) for M1. B) Overall LI sorted by landmark direction for M1. The green circle at the center represents target location, whereas the outer circle (blue) represents the set of possible landmark locations. The mean LI for a given direction is represented by the intersection point of the red curve with the black line segment corresponding to each direction. The red curve is a cubic spline interpolation of the LI for each direction and serve as a visual guide for the data. Data for closer and further from initial gaze position are represented in the left and right semicircles, respectively. C) Comparison of the mean LI (Y axis) between allocentric landmarks positioned closer or further from the initial gaze position (X axis) for M2. D) Overall LI sorted by landmark direction for M2. Same convention as Figure 8B. Error bars indicate one standard error of the mean, statistical significance is denoted by (*) above the bar graphs.

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Effect of Allocentric Landmark Shift

Once we confirmed that the allocentric landmark was, in fact, affecting gaze behaviour, we recorded both monkeys while they performed the cue conflict task. See Figure 9 for the conversion of raw gaze trajectories to allocentric weights (AW). First, we collected gaze trajectories from the 'no shift' condition, and found the average gaze endpoint for each initial target location (Figure 9A). To account for systematic biases in the monkeys' gaze behaviour, we determined the mean gaze errors, which are the vectors between each initial target location and the corresponding 'no shift' mean gaze endpoint location. Mean gaze endpoints in the 'shift' condition were calculated (Figure 9B), and then corrected by extracting the mean gaze error for the corresponding target (Figure 9C). We performed this correction for each individual recording session. Each trial in the 'shift' condition was then normalized for landmark shift direction and amplitude (Figure 9D) in order to calculate their AW (Figure 5B).

If the monkeys were making gaze shifts toward the original, egocentric target location, we would expect an AW of 0. On the other hand, if they were making gaze shifts toward the shifted, allocentric target location, AW would equal to 1. Figure 10 shows histograms of AW distribution, we categorized the AW of each monkey into 40 bins, each with a size of 0.1. Overall, there was a significant allocentric shift in gaze endpoints in the 'shift' condition relative to the 'no shift' condition ($p < 0.01$), with a mean AW of 0.27 in M1 and 0.23 in M2. The results revealed a normal

distribution around the mean AW. Since neither end of the distribution were terminated prematurely, it is evident that our tolerance window did not restrict natural gave behaviour in the animal. These results suggest that internal representations of gaze targets are weighted between egocentric and allocentric cues.
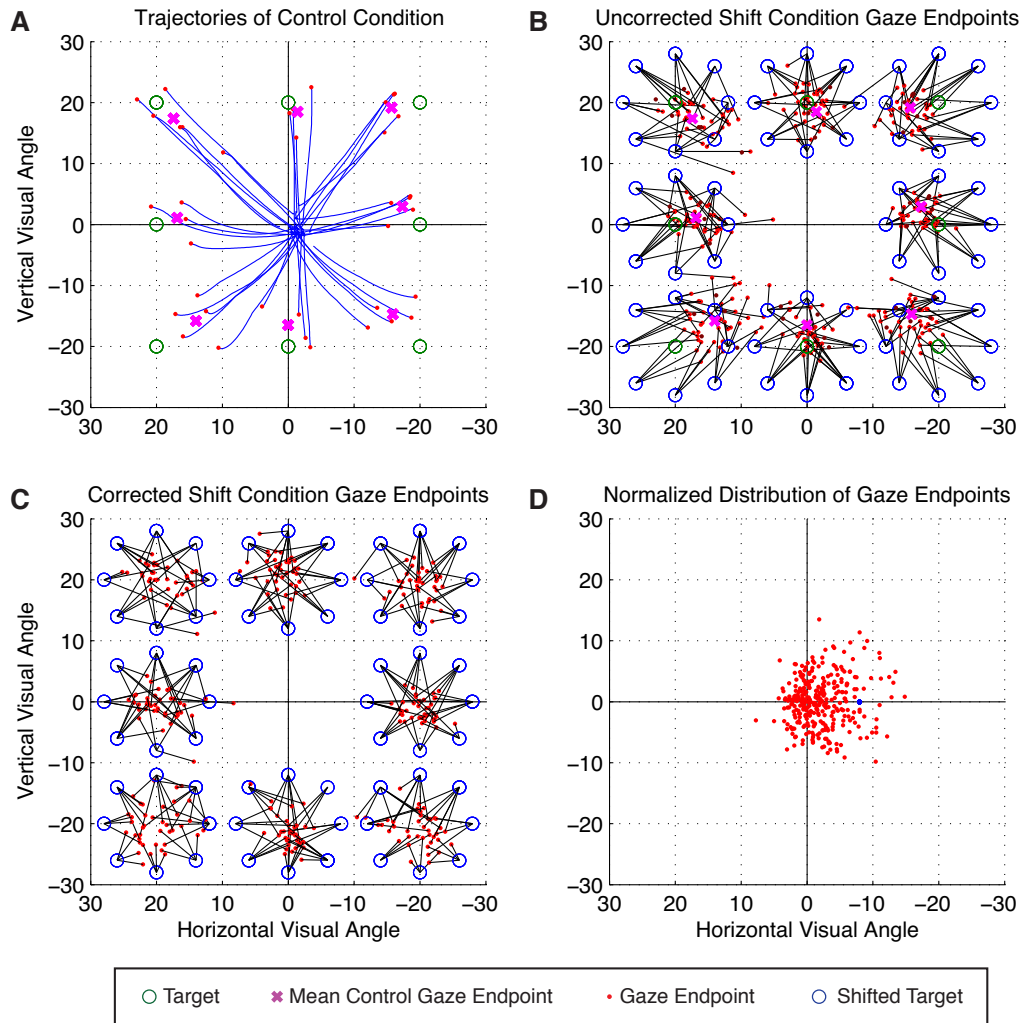
Figure 9. Converting raw data to allocentric weight, sample session. A) Gaze trajectories in the 'no shift' condition are shown in blue. Target locations are represented using dark green circles. Mean gaze endpoints, magenta crosses, are calculated for each target location. B) Uncorrected gaze endpoints in the "shift" condition are shown in red. Shifted target locations are represented using blue circles. Black lines connect gaze endpoints to their corresponding shifted targets. C) Corrected gaze endpoints for the 'shift' condition. D) Each group of original target, shifted target, and gaze endpoint from Figure 9C is transformed to control for landmark shift direction and amplitude. Original target location is centered

at the origin, the shifted target location is represented by the blue dot, and each red dot represents the gaze endpoint of a unique trial in this sample session.
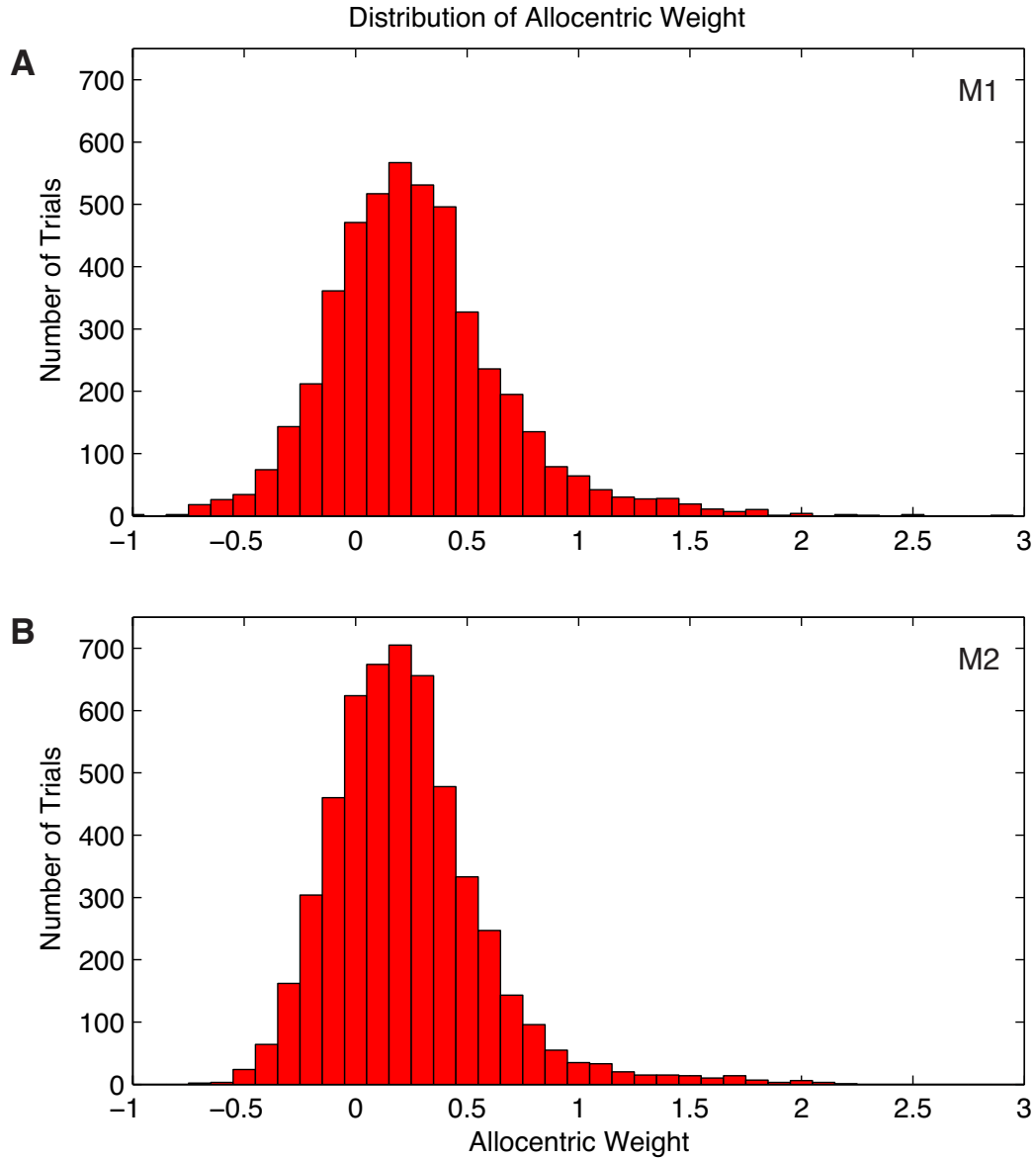
Figure 10. Distribution of allocentric weights. A) Histogram showing the distribution of allocentric weights for M1 (X axis) plotted against the number of trials (Y axis). B) Histogram showing the distribution of allocentric weights for M2.

Gaze Parameters Influence Allocentric Weight

Lastly, we examined the impact of gaze parameters on AW by comparing the weights between various combinations of target, allocentric landmark, landmark shift, and gaze shift directions and magnitudes using multifactorial ANOVAs. We found that AW is dependant on allocentric landmark position (Figure 11) and shift direction (Figure 12) relative to initial gaze position, and is also dependent on cue shift direction relative to target position (Figure 13).

To examine allocentric landmark position and shift direction relative to initial gaze position, each 'shift' trial was normalized for the gaze shift direction and amplitude. For allocentric cue position, we separated the trials based on the landmark eccentricity relative to the initial gaze position. Post hoc Bonferroni corrections revealed a significant increase ($p < 0.01$) in AW when the landmark is located closer in comparison to further, to the initial gaze position in both M1 (Figure 11A) and M2 (Figure 11C). We then separated the trials based on their direction of landmark shift relative to the initial gaze position. Post hoc Bonferroni corrections revealed a significant increase ($p < 0.01$) in AW when the cue shifts away from the initial gaze position in both M1 (Figure 12A) and M2 (Figure 12C). To study cue shift direction relative to target position, we normalized the landmark shift direction. Here, we separated the trials based on the direction of landmark shift relative to the target position. Post hoc Bonferroni corrections revealed a significant increase ($p < 0.01$) in

allocentric weight when the landmark shifts away from the initial target position in both M1 (Figure 13A) and M2 (Figure 13C).
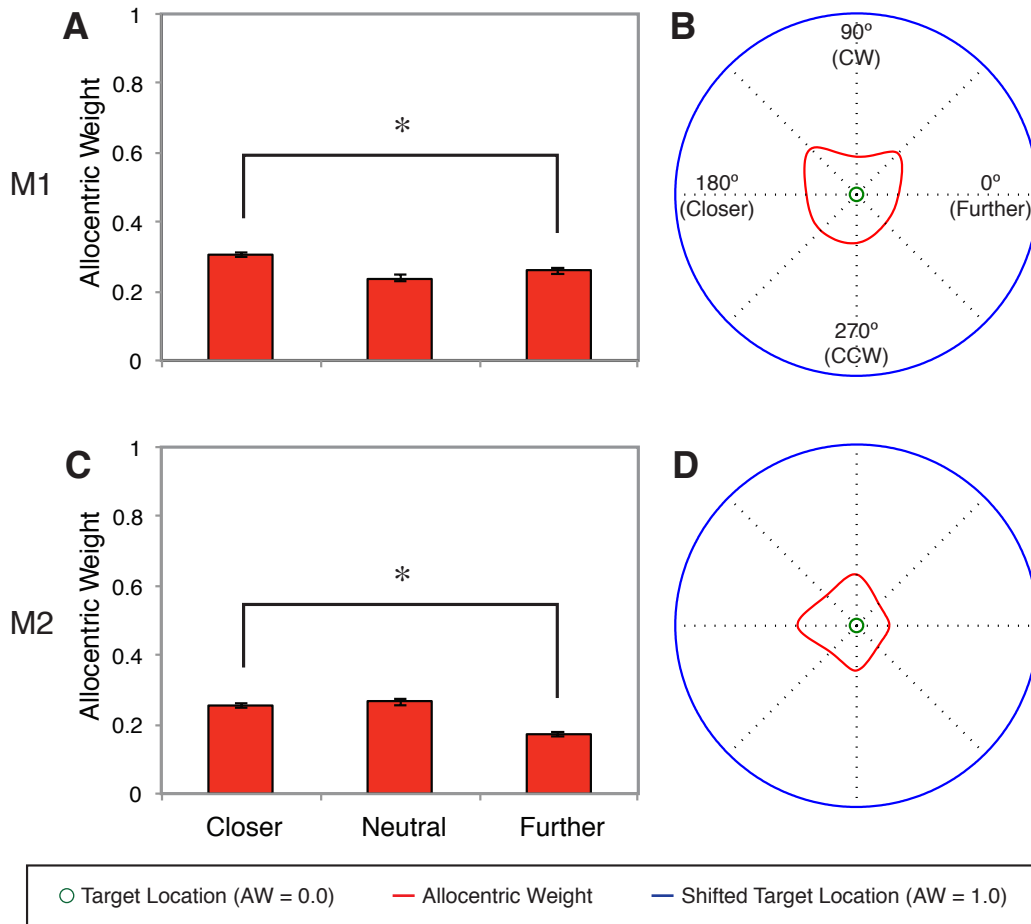
Figure 11. How distance between the allocentric cue position and the initial gaze position affects allocentric weight. A) Comparison of the mean AW (Y axis) between allocentric landmarks positioned closer or further from the initial gaze position (X axis) for M1. B) Overall AW sorted by landmark direction for M1. The green circle at the center represents target location, whereas the outer circle (blue) represents the set of possible shifted target locations. The mean AW for a given direction is represented by the intersection point of the red curve with the black line segment corresponding to each direction. The red curve is a cubic spline interpolation of the AW for each direction and serve as a visual guide for the data. Data for closer and further from initial gaze position are represented in the left and right semicircles, respectively. C) Comparison of the mean AW (Y axis) between allocentric landmarks positioned closer or further from the initial gaze position (X axis) for M2. D) Overall AW sorted by landmark direction for M2. Same convention as Figure 11B. Error bars indicate one standard error of the mean, statistical significance is denoted by (*) above the bar graphs.
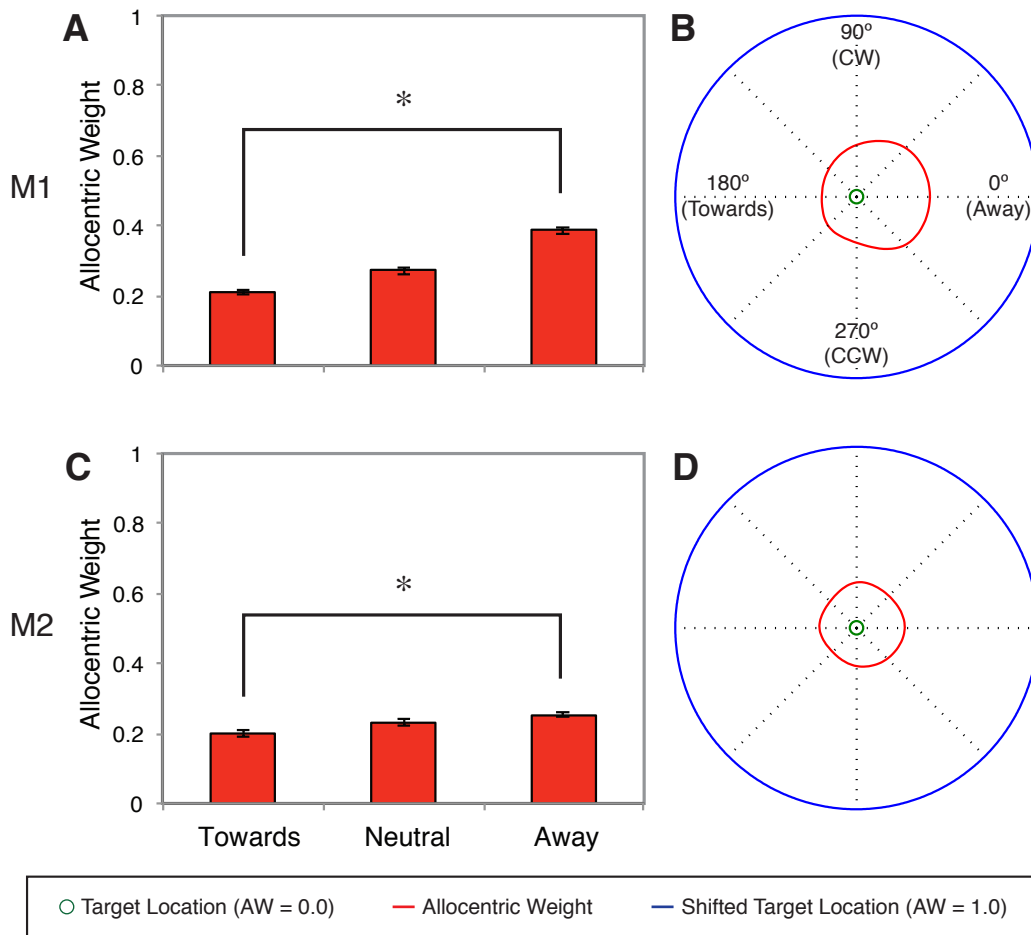
Figure 12. How the direction of cue shift relative to the initial gaze position affects allocentric weight. A) Comparison of the mean AW (Y axis) between allocentric landmarks that shift towards or away from the initial gaze position (X axis) for M1. B) Overall AW sorted by landmark shift direction for M1. Same conventions Figure 11B. C) Comparison of the mean AW (Y axis) between allocentric landmarks that shift towards or away from the initial gaze position (X axis) for M2. D) Overall AW sorted by landmark shift direction for M2. Same convention as Figure 11B. Error bars indicate one standard error of the mean, statistical significance is denoted by (*) above the bar graphs.
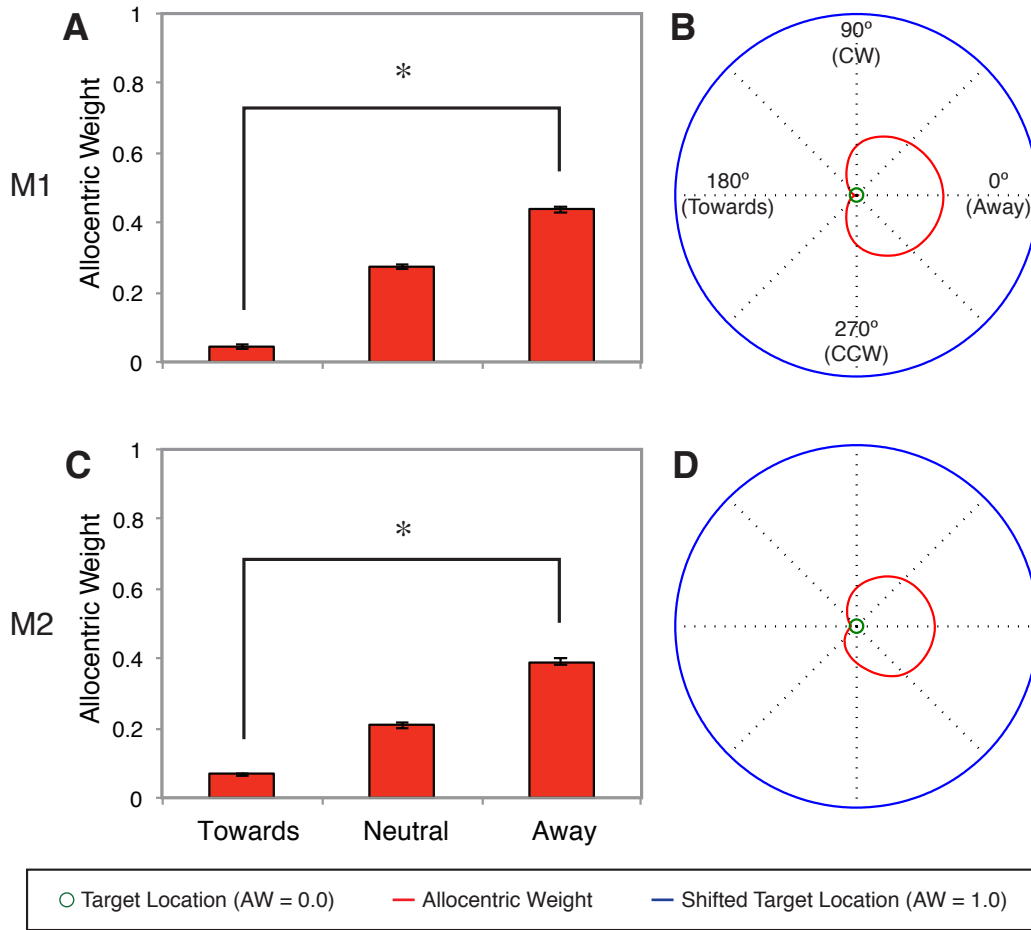
Figure 13. How the direction of cue shift relative to the initial target position affects allocentric weight. A) Comparison of the mean AW (Y axis) between allocentric landmarks that shift towards or away from the initial target position (X axis) for M1. B) Overall AW sorted by landmark direction for M1. Same conventions Figure 11B. C) Comparison of the mean AW (Y axis) between allocentric landmarks that shift towards or away from the initial target position (X axis) for M2. D) Overall AW sorted by landmark direction for M2. Same convention as Figure 11B. Error bars indicate one standard error of the mean, statistical significance is denoted by (*) above the bar graphs.

DISCUSSION

In this study, we designed the cue conflict task to investigate the effect of large-scale allocentric landmarks on gaze shifts towards remembered target locations. Our goal was to bridge the gap between previous studies that compared egocentric and allocentric frames of reference in the human reach model and future electrophysiological studies in nonhuman primate gaze models to reveal the underlying neural substrates responsible for encoding information via the reference frames. The cue conflict task was designed to create a dissociation between egocentric and allocentric information by shifting the allocentric landmark. We calculated a measure of allocentric weight to quantify behavioural reliance on both egocentric and allocentric information.

Our results demonstrated that large-scale allocentric landmark have an attractive influence on gaze behaviour both when it is stable and when it is shifted. This influence fluctuates with different gaze parameters such as the eccentricity of the landmark location and shift direction relative to the initial gaze position. These results corroborate our hypotheses, which were derived from literature on human reach models of egocentric versus allocentric frames of references.

Landmark vs. No Landmark

Humans are capable of encoding object and target locations relative to a part of their body (Crawford et al., 2004; Henriques et al., 1998; Lemay and Stelmach,

2005; McIntyre et al., 1998; Pouget et al., 2002; Vindras and Viviani, 1998), and they can also encode these locations relative to surrounding landmarks and stimuli (Brouwer and Knill, 2007; Burnod et al., 1999; Carrozzo et al., 2002; Goodale and Haffenden, 1998; Obhi and Goodale, 2005; Olson, 2003). Typically, both types of information are available in the natural environment to be utilized for spatial coding. Allocentric information provides an additional frame of reference, given that it is available at the same time as the target and within a close proximity (Chen et al., 2011; Diedrichsen et al., 2004). Previous studies have shown that the brain will use allocentric information to improve target localization when a target is surrounded by other objects in space (Hay and Redon, 2006; Krigolson and Heath, 2004; Lemay et al., 2004; Obhi and Goodale, 2005).

Previous studies demonstrated that the presence of allocentric landmarks improves both the accuracy and precision of the action (Krigolson and Heath, 2004; Krigolson et al., 2007; Obhi and Goodale, 2005; Thaler and Goodale, 2011). Results from the present study revealed an improvement in precision but not accuracy when monkeys made gaze shifts towards remembered target locations in the presence of a large-scale allocentric cue. One possible explanation for the lack of improvement in gaze accuracy may be interspecific differences between humans and nonhuman primates and their abilities to make use of allocentric information. A more likely explanation is that our experiment introduces only a single allocentric landmark, whereas multiple allocentric landmarks are available when viewing natural scenes. Because allocentric landmarks have an attractive bias on gaze endpoint, a lone

landmark can be distracting for the subject. Not only do multiple landmarks provide a more reliable allocentric reference frame for the subject (Fiehler et al., 2014), they could also cancel out the cue attraction effect, thereby improving gaze accuracy.

Subsequently, we quantified the influence of the allocentric landmark on gaze behaviour and found that the landmark exerts an attractive influence on the mean gaze endpoint, with mean LIs of 0.14 (M1) and 0.17 (M2). On average, gaze behaviour moves around 15% of the total distance between the remembered target location and the landmark in cued versus non-cued conditions. Similarly, a previous study by Diedrichsen et al. (2004) found that human reach behaviour tends to be biased towards nearby landmark(s) in memory-guided reach tasks.

Our data showed a significant difference between high and low landmark eccentricities. When landmarks are located closer to the initial gaze position, they have a greater attractive influence on the gaze endpoint. A simple explanation for this relies on the fact that allocentric landmarks increase in reliability when they are closer to the fixation point. Consequently, the brain assigns more weight to allocentric information when processing the final action command (Byrne and Crawford, 2010).

Shift vs. No Shift

The cue conflict task was designed to introduce a dissociation between egocentric and allocentric information. In this task, various spatial and gaze parameters can be controlled to assess their influence on egocentric and allocentric weighting. The current study manipulates the eccentricity of the allocentric landmark

to the fixation point and the direction of cue shift relative to the fixation point and the target locations. But it is capable of varying other parameters such as delay duration, eccentricity of initial target locations, or the eccentricity of landmarks relative to target.

Given our current configurations, we reported mean AWs of 0.27 (M1) and 0.23 (M2), which were roughly 75% egocentric and 25% allocentric. Present results support previous findings in human reach models where the egocentric and allocentric reference frames are combined based on their relative reliabilities (Byrne and Crawford, 2010; Fiehler et al., 2014; Thompson and Henriques, 2010). Data from these reach models established mean AWs between 0.3 and 0.5, which is higher than the current result of 0.25. However, we cannot attribute this difference to differences in reach and gaze control. In the current data, certain combinations of parameters that maximize allocentric reliability can also push the allocentric weight to above 0.4. It is also important to note that human studies often used longer delays (5 to 10 s) relative to our study (0.5 to 1.2 s), leading to the decay of egocentric information, which incentivizes the use of the allocentric reference frame.

We assessed three gaze parameters: the eccentricity of the allocentric landmark to the initial gaze location (fixation point) and the directions of cue shift relative to the initial gaze and target locations. For landmark eccentricity, the results were comparable to the cue versus no cue experiment: dependence on allocentric information increases with the proximity of the landmark to the initial gaze position.

For the direction of landmark shift, AW increases when the cue shifts away from the fixation point or the target. This can also be explained using the theory of relative reliabilities. Since the monkeys must attend to the fixation point and target locations during this task, any landmark shifts towards these locations were more likely to be perceived as apparent motion. Although we hid the landmark shift behind the mask, the mask duration might not be enough to conceal apparent motion of the landmark towards attended regions on the screen, reducing allocentric reliability, thereby resulting in the current dataset. Mask duration can be varied in a future study to examine this possibility.

Another possible cause for the decrease in AW when the landmark is shifted towards the initial target location may be due to the conflict of egocentric and allocentric information, as both remembered target location and landmark location are adjacent post-landmark shift. Previous studies have shown that egocentric information decays over the course of 2 to 5 seconds and people are more reliant on allocentric information when the memory delay increases (Carrozzo et al., 2002; Glover and Dixon, 2004; Goodale and Haffenden, 1998; Lemay et al., 2004; McIntyre et al., 1998; Obhi and Goodale, 2005). The current study used delays between 0.5 to 1.2 seconds, consequently, the monkeys preferred egocentric information when there is a conflict between the reference frames. I would expect to see a gradual transition to allocentric information with prolonged memory delays. Unfortunately, it is difficult to maintain the monkeys' motivation throughout longer trials.

It is interesting to note the differences in the spread of gaze endpoints between cardinal and orthogonal targets (Figure 9B) – gaze spreads further away from the orthogonal axis in comparison to the cardinal axis. Given the fact that there are extraocular muscles (media, lateral, superior and inferior rectus) along the cardinal axis, gaze shifts to cardinal targets can be achieved by activating a single pair of synergistic muscles (Porter et al., 1995), effectively minimizing directional error. On the other hand, gaze shifts to orthogonal targets make use of all three pairs of extraocular muscles (Porter et al., 1995), drastically increasing directional error.

Limitations

We minimized the possible effect of confounding cues in the experimental setup by training and recording in complete darkness. Some limitations to my experimental procedures include: training the monkeys to understand the importance of the landmark, and training in an unnatural laboratory setting.

We trained the monkeys to recognize the importance of the allocentric landmark because our goal is to decipher the neuromechanisms responsible for encoding allocentric information. Some might argue that this biases gaze behaviour towards the allocentric landmark, inflating allocentric weight. While there was evidence of improved mean allocentric weight of up to 0.5 during training, this mean returns to a plateau around our result of 0.25 post training.

Another limitation of this study was that it was conducted in an unnatural environment. A more ecologically sound experiment was done by Fiehler et al.

(2014) in human reach. Natural scenes (breakfast arrangement) were shown to subjects who were instructed to point at a missing object in the subsequent image, while other objects were moved according to several parameters. They found that AW increased with the number of task relevant objects that were displaced in the second image. This study suggests that perhaps multiple allocentric cues will raise allocentric weight. The monkeys' natural habitat contains many more stimuli and landmarks that can all be used as allocentric cues, unfortunately, this is difficult to mimic in the laboratory setting.

Possible Neuromechanisms

Neural representation of egocentric and allocentric reference frames have been studied as a part of the dorsal and ventral streams of the two-stream hypothesis, respectively. Both streams originate from early visual areas (area V1) and project dorsally to the posterior parietal cortex (PPC) or ventrally to the interior temporal cortex (IT) (Carey et al., 2006; Goodale and Humphrey, 1998; Goodale et al. 2004; Merigan and Maunsell, 1993; Schenk, 2006). The dorsal (action) stream has been suggested to represent and update visual target locations in gaze-centered coordinates in the PPC for action planning (Batista et al., 1999; Crawford et al., 2004; Fernandez-Ruiz et al., 2007; Medendorp et al., 2003; Pouget et al., 2002). Several neurophysiology studies have also shown projections from the ventral stream including area V4 (Ungerleider et al., 2008) and posterior inferior temporal area (TEO) (Distler et al., 1993; Webster et al, 1994) to the lateral intraparietal cortex

(LIP) in the PPC. Chen et al. (2011) proposed that allocentric information about a remembered target location is transformed into egocentric information at the earliest opportunity to be included in action planning.

Allocentric information can also be processed in the frontal cortex. Olson et al. (Moorman and Olson 2007a, 2007b; Olson and Gettner, 1995; Olson and Tremblay, 2000; Tremblay et al., 2002) showed object-centered responses in the supplementary eye fields (SEF) in monkeys trained in object-centered saccade tasks. Granted, SEF projects reciprocally with LIP, making it hard to discern their unique roles. However, a study by Sabes et al. (2002) using a similar object-centered saccade task found no object-centered responses in the LIP, rather, there was a retinotopic movement oriented correlation with neuron firing rate.

This information suggests the possibility that allocentric information enters through the SEF and then projected to the LIP where it is converted into an action plan. Therefore, to understand neurophysiological representation of allocentric information, one must start at the SEF.

CONCLUSION

In addition to playing a critical role in our everyday lives (e.g. driving), allocentric representation is an essential part of the discourse in understanding the two-stream hypothesis, and the dissociation of action and perception.

Clinical implications of the two-stream hypothesis include patients suffering from optic ataxia, visual agnosia, and hemispatial neglect where either action or perception streams has been damaged. Efforts by Harvey M et al. (2012; Opolka et al., 2013) have shown that, using a rod bisection task, it is possible to train perception via action in patients with hemispatial neglect. Perhaps a deeper understanding of the ventral (perception/allocentric) stream will aid in the development of better training intervention programs for these patients.

A large number of studies have studied neural representation of egocentric and allocentric information in human reach models using functional magnetic resonance imaging. To our knowledge, no one has yet applied electrophysiological techniques to examine the underlying neuromechanisms interconnecting egocentric and allocentric representations of remembered target locations. This study aims to bridge the gap between these two methods by bringing reach literature into the gaze control system. We have confirmed our hypotheses that the reliability of a large-scale allocentric landmark is weighed by an internal process and combined with egocentric information to improve precision and accuracy of gaze shifts towards remembered

target locations. This weighting process is dependent on gaze parameters that influence the reliability of the allocentric cue.

Finally, the next step in this line of research will be to use electrophysiological techniques to record from the aforementioned SEF. Ultimately, the goal is to collect neuron data and decode the neural substrates of allocentric representation.

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