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Preparing Non-Human Primates to Study Hand-Eye Coordination in Frontal Eye Fields (FEF) During Delayed Movement Task

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WASHINGTON UNIVERSITY IN ST. LOUIS

McKelvey School of Engineering
Department of Biomedical Engineering

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by
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A thesis presented to
the McKelvey School of Engineering
of Washington University in
partial fulfillment of the
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Juliusz Cydzik

Washington University in St. Louis

May 2023

ABSTRACT OF THE THESIS

Preparing Non-Human Primates to Study Hand-Eye Coordination in Frontal Eye Fields (FEF) During Delayed Movement Task

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Master of Science in Biomedical Engineering

Washington University in St. Louis, 2023

Professor Lawrence Snyder, Chair

Hand-eye coordination enables humans and non-human primates to use their hands and eyes to perform various tasks. We are interested in coordination at the systems level, where saccades and reaches are encoded. The parietal reach region (PRR), situated at the posterior end of the intraparietal sulcus (IPS) and overlapping portions of the medial intraparietal area (MIP) and V6a, is commonly attributed as an area which contains cells that encode the direction or endpoint of an upcoming reach, particularly for the contralateral arm [17][6][15]. Similarly, the lateral intraparietal area (LIP), located midway along the lateral bank of the IPS, is commonly attributed as an area containing cells that encode the direction or endpoint of an upcoming saccade [16][11][7][4][18]. Coordinated behavior is often stereotyped in research, many unimanual reach studies have brought forth findings based on stereotyped behavior in LIP and PRR, in the Free Choice task LIP cells encoded the direction or endpoint of an upcoming saccade. A stereotyped

behavior is a behavior instructed by experimenters which always occurs in a manner that would be unlikely to happen in nature. We want to train subjects in non-stereotyped, bimanual reaching tasks to be able to study how saccadic behaviors are naturally coded in FEF.

Animals naturally make a saccade first to one target and then the other on separate trials prior to a hand movement, creating different patterns of limb–gaze coordination on different trials [14]. These results suggest that the parietal cortex plays at best only a permissive role in some aspects of eye–hand coordination and makes the role of LIP in saccade generation unclear. Previously LIP activity was attributed as an area that coded saccades as they reached targets, providing distinguishable activity between different targets. In our experiment, saccades could go to either arm's target, yet LIP did not distinguish between those two cases (saccade to the target of the right arm versus saccade to the target of the left arm) prior to the actual onset of the saccade. Frontal eye fields (FEF) an area located in the frontal cortex, specifically in Brodmann's area 8a in primates, receives projections from temporal and parietal cortices and has direct projections to the superior colliculus [8]. One study which induced monkeys to make saccades in the absence of visual targets classified three types of perisaccadic activity in FEF and found that the activity could account for saccadic generation [5]. More recently, a study found that responses in FEF are suppressed when the animal maintains fixation for longer durations during a visual foraging task [13].

Based on the literature mentioned, we believe that FEF may play a role in saccade generation. We would like to determine if FEF encodes saccadic movements made to targets cued for the left hand versus targets cued for the right hand during a "bimanual apart task". In this study we defined, assessed, and influenced saccadic behavior in one subject during the bimanual apart task. We found that non-human primate subjects preferred certain saccade targets over others in the bimanual apart task. This finding indicated that the subject needs further training for us to study saccade generation in FEF. We believed that we could alter behaviors, in particular choice making during a task by adding rewards and altering viii stimuli/targets. We trained non-human primates to choose both targets in the bimanual apart task for two of the target combinations used in the task. If we successfully train the subject to saccade to both targets on the remaining combinations with our Bimanual Apart Flash Period Task, the behavioral paradigm can serve as a useful task to study FEF. This model will allow us to test the hypothesis that FEF encodes upcoming saccades when animals reach for two targets.

Chapter 1: Materials and Methods

1.1Procedures

All procedures conformed to the guide for care of and use of lab animals and are approved by Washington University Institutional Animal Care and Use Committee. One rhesus monkey served as a non-human animal subject.

1.2 Behavioral Tasks

We designed 5 visually guided tasks to train and test on the subject. For each task the subject was first instructed to fixate (±3°) on a circular white stimulus (1.5° × 1.5°) centered on the screen in front of them. Left and right hands touched home pads situated at waist height and 20 cm forward of each shoulder (Fig 1a). After 500 milliseconds (ms) a selected target or a combination of two targets appeared on the screen and remained present until the end of the delay period. We set a fixed delay of 1500 ms and a random delay of 500 ms. Once this delay period ended the circular white stimulus or "go cue" was extinguished indicating that the subject should now make a saccade and/or a reach (Fig 1c). The tasks consisted of a one arm left or right reach to a target elicited by a red or green (right and left cues) target (unimanual reach task), only a saccade made to a target elicited by a white target (saccade task), a reach with both arms made to one target elicited by a blue target (bimanual together reach task), a reach with both arms made to separate targets elicited by a combination of green (left cue) and red targets (right cue) presented together (bimanual apart task) (Fig 1b). All targets presented were (5° × 5°) located at one of eight equally spaced locations and bimanual apart targets were diametrically opposite to one another. Throughout saccade and unimanual reach trials, the hand(s) that were not instructed to move were required to remain on the home pad(s). On unimanual reach trials, eye movements to the target of the reach were required. On bimanual reach trials, eye movements were unconstrained, once the subject was cued to initiate the movement, the left and right hands were required to hit one of eight possible target combinations within 500 ms of one another. We created three separate tasks almost identical to the bimanual apart task. In these tasks we observed the subjects eye position, we measured when the subject made the first saccade, its location (preferred vs non preferred target), and duration. On the bimanual apart reward task, the subject was given an additional conditional reward for eye movements made to the non-preferred target; the reward was available for a period of 180 ms after the go cue. On the bimanual apart reward task, the subject was given an additional conditional reward for eye movements made to the non-preferred target. On the bimanual apart flash task, the subject was given an additional conditional reward for eye movements made to the non-preferred target and the non-preferred target flashed green or red light rapidly for 100ms. On the bimanual apart flash period task, the subject was given an additional conditional reward for eye movements made to the non-preferred target and the non-preferred target flashed green or red light rapidly for 300, 250, 200, 150, and 100 ms. The flash period was adjusted manually and was dependent on the subject's behavior. On all tasks successful trials were rewarded with a drop of water or juice.

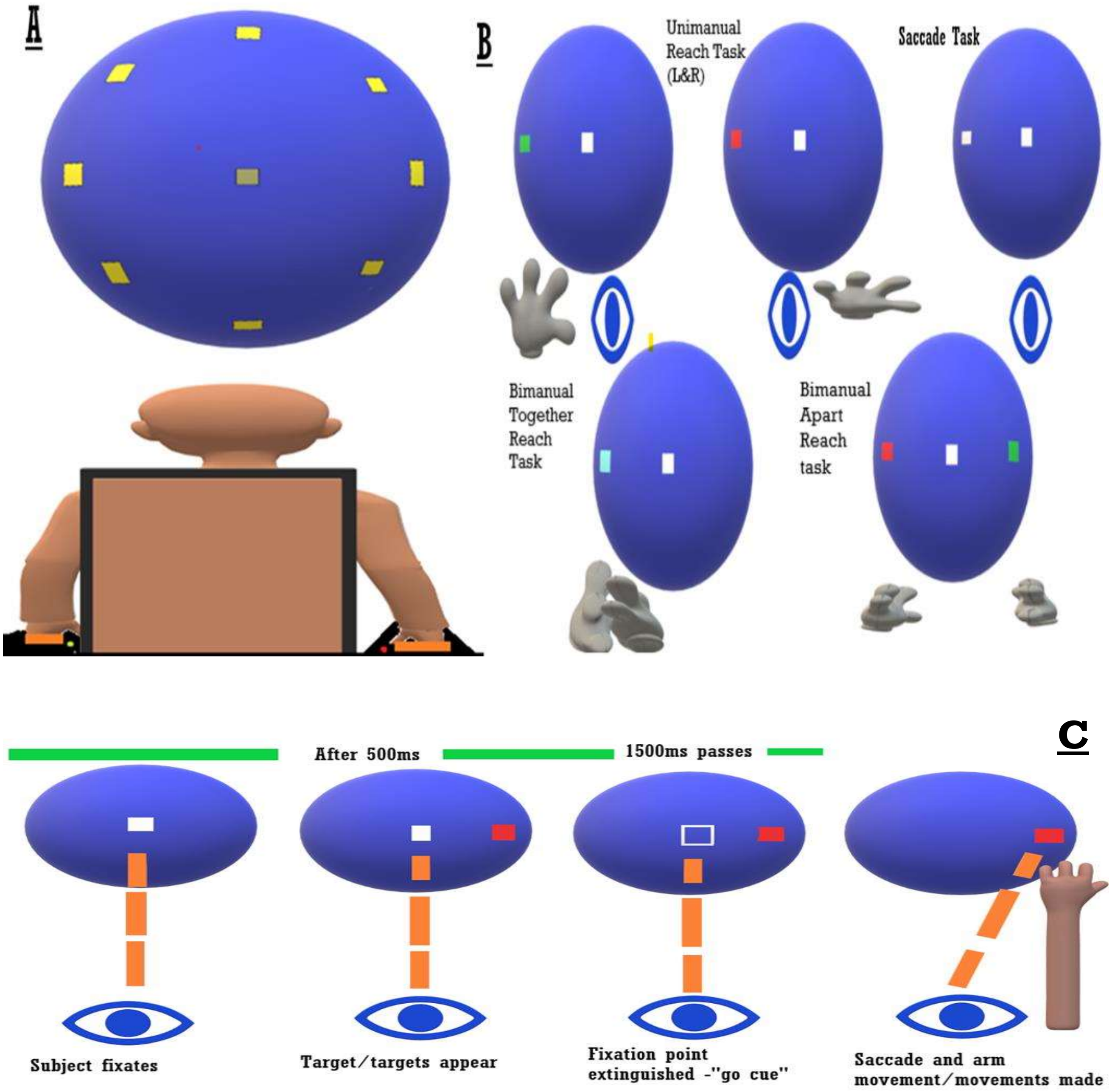

A
B
Unimanual Reach Task (L&R)
Saccade Task
Bimanual Together Reach Task
Bimanual Apart Reach task
C
After 500ms
1500ms passes
Subject fixates
Target/targets appear
Fixation point extinguished -"go cue"
Saccade and arm movement/movements made

Figure 1: Behavioral Setup and Task Visual: Subject are placed in a chair, with arms unconstrained, instructed to put two hands onto home buttons with a screen in front of them (1a). On that screen 1 fixation target and 8 peripheral targets are presented through lighted buttons. In all 5 tasks (and 3 additional bimanual tasks) (1b) animal fixates, we set a delay period, after 500ms peripheral target or targets appear. Once the delay period ends the fixation point is extinguished ("go cue") and saccades and arm movements begin(1c).

1.3 Eye tracking

ISCAN RK-726PCI Pupil/Corneal Reflection Tracking System, set to accept 120Hz signal, was used for non-invasive infrared eye tracking (Fig 2). All eye tracking data was saved and used in the analysis.

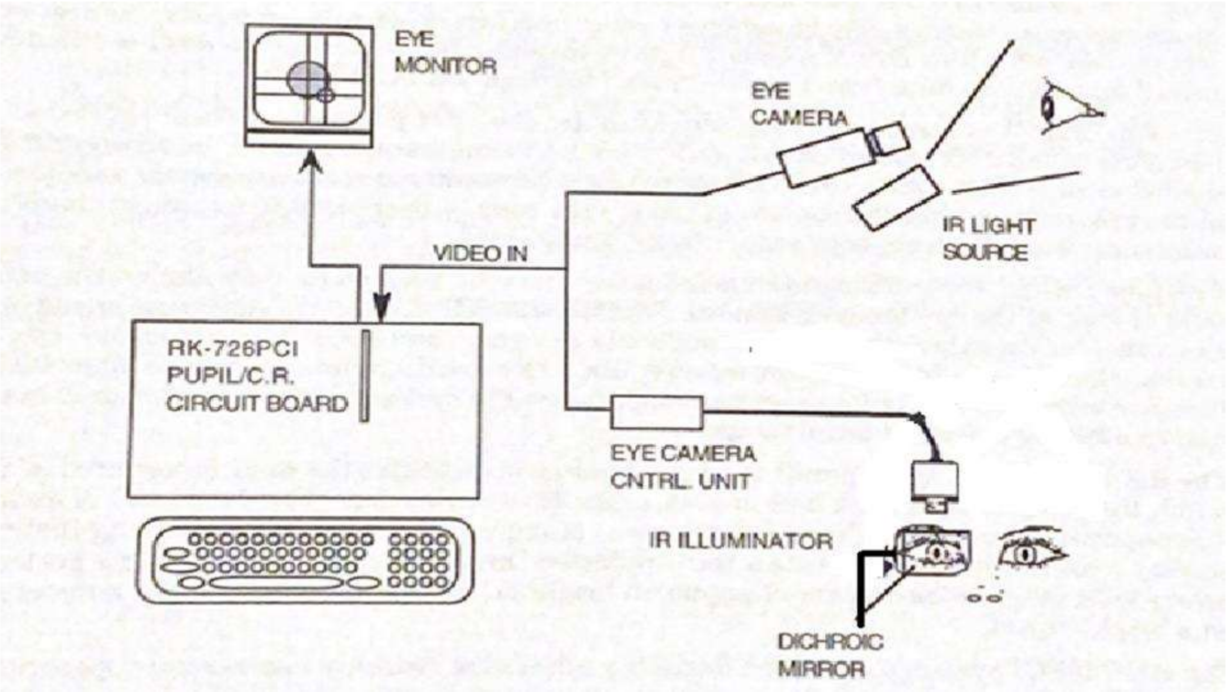


Figure 2: Eye Tracker Visual

1.4 Analysis

All analysis was done in MATLAB.

We calculated Accuracy as follows:

(correct/ (correct +run error) *100) =accuracy

We calculated Ratios for all 8 target combinations individually:

x*= saccade values preferred direction per a session*

y*=saccade values non preferred direction per a session*

$X=(\mu x/(\mu x+\mu y)100)$ $\qquad$ $Y=(\mu y/(\mu x+\mu y)100)$

$X:Y$

We took the mean of all ratios per a target combination individually:

$\mu(X):\mu(Y)$

We conducted Wilcoxon signed rank test for all combinations for the initial 18 months of sessions and last 4 sessions:

Xi*=preferred mean 18 months* ***Xj****=preferred mean last four sessions*

$$\mathbf{p2}=\mathbf{Pr}\left(\frac{1}{2(Xi-Yi+Xj-Yj)}>0\right)$$

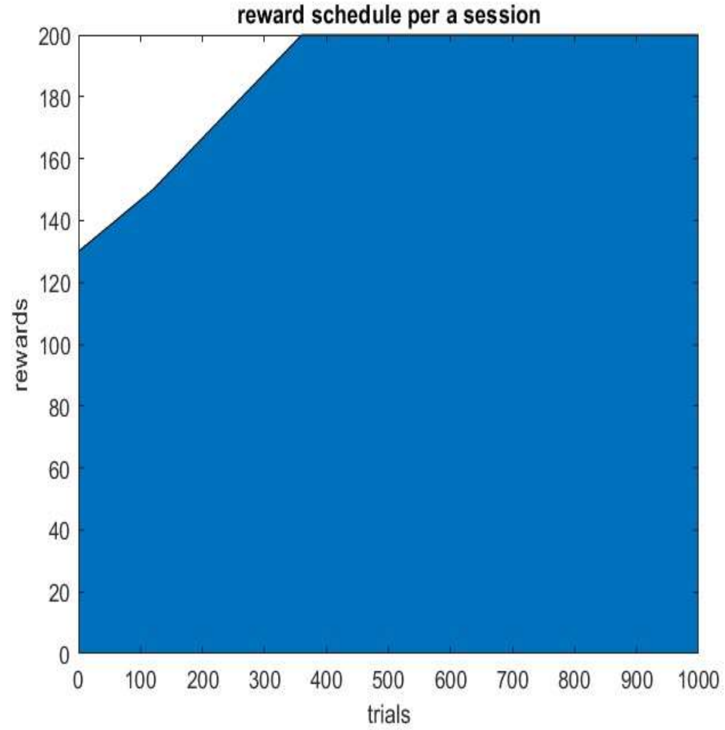
Chapter 2: Initial Assessment of Subject

2.1 Introduction

We ultimately asked can the subject be used to study saccadic behavior in FEF? For the subject to be used he would have to make the first saccade to both targets during a session in a ratio that falls between 25% and 75% of saccades made to preferred to non-preferred direction. Between 25% and 75% of saccades made to preferred to non-preferred direction, was the widest ratio found in subjects in our previous study [14]. To properly record and analyze neural activity for both targets, we need to collect a similar number of trials for both preferred and non-preferred targets. With a wide ratio we would have to collect many more trials than if the subject had a narrow ratio. Subjects were previously trained with operant conditioning; a subject is given a reward for correct behavior. In our case we use liquid rewards. When a subject first learns a task, it is taught to perform the task quickly and is given a liquid reward for 130-300 ms after completion. NHP subjects and humans have no direct method of educational communication, we need to ensure the subject is performing the task correctly and understands what is expected using time, stimuli, and reward. In this chapter, we defined, assessed, and influenced the subject's saccadic behavior using tasks and the measurements taken during these tasks.

2.2 Delay

The delay period is a period when the subject is instructed to wait before performing any of the tasks described in our methods section. The delay period starts at the beginning of the "go cue", throughout the period the targets are turned on and the animal fixates on the "go cue", once the delay period ends the "go cue" is extinguished. When we first evaluated the subject's delay, we noticed that the subject worked at a delay under 1500ms on all of our tasks. Our subject was trained to perform the task but was not trained for us to study saccade generation in FEF. We wanted to know if the subject can perform tasks at a delay of 1300ms to 1500ms. Subjects perform better when given more time to prepare tasks [3]. To increase the delay period, we initiated a new reward schedule, we increased the subject’s rewards as he completed a block of 120 trials of all of our tasks interleaved (Fig 3). Once the subject completed 4 blocks (480 trials) we increased the reward to 200ms. We sometimes changed the reward from water to juice, but the subject did not seem to have a preference. We saw that our subject can work at a delay of 1500ms (Fig 4).



rewards	trials
130ms	120 trials
150ms	120 trials
175ms	120 trials
200ms	≥240 trials

Figure 3: Reward Schedule per Individual Sessions: liquid rewards per a block of trials (120 trials each) until maximum reward is given. After 240 trials the animal typically remains at a reward of 200ms.

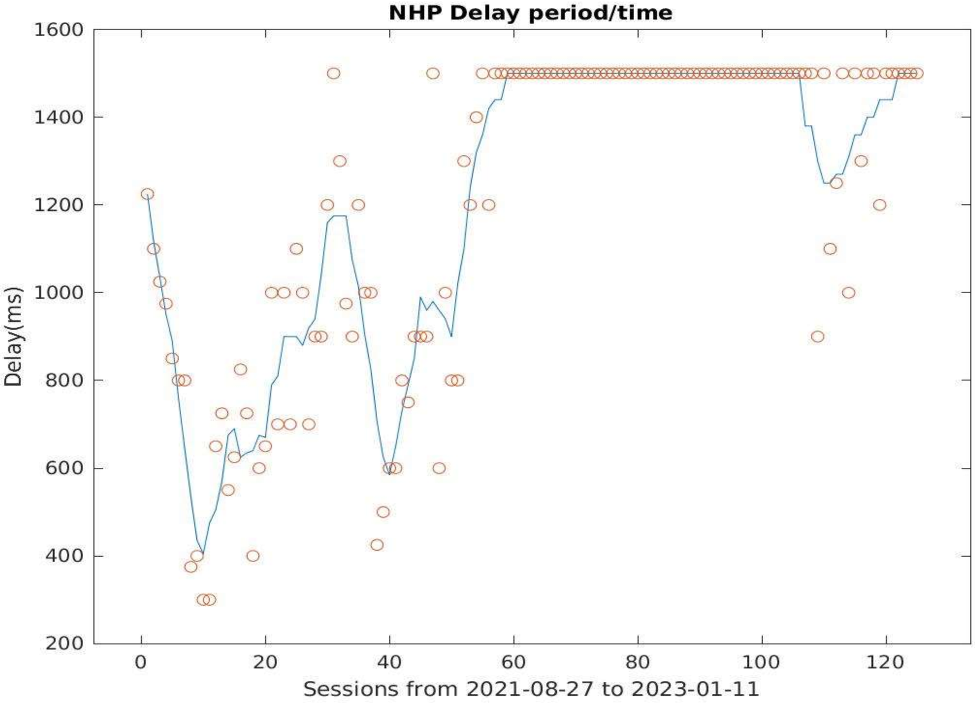


Figure 4: NHP Delay over Time: Subjects delay over an 18-month period. Points (orange) represent each session. Generally, one session occurred per a day with some cases of two sessions per one day.

2.3 Accuracy

Simultaneously we reviewed the subject's accuracy; the accuracy is the rate at which the subject performs the trials correctly. We wanted to know if the subject can accurately perform the task at an increased delay. In our experiment the subject can perform two kinds of errors an error for not starting the task or a run error during the task. With increased delay the animal's accuracy was slightly affected, in the first 9 months we had a mean accuracy of 72% and on the next 9 months we had a mean of 68%. (Fig 5)

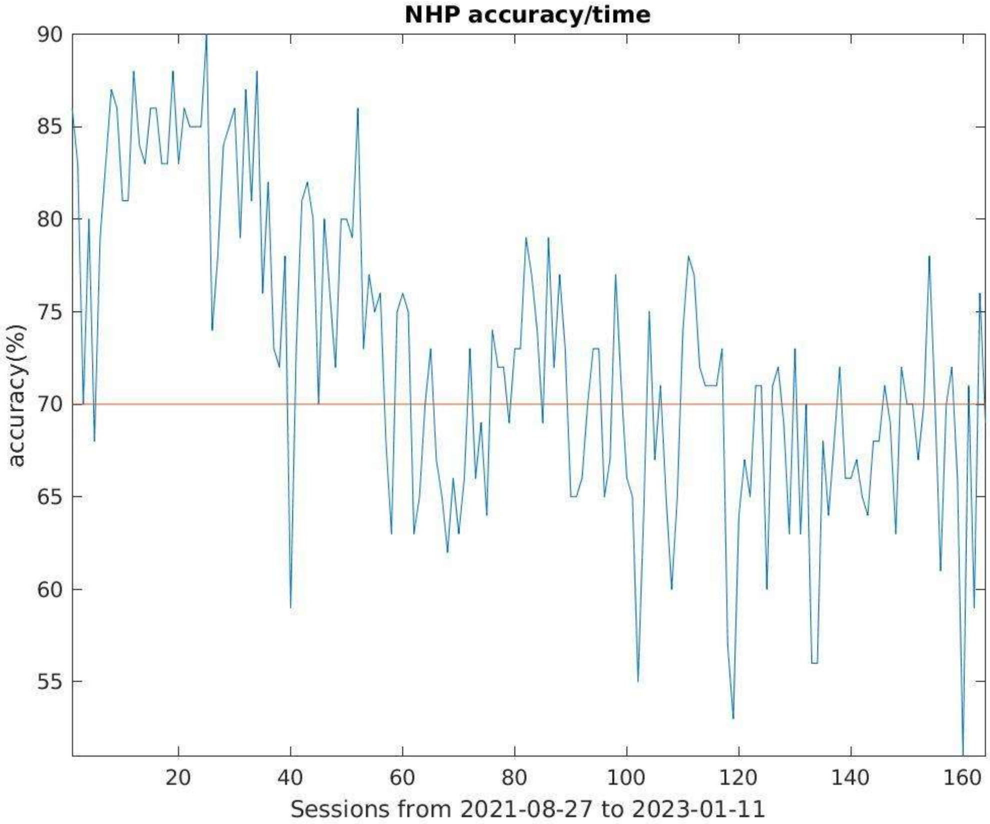


Figure 5: NHP Accuracy over Time: accuracy of task performance, measurement taken concurrently with delay.

2.4 Initial ratio

After 18 months of training the subject, we calculated a ratio of saccade choices only during the bimanual apart task. A choice is a behavior where the subject can voluntarily decide what action to take. Our subject was instructed to move both arms to separate targets, to a total of eight different target combinations (Fig 6). We never instructed the subject to make specific eye movements to a given target, but we still logged the subjects saccadic eye movements. We were interested in the first saccade an animal makes on a trial. We asked if all saccadic eye movements to targets of the lefthand and targets of the righthand fall in between a ratio of 25% and 75%? We found the subject making saccadic movements to the target combinations in ratios that favored one target over the other (Fig 7). None of our ratios came close to our boundary, we determined the animal cannot be used to study saccadic behaviors in FEF without further training.

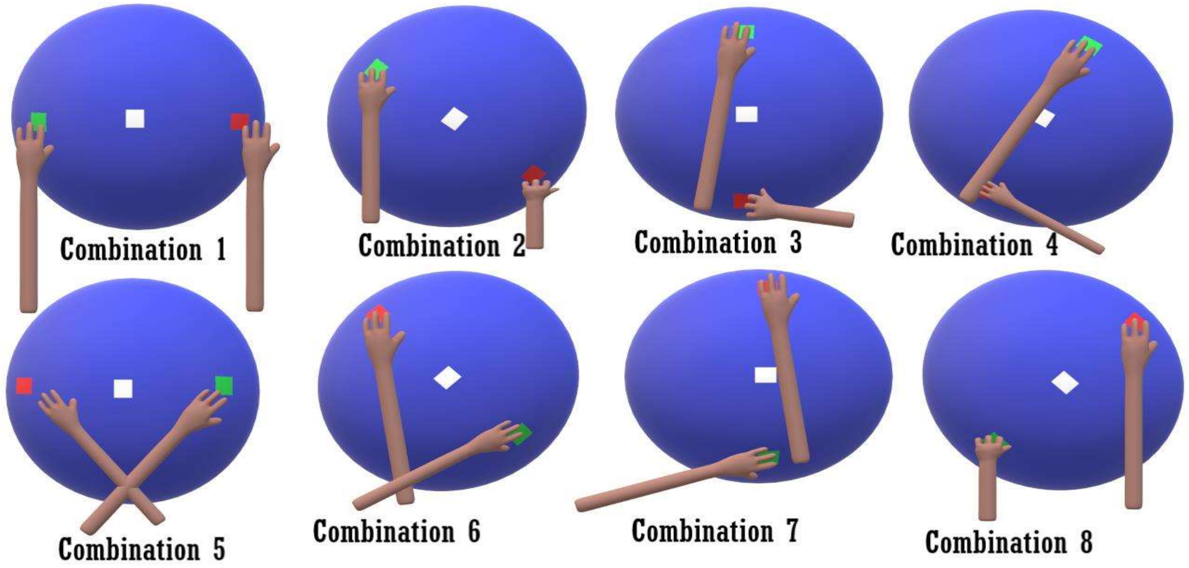


Figure 6: Combinations of Targets: This figure shows how target combinations are presented to the subject together in the bimanual apart task. The red target calls movements of the right arm, and the green target calls movements of the left arm.

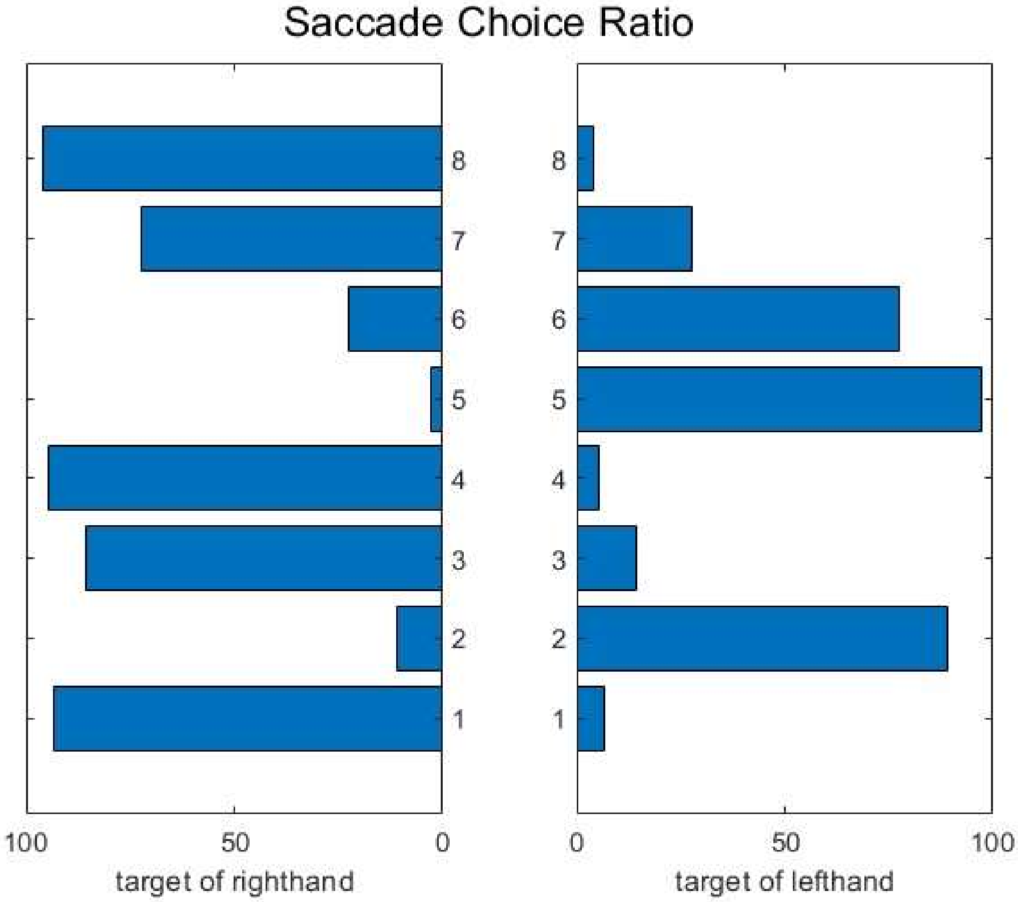


Figure 7: Ratio of Saccade Choices: Mean ratio of saccadic eye movements made to the left handed or right-handed targets for only the bimanual apart task.

Chapter 3: Behavioral Training

3.1 Introduction

In the past chapter we successfully trained the animal to perform all tasks at a delay of 1500ms and identified a preference for certain targets when the subject performed the bimanual apart task after a period of 18 months. Due to the large saccadic choice ratios (Fig 7), we determined that the subject cannot be used to study saccadic behaviors in FEF during the bimanual apart task. In this chapter we will retrain the subject for us to study saccadic behaviors in FEF, focusing on lessening the preference for certain targets. Can we alter saccade behaviors during a task, in particular choice making by adding rewards and altering stimuli/targets? We created three tasks, the bimanual apart reward task, the bimanual apart flash task, and the bimanual apart flash period task. We had five copies of the bimanual apart flash task with varying flash periods. To confirm our results, we took the ratio data from the 18-month period and compared it to four final sessions conducted with the original bimanual apart task.

3.2 Bimanual Apart Reward Task

We used the bimanual apart reward task (Fig 8), to try to change the subject's saccadic behavior. Originally the reward was available 150 ms after the go-cue, for no more than 180 ms. We checked how many rewards the subject earned at the end of each session. At first, the subject rarely received rewards and those rewards that he did receive were sometimes incorrect rewards for fast double saccades. A fast double saccade is a saccade made from the preferred target to the non-preferred target in time for the subject to earn an additional reward. For the first two sessions conducted, we allowed the subjects to make fast double saccades, so that it is aware of the reward being available. Once we saw the subject making those saccades, we shortened the window of how long the reward is available. If the animal did not earn the reward, we would shift the time at which it becomes available. As the animal started making some saccades we increased the reward per each target, to encourage the animal to make more saccades there and decreased the reward if we saw the animal making more frequent saccades. We compared and plotted the ratios over 18 months together with the Bimanual Reward Task. The task was unsuccessful, we still saw the same preference as in our initial assessment (Fig 9).

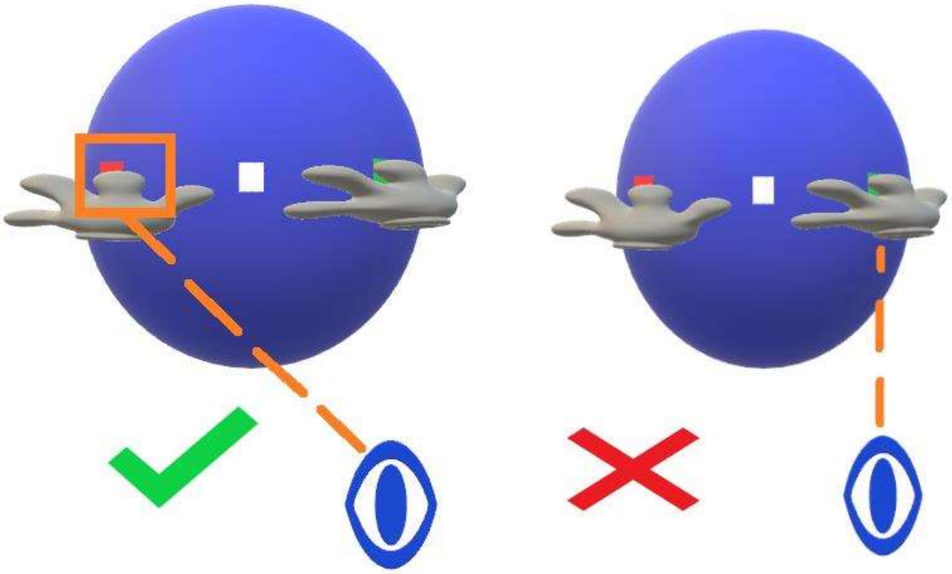


Figure 8: Bimanual Apart Reward Task: The task allows the animal to earn an extra liquid reward for saccades made to the non preferred target. To start,the reward is available 150 ms after the “go cue” for 180 ms.

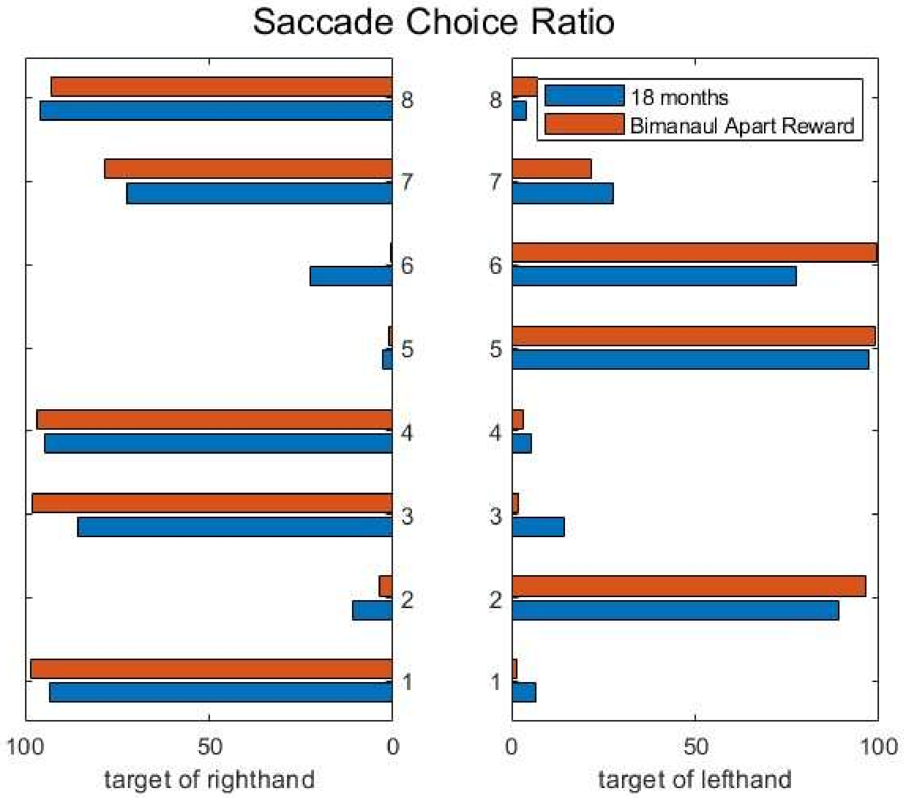


Figure 9: Ratio of Saccade Choices during Bimanual Apart Reward Task: Mean ratio of saccadic eye movements made to the target of the left hand or target of the right hand for our initial assessment over 18 months and our bimanual reward task.

3.3 Bimanual Apart Flash Task

Next, we used the bimanual apart flash task to further encourages saccades to the targets with ratios that did not favor one side over the other. We saw change in the subject's behavior, but we still saw that the subject preferred certain combinations (Fig 10). Once again, we increased the reward for each target to encourage the animal to make more saccades towards the non-preferred direction and decreased the reward if we saw the animal making more frequent saccades. We started to see shifts for certain combinations, some of these shifts towards our ratio and others just signifying a change.

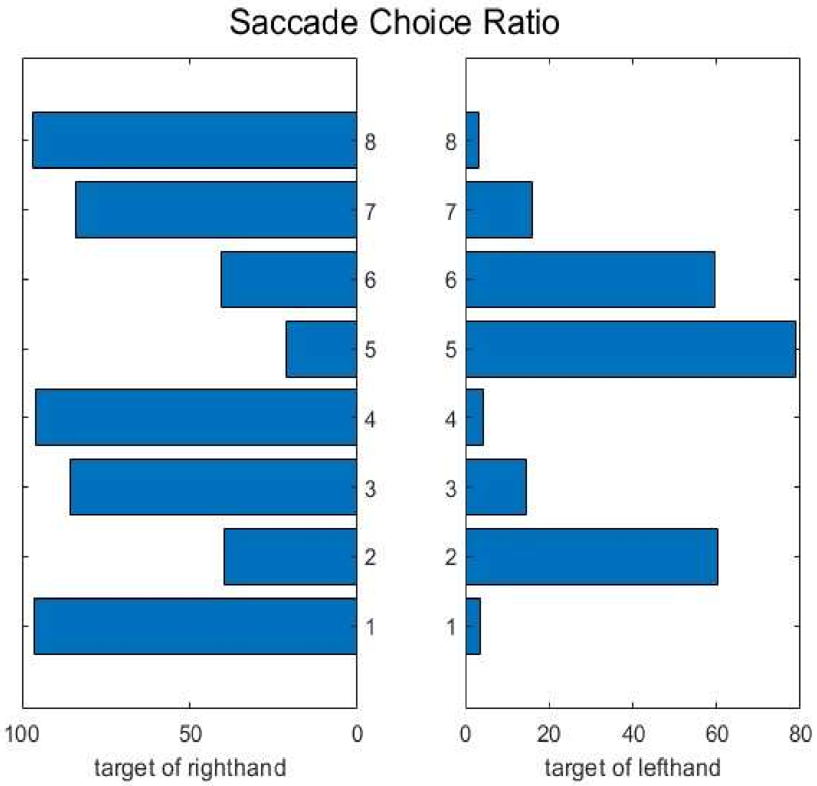


Figure 10: Ratio of Saccade Choices during Bimanual Apart Flash Task: Mean ratio of saccadic eye movements made to the left handed or right handed target during Bimanual Apart Flash Task. Notice how with training, combinations 2 and 6 have more equal ratios.

3.4 Bimanual Apart Flash Period Task

Next, we tried to extinguish both targets in two different variations of the task. We observed the animal making the saccade to the non-preferred target as we extinguished it. The animal did not perform well nor saccade to the non-preferred target on the trials where we turned off the preferred target. Since we already flashed the target on previous trials and the subject responded to extinguishing the non-preferred target, we decided that we could manipulate the period that the target is flashing.

We conducted 2 sessions with an array of different flashing periods. We created tasks with different flashing periods, the targets flashed for 300, 250, 200, 150, and 100 ms. If the subject did not perform well on the first introduction of these tasks, we planned to step him down from 300 ms flashing to 200 ms flashing, from 200 ms flashing back to no flashing. If he performed well and we noticed five consecutive failures, we stepped him down by 50 ms on each occurrence. In this task we noticed a ratio of nearly 50:50 for combinations 4, 5, and 6 and a reverse in polarity for combinations 2 and 3 (Fig 11).

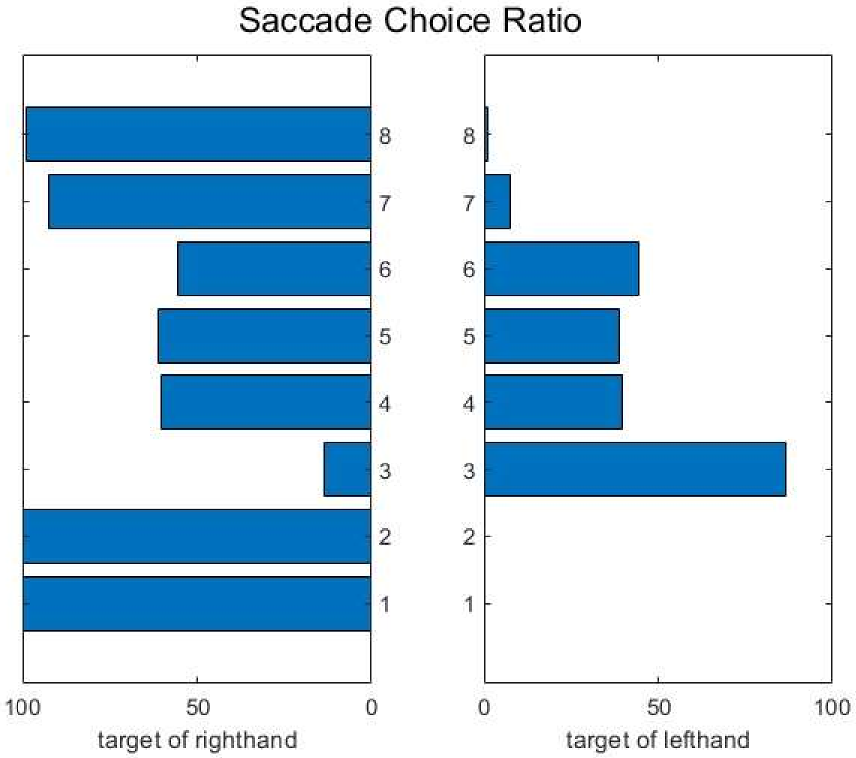


Figure 11: Ratio of Saccade Choices during Bimanual Apart Flash Period Task: Mean ratio of saccadic eye movements made to the left handed or right handed target during flash period task.

3.5 Final Results

To confirm our result, we conducted four final sessions with the original bimanual apart task. We calculated that the subject had a ratio of 51:50 for combination 3 and a ratio of 71:29 for combination 2. For combination 2 the ratio flipped from left-handed saccade targets to right-handed saccade targets (Fig 12).

To really see if a change occurred, we plotted the ratios from the first 18 months (blue) with the ratios from the last four sessions (red) to see if the ratio shifted (Fig 13). We eliminated all target combinations with an N of less than 16 trials. We had 321 combinations for the first 18 months and 32 combinations for the last four sessions. We conducted a two-sided sum rank test. For Combination 2 we received a significant result ($p<0.05$) and for combination 3 we received a trend ($p=0.05$). This result showed us that we did see a shift of saccade choices that fell within our boundary of 75% (Yellow Diamond at the top of y axis Fig 13) and 25% (Yellow Diamond at the bottom of y axis Fig 13) for combination 2 and combination 3. A change had clearly occurred, we were able to adjust saccade choice preference for two of our combinations. For our other 6 combinations we did not see a change in saccadic choices that fell within our boundary. For data to be significant it needed to meet two criteria, 1) a significant *p*-value 2) a ratio within our boundary.

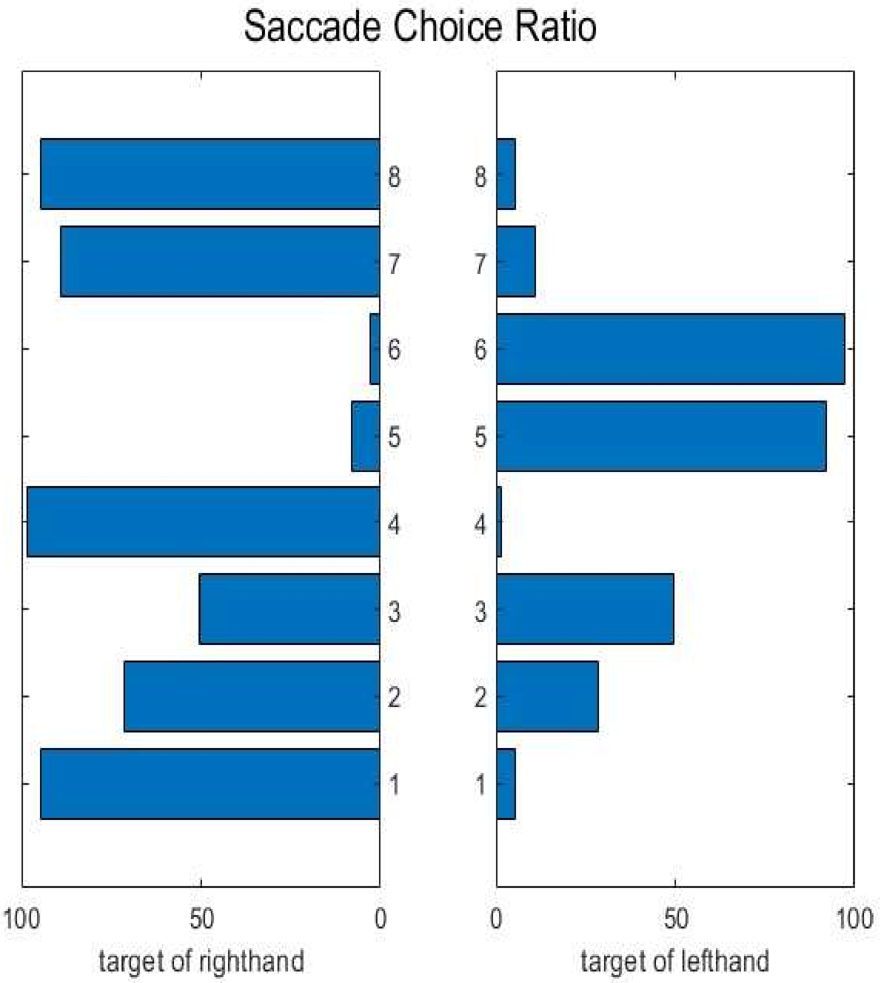


Figure 12: Ratio of Saccade Choices during 4 Final Sessions: Mean ratio of saccadic eye movements made to the target of the left hand or right hand during the last 4 sessions

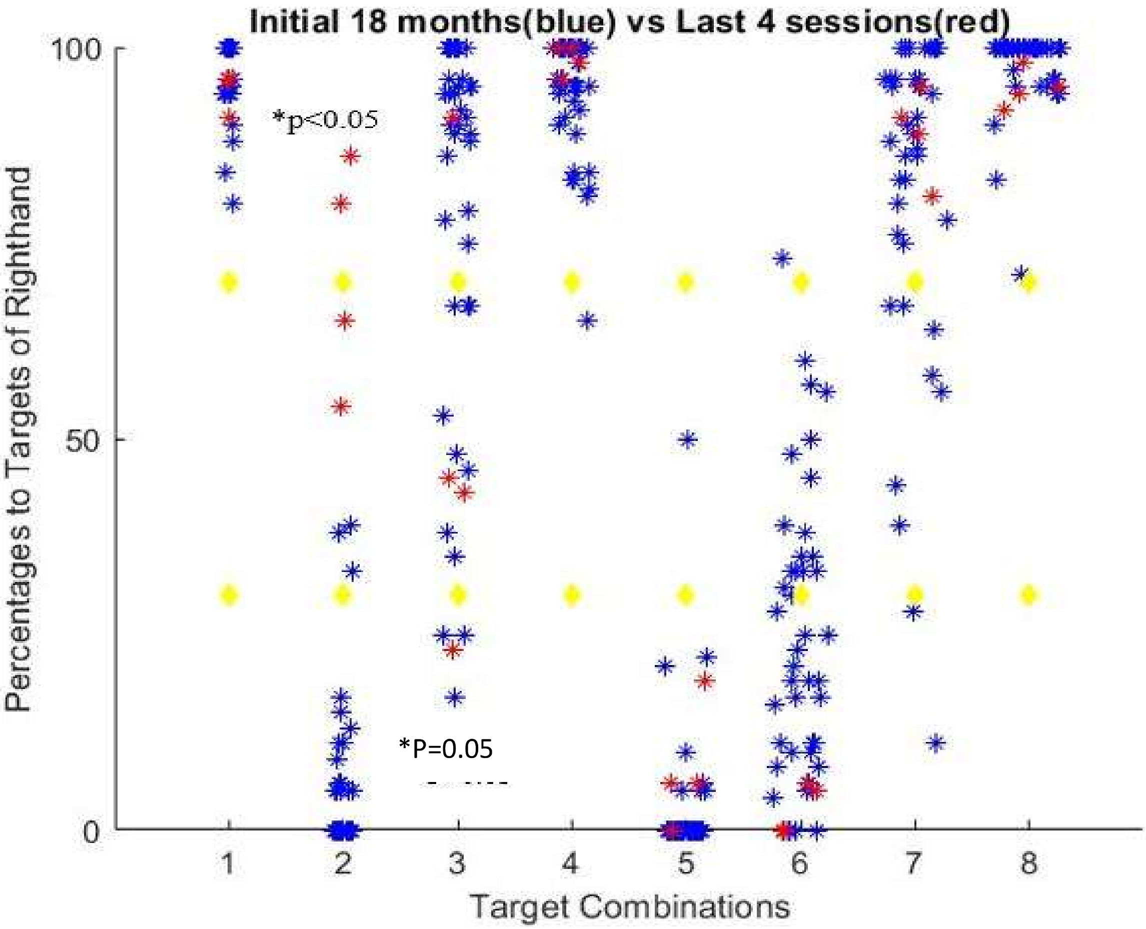


Figure 13: Scatter Plot of Saccade Choices (First 18 months vs Last 4 Sessions):

Upper yellow diamonds represent the boundary of 75% and lower represent 25%, points between these two boundaries are within the desired ratio for our experiment. Combination three showed a trend and combination two showed significant change ($p<0.05$).

Chapter 4: Next Steps and Discussion

Here we showed that the monkey does not always make the same movement. We identified that the monkey preferred certain targets over others during the bimanual apart task. We created tasks which added rewards and altered stimuli/targets, using these tasks we showed a change in preference for target choices. After using these tasks, we reverted back to our original task to show a change in target choices. We found a change in two combinations in our final four sessions with the original task.

In combination two and three we successfully trained the subject to make saccades between a ratio of 25% and 75%. Through further training we can achieve this ratio for all combinations. Throughout our training we saw the ratio shift several times. This shift clearly tells us that saccadic behavior during the bimanual apart task is not stereotyped permanently, the subject is choosing which target to saccade towards.

We only used the Bimanual Flash Period task for two sessions, within those two sessions we received a shift in combination 2 and 3 and we received a ratio of nearly 50:50 for combinations 4, 5 and 6. We speculate that with more sessions the subject's ratio will change for all combinations. Once the ratios are all relatively balanced, we can move on to electrophysiological recording from FEF. In [14], the subjects all had ratios which fell between 25% to 75% so the preference was only listed. The study analyzed the saccade direction during the bimanual-apart task, focusing on activity before the first saccade. Trials were sorted based on whether the initial saccade was directed to the target inside or outside the response field (RF) and referred to as "eye-in" (Ein) and "eye-out" (Eout) trials. In a secondary analysis, trials were sorted based on whether the contralateral arm moved to the target inside or outside the RF and referred to as “arm-in” (Ain) “arm-out” (Aout) trials. Thus, there were four possible trial types: EinAin, EoutAin, EinAout, and EoutAout. Reach directions were instructed, such that we obtained equal numbers of Ain and Aout trials for each cell. Saccade direction was freely chosen by the animal on each trial, so the relative numbers of Ein and Eout trials varied from cell to cell. For example, if the animal always chose to saccade to the right in a particular recording session, only EoutAin and EoutAout trials for that cell would be collected. They were able to obtain two, three, or four different bimanual-apart trial types for a given cell; restricting analysis to cells where at least two EinAin and two EoutAin trials or at least two EinAout and two EoutAout trials were collected. In our case we have a subject with a strong preference for certain targets, so we will not have to worry about accounting for any behavioral preferences during recording if we can reach ratios less than between 25% to 75%, we will only have to worry about the subject’s response field and the cells preference. If all of our ratios fall right to 25% and right at 75% we may have to initiate a similar strategy.

For recording the animal will receive a recording chamber above FEF, the dura mater will be exposed. FEF cells will have to be mapped; previous study [12] confirmed FEF locations by evoking saccades using low current microstimulation while subjects performed a blink task. We will map out FEF with a single electrode through the use of microstimulation with our saccade task. We will then use multiple single electrodes or one electrode array to record action potentials in FEF during the bimanual task. We will compare this activity to the activity described in [14], giving us the ability to define the role of FEF in saccadic generation. This work will help define the role of FEF in hand eye coordination and maybe even help us develop a neurotypical model of electrophysiological activity at the systems level for LIP, FEF, and PRR in non-human primates.

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