BEHAVIORAL TRAINING AND SACCADIC ADAPTATION IN MARMOSETS.

by
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ABSTRACT

The common marmoset (*Callithrix jacchus*) is a promising non-human primate model for neuroscientific research. Like other primates, they are able to foveate and use saccadic eye movements to explore their environments. Previous studies have demonstrated their ability to produce goal-directed saccades under head-fixed conditions, however the number of trials completed per session have been insufficient for behavioral or neurophysiological investigation. In this paper, we report on the long-term feasibility of our behavioral training protocols and carefully calibrated food-regulated diet, which has resulted in trained marmosets that are capable of performing ~1,000 trials on a daily basis while maintaining their health. Additionally, we present previously unreported evidence of saccadic adaptation and savings in two marmosets that take part in three different saccade tasks: gain down, gain down savings and a control task.

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INTRODUCTION

When selecting an animal model for scientific research, several factors are taken into consideration, such as animal welfare, practicality and scientific suitability (Kishi et al. 2014). Neuroscientific researchers have become increasingly interested in the use of the common marmoset (*Callithrix jacchus*) as a primate model due to their small size and easy handling, a lack of reported lethal zoonotic diseases that are transmittable to humans, and have a short gestation period (~5 mo.) regularly giving birth to twins or triplets, giving them potential for transgenic manipulation (Kishi et al. 2014; Wakabayashi et al. 2018). Socially and biologically they share similarities with humans, like having strong family relationships and relying heavily on vocal and visual cues during social interactions (Mitchell and Leopold 2015; Solomon and Rosa 2014). They are known to have a well-developed visual system with the ability to foveate as well as showing evidence of homologous frontal and parietal areas that have direct connections to the midbrain superior colliculus (SC), an oculomotor structure critical for saccade initiation (Johnston et al. 2018; Mitchell and Leopold 2015).

Since human cognition is highly dependent on vision, the oculomotor system is a key model for studying the principles of brain functionality (Mitchell and Leopold 2015) and the field of visual neuroscience could potentially benefit from studying the marmoset. These new world primates have the ability to bring forth new evidence on the mechanisms of visual cognition and could lead to a deeper understanding of social communication and neurological disorders. However, despite the attractive attributes of the marmoset, there are still questions on whether they can learn to intentionally control their fixation behavior and perform visual

discrimination tasks under head-fixation (Mitchell et al. 2014); and if so, will it be enough to investigate the neural basis of goal-directed behavior (Sedaghat-Nejad et al. 2019)?

In a recent study that trained marmosets to perform saccade tasks, they found that, on average, subjects completed 80-100 trials per session (Johnston et al. 2018). Three other studies reported that, on average, marmosets were able to complete 300-800 trials per session (Mitchell et al. 2014), 47.2-49 trials per session (Mitchell et al. 2015), and 200 trials per session (Ma et al. 2020). Therefore, although it has been shown that marmosets can be trained to make saccadic and smooth pursuit eye movements (Mitchell and Leopold 2015), they exhibit a decreased oculomotor range when compared to humans and macaques (Mitchell et al. 2014) and are only capable of performing a limited number of trials per session.

In our previous work (Sedagaht-Nejad et al. 2019) we documented the development of our marmoset laboratory which was aimed at developing behavioral and neurophysiological recording protocols that would allow for electrophysiological recording from the cerebellum in awake and behaving head-fixed marmosets. Behaviorally, our goal was to determine if marmosets could be trained to produce a sufficient number of rewarded trials. To do so, we had strategically designed a calibrated food-regulated diet that would keep the marmosets motivated to complete a sufficient number of goal-directed saccades 5 days/week while also maintaining their health (Sedagaht-Nejad et al. 2019).

The accuracy of a goal-directed saccade is defined by its gain, or the ratio of the saccade amplitude to the desired saccade amplitude. Under normal conditions, it is common to see a baseline gain of 0.9 due to their hypometric nature (Henson, 1978; Rahmouni and Madelain 2019). Our saccades remain accurate throughout the duration of our lives due to the constant

recalibration of our saccade gain by a learning mechanism referred to as saccadic adaptation. Saccadic adaptation is believed to be a form of motor learning driven by visual errors that are recognized at the end of the saccade (Kojima et al. 2004). Observation of these visual errors associated with motor performance is done by utilization of adaptation mechanisms which allow us to observe the iteratively updated relationship between target location and the processing of information needed to re-align our sight to the target.

Back in 1967, McLaughlin was the first to explore this concept with the introduction of the double-step paradigm, whose main goal was to stimulate a spatial error in saccadic generation by changing the target location during saccade execution. During the initial trials these corrective saccades, which are encouraged by the spatial error, occur more frequently and have an amplitude close to that of the target shift. Repetition of the intra-saccadic step (ISS), over the course of consecutive trials, causes a change in the amplitude and/or direction of the primary saccade and a decrease in the frequency and amplitude of the corrective. This is because the primary saccade is now landing closer to the shifted target and the need for this error-correcting saccade becomes less necessary.

These adaptations elicited by the ISS have been found to have an exponential characteristic with a rate constant of 100-800 saccades, however this is variable across animals and experiments in the same animal (Fuchs et al. 1996; Kojima et al. 2004; Straube et al. 1997; Scudder et al. 1998). Therefore, we need to be able to collect a sufficient number of adaptation trials from the marmoset in order to answer the question, can marmosets learn? One way to explore this question is the gain down paradigm, in which the primary amplitude decreases due to a target shift in the opposite direction of the saccade.

Associated with learning, there is another phenomenon known as savings. This phenomenon has been shown in the motor learning task known as eye blink conditioning (Medina et al. 2001), in a saccade adaptation task (Kojima et al. 2004), and in a rotation adaptation for reach movements (Krakauer et al. 2005). In a savings paradigm, adaptation is followed by extinction training. In the subsequent re-adaptation, savings is defined as experiencing a rate of re-adaptation that may be faster than the original adaptation (Frey and Ross 1968; Naiper et al. 1992). Thus, despite extinction (return of behavior to near baseline), a memory of the initial adaptation remains, allowing for a faster re-learning (Kojima et al. 2004).

In this paper, we report on the long-term feasibility of training of marmosets on a saccade task, with the aim of asking whether they can consistently perform ~1,000 trials per session. From these results we ask, during a 1,000 trial session, can one study saccadic adaptation? We went after our question utilizing the two paradigms previously mentioned: gain-down and savings.

METHODS

Subjects. Two marmosets participated in our procedures: one female (*subject M*: 350g, 4 yr old) and one male (*subject R*: 360g, 4 yr old). Both subjects were born and raised in the Johns Hopkins School of Medicine colony which has been maintained by Prof. Xiaoqin Wang. All experimental procedures were evaluated and approved by the Johns Hopkins University Animal Care and Use Committee, and in accordance with the guidelines of the US National Institutes of Health.

Behavioral training. Prior to the start of the food-regulated diet, the marmosets underwent surgery to implant a head-fixation post. The post was designed using preoperative CT imaging to fit the subject-specific skull geometries. The images were loaded into 3D slicer, an open source imaging analysis and visualization software (Fedorov et al. 2012), to generate a 3D volume of the skull. This was then imported into a CAD environment (SolidWorks and Autodesk Fusion 360) with which we designed the titanium head-post and base chamber for recording. The head-post and base chamber were 3D printed with laser-melted grade 5 titanium (6AI-4V; Sculpteo) and then implanted using procedures described earlier (Sedaghat-Nejad et al. 2019).

Following recovery from surgery, subjects were placed on a food-regulated diet. Behavioral training began once weight had been reduced to approximately 90% of the pre-surgery weight. During training, for 5 days/week they were fed a liquid meal as reward for completing the task. The meal consisted of 15 g of laboratory diet powder and 10 g applesauce mixed in 30 g of water. This produced a net total of 40 mL of food. On the weekends, each monkey was given 25 or 30 g of solid laboratory diet per day, depending on their current weight.

Weight was checked daily to monitor the health of the subjects. A healthy weight was considered to be between 85-100% of their average weight prior to being placed on food regulation. If the subject's weight dropped below 85%, they were taken off food regulation and were fed in the colony until they were back to their 90% weight. To maintain an accurate log of the subjects' weight, we recorded their weight at the same time every weekday.

We found that motivating the animals to perform at least 1,000 trials per day was dependent not only on their weight, but on other factors such as time of day, comfort in the chair, and system calibration. To ensure that the animals were hungry when entering the recording room, and motivated to complete the task, we controlled the subjects' daily schedule in terms of feeding times: one subject was trained and fed in the morning, while the other in the afternoon.

The animal's chair and recording system were described previously (Sedaghat-Nejad et al. 2019). We found that the animals differed in their preference regarding head position and target positions on the screen. Finding a posture and center fixation position that was suitable for each animal appeared to be just as impactful on their performance as their weight. If they were not comfortable, they would refuse to perform for extended periods of time.

Training occurred 5 days/week and transitioned from behavior only to behavior and neurophysiology. Visual targets were presented on a curved monitor (model AG32CQ, 32 in., 144 Hz; MSI) while binocular eye movements were tracked using an EyeLink 1000 eye tracking system (SR Research). After chair acclimation and fixation/pursuit training was completed, as previously described (Sedaghat-Nejad et al. 2019), we began training the subjects to perform the saccade task.

Behavioral paradigm. Trials began with a fixation dot (0.5˚x0.5˚) for which they had to fixate for approximately 200 ms within a 1.5˚-2.0˚ radius of the target (Fig. 2A). Following fixation, an auditory beep was presented along with display of the primary target at 6.5˚ to the right or left (Fig. 2B). Once saccade onset was detected (thresholding of 75 deg/s), the primary target was erased and a secondary target was placed at a displacement of 3˚ with respect to the

primary target (as shown in Fig. 2B), thus encouraging a corrective saccade. A reward was administered if the primary saccade was followed by a corrective saccade that landed within a 1.5˚-2.0˚ radius of the secondary target and fixation was maintained for 200 ms.

Odd trials always began at the center fixation position. There was a 50% chance that the subject would be cued to the left or the right of the start fixation point. At the end of this center-out trial, the position of the target became the new start position. Thus, odd trials were center-out and even trials were out-center (as shown in Fig. 2B). After the completion of the out-center trial, the fixation point was again at the center of the screen.

Correct trials generated an auditory tone and engaged the food pump, which dispensed food at a rate of 0.015-0.025 mL/trial. Sessions began at 0.015 mL of food per trial. This low rate encouraged the animals to perform 4 or more correct trials before licking the reward tube. As the trials continued, we increased the food rate to maintain motivation.

Subjects were trained in various forms of saccade adaptation (Fig. 2C). In Experiment 1 we measured performance during a standard gain-down task. This experiment consisted of 100 baseline, 800 adaptation, and 100 washout trials. In Experiment 2 we measured performance in a savings paradigm, which consisted of 50 baseline, 300 adaptation, 300 washout, 300 re-adaptation, and 50 washout trials. The control experiment consisted of 1,000 baseline trials. In baseline and washout trials only a primary target was displayed (i.e., no target-jump). A session was considered complete only if the subject performed all 1,000 trials correctly.

Data acquisition and analysis. Eye position data was acquired via an infrared camera and sampled at 1000 Hz (Eye Link). Primary and corrective saccades were detected based on

speed thresholds and were confirmed by aligning the speed trace to the horizontal eye trace. Saccade gain was defined as eye displacement during the primary saccade divided by target displacement (with respect to eye position before the start of the primary saccade).

Statistics. Comparison of the gain down paradigm to the control task for each subject required performing a weighted two-way RM-ANOVA using a type 2 sum of squares looking at the dependence of the gain on the factors experiment and trial as well as their interaction. This was done to compensate for the unequal sample size between the two experiments. *Subject R* completed 7 sessions of the control experiment and 6 sessions of the gain down. *Subject M* completed 7 sessions of the control experiment and 10 sessions of the gain down. To compare each of the subject's performance in block 1 of the savings paradigm to block 2, we ran a within subject three-way RM-ANOVA looking at the dependence of gain on the factors session, trial and block and their interactions. Each subject performed 12 sessions of the savings paradigm allowing for equal sample sizes. To compare the dependence of gain and primary reaction time on the odd and even trials we performed a one-way RM-ANOVA for both subjects on all three experiments.

RESULTS

Performance results. Figure 1A and 1B show the relationship between weight and number of trials for *subject M* and *subject R*. Day zero on both plots marks when each subject had under-went head-post surgery. Post-surgery, *subject R* began food regulation 27 days later while *subject M* started 28 days later. Behavioral training for *subject M* began 99 days after surgery and 71 days after the start of food regulation compared to *subject R* who began 31 days after surgery and 4 days after start of food regulation. They both continued their training until

their burr hole surgery (329 days post-surgery for *subject M* and 111 days post-surgery for *subject R*) for which their neurophysiological recording sessions began

4 days after for *subject M* and 2 days after for *subject R*.

Prior to beginning food regulation, *subject R's* average initial weight was 415.0 +/- 1.99 g and *subject M's* weight was 393.9 +/- 1.49 g. *Subject R* was placed on the diet for a total of 281 days and maintained an average weight of 356.4 +/- 0.929 g (85.9% of the average initial weight). *Subject M* was placed on the diet for 708 days and maintained an average weight of 353.5 +/- 0.440 g (89.8% of the average initial weight). *Subject M's* weight showed a spike around day 480 due to a short period of time (three days) that she was taken off food restriction, causing her weight to increase. However, only a few days back on the regiment and her weight went back down. Both subjects were removed from food restriction (day 745 for *subject M* and day 310 for *subject R*) and after being off the diet for 29 days, *Subject R's* new average weight was 387.8 +/- 1.39 g while *Subject M's* new average was 378.1 +/- 1.60 g.

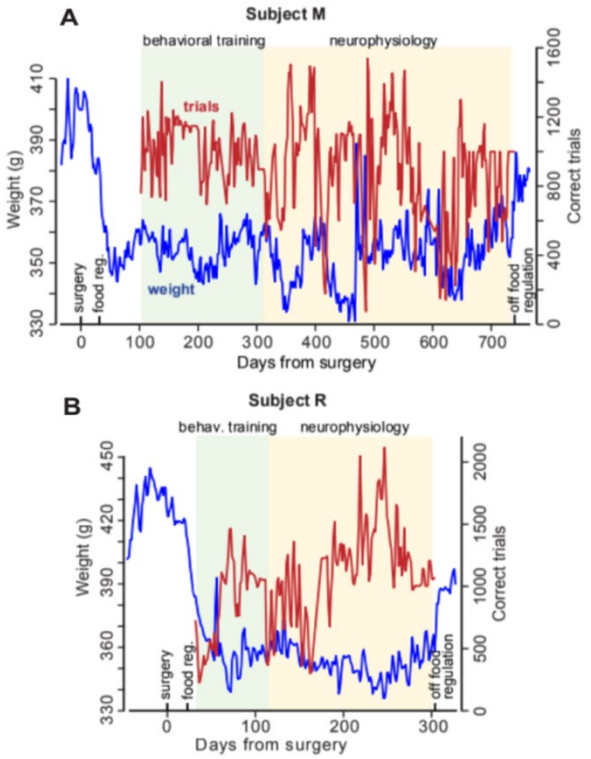

Figure 1. Weight patterns and number of correct trials after the start of food regulation. A: record of weight (blue) and correct trials (red) in subject M. B: weight and correct trial data in subject R. Data for correct trials represent a running average of bin size 2. Green shading indicates periods of food regulation and behavioral training. Yellow shading indicates periods of food regulation and neurophysiological recordings.

During the food restriction periods both animals remained healthy as suggested by their stable weight and lack of complications. While on the diet, *subject R* had a total of 167 sessions completing on average 1,047.8 +/- 31.0 trials per session. Of his total sessions 70% had 1,000 or more trials with a peak performance of 2,191 trials in one session. *Subject M* had a total of 344 sessions completing on average 958.6 +/- 15.6 trials per session. Of her total sessions 57% had 1,000 or more trials with a peak performance of 1,762 trials during a single session.

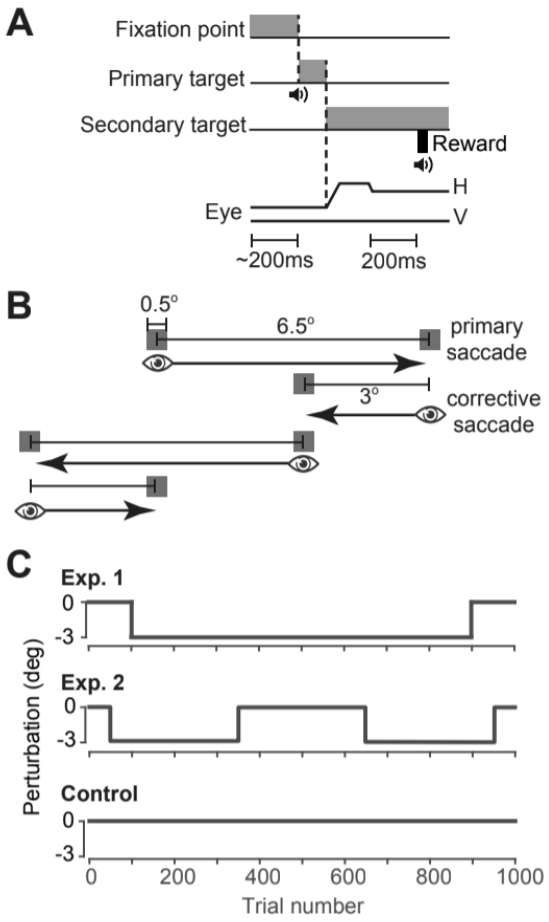

Figure 2. Task design and effect on primary saccade. A: a trial began with a 200 ms fixation, followed by presentation of a primary target at 6.5˚. During the primary saccade, the target was erased, and a secondary target was presented at a 3.0˚ displacement with respect to the primary target. Reward was presented following 200-ms fixation of the secondary target. H, horizontal; V, vertical. B: odd trials trial began at a 0.5˚X0.5˚ fixation point at the center of the screen followed by the 6.5˚ horizontal primary saccade. The 3.0˚ corrective saccade was induced by a 3.0˚ target jump 180˚ relative to the primary target which became the new start position. After completion of the even trial, subjects began at the center of the screen again. During odd trials, there was a 50% chance they would be cued either to the left or the right of the target. C: for experiment 1 is comprised of 100 baseline trials 800 adaptation trials and 100 washout trials. Experiment 2 is comprised of 50 baseline, 300 adaptation, 300 washout, 300 re-adaptation, and 50 washout. The control is comprised of 1,

Behavioral results. Figure 2A and 2B illustrates the gain down paradigm (exp. 1) that the subjects performed. At the beginning of a trial the subjects were instructed to fixate on the target for ~200 ms after which they would make a primary saccade to the peripheral target at 6.5˚ followed by a corrective saccade with a 3˚ displacement. In Figure 3A, we have selected four trials that span the 800 trials of the adaptation block in a single gain down session from *subject R*. The amplitude and velocity of the primary and corrective saccades progressively decrease from trial 114 to trial 891.

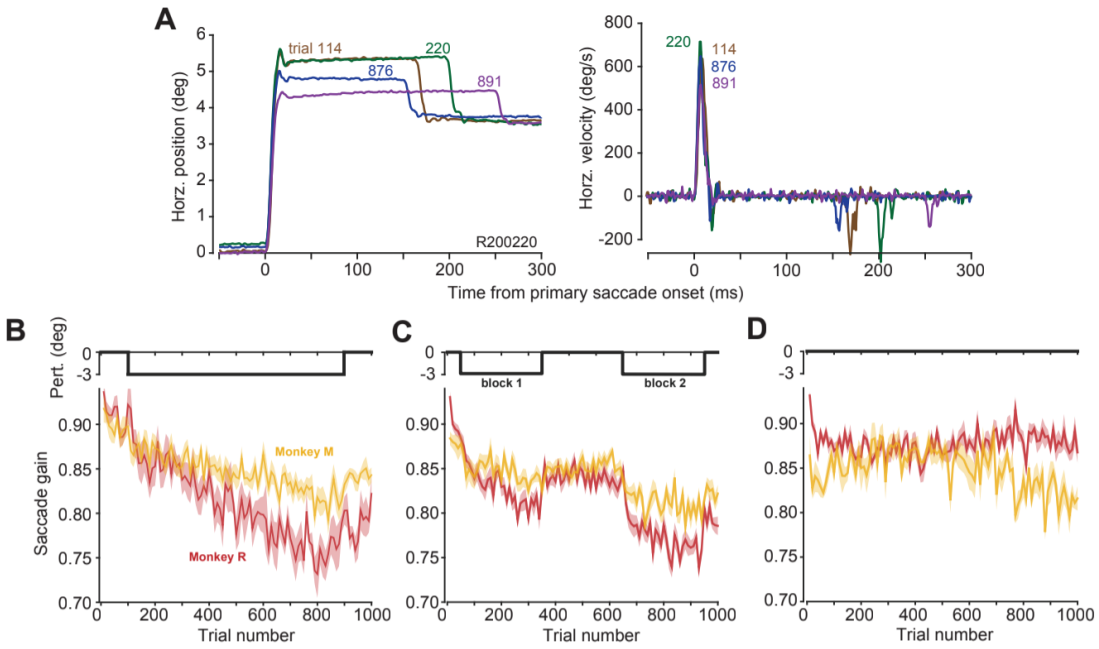

Figure 3. Behavioral results. A: four trials selected from a single gain down session from subject R showing the horizontal eye position and velocity aligned to primary saccade onset. B: saccade gain for the gain down paradigm for subject M (yellow) who completed 10 sessions and subject R (red) who completed 6 sessions. Task consists of 100 baseline, 800 adaptation, and 100 washout. C: saccade gain for the gain down savings paradigm where both subject M and R completed 12 sessions of the task. Task consists of 50 baseline, 300 adaptation, 300 washout, 300 re-adaptation, and 50 washout. D: saccade gain for the control task where both subjects completed 7 sessions. Task consist of 1,000 baseline trials. Bin size for figures B, C and D is 10 trials.

At trial 114 and 220 the primary saccade is landing around 5.5˚. At trial 876 the primary is landing closer to 5˚ and at trial 891, nine trials away from the completion of the adaptation block, the primary is landing at 4˚. Due to the primary saccade landing closer to the jumped

target, at 3.5˚, the need for the corrective saccade becomes less necessary and so the corrective amplitude becomes shorter. All of the trials finish around the 3.5˚ mark, so we can clearly see the decrease of the corrective amplitude from trial 114 to 891. The change in the metrics of the primary and corrective saccade are hallmarks of saccadic adaptation, thus suggesting that marmosets can demonstrate saccadic adaptation within about 1,000 trials (800 trials of adaptation).

During the gain down paradigm, shown in Figure 3B, *subject R* had a total of 6 sessions and learned to compensate for around 75% of the 3˚ perturbation while *subject M* had a total of 10 sessions and learned to compensate for about 81% of the perturbation. As this is a gain down paradigm and the amplitude of the primary saccade should be decreasing, the less the percentage of the error, the farther the subjects are landing from the Primary target and the closer they are to the jumped target. That is, the lower the percentage, the greater the error learned. If we compare these values to the control task (Figure 3D) *subject R*, who had a total of 7 sessions, remains around the 88% mark while *subject M*, also with a total of 7 sessions, remains around 85% but does begin to decrease around trial 600. This decrease in the gain could be due to the monkey becoming exhausted and using the full advantage of the reward area they are given (1-5˚-2.0˚). With a 6.5˚ saccade of to the left and right of the center, we have them spanning a total of 13˚ in the horizontal axes and performing saccades consecutively could be strenuous on their eyes due to their decreased oculomotor range.

Performing a two-way RM-ANOVA using type 2 sum of squares both *subject R* ($F(1,500) = 504.6370$, $p < 2.2e\text{-}16$ ***) and *subject M* ($F(1,600) = 12.6267$, $p = 0.0004102$ ***) show a significant difference between the two types of experiments: gain down and

control. Moreover, *subject R* ($F(99,500) = 3.6167$, $p < 2.2e\text{-}16$ ***) and *subject M* ($F(99,600) = 2.4063$, $p < 1.029e\text{-}10$ ***) return a significant interaction between experiment and trial. From these statistics, we can infer that, for both subjects, depending on which experiment they were performing (gain down or control) there is significant difference in their trial by trial behavior (slope) and therefore show evidence of saccadic adaptation in the gain down and not in the control. Therefore, from these results we can conclude that by giving them a task where we introduce a perturbation, they are making these error-correcting saccades for which they gradually learn the error.

Figure 3C, shows the learning plots for the gain down savings paradigm (exp. 2) for which we do see potential evidence of savings where *subject R* and *subject M* both completed a total of 12 sessions. Moreover, we can see that by the end of the second adaptation block, both subjects had learned relatively the same amount of the perturbation as they did during the subjects appear to have learned the same amount of the perturbation in fewer adaptation trials (600 trials for savings and 800 trials for gain down). The ability for them to learn the same amount in fewer trials, after a period of extinction, could be the consequence of a faster rate of adaptation caused by the retention of the memory of the learned error.

Primary and corrective reaction times for the gain down (Figure 4A), savings (Figure 4B) and control (Figure 4C) can be seen for both subjects. *Subject R*'s average primary reaction times were: 207.8 +/- 14.8 ms for gain down, 195.3 +/- 8.78 ms for savings and 173.8 +/- 11.4 ms for the control task. *Subject M's* primary reaction times were: 163.7 +/- 5.04 ms for gain down, 159.1 +/- 4.52 ms for savings and 168.2 +/- 9.62 ms for the control task.

Corrective reaction times for *subject R* were: 149.7 +/- 4.64 ms for gain down and 153.8

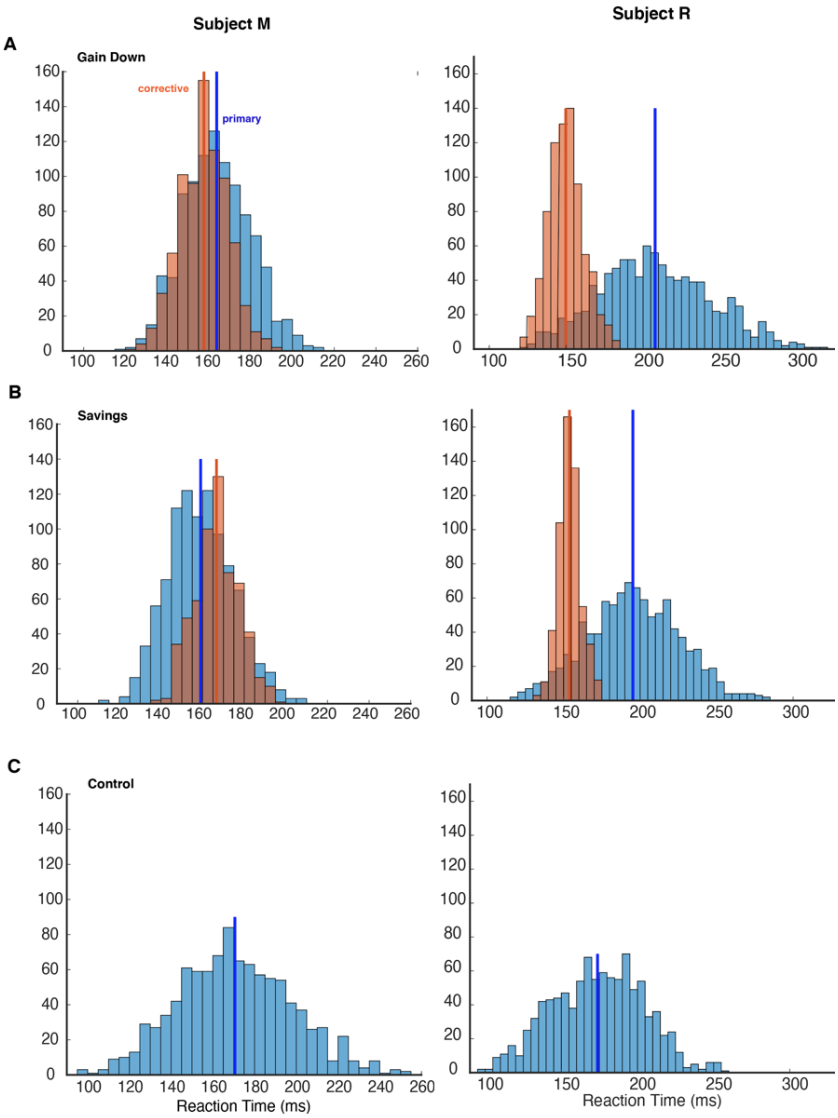

Figure 4. Reaction times. A: Gain down (exp. 1) primary (blue) and corrective (orange) reaction times (ms) for both subject M (top) and subject R (bottom). B: Savings (exp. 2) primary and corrective reaction times for subject M and subject R. C: Control primary reaction times for both subject M and subject R. By nature of the control task, there are no corrective saccades to report. All histograms are plotted with 5 ms bins.

no corrective saccades in the control task.

Looking at Figure 5A for both subjects, we can see that for the gain down paradigm the more they learn of the adaptation, the slower their reaction times become and instantly increase again as they enter a period of washout (trial 900). Figure 5B shows the savings paradigm where in both subjects you can see the reaction times become faster as they enter their first washout block (trial 350). Then as they continue through the rest of the washout and into the second adaptation block, the reaction times continue to get slower and the increase in reaction is not as spontaneous. *Subject R* seems to be much more affected by the washout periods as demonstrated by his gain down (Figure 5A) and gain down savings (Figure 5B) as compared to *subject M* who exhibits a less dramatic increase going into periods of washout. The control paradigm (Figure 5C) for each

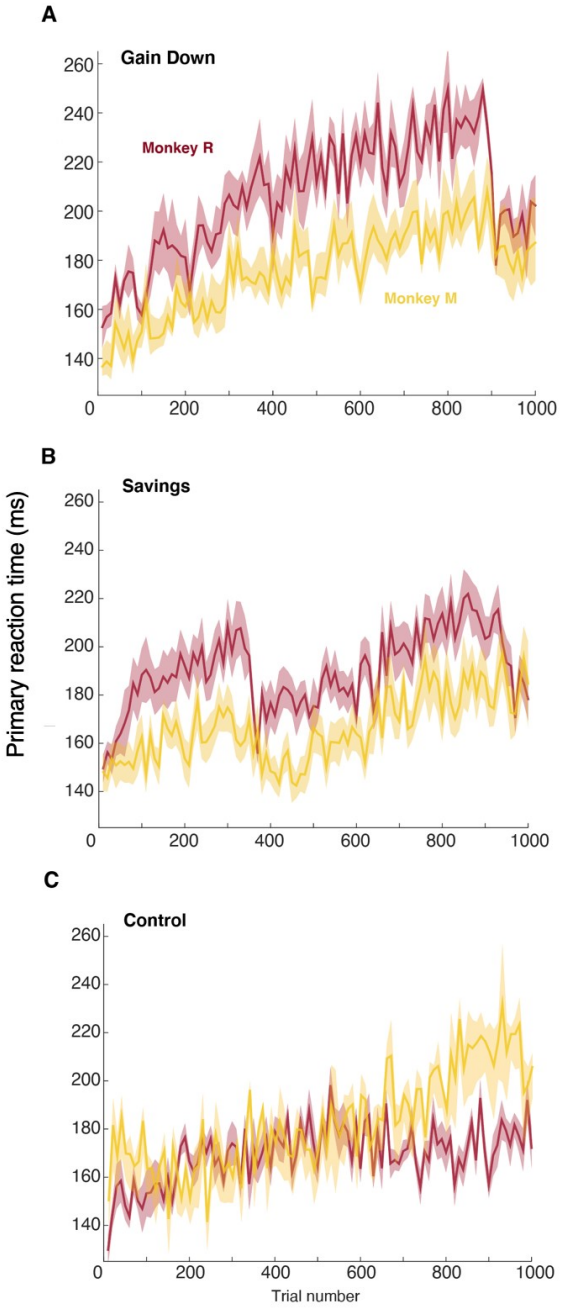

Figure 5. Primary reaction times. A: Gain down (exp. 1) primary saccade reaction times (ms) for subject R (red) and subject M (yellow). B: Savings (exp. 2) primary saccade reaction times for subject R and subject M. C: Control primary reaction times for subject R and subject M. Bin size for all plots is 10 trials.

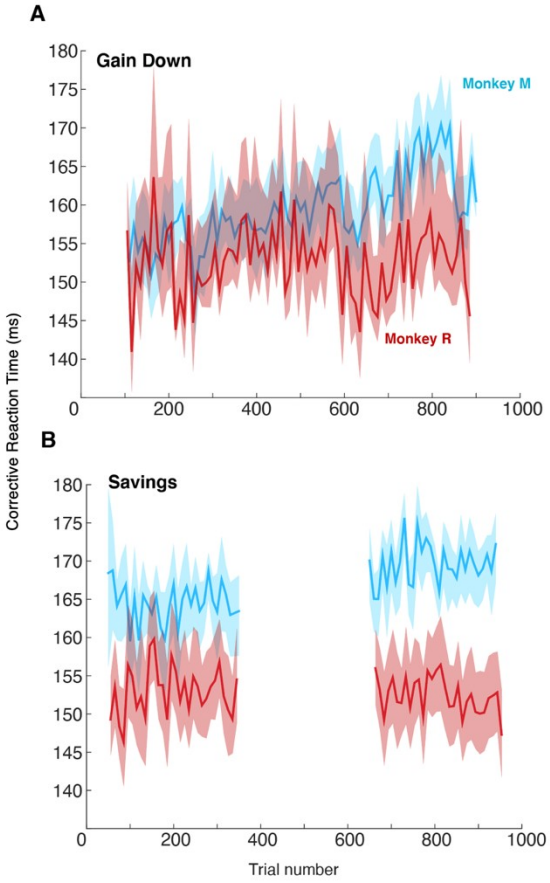

Figure 6. Corrective reaction times. A: Gain down (exp. 1) corrective saccade reaction times (ms) for subject R (red) and subject M (blue). B: Savings (exp. 2) corrective saccade reaction times for subject R and subject M. Bin size for all plots is 10 trials. M. Bin size for all plots is 10 trials. M. Bin size for all plots is 10 trials.

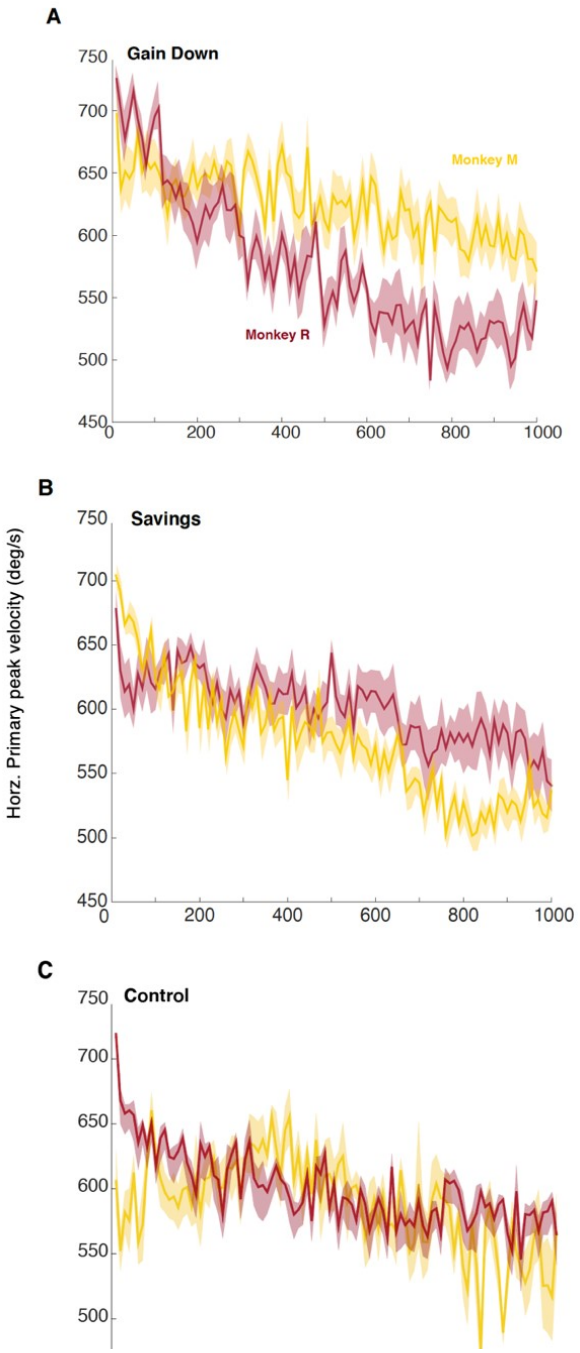

Figure 7. Horizontal primary peak velocity. A: Gain Down (exp.1) primary peak velocity (deg/s) for subject R (red) and subject M (yellow). B: Savings (exp. 2) primary peak velocity for subject R and subject M. C: Control primary peak velocity for subject R and subject M. Bin size for all plots is 10 trials.

subject show less of a decrease in the reaction times with *subject R's* fluctuating around 170 ms and *subject M* fluctuating around 165ms and then begins to show a decrease in reaction time around trial 600, similar to the trend we saw in Figure 3C.

Looking at the corrective reaction times for the gain down paradigm (Figure 6A) we can see that *subject R's* appear to fluctuate around 145-150 ms. However, *subject M* shows a slight increase in her reaction times as she learned the perturbation. Corrective reaction times for the savings paradigm (Figure 6B) show similar trends to their gain down. That is, *subject R* fluctuates around150-155 ms with no obvious dependence on trial number. *Subject* M, however, does show a decrease from 165 to 170 ms across the two adaptation blocks

We can see that the horizontal primary peak velocity for the gain down (Figure 7A) and control (Figure 7C) take on similar shapes as the learning plots (Figure 3A and 3C). For the savings paradigm (Figure 7B), there is no distinct

change in peak velocity between the adaptation and washout blocks, but for both subjects their peak velocities end at the same value across the two experiments.

For both subjects, we can see that the corrective peak velocity for the gain down paradigm (Figure 8A) also follows the shape of the learning plots. In the savings paradigm (Figure 8B), again, we see that both subjects' corrective peak velocities decrease as they continue through that adaptation block.

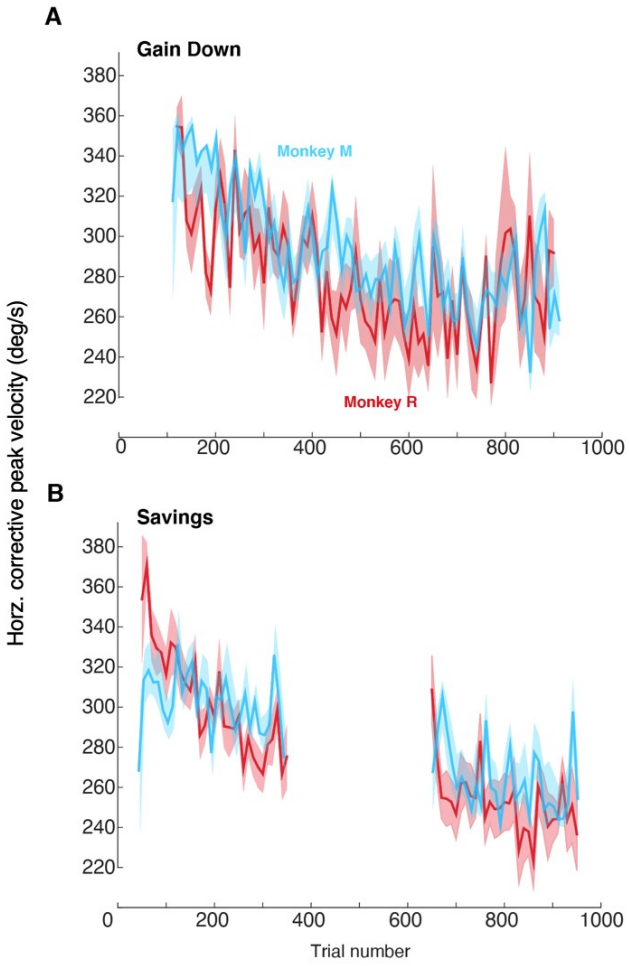

Figure 8. Corrective peak velocity. A: Gain down (exp. 1) corrective peak velocity (deg/s) for subject R (red) and subject M (blue). B: Savings (exp. 2) corrective peak velocity for subject R and subject M. Bin size for all plots is 10 trials.

To explore the relationship between the wo adaptation blocks of the savings paradigm, we can compare the rates of learning, or the slopes, that each subject exhibit between the two blocks. To do so, we took an average of the last 20 trials of the baseline and first washout period and subtracted that value from all the trials of the preceding adaptation block in order to eliminate the change in baseline.

This is shown in Figure 9 where we have plotted the last two points of the baseline and washout periods with their preceding adaptation block. To check that there is a significant difference in the rates of learning, we performed a three-way within subject RM-ANOVA and

found: no effect of session ($F(11,11) = 0.96$, $p = 0.526$), an effect of block ($F(1,1) = 335.6$, $p = 0.0347$ *), an effect of trial ($F(29,29) = 3.907$, $p = 0.000223$ ***), a block x trial interaction ($F(29,29) = 2.23$, $p = 0.0173$ *), and no interactions involving sessions came back as significant. Since there is no effect of session, we can state that there is no meta-learning occurring the longer the monkeys perform the tasks.

Additionally, the block by trial interaction indicates that depending on which block they were in, there is a significant difference in the slopes, meaning there is promising evidence of savings being shown in both subjects.

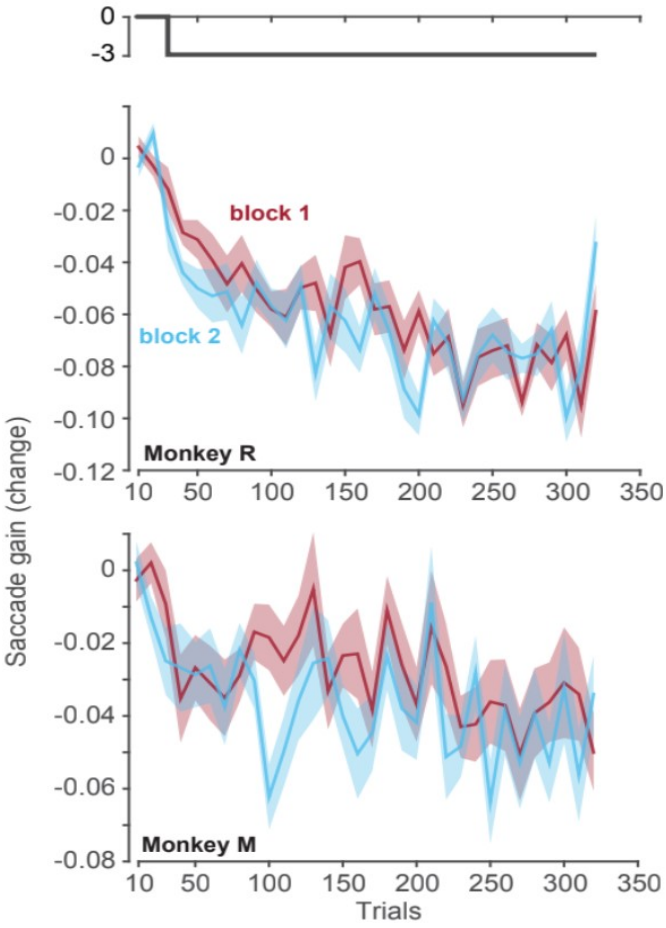

Figure 9. Change in saccade gain relative to baseline in block 1 (red) and block 2 (blue) from experiment 2. Top plot is subject R and the bottom is subject M. We have plotted the last 2 points of their respective baseline/washout blocks and have subtracted an average of 20 trials from the points in order to account for the change in baseline. Bin size for all plots is 10 trials.

To compare the odd (center-out) to even (out-center) trials we separated the trials based on type and looked at their behavior as shown in Figure 10. Performing a one-way RM-ANOVA to look at the effect that the uncertainty in the odd trials had on the gain it is found that, for *subject R's* there is no effect of trial type for the gain down (Figure 10A) ($F(1,598) =$

0.706, p = 0.401) and savings (Figure 10B) (F(1,1195) = 2.772, p = 0.0962) experiments but there was an effect of trial type for the control (Figure 10C) (F(1,698) = 8.665, p = 0.00337 **). For *subject M* we find that there is no effect of trial type for the gain down (Figure 10A) (F(1,998) = 0.012, p = 0.913), savings (Figure 10B) (F(1,1198) = 3.217, p = 0.0731) or the control (Figure 10C) (F(1,698) = 2.362, p = 0.125).

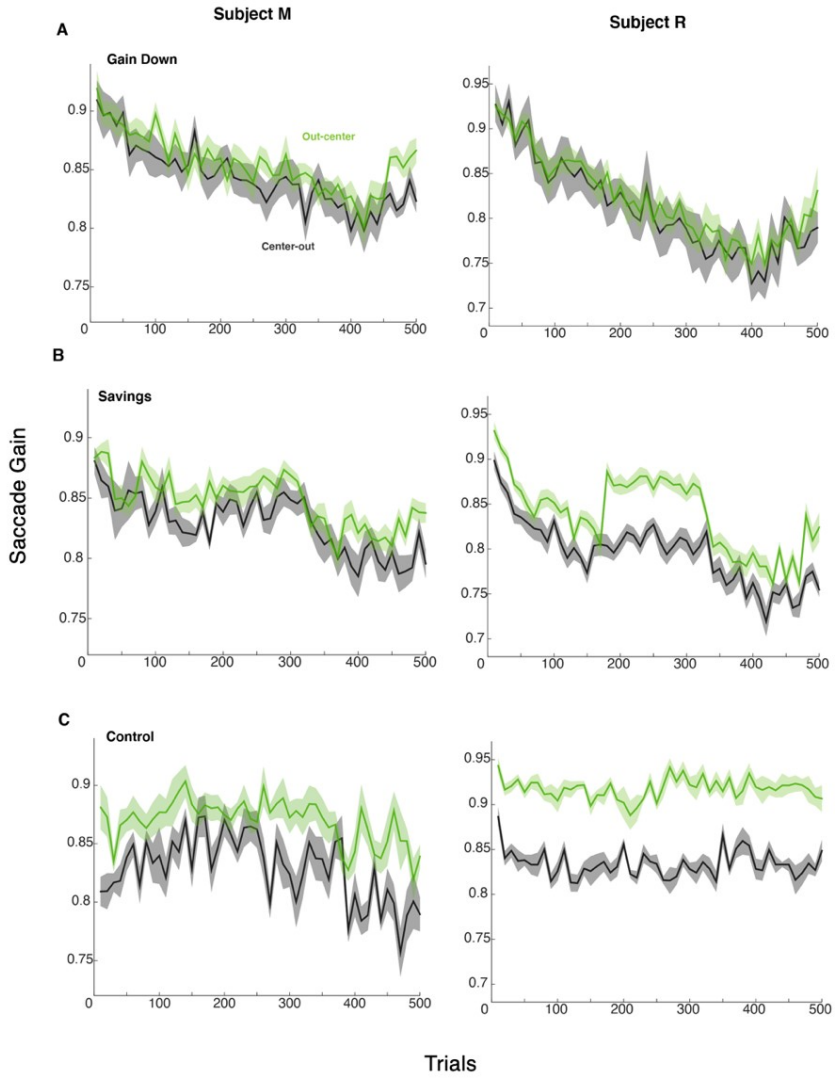

Figure 10. Odd even trial saccade gain. A: Gain Down (exp. 1) gain comparison for the odd (black) and even (green) trials for subject M (left) and subject R (right). B: Savings (exp. 2) gain comparison of odd and even trials for subject M and subject R. C: Control gain comparison for the odd and even trials for subject M and subject R. Bin size for all plots is 10 trials.

In Figure 11 we see the comparison on reaction time as a function of trial depending on which type of trial they were performing. To check if the trial type has a significant effect on reaction time, we performed a one-way RM-ANOVA. For *subject R* we found a significant effect on reaction time for the gain down (Figure 11A) (F(1,598) = 161.6, p < 2e-16 ***), savings (Figure 11B) (F(1,1195) = 551.4, p < 2e-16 ***), and control (Figure 11C) (F(1,698)

= 576.3, p < 2e-16 ***). For *subject M* we find similar results that there is an effect on reaction time depending on trial type for all experiments: gain down (Figure 11A) (F(1,998) = 4.153, p = 0.0418 *), savings (Figure 11B) (F(1,1198) = 31.47, p = 2.51e-08 ***), and the control (Figure 11C) (F(1,698) = 222.8, p < 2e-16).

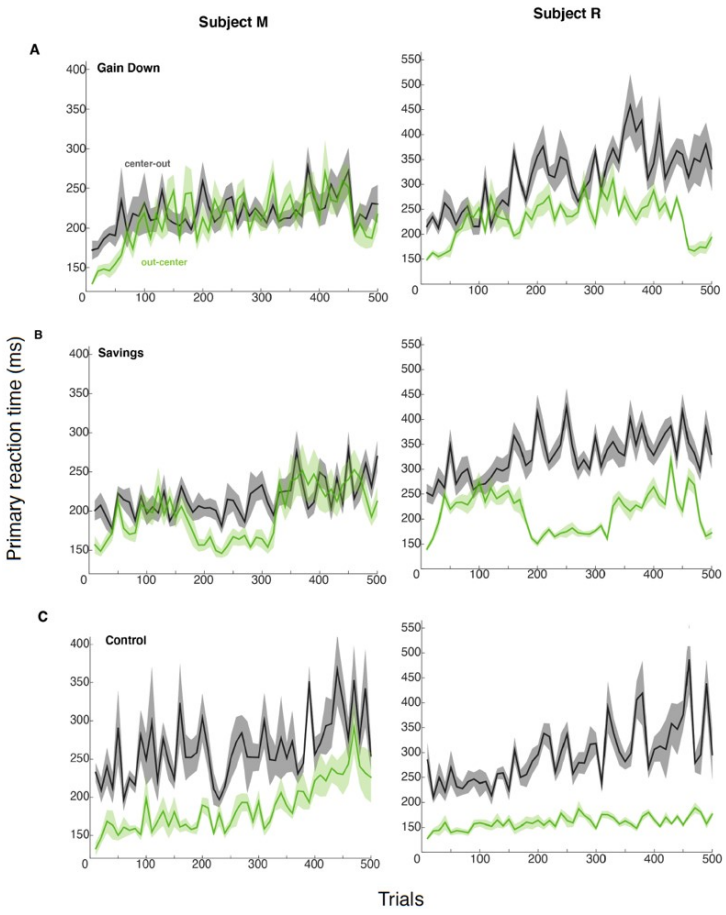

Figure 11. Odd even trial primary saccade reaction times (ms). A: Gain Down (exp. 1) reaction time (ms) comparison for the odd (black) and even (green) trials for subject M (left) and subject R (right). B: Savings (exp. 2) reaction time comparison of odd and even trials for subject M and subject R. C: Control reaction time comparison for the odd and even trials for subject M and subject R. Bin size for all plots is 10 trials.

We can see that for both subjects and all three experiments, the out-center trials have faster reaction times than the center-out trials. *Subject R's* gain down had an average primary reaction time of 282.9 +/- 32.6 ms for the center-out trials and 215.8 +/- 21.8 ms for the out-center trials. For the savings paradigms he had an average of 324.4 +/- 27.3 ms for center-out trials and 205.5 +/- 14.6 ms for out-center trials and for the control he had 216.5 +/- 17.3 ms for center-out and 153.5 +/- 11.3 ms for out-center. *Subject M's* gain down had an average primary reaction time of 208.1 +/- 11.5 ms for the center-out trials and 197.6 +/- 13.5 ms for the out-center trials. For the savings paradigms she had an average of 208.7 +/-11.2 ms for center-out trials and 182.3 +/-

10.6 ms for out-center trials and for the control she had 240.9 +/- 23.2 ms for center-out and 173.5 +/- 14.5 ms for out-center. This indicates that the presence of uncertainty has an effect on the subject's reaction times, but it does not appear to affect the characteristic of the learning plots, although there is a significant effect on the gain for *subject R's* control.

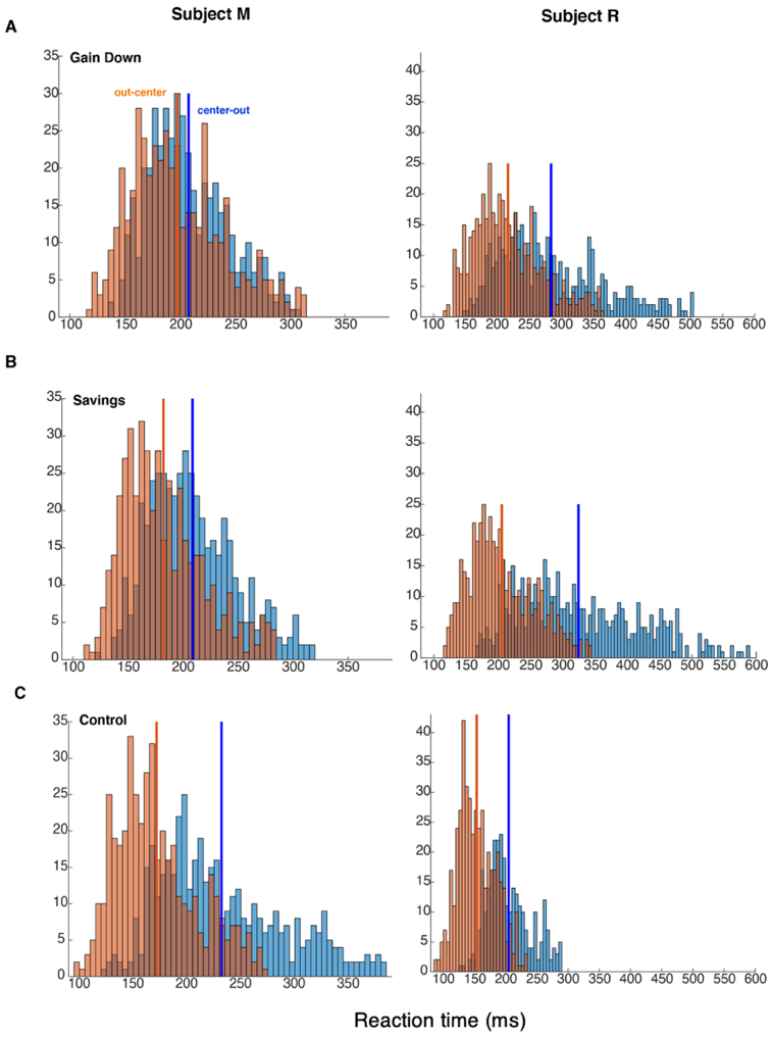

Figure 12. Odd and even primary reaction times. A: Gain down (exp. 1) primary saccade reaction times (ms) for the odd (blue) and even (orange) trials for subject M (left) and subject R (right). B: Savings (exp. 2) primary saccade reaction times for the odd and even trial for subject M and subject R. C: Control primary saccade reaction times for odd and even trials for subject M and subject R. All histograms are plotted with 5 ms bins.

DISCUSSION

The marmoset is a promising non-human primate model for neuroscientific research due to their desirable characteristics and having behavioral and biological similarities to humans. These similarities give them versatility in the types of studies they can be utilized in, such as cognitive control of motor and social behavior (Mustoe et al. 2015; Pomberger et al. 2019; Takahashi et al. 2017), saccade tasks (Johnston et al. 2018; Ma et al. 2020; Mitchell et al. 2015; Mitchell et al. 2014; Sedaghat-Nejad et al. 2019), auditory physiology (Wang 2018), and vocalization (Eliades and Wang 2013; Eliades and Miller 2017; Roy et al. 2011). However, there are still concerns on whether the marmoset can produce a sufficient amount of trials, and if so; do they show evidence of saccadic adaptation? Previous studies working with head-fixed marmosets have reported on average a range from 47-800 trials per session (Johnston et al. 2018; Ma et al. 2020; Mitchell et al. 2015; Mithcell et al. 2014;). These low numbers lead to questions on the ability to motivate these marmosets to perform a sufficient amount of trials. To address these questions, our lab had documented our creation of our marmoset laboratory in our methods paper (Sedaghat-Nejad et al. 2019) for which we improved these results. In this paper, we show the continuation of our behavioral training procedures, reporting on the long-term feasibility of training marmosets to consistently complete ~1,000 trials per session while maintaining their health. We have shown that this is possible and with these sufficient amounts of trials, we see evidence of saccadic adaptation during the gain down paradigm, as well as evidence of savings.

Performance results. The food regulated diet that we had placed our marmosets on was able to maintain their health within the desired range of 85-100% of their average initial weight (*subject R's* weight was maintained at 85.9% of their average initial weight while

subject M's weight was maintained at 89.8% of their average initial weight). By controlling their daily schedule and monitoring their weight at relatively the same time 5 days/week, we have been able to keep track of their health and ensure they are in healthy conditions, as suggested by the stabilization of their weight and lack of complications. Additionally, by giving them a structured daily routine (morning-afternoon cycles), we are able to guarantee that they would be motivated to perform on a daily basis. We implemented an adaptive style of training; in that we paid attention to the animals' experience and general performance and used these observations to calibrate our process accordingly. Both subjects have unique personality characteristics that made training and handling each one of them slightly different, in that they responded to differently to our motivational "tricks". By paying close attention to their personalities we were able to create more subject specific training that assisted in keeping motivation high.

Previous studies which used food regulation as a means of motivation used relatively higher food rates, feeding them 0.07 mL per trial (Johnston et al. 2018), 0.05-0.06 mL per trial (Mitchell et al. 2014) or 0.1-0.2 mL per trial (Osmanski and Wang 2011; Osmanski et al. 2013; Remington et al. 2012). We decreased this rate to a range of 0.015-0.025 mL per trial which showed to keep them from becoming full too early in a session. They have a small stomach capacity and when full can become lethargic and sleepy. The range of rates allowed us to manipulate their food rate throughout the session to keep motivation up and to make sure they were fed close to their 25 mL of food in the chair within a 1,000 trial session. This was done to prompt them to fully associate the chair with their meal by limiting how much we fed them in the colony after a session. We believe this association of the chair with food is another key

factor in motivating the marmosets to continue to work each time they enter the chamber. The lower food rates also encouraged the marmosets to perform about 4 or more trials between eating in order to get the food all the way to the tip of the tube before harvesting their reward. We believe this also played an important role in keeping their motivation high since they were working towards a goal (larger quantity of food at one time). Utilization of our food regiment as well as paying close attention to their personalities allowed us to get ~1,000 trials per session out of both marmosets over a long period of time (277 days for *subject R* and 637 days for *subject M*).

Behavioral results. One of the main questions people have is, if these marmosets can complete a sufficient amount of trials, will it be enough to show evidence of saccadic adaptation, or learning. We went after this question by utilizing the gain down paradigm for which we saw evidence of learning in both marmosets within 800 adaptation trials, as demonstrated by each subjects' ability to learn a noticeable amount of a 3˚ error. The definition of saccadic adaptation, for the gain down paradigm, is a decrease in the amplitude of the primary and corrective saccades and can be quantified using the saccade gain. *Subject R* showed to learn 75% of the error while *subject M* had shown to learn a total of 81% of the error. Recalling the nature of the gain down task, we expect to see a decrease in the primary amplitude, therefore the lower the percentage learned, the greater the decrease in the primary amplitude and consequently leading to a greater decrease in the corrective amplitude as well, which can be seen in Figure 3A.This reduction in the primary amplitude is representative of the eye landing closer to the jumped target and demonstrating their ability to gradually learn the perturbation. Moreover, they both showed a significant effect based on the experiment and

returned a significant experiment by trial interaction, meaning there is a significant difference in their slopes between the gain down and control experiments. This allowed for us to more definitively state that marmosets are able to show evidence of saccadic adaptation within 800 trials.

In addition to saccade gain, we looked into the changes of the saccade dynamics as a function of trial. When looking at their primary reaction times for the gain down experiments, we can see that over the duration of the adaptation block, their reaction times increase, that is the time it takes for them to respond to the stimulus takes longer, then begins to decrease once they enter a period of washout. In the savings experiment, we again see this decrease going from adaptation blocks to washout blocks for *subject R* but not present for the second washout block in *subject M*. The primary reaction times for the control experiment show an increase as they continue to make their 6.5˚ saccades. This increase in the control experiment shows evidence that they are becoming fatigued as they continue through all 1,000 trials, of ~40 ms for both subjects. However, when performing the gain down and gain down savings, it is unclear why we see an increase when they enter periods of washout.

Both subjects showed the same relationship between their peak velocities and the amount of perturbation they had learned. That is, the more they adapted to the perturbation, the greater the decrease in their peak velocities for both the primary and corrective saccades, which an example can be seen in Figure 3A. Straube et al. (1997) had shown that between their animals, the subject that had become more adapted expressed an increase in duration and decrease of the peak velocity. Catz et al. (2008) explored the relationship between saccade amplitude and peak velocity in humans. They had reported that a decrease in saccade

amplitude, as a result of a gain down perturbation, was correlated to a decrease in peak velocity. However, this study lacks a control experiment so they could not definitively claim this relationship and could still be caused by fatigue. If we compare our primary peak velocity plots to their corresponding learning plots, we see that the plots take on similar shapes, however, the presence of the washout is not seen in the peak velocity. Peak velocity continues to decrease throughout the duration of the experiment which leads to the assumption this is mainly affected by the fatigue the subjects are experiencing and not solely an effect of the perturbation.

Associated with the phenomenon of learning, we also explored if these marmosets showed any evidence of savings in the gain down savings paradigm (exp. 2) and found that they do. In Figure 3C we notice that they do not fully return to baseline during their first washout block, so in order to account for this change in baseline, we subtracted out their respective baseline periods and compared their rates of learning by performing a three-way within subject RM-ANOVA. The results showed no significance of session, a significance in trial, block and trial by block interaction. This allows us to make the assumption that depending on which block of the adaptation the subjects were in, their rates of learning were affected. That is, by being in block 2, they experienced a faster rate of learning which indicates the potential presence of a memory of the previously learned adaptation.

The difference in even and odd trials in our tasks consequently added an uncertainty aspect for the odd (center-out) trials since the subjects were unsure of the direction they would be cued (right or left of the target) as compared to the even (out-center) where they knew they would be cued back to the center. The variation in these two types of trials had shown a

significant effect on the primary reaction times for all three paradigms, as well as an increase in the odd trial's reaction times. This decrease in reaction times for even trials was expected since they had more information on where they would be cued and could theoretically react to the stimulus quicker. When they start at the center, the uncertainty of the direction the saccade is going to be made adds a delay period in order for them to register the direction they need to make their voluntary (primary) saccade.

There was no significant difference in saccade gain between the two types of trial for all three experiments for *subject M* and for the gain down and savings for *subject R* but significant for the control. One interpretation of this significant decrease for *subject R's* control and the decrease (although insignificant) in the odd trials gain, could be a result of the marmoset's ability to make a saccade from the center-out is more strenuous than returning back to the center, their natural resting point. Marmosets are notorious for using their heads to explore their environments. Having them perform saccades under head-fixed conditions is against their normal behavior when it comes to making saccades. One study that explored the oculomotor range of the marmoset under head-fixed conditions found that they were able to make saccades up to 10 degrees from the central point, which is adequate when it comes to studies of eye movements and visual cognition. However, they also found that during tasks that have a central fixation point, this limited range can cause a greater spatial bias, or cause them to become unresponsive if the stimulus is far from their natural position of rest and should be taken into consideration when training them to perform such tasks (Mitchell et al. 2014).

This increase in spatial bias could be the reason we are seeing an increase in the saccade gain in the center-out trials since we are having them perform a 6.5˚ saccade, which is close to

the reported oculomotor range. This effect is most likely not significant when the perturbation is turned on the longer they are exposed to the error, the more their primary amplitude decreases and the task theoretically is becoming easier for them to complete. As we can see in Figure 10B, *subject R* appears to be more sensitive to this strain and could be the reason we see a more dramatic difference between his odd and even trials during periods of washout during the savings experiment. His even trials show a more dramatic increase in gain, meaning he is now landing close to the 6.5˚ primary target again and has washed out, however, we do not see this as much for his odd trials. We can make the assumption that it is slightly more difficult for him to look 6.5˚ to the left or right.

In summary, we have shown that we are able to motivate our marmosets by use of our calibrated food-regulated diet while keeping them healthy. This is demonstrated by the stabilization of their weight within the desired range of 85-100% of their average initial weight and lack of presence of any complications. Use of our training protocol as well as paying close attention to the marmoset's individual behaviors and adjusting accordingly to make them comfortable in the chair has ensured that they can complete ~1,000 trials per session. From these findings, we were able to have both subjects complete three different experiments (gain down, gain down savings and a control) for which within a 1,000 trial session, we show that marmosets are capable of showing evidence of saccadic adaptation and savings.

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CURRICULUM VITAE

EDUCATION

MSE in Biomedical Engineering: Imaging and Instrumentation
Johns Hopkins University, Baltimore, MD (Aug. 2018 – Present)

B.S. in Chemical and Biomedical Engineering
Florida State University, Tallahassee, FL (Aug. 2013 – May 2018)

RESEARCH EXPERIENCE

Graduate Research Assistant
Laboratory for Computational Motor Control, Johns Hopkins University, Baltimore, MD (Aug. 2018 – Present)

- Conducting oculomotor control based psychophysical research in humans and non-human primates.
- Developed a primate specific, image guided, targeted recording system through manual co-registration of CT and MR imaging to establish a series of electrode guidance trajectories in 3D Slicer.
- Performing image segmentations of relevant brain structures and the skull, in 3D Slicer, for the development of 3D models for the design of implantable neurophysiological apparatus and surgical practice.
- Conceived, designed and programmed oculomotor behavioral experiments in C++ and Python.
- Development and optimization of behavioral protocols and training of marmoset monkeys in error-dependent learning tasks.
- Analyzing experimental psychophysical data in MATLAB.

Undergraduate Research Assistant
Neurodegenerative Diseases Laboratory, National High Magnet Field Laboratory, Tallahassee, FL (Jan. 2017 – May 2018)

- Handled care and preparation of samples for ex vivo MRI data acquisition.
- Performed set-up operations of all hardware and software associated with 500MHz and 900MHz MRI.
- Ran high resolution MRIs of transgenic 5xFAD mice brains using 500MHZ and 900MHz magnets to detect Amyloid-Beta Plaque burden associated with Alzheimer's Disease.
- Developed novel method for plaque detection using post processing of MRIs in AMIRA.

SKILLS

Animal work: marmoset monkey handling
Engineering Software: 3D slicer, AMIRA, Aspen, Fritzing, and ParaVision
Hardware: hardware filters, operational amplifiers and soldering
IDE: MATLAB and RStudio
Operating systems: Linux (Ubuntu), MAC and Windows
Programming: Arduino, C++, MATLAB, Python and R

PUBLICATIONS

[1] Sedaghat-Nejad. E, Herzfeld. D, Hage. P*, Karbasi. K, **Palin. T***, Wang. X, and Shadmehr. R "Behavioral Training of Marmosets and Electrophysiological Recording from the Cerebellum." *Journal of Neurophysiology,* 7 Aug. 2019, doi:10.1101/683706

[2] Hike. D, Boebinger. S*, **Palin. T***, and Grant. S "High Resolution MR Imaging and DTI-based Network Analysis of APP/PS1 Mouse Brains with Respect to Age and Sex." *(In progress)*

PROJECTS

Introduction to Neuro-Image Processing, Johns Hopkins University, Baltimore, MD (Jan. 2019 – May 2019)

- Post processed MRIs of human subjects' brains in MATLAB to perform histogram equalization and various types of smoothing filters.

Imaging Instrumentation, Johns Hopkins University, Baltimore, MD (Jan. 2019 – May 2019)

- Improved depth of field of microscopic images using MATLAB for post processing.

Biomedical Instrumentation, Johns Hopkins University, Baltimore, MD (Aug. 2018 – Dec. 2018)

- Designed and developed an arthritis detection glove.
- Designed and developed a biosecurity device to detect veins in finger.

Robot Devices Kinematics Dynamics and Control, Johns Hopkins University, Baltimore, MD (Aug. 2018 – Dec. 2018)

- Programmed a robotic arm to draw the state of Maryland in MATLAB.

Quantitative Anatomy and Systems Physiology II, Florida State University, Tallahassee, FL (Jan. 2017 – May 2017)

- Designed and developed a functional ECG for human measurements which was functionally tested in human trials.

Chemical Engineering Senior Design, Florida State University, Tallahassee, FL (Jan. 2018 – May 2018)

- Designed and simulated a Cumene production facility while leading a group of 4 students.
- Performed cost analysis to ensure that plant would be lucrative.
- Performed an environmental analysis to ensure the facility would be carbon negative.

PRESENTATIONS

Bachelor's Honors Thesis Defense – Oral Presentation
Florida State University, Tallahassee, FL (Apr. 2018)

- High Resolution MR Imaging of Amyloid Deposition in a Genetic Model of Familial Alzheimer's Disease

President's Showcase of Undergraduate Research Excellence – Poster Presentation

Florida State University, Tallahassee, FL (Oct. 2017)

- High Resolution MR Imaging and DTI-based Network Analysis of APP/PS1 Mouse Brains with Respect to Age and Sex

AWARDS

Nancy Casper and Mark Hillis Undergraduate Research Award
Florida State University, Tallahassee, FL (Mar. 2017)

- Research grant fund to work on bachelor's Honors Thesis.

Florida State University Star Student
Florida State University, Tallahassee, FL (Aug. 2017)

- Awarded to 20 of the most accomplished students annually as recognition for achieving distinction in their academic area: https://news.fsu.edu/student-stars/2017/12/04/tara-palin/