# ADAPTIVE CONTROL OF SACCADES VIA INTERNAL FEEDBACK

by

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# Abstract

Our brain monitors motor commands and, through internal feedback, corrects for anticipated errors. Saccades provide a powerful way to test this process because saccades are completed too quickly for sensory feedback to be useful. I first show that motor commands that move our eyes show variability and that this variability is not random noise, but is due to the cognitive state of the subject. Healthy people showed within saccade compensation for this variability with commands that arrived later in the same saccade. However, in people with cerebellar damage, the same variability resulted in dysmetria. This ability to correct for variability in the motor commands that initiated a saccade was a predictor of each subject's ability to learn from endpoint errors, suggesting that maintenance of saccade accuracy in daily life and short-term saccade adaptation have shared neural mechanisms. I then present a novel tool for studying feedback control of saccades: transcranial magnetic stimulation during a saccade perturbed the eye's trajectory, causing a reduction in velocity or an outright pause. This perturbation was corrected within the same saccade with motor commands that compensated and brought the eyes near the target. As this correction occurred even without visual input (in conditions where the target was removed), it appears that the correction is due to an internal feedback process that has an estimate of the current state of the eye. Furthermore our findings emphasize that TMS can have non specific, presumably "startle," effects on motor behavior, and these effects should be taken into account when interpreting the effects of TMS on brain function.

ABSTRACT

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# Chapter 1

# Introduction

To control our movements, our brains rely on sensory feedback. This feedback is thought to take two forms: one from sensory sources (vision and proprioception) that measure the state of our body and our environment, and a second from a process that predicts that state using the motor commands (efference copy) that we send out to move our body and "forward models" (FM) of our body and environment. From simple tasks such as picking up a cup of coffee to more advanced maneuvers like half-pipe snowboarding, we rely on these two sources of feedback to guide coordinated and accurate movements.

While the idea of a FM is attractive from a theoretical perspective, there is as yet no experiment that demonstrates that control of movements depends on a FM. This is because most previous experiments have focused on reaching, a movement in which it is difficult to dissociate effect of a FM vs. actual sensory feedback. Yet, testing the hypothesis of FMs is crucial because while many have argued that the cerebellum plays a role in computing FMs, there is scant evidence that control of movements depends on FMs.

To solve this problem, a better approach may be to consider control of saccadic eye movements. We make saccades to explore our world, such as looking at a picture of Queen Nefertiti (Figure 1.1, from Yarbus 1967). Our eyes quickly dart from one

Figure 1.1: Saccades when viewing a picture (Yarbus 1967).

fixation point to another. These movements are typically completed within 60ms and are too fast for external sensory feedback to be useful. For this reason, saccades are often thought to be stereotypical, ballistic movements. However, I will show that the motor commands that initiate saccades are in fact highly variable, due to top-down factors such as motivation and reward. For example, in the picture of Queen Nefertiti, we are attracted to certain features of the image. These biases not only determine where we look, but could influence how make the movement to look there, reflected in the speed of these movements (Chapter 2). If left uncompensated, these internal sources of variability would causes dysmetria in our saccades. Yet, saccade endpoints appear immune to this variability, consistent with the idea that control of saccades depends on a FM that monitors the outgoing motor commands and steers the eyes. I examine the neural correlates of the forward model by testing the response to variability and response to endpoint errors in control of saccades in cerebellar patients (Chapter 3). Instead of simply relying on the brain's own variability, we then used transcranial magnetic stimulation (TMS) to perturb saccades in a more controlled manner to study. We show that a single pulse of TMS during a saccade perturbs the eye's trajectory, causing a reduction in velocity or an outright pause. This perturbation is corrected within the same saccade by motor commands that

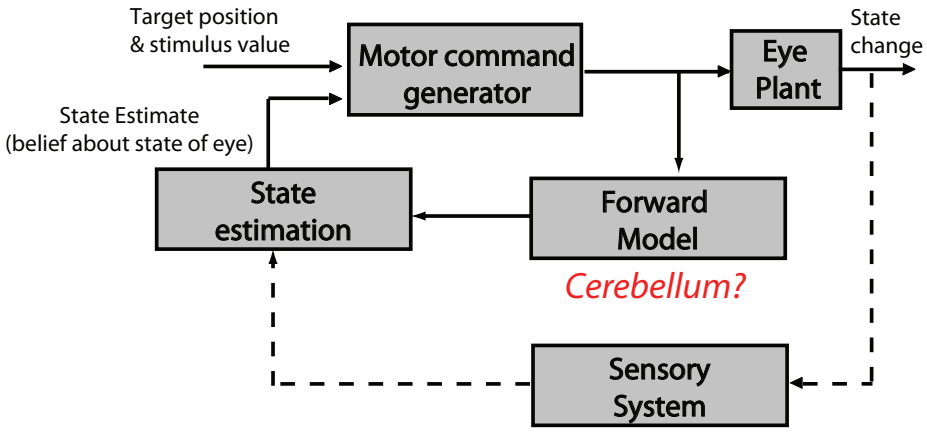


Figure 1.2: Schematic of feedback controller of saccades. Saccadic eye movements are useful for studying the role of forward models in motor control because they are too fast to rely on sensory feedback during the movement.

compensate and bring the eyes to the target, perhaps relying on a feedback process that has an estimate of the current state of the eye (Chapter 4).

## 1.1 Forward models and the cerebellum

The idea that the brain controls movements through a system that predicts sensory consequences of motor commands using a forward model is a very well accepted concept in motor control (Figure 1.2). Indeed, investigators who study control of limb movements have concluded that an internal feedback process is probably at work in the control of reaching [1, 2]. However, testing this framework in limb movements has proven to be very difficult because such movements always benefit from sensory feedback. Teasing apart contributions of sensory feedback and internal feedback is very difficult from analysis of limb trajectories. Control of saccades, on the other hand, seems ideally suited as an experimental paradigm for testing the mechanisms of internal feedback.

In order for forward models to be useful, they must be accurate representations of our body and environment. That is, these models must undergo constant recalibration

in response to growth, injury, and disease. A better understanding of the neural structures and mechanisms involved in forming accurate forward models could help us design better rehabilitation strategies for patients with motor disorders.

Many studies have implicated that the cerebellum as the site of internal models. For example, cerebellar lesions disrupt compensation of the interaction torques between different segments of a limb, implying that the cerebellum contains a model of arm kinematics and dynamics that allows it to predict and counteract interaction torques [3]. Cerebellar patients cannot form new models of arm dynamics, when reaching in a novel force field [4]. A study in monkeys showed that cerebellar neurons can disambiguate tilt and torsion signals from semicircular canals and otolith neurons, implying that the cerebellum creates an internal model of the physics of the world [5].

## 1.2 Feedback control of saccades

Saccades differ from other kinds of movements in that they are too fast to be influenced by sensory feedback. In fact, the brain actively suppresses visual processing during saccades [6]. Furthermore, proprioceptive signals from the eyes do not play any significant role in controlling saccade trajectories [7, 8]. However, saccades are not open-loop movements. For example, the brain is able to compensate for both natural and drug-induced variability in peak saccade velocity to maintain saccade endpoint accuracy [9]. That is, the variability due to motor commands that initiate the saccade appear to be partially corrected as the saccade progresses [10]. These results are consistent with a hypothesis that David Robinson [11] first put forth, which stats that saccades are controlled online by a feedback controller that monitors ongoing motor commands and corrects for predicted errors.

Many neural structures and pathways have been implicated in the generation of saccades. Different structures may be involved in generating different kind of saccades.

In this work, we consider reactive saccades in response to suddenly appearing targets (Figure 1.3. The brainstem burst generator is common to all saccades and directly innervates the oculomotor muscles to move the eyes. The burst generator receives its input directly from the superior colliculus and indirectly from the superior colliculus via the oculomotor cerebellum. This indirect pathway receives a copy of the motor command from the superior colliculus and adjusts the eye movement as needed.

One interpretation of this pattern of connections is that the direct pathway provides the initial drive to saccades while the indirect pathway receives a copy of the motor commands and corrects saccade trajectories if needed. Lesion studies support this interpretation. Lesion of superior colliculus leads to enduring increased reaction time and slowed saccades, but the accuracy of saccades recovers [12]. Lesion of the cerebellum leads to enduring dysmetria [13, 14]. When the cerebellar vermis is lesioned, monkeys' saccadic amplitudes become more variable [15, 16]. These monkeys have impaired ability to adaptively adjust saccade amplitudes in response to intra-saccadic target jumps. Studies of cerebellar patients show that their saccades are dysmetric [17] and that they are impaired in short term saccade adaptation [18, 19]. This dysmetria could be a reflection of an inability to compensate for the natural variability in motor commands that initiate the saccade.

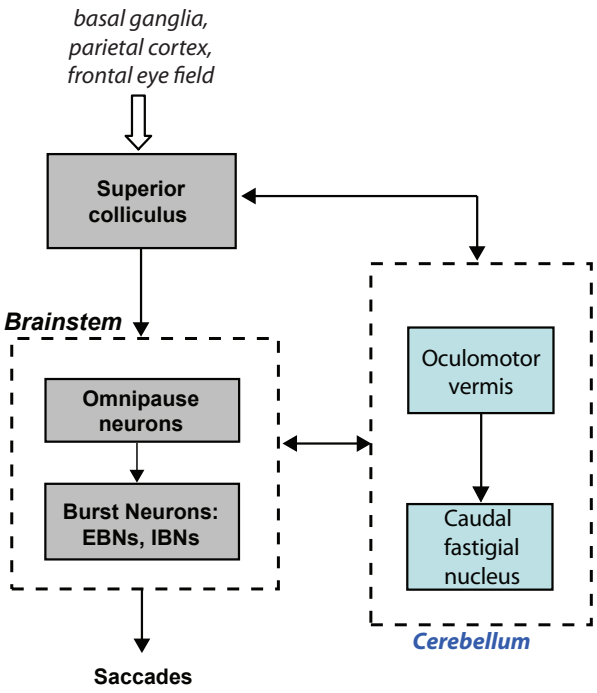


Figure 1.3: High-level diagram of brain areas involved in saccade generation

# Chapter 2

# Factors that affect saccade velocity

## 2.1 Introduction

When we view a work of art, the face of a friend, or read this text, our brain shifts our gaze from one point to another, rapidly moving our eyes. Each movement is a saccade that positions the eyes so that the fovea can sample the currently most interesting part of the visual space. In performing these movements, the brain solves two kinds of problems: first, it selects where to look, and next, it programs the motor commands that move the eyes to that location.

Regarding the first problem, it has long been recognized that the scan sequence is not random [20] and that task demand, potential reward, uncertainty and risk, among other cognitive factors greatly influence where we look (Hayhoe and Ballard, 2005). For example, in viewing a scene consisting of faces and non-face objects, we are naturally drawn to the face regions first and spend longer looking at faces compared to the rest of the scene [21]. This suggests that our brain may continuously assign a value (integrating various cognitive factors) to every part of the visible space forming a priority or salience map [22, 23], and each saccade is our brain's attempt to direct our fovea to the region where currently, the value is highest. Because people

are naturally drawn to faces, the implication is that faces may have an intrinsically higher value than other images.

The second problem, the problem of how to move the eyes during a saccade, was thought to be independent of the value that the brain might assign to the stimulus. Saccades are so short in duration (50-70ms) and so high in velocity (300-400°/s) that they were thought to be pre-programmed, ballistic processes, resulting in a stereotypical relationship between amplitude and velocity termed the "main sequence" [24]. However, recent results suggest saccade kinematics are not stereotypical. For example, monkeys that make a saccade to a remembered target location have higher saccade velocities and shorter durations when that target is also associated with a food reward [25]. If an object is the target of a reaching movement, saccades that accompany the reach exhibit higher velocities and shorter durations [26, 27]. If there is information that one needs to acquire at the visual target, saccades to that target exhibit higher velocities and shorter durations [28]. Finally, repeatedly making saccades to the same visual stimulus produces eye movements with smaller velocities and longer durations [19,29]. It is possible that these manipulations (food, repetition, etc.) alter the implicit value that the brain assigns to the visual stimulus, and that in turn affects the saccade's trajectory. Indeed, one of the fundamental predictions of the optimal control framework is that the trajectory of saccades depends on the value of the visual stimulus . In this framework (Niv et al., 2007a), the trajectory of a saccade is affected by two kinds of costs: costs associated with the motor commands, and costs associated with the time that passes before the target is foveated. If the value of the stimulus is high, this second cost is also high, which should result in high velocity, low duration saccades.

Here, we attempted to test the prediction that the hypothetical intrinsic value associated with a visual stimulus affects control of saccades. To approach our problem, we considered reflexive (rather than voluntary) saccades, as they are thought to be a low-level orienting reflex. Instead of supplying the stimulus value externally by using

money or food as reward, we tested whether visual images of social relevance alter the kinematics of the orienting reflex.

## 2.2 Materials and Methods

### 2.2.1 Subjects

Twelve subjects (6 female, mean age 27, range 21-44 years) were recruited from the Johns Hopkins medical school community. All subjects gave written consent to protocols approved by the Johns Hopkins Institution Review Board.

### 2.2.2 Experimental procedure

We used a single-axis scleral search coil system (Skalar Medical, Delft, The Netherlands) to record horizontal and vertical eye movements at 1000 Hz from either the right or the left eye [30]. Subjects sat in a dark room with their head restrained by a dental bite-bar. Raw coil signals were filtered in hardware (90-Hz low-pass Butterworth), digitized (1,000Hz), and saved on computer for later analysis. Saccade targets were presented with a red laser (0.25° in visual angle) that was rear-projected onto a translucent screen located 1 m in front of the subject. The position of the beam was jumped using a galvo-controlled mirror, which had a step response of 10ms. Images were presented via a projector (Sharp Notevision PG-M20X, 60 Hz refresh rate). The projector provided some ambient light in the room but otherwise the room had no other sources of light.

The idea of our experiment was to have people make reflexive saccades to foveate a laser light in a darkened room. However, we wanted to control the "expected reward" of each saccade. We did this by controlling the image that the subject would see after completion of the saccade. The trial sequence is shown in Fig. 2.1A and Fig. 2.1B.

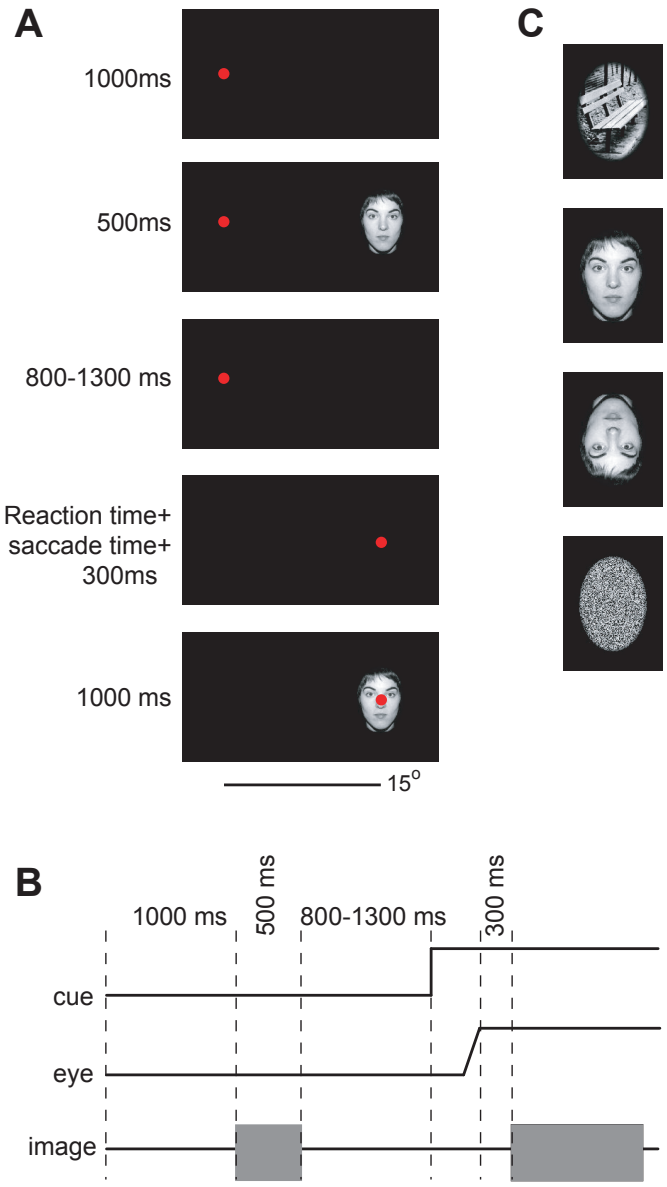


Figure 2.1: A. A trial began with subjects fixating a red laser light. After a period of 1000ms, an image was displayed for 500ms centered at 15o with respect to fixation. Subjects continued to maintain fixation at the red laser. After an additional 800-1300ms fixation period, the laser moved by 15°, and the subject made a saccade to the new target location. After an additional 300ms fixation period, the same image was displayed again. B. Timing of the events. C. On each trial, the image was randomly chosen from one of four image types: faces, objects, inverted faces, or random pixels.

Participants made 15° horizontal saccades symmetric about the primary position between +7.5° and -7.5°. When the trial started at -7.5°, the target was 15° to the right and when the trial started at +7.5° the target was 15° to the left. Participants fixated a target (red laser) located at +/-7.5° for 1000ms. After this period, an image centered at 15° away with respect to fixation on the other side of midline was presented for 500ms. Subjects continued to maintain fixation. After a random delay of 800-1300ms the laser moved and subjects made a saccade crossing the midline to fixate the new target location. Around 300ms after completion of their saccade, the image was re-displayed at the location of the target (200 ms plus delay introduced by the projector, which was 104+/-7ms SD). Therefore, the saccade was "rewarded" with the image that the subject had initially seen in the periphery. In this way, we hoped that the expected value of each saccade could be controlled on a trial-by-trial basis via the image that first appeared in the periphery.

Subjects made six blocks of 40 saccades. We considered four types of images: faces, inverted faces, objects, and random pixels (Fig. 2.1C). One image type, selected at random, was presented on each trial. Thirty different images were used for each image type. Thus each image was used twice during the experiment. The images were constructed from the Psychological Image Collection of University of Stirling database (http://pics.psych.stir.ac.uk). All images were histogram equalized to have the same overall intensity values. The image size was 4.5° by 6.5° in visual angle.

### 2.2.3 Data analysis

The duration of saccades was determined by a 16°/s speed threshold. Abnormal saccades were excluded from analysis using global criteria that were applied to all subjects: 1) Saccade amplitude less than 11° (73% of the target displacement) or greater than 16°. 2) Saccade duration less than 50ms or greater than 150ms 3) saccade reaction time less than 50ms or greater than 500ms. 4) peak saccade velocity

less than 150°/s or greater than 550°/s. For each subject, outliers for amplitude, duration, and peak velocity are those outside of 1.5 times the inter quartile range; these outliers were also removed. Trials in which the subject broke fixation by reacting to flashing of the image were also excluded from analysis. Overall, 10% of saccades were excluded from analysis.

## 2.3 Results

Reflexive saccades made in anticipation of viewing a face were generally faster and had a shorter duration than saccades for other images. Fig. 2.2A illustrates the average saccade trajectory of a single subject in the face and random-pixel trials. The saccades in the two types of trials were approximately the same amplitude ($p = 0.29$, paired t-test), yet in the face trials the peak velocities were higher ($p < 0.05$) and the durations were shorter ($p < 0.05$, paired t-test).

These differences were also present in the population data. Fig. 2.2B illustrates within subject changes in saccade parameters with respect to face trials in the inverted face, object, and random-pixel trials. We found that saccade durations and peak velocities were significantly affected by image type (ANOVA with image type as the within subject factor, $F(3, 33) = 3.4$, $p < 0.05$ for durations, and $F(3, 33) = 3.6$, $p < 0.05$ for peak velocities). There was also a trend toward significance for peak deceleration and time of peak deceleration ($F(3, 33) = 2.73$, $p = 0.059$ for peak deceleration, and $F(3, 33) = 2.68$, $p = 0.063$ for time of peak deceleration). Post hoc pair-wise t-tests using the Bonferroni correction revealed that saccades in face trials had significantly higher peak velocities (5.48°/s, corrected t-test $p = 0.01$) and shorter durations (1.73 ms, corrected t-test $p = 0.04$) than saccades in random-pixel trials. In contrast, we did not observe an effect on saccade amplitudes ($F(3, 33) = 0.77$, $p = 0.52$), endpoint variability ($F(3, 33) = 0.201$, $p = 0.895$), or reaction times ($F(3, 33) = 1.21$, $p = 0.32$). Figure 2.2 shows the result of pair-wise t-tests with

and without Bonferroni corrections. Subjects made equal number of leftward and rightward saccades. Equal numbers of each image type were presented for leftward and rightward saccades. In addition, we had half of the subjects wear the coil in the left eye to counterbalance any differences in the eye recorded. Analysis showed no difference between rightward and leftward peak velocity within subject ($p = 0.75$, 2 tailed paired t-test), duration ($p = 0.66$), amplitude ($p = 0.66$), and reaction time ($p = 0.82$).

Collewijn et al. [31] found that for saccades about the primary position, the temporal/abducting eye made saccades of higher amplitude, higher velocity, shorter duration, and less skewed than the nasal/adducting eye. However, we found no significant difference between temporal and nasal bound saccades ($p = 0.14$), although the trend was in the direction suggested by Collewijn et al. [31]. Regardless, we had an equal number of temporal and nasal bound saccades, thereby counterbalancing any potential differences.

The data presented in Fig. 2.2 reflects average saccade kinematics as measured over six blocks of 40 trials. Our earlier work had suggested that the repetition of saccades tends to produce a fatigue-like effect so that set after set, the peak velocities tend to drop. We wondered whether the differences that we had seen in the pooled data (Fig. 2.2), i.e. the differences in saccade kinematics between face and random pixels, were present from the early trials, or were they due to a differing rate of fatigue. To answer this question, for each subject we found the average speed and duration of face saccades in block 1 and then compared the random pixel saccades to these measures. This difference with respect to face saccades of block 1 is plotted in Fig. 2.3. The data suggests that whereas repetition induced a fatigue-like effect on both face and random pixel saccades (ANOVA, main effect of block, peak velocity $F(5, 55) = 4.6$, $p < 0.01$; duration $F(5, 55) = 3.76$, $p < 0.01$), faces elicited a consistently faster saccade with a shorter duration (ANOVA, main effect of image type, peak velocity $F(1, 11) = 9.7$, $p < 0.05$; duration $F(1, 11) = 5.96$, $p < 0.05$), and this difference did not change

markedly as a function of repetition (ANOVA, block by image type interaction, peak velocity $F(5, 55) = 0.56$, $p = 0.7$; duration $F(5, 55) = 0.64$, $p = 0.7$).

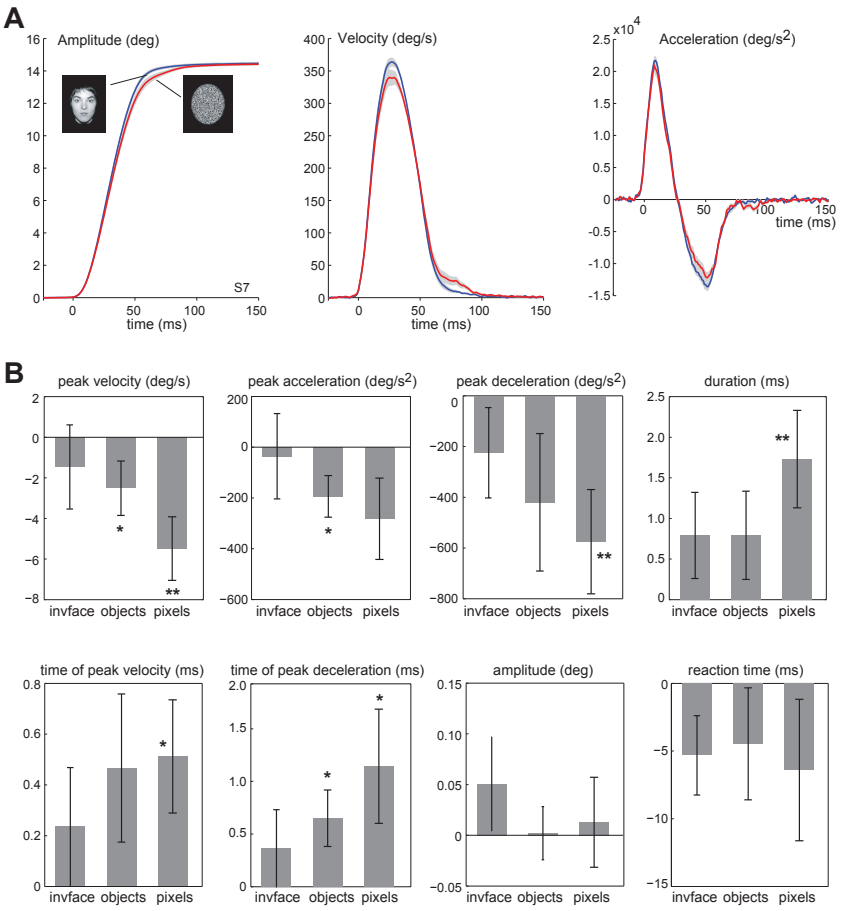


Figure 2.2: In anticipation of foveating an image of a face vs. an image that contained random pixels, reflexive saccades tended to have higher velocities, shorter durations, higher accelerations, and lower decelerations. A. Average saccade trajectory of one subject for face trials (blue traces) and random-pixel trials (red traces). Gray region is SEM across trials. B. Within subject change in saccade parameters for the various images with respect to face (error bars are SEM across subjects, asterisk indicate $p < 0.05$, one-sided t-test). For example, subjects on average had a 1.8ms longer duration saccade in random-pixel trials as compared to face trials. ($^*p < 0.05$ uncorrected comparison, $^{**}p < 0.05$ Bonferroni corrected comparisons)

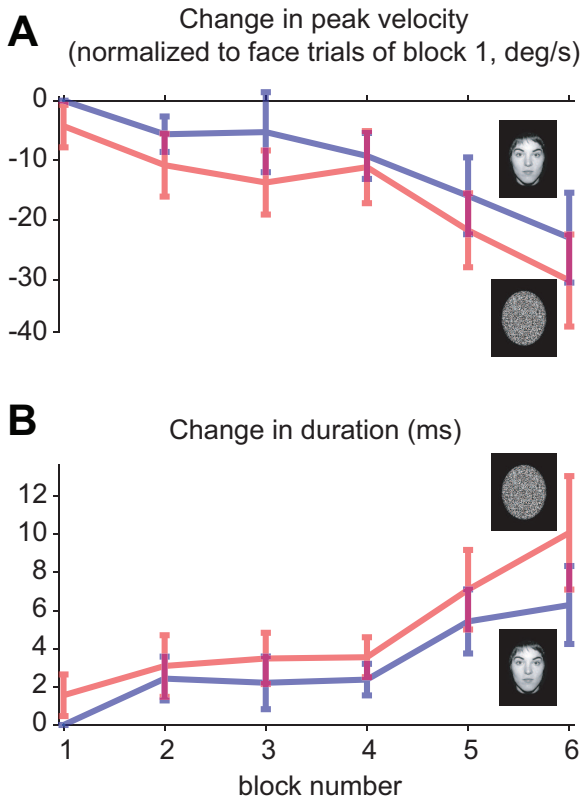


Figure 2.3: A fatigue-like effect on saccade kinematic parameters over blocks. For each subject, we computed the average peak velocity and duration for face trials in block 1, and then compared the saccades to faces and random pixel during other blocks to these measures. A. Change in peak velocity. B. Change in duration. Error bars are SEM across subjects. (Without Bonferroni correction: $^{*}p < 0.05$, With Bonferroni correction $^{**}p < 0.05$)

## 2.4 Discussion

In our experiment, people made a reflexive saccade to foveate a point of light in a dimly lit room. After completion of the saccade, they were presented with an image centered on their fovea. We found that saccades that were made in anticipation of viewing a face had higher velocities and shorter durations than saccades that were made in anticipation of viewing an image consisting of random-pixels. It is important to note that the image types were not associated with an experimenter controlled value; rather, our intention was to ask whether there was some inherent property of

the image that would affect saccade kinematics. Our results suggest that the brain assigns a value to the stimulus of the saccade, and this in turn affects the motor commands that orient the eyes toward that stimulus. While earlier work had found some evidence for the role of stimulus value in voluntary saccades of monkeys, for example, in anticipation of food [25, 29], our results may be the first to demonstrate an effect of natural images.

### 2.4.1 Can images have an intrinsic value?

Instead of supplying the stimulus value externally by using money or food as reward, we tested whether visual images of social relevance altered the vigor of the orienting reflex. Visual images have been shown to elicit short latency responses in midbrain dopaminergic neurons [32], and images can serve as positive reinforcement for animal behavior [33]. Images conveying social information such as social status [34] and potential mate [35] can modulate gaze behavior. Face images in particular are known to produce reward-like neuronal responses. Hayden et al. [36] found that the opportunity to look at another person is a valued commodity and that physical attractiveness is one dimension along which value rises. Indeed, attractive faces can activate the reward circuitry of the brain [37, 38].

### 2.4.2 Small effect on kinematic parameters

The modulation that we were able to elicit with different image types was significant but quite small (5°/s in velocity and 1-2 ms in saccade duration). Foveating a target a few milliseconds earlier may not be crucial for survival. However, it is possible that our results are a reflection of a general framework of how the brain controls movements: the brain assigns a value to sensory stimuli and this value is reflected in the vigor with which movements are performed.

This view helps explain a number of previously published observations. For ex-

ample, saccades accompanied by reaching movements [26,27] or followed by a perceptual task [28] are faster than saccades without subsequent tasks. Saccades made to repetitive stimuli become slower as the stimulus repeats [29, 39]. Predictive saccades (predictive in amplitude, direction, and timing) are slower than reflexive saccades [40].

To explain these results, let us suppose that the stimulus that elicits the saccade holds more value if useful information is expected at the endpoint. Both predictive saccades and saccades to repeated targets offer little new information; potentially explaining why the accompanying saccades are slower. In contrast, saccades guiding a reaching movement or a perceptual task provide useful information that can help accomplish the task; potentially explaining why the accompanying saccades are faster.

However, the effect that we observed was quite small. For example, when saccades are accompanied with a reaching movement, velocities can be about 4% faster, while here image content had about a 1% effect. What might account for our smaller effect? One possibility is that we focused on reflexive saccades (driven by the sudden onset of external stimulus), whereas the effect of stimulus value may be much higher for voluntary saccades (the brain voluntarily chooses the target location of the saccade). The neural control of reflexive saccades is distinct from voluntary saccades [27,41], and it is likely that the effect of value on saccade velocities might be greater for voluntary saccades because voluntary saccades rely more heavily on basal ganglia structures, structures that in monkeys are modulated by the value of the stimulus [42]. Indeed, monkeys make faster voluntary saccades (by about 7%) to stimuli that produce more food [25]. In contrast, our task was a low-level orienting reflex.

Another possibility is that our task relied on the intrinsic value of images, and not on any specific task that subjects needed to perform after observing the image. During each trial, the subject was led to anticipate a certain image by flashing that image for 500ms at 15° with respect to the fovea. After the image was removed, the saccade was elicited by a step change in a red laser dot. Therefore, the saccade was ultimately made in reaction to a jumping red target.

### 2.4.3 Reaction time and peak velocity

Many previous reports have focused on the relationship between target value and saccade reaction times [43–45]. These reports have generally not considered the effect of value on saccade kinematics. Here, we did not observe an effect of image type on reaction times. This could be because we were not able to induce a large enough range of stimulus values, or because we focused on reflexive rather than voluntary saccades. The correlation between peak velocity and reaction time in our experiment was very small ($-0.2837 < r < 0.0859$). The lack of correlation between saccade peak velocity and reaction have been observed in other tasks [46]. For example, repetition induced slowing of saccades produces up to 10% reduction in saccade velocities with little or no changes in reaction time. It is possible that for reflexive saccades, stimulus value more strongly affects saccade velocities as compared to reaction times.

### 2.4.4 Attention vs. reward

The different image types capture different amounts of attention and this can alter the motivation for the subsequent eye movements. Bindemann and Burton [47] showed that faces retain more attention than images of other categories (inverted images, objects). The question of whether saccade velocities are modulated because of changing attention or because of an intrinsic reward associated with that image is very difficult to answer [48]. However, whether the attention or the reward system is engaged, both could translate to a value assigned to the upcoming movement.

### 2.4.5 Low level differences in the images

Our images were equalized for overall intensity, but not contrast or spatial frequency. This is because normalization for contrast and spatial frequency tends to make the images unrecognizable at the eccentricity that we presented them. Regard-

less, our experiment attempted to account for this potential confound by making the stimulus that guided the saccades a uniform laser light. That is, the saccade kinematics varied not because of the image on the fovea that elicited the saccade, but because of the memory of an image that would be presented after saccade completion. This may be analogous to the memory of a rewarding piece of food that is expected to be received after completion of a movement. Although we have not ruled out the possibility that low-level features in visual memory could influence saccade kinematics, there is evidence that high level task demand rather than low level image features modulate saccade kinematics. For example, catch-up saccades during smooth pursuit to bright and dim targets showed similar main sequence relationships while a condition in which the target changed between bright and dim as a form of task feedback actually resulted in faster catch-up saccades [49].

### 2.4.6 Optimal control framework

It is reasonable that our brain should incorporate some concept of value in motor planning. Actions with more social priority such as looking to faces could benefit from being performed faster. Optimal control models incorporate the concept of value [50]. In these models, movement duration and velocity depend on the combined effect of two types of cost: a cost associated with the motor commands in which larger commands are penalized because they cause endpoint inaccuracy (encouraging slower movements), and a cost associated with passage of time in which longer duration movements are penalized (encouraging faster movements). The ratio of these two costs determines movement duration. Stimulus value increases the cost of time, encouraging faster movements with shorter duration. It is not enough to model movements simply with the constraint of endpoint variance [51]. A much richer set of motor behavior can be explained with the incorporation of value of the action.

### 2.4.7 Neural correlates of value

Neural signals reflecting value and action selection in the context of eye movements have been found in many brain regions including the basal ganglia [52], the posterior cingulate cortex [53], and the amygdala [54]. These signals can subsequently influence motor output: for example, the basal ganglia has direct projections to the superior colliculus which influences saccade kinematics. These signals are also important in implementing reinforcement learning of the optimal control policy with dopamine as a strong candidate for mediating reward based learning [55, 56]. Our work here may reflect the optimized behavior of responding with more vigor to biologically salient images.

In summary, our findings suggest that the brain assigns an internal value to our actions, even for low level orienting reflexes that orient the eyes in anticipation of viewing a natural image. Movements which carry more value are executed with more vigor, i.e., faster.

# Chapter 3

# Cerebellar contributions to adaptive control of saccades in humans

## 3.1 Introduction

It is thought that saccades are highly practiced, optimized examples of ballistic movements. Yet, the motor commands that initiate an eye movement to a given target are variable, and this variability is not random noise. For example, people make saccades with higher velocities in anticipation of seeing a more interesting visual stimulus [57]. Repeating a visual target or reducing the reward associated with it reduces saccade velocities [29, 39]. On the other hand, increasing the reward associated with the target or making the target the goal of both the eye and the arm movements increases saccade velocities [25, 27, 58]. Despite this variability in the motor commands that initiate saccades, the brain accurately guides the eyes to the target. How is this accomplished? Perhaps endpoint accuracy is possible because the brain incorporates an internal feedback process that monitors the motor commands

and corrects them online [11]. If the internal feedback is intact, variability in the commands that initiate the saccade might be compensated via commands that arrive later during the same saccade. However, for this internal feedback to be effective, it needs to be adaptive and learn from endpoint errors. A computational framework that captures these ideas is one in which motor commands are monitored via a forward model, predicting sensory consequences and allowing for within saccade compensation. Endpoint errors should produce adaptation in the forward model because they reflect a prediction error. If there is such an internal feedback process, damage to it might produce both an inability to compensate for the variability in the motor commands that initiated the movement, and an inability to learn from endpoint errors. That is, the two abilities should be correlated. Previously we observed that when a visual target on the horizontal meridian was moved vertically as a saccade is made toward it (cross-axis paradigm), saccades became curved [29]. This suggested that the forward model was learning from endpoint errors, steering the saccade to the target. Here, we looked for the neural basis of this hypothetical internal feedback process by examining saccades of cerebellar patients, as their saccades are dysmetric, and the cerebellum has long been hypothesized to function as an internal feedback pathway that steers the eyes to the target [13, 14, 17]. Our subjects were a group of patients who suffered from spinocerebellar ataxia (SCA-6), a neuro-degenerative disease that targets the Purkinje cells of the cerebellum [59–61]. Our experiment (the cross-axis paradigm) involved repetition of a visual target, something that we had found to produce structured variability in the motor commands that initiate the saccade [29]. We wondered whether this natural variability would also be present in the motor commands that initiated saccades of cerebellar patients, and if so, whether these subjects would show a reduced ability to compensate for that variability. A second part of our experiment was focused on the endpoint errors that were caused by jumping of the target. We had earlier found that the adaptive response to errors appeared to involve two or more timescales: a fast timescale that learned a great deal

from error but had poor retention, and a slower timescale that learned little from error but had good retention [62]. Cerebellar damage is known to profoundly impair the ability to adaptively control saccades [18, 19]. Here, we wondered whether these two timescales were uniformly affected by cortical cerebellar damage, or was there a greater impairment in one timescale of the adaptive process than in the other.

## 3.2 Materials and Methods

### 3.2.1 Experimental setup and design

Subjects sat in a dark room with their head restrained using a dental bite-bar. We used a scleral search coil system (Skalar Medical, Delft, The Netherlands) to record horizontal and vertical eye movements at 1000Hz from either the right or the left eye [30]. Raw eye position information from the coils was filtered in hardware (90Hz low-pass Butterworth), digitized (1,000Hz), and saved on a computer for later analysis. A 0.2° red laser beam was rear-projected onto a translucent screen located 1 m in front of the subject. Target position was varied by a galvo-controlled mirror. The experiment is summarized in Figure 3.1A. It consisted of 5 blocks: pre-adaptation oblique (112 trials), pre-adaptation error-clamp (error-clamp I, 60 trials), counterclockwise (CCW) cross-axis adaptation (500 trials), clockwise (CW) de-adaptation trials (80 trials), and post-adaptation error-clamp trials (error-clamp II, 140 trials) (Figure 3.1). The experimental blocks are explained in detail below. Each block was further divided into short sets of 60 trials (1.5 sec inter-trial interval). On each trial, the saccade crossed the vertical meridian. The sets were separated with a break typically of 30 seconds. During set breaks the subjects sat quietly, usually with their eyes closed, except for occasional breaks that were 2-3 minutes long to administer eye drops to the subject. Oblique trials: The experiment began with two sets of oblique trials (Figure 3.1A). The target locations were always 15° away from fixation in the horizontal direction

and 0, 1, 2, or 3° above or below the meridian vertically. The targets appeared randomly within the set. Saccades alternated rightward and leftward symmetric about the midline. Error-clamp trials: The target T1 was presented at 15° to the left or right of fixation. Once the saccade began, T1 disappeared. At 500ms later, a fixation point appeared with a horizontal position the same as that of T1 and a vertical position of the eye from 10ms prior. Therefore, in error-clamp trials we attempt to assay the motor output after adaptation while preventing further learning by minimizing the endpoint errors. Because in the cross-axis paradigm, learning takes place in the vertical direction, the error-clamp trials clamp the vertical error to zero but do not affect the horizontal error. To prevent accumulation of a large vertical offset, we restricted the target position to within +/-10° range vertically. Once outside of this range, the vertical position of the target was reset to 0° for the next trial. There were two error-clamp sets of trials, one before the adaptation sets (error-clamp I) and one after (error-clamp II). Cross-axis trials: The pattern of target positions is shown in Figure 3.1A. A target was projected at 15° with respect to fixation (T1). As soon as the saccade began, the target jumped 5° vertically to a new location (T2). In the adaptation trials, the jump direction was consistently counterclockwise to the orientation of T1. T2 then served as the fixation point (F) for the next trial. In de-adaptation trials, the jump direction was clockwise to the orientation of T1. The primary saccade to T1 was always followed by a secondary corrective saccade that brought the eyes to T2. The data presented here represents characteristics of only the primary saccade. The transition between CCW to CW adaptation trials occurred mid-set without a break: the 9th adaptation set began with 20 CCW trials but then suddenly changed to CW training (40 trials). Similarly, the transition from CW to error-clamp was mid-set without a break: the 10th adaptation set began with 40 CW trials but then suddenly changed to error-clamp trials (20 trials).

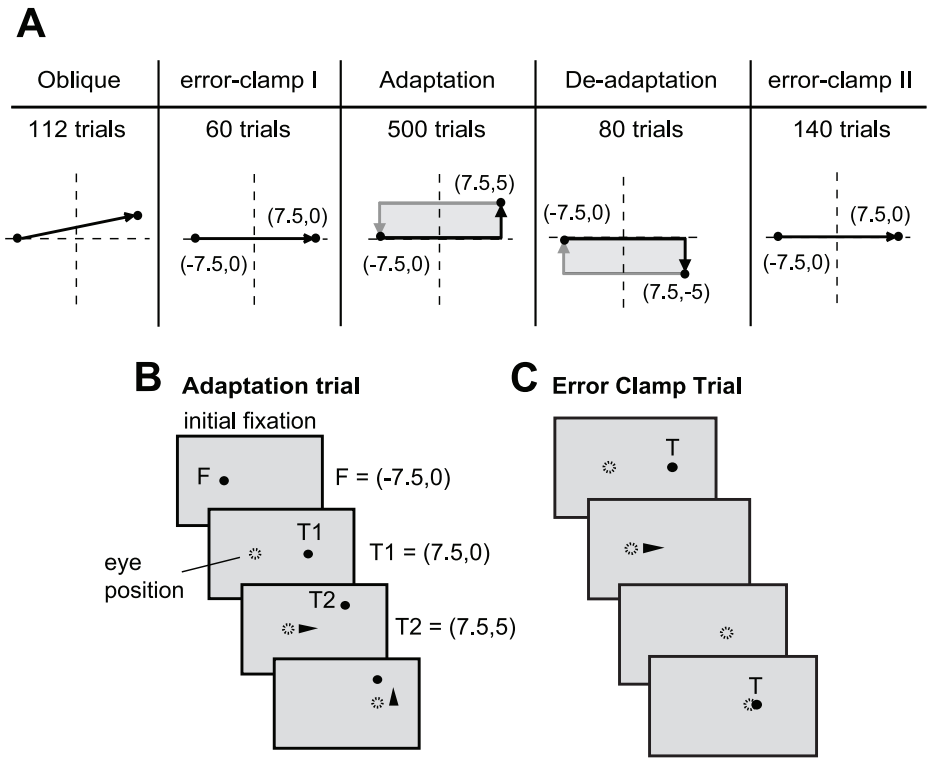


Figure 3.1: Experimental procedures. (A) Subjects were trained on a cross-axis adaptation task. The experiment consisted of five blocks: trials in which saccade targets were presented at various oblique angles, 60 pre-adapt error-clamp trials in which targets were always at 15° horizontal (error-clamp I), 500 adaptation trials (target jump is counter-clockwise), 80 de-adaptation trials (target jump is clockwise), and 140 post-adapt error-clamp trials (error-clamp II, targets again at 15° horizontal). During error-clamp trials, the target did not jump but disappeared after saccade onset and reappeared 500ms later at the current eye position. The dashed lines indicate axes centered on straight ahead. (B) Adaptation trials. Filled circles indicate current laser position. Arrowheads indicate when a saccade began. A target was projected 15° away from fixation (T1). As soon as the saccade began, the target jumped 5° vertically to a new location (T2). The jump direction was consistently counterclockwise to the orientation of T1. T2 then served as the fixation point (F) for the next trial. In de-adaptation trials, the jump direction was clockwise to the orientation of T1. (C) Error clamp trials. T1 was presented at 15° to the left or right of fixation. Once the saccade began, T1 disappeared. 500ms later, a fixation point appeared with a horizontal position the same as T1 and a vertical position of the eye from 10ms prior.

### 3.2.2 Subjects

Nine individuals with cerebellar degeneration participated in the study (Table 3.1). All but one were diagnosed with Spino-Cerebellar Ataxia Type 6 (SCA6), a neurodegenerative disease that primarily affects the Purkinje cells of the cerebellum, particularly in the vermis [59, 60]. MRI scans confirmed that these patients had global degeneration of the cerebellum including the vermis and the hemispheres. The one patient without a genetic diagnosis (P2) had a clinical picture indistinguishable from the others with a genetically-confirmed diagnosis. SCA6 is caused by mutations in a gene that encodes a calcium channel in Purkinje cells. In the cell culture models of this mutation the result is premature death of the Purkinje cells. In the surviving cells, excitability is decreased. Postmortem examination of the brain shows a severe loss of Purkinje cells, with very mild loss of granule, stellate, and basket cells, as well as little or no loss of cells in the inferior olive [63]. The mutation is a trinucleotide repeat of CAG, with longer repeats resulting in symptoms beginning at an earlier age [64]. Table 3.1 summarizes the patient information. Control 1. Eleven age matched control subjects also took part in our experiment (six female and five male; mean age 57 years, range 45-69). All subjects gave written consent to protocols approved by the Johns Hopkins Institution Review Board. Control 2. In our age-matched control group 1 we noted a trend in which the ability to control for horizontal variability correlated with the ability to learn in the cross-axis adaptation paradigm. To improve our power to detect such a pattern, we enlarged our control group by adding six non-age-matched control subjects (age range 20 to 43 years). This younger group allowed us to validate the previous correlations that we had seen in Control 1.

### 3.2.3 Data analysis

The beginnings and ends of saccades were determined by a 16°/s speed threshold. Criteria for including saccades in analysis were as follows: 1) Saccade amplitude must be greater than 50% of the target displacement. 2) Saccade duration must be within 50 to 150ms. 3) Saccade reaction time must lie within 100 to 500ms. 4) Peak horizontal velocity must be $> 100$°/s. On average, control subjects had 13% of their saccades excluded while patients, with their more variable saccades, had 26% excluded. We use a constant bin width (bw) of 4 trials to show the effect of stimulus repetition and learning that evolves over the entire course of the experiment (Figures 3.6A, 3.6D, 3.7A, and 3.8A). We then used a smaller bin width of 2 trials to show the rapid changes that take place at set breaks and sudden changes in trial-type (Figures 3.6B, 3.6C, 3.6E, 3.6F, 3.7C, 3.7D, 3.8C, and 3.8D). The amount of adaptation was assessed by comparing (using a paired, 2-tailed t-test) the vertical eye movement averaged over all the baseline error-clamp trials with the vertical movement averaged over the last 60-trial set of the CCW cross-axis adaptation block. Likewise, the recovery of the previous adaptation that occurred following the brief de-adaptation block was assessed by comparing the vertical movement in the baseline trials with the vertical movement averaged over the first set of post adaptation error clamp trials. We used a significance level of $p < 0.05$ for each pair-wise comparison. We used a 2x1 repeated-measure ANOVA design to compare the effect of group (control and cerebellar) and the within subject factor of set number on saccade horizontal parameters (peak horizontal velocity and amplitude). Significance level was set at $p < 0.05$. Two-sided unpaired t-tests were used to assess the differences in adaptation and recovery levels between groups. The vertical bias (in Fig. 3.9) was calculated as the difference between the absolute(vertical endpoint) - absolute(target vertical position). For example a vertical endpoint of -2.5° to a target with vertical eccentricity of -3° had a bias of -0.5° which is undershooting. The standard error of various parameters (error bars in Figure 3.8) were calculated as follows. The standard error

of the adaptation amount $s$ is approximated as $s/\sqrt{n}$, where n is the number of trials used to calculate this measure. The standard errors of horizontal and vertical variability as measured by standard deviation $\sigma$ are approximated as $0.71\sigma/\sqrt{n}$.

| | Age | Gender | Ataxia type | Disease duration (yrs) |
|---|---|---|---|---|
| P1 | 45 | F | SCA6 | 7 |
| P2 | 35 | F | SCA, type unknown | 13 |
| P3 | 53 | F | SCA6 | 11 |
| P4 | 55 | F | SCA6 | 6 |
| P5 | 74 | M | SCA6 | 35 |
| P6 | 59 | F | SCA6 | 14 |
| P7 | 63 | M | SCA6 | 12 |
| P8 | 67 | F | SCA6 | 15 |
| P9 | 64 | F | SCA6 | 4 |

Table 3.1: Cerebellar subjects information

## 3.3 Results

We will first focus on the horizontal component of eye movements to illustrate that there is variability in the motor commands that initiate saccades, and that the cerebellum plays a role in the within saccade compensation for this variability. We will then focus on the vertical direction and the process of adaptation.

### 3.3.1 A role for the cerebellum in compensating for the variability in the motor commands that initiate saccades

Figure 3.2A shows the horizontal component of the saccades kinematics from the first and last error-clamp sets for a typical healthy control (C5) and a representative cerebellar patient (P4). In the control subject, the amplitude of the movement was the same in the first and last sets ($p = 0.34$). However, the amplitude dropped by 2.2° for the cerebellar patient ($p < 0.001$). The peak velocity dropped in both subjects from the first to the last set: the control subjects saccades slowed by 68.3°/s or 21% ($p < 0.001$) and the cerebellar patients saccades slowed by 68°/s or 24% ($p < 0.001$). In the control subject, the saccades in the last set started with reduced peak velocities but then were completed with an increased velocity late in the same saccade. In the cerebellar patient, the reduction in peak velocity was left uncompensated. Saccade peak accelerations showed similar drops for both subjects: 20% ($p < 0.001$) for the control subject and 18% ($p < 0.001$) for the cerebellar patient. The deceleration pattern, however, was strikingly different. The peak value of deceleration of the control subject was less and occurred later than the cerebellar patient. Therefore, from the first to the last set, the magnitude of the motor commands that initiated saccades dropped for both subjects, but only the control subject was able to maintain amplitude by compensating late in the saccade's time course.

Figure 3.2B summarizes some of these changes in the horizontal direction through the course of the experiment. Both groups made slower saccades as the experiment proceeded. In control subjects, saccades slowed by 11.1% or 33°/s ($p < 0.005$). In cerebellar patients, saccades slowed by 12.9% or 40°/s ($p < 0.01$). Repeated measure ANOVA on peak velocity showed an effect of set ($p < 0.001$), no effect of group, and no interaction between group and set. Therefore, saccades slowed by a similar amount in the two groups. Repeated measure ANOVA of horizontal amplitude showed an

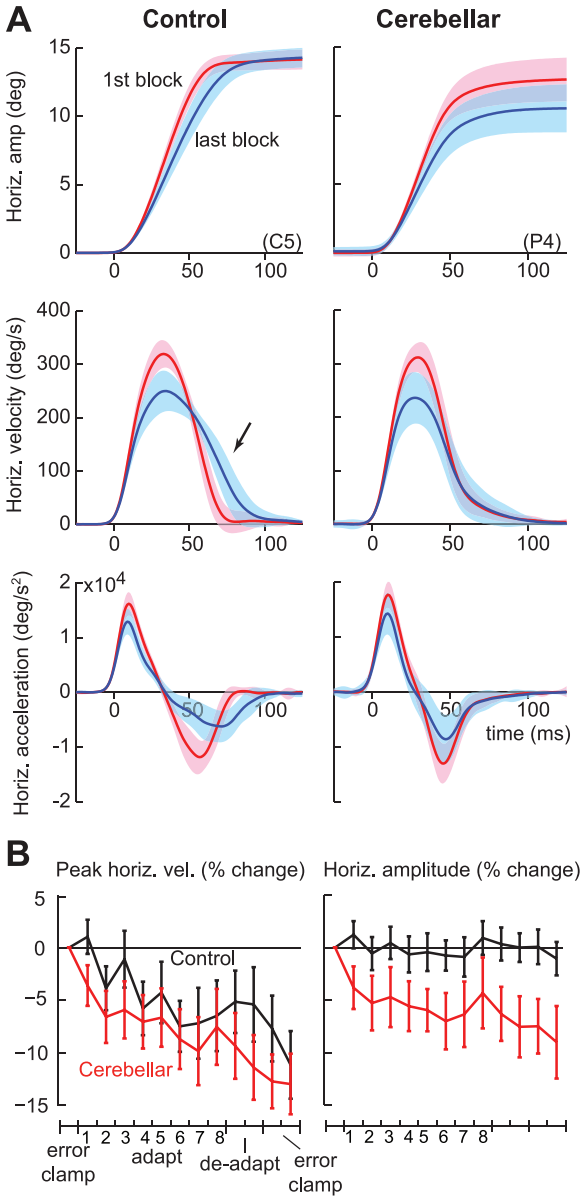


Figure 3.2: Cerebellar patients could not correct for variability in the motor commands that initiated saccades. (A) The average horizontal amplitude, velocity, and acceleration traces from the first and last error-clamp blocks (error clamp I and II), in response to a target at 15°, for two representative subjects. In the last block, the saccades of both the control subject (C5) and the cerebellar patient (P4) were initiated with reduced velocities, but the control subject compensated later during the same saccade. Shading indicates standard deviation. (B) Group data for horizontal peak velocity and amplitude changes. Percentage change is with respect to the first error-clamp block (error clamp I). Each point is the average from one set of 60 trials. Error bars indicate SEM.

effect of set ($p < 0.01$), group ($p < 0.05$), and group by set interaction ($p < 0.05$). Control subjects were able to maintain endpoint amplitude from first to last set ($p = 0.43$) while cerebellar patients showed a drop in amplitude by 9.0% or 1.06° ($p < 0.05$).

An analysis of saccade timing parameters demonstrated that control and cerebellar subjects differed most in the deceleration phase of saccades (Figure 3.3). The time of peak acceleration remained unchanged in both groups ($p = 0.45$ for controls and $p = 0.59$ for patients). In the control group, the time of peak velocity (shift = 1.7ms, $p < 0.01$) shifted to a later time, time of peak deceleration (shift = 6.5ms, $p < 0.01$) shifted to a later time, and duration of the saccade (shift = 8.4ms, $p < 0.001$) increased. For cerebellar patients, however, time of peak deceleration showed less than half the change seen in controls (shift = 2.9ms, $p < 0.01$) while time of peak velocity and duration of saccades showed no significant changes. As a result, while in both groups the commands that accelerated the eyes along the horizontal dimension

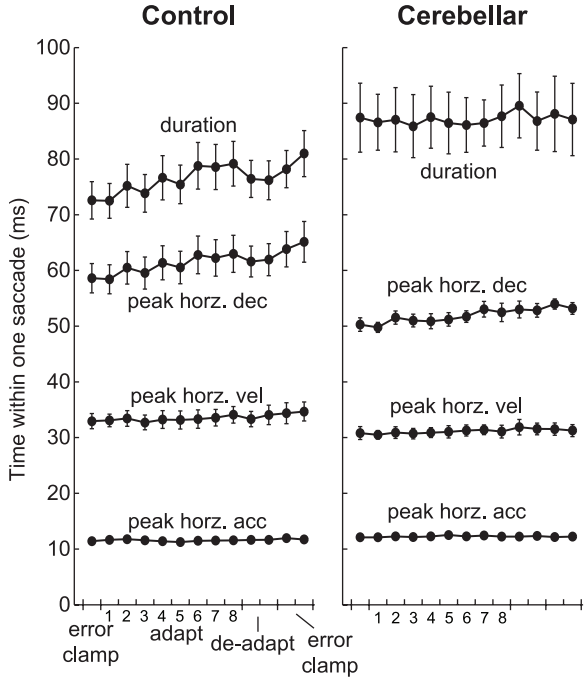


Figure 3.3: The plots show the changes in the timing of saccade parameters. Position, velocity, and acceleration refer to horizontal components of the movement. Each point is the average from one set of 60 trials. Error bars indicate SEM.

decreased from the first to the last set of the experiment, the healthy subjects were able to maintain horizontal amplitude by compensating later in the saccade.

In the above data we averaged saccade parameters in each set, and then displayed the results across sets. However, there were also consistent changes that occurred within each set. Each set consisted of 60 trials (inter-trial interval of $1.5s$). Between the sets our subjects rested for $30s$ and closed their eyes. As in our previous studies of cross-axis adaptation [29], on-axis adaptation [62], or simply control studies in which targets did not jump [29], we found that the peak horizontal velocity dropped within each set and then sharply increased in the first saccade after the set break (Figure 3.6A). On average, the healthy subjects showed 49.8°/s or 16.3% increase in peak horizontal velocity (last two saccades before set break vs. first two saccades after set break, $p < 0.001$) and 10.0ms or 15.4% decrease in duration ($p < 0.001$), as shown in Figure 3.6B. The set breaks also produced a small increase in the horizontal amplitude (0.6° or 4.6%, $p < 0.05$, Figure 3.4) and a small decrease in saccade latencies ($p < 0.05$, Figure 3.4). The small but significant increase in amplitude at set breaks suggests that even in healthy people, some of the variability in motor commands that accelerated the eyes was left uncompensated. This is a crucial finding for us as we will later show that the amount of within saccade compensation in the horizontal direction is a predictor of the ability of that subject to learn from endpoint errors in the vertical direction.

Similar to control subjects, cerebellar patients showed an obvious structure in their saccade velocities: set breaks induced an increase of 28.0°/s or 9.3% in peak horizontal velocity ($p < 0.01$, Figure 3.6E). This was a clear finding, as set breaks induced an increase in peak horizontal velocity in 7 out of 9 cerebellar subjects (5 subjects with $p < 0.05$ and 2 subjects with $p < 0.1$), and in 7 out of 9 set breaks (Figure 3.5). However, unlike controls, the cerebellar patients did not decrease the saccade durations to compensate for this increased velocity ($p = 0.92$).

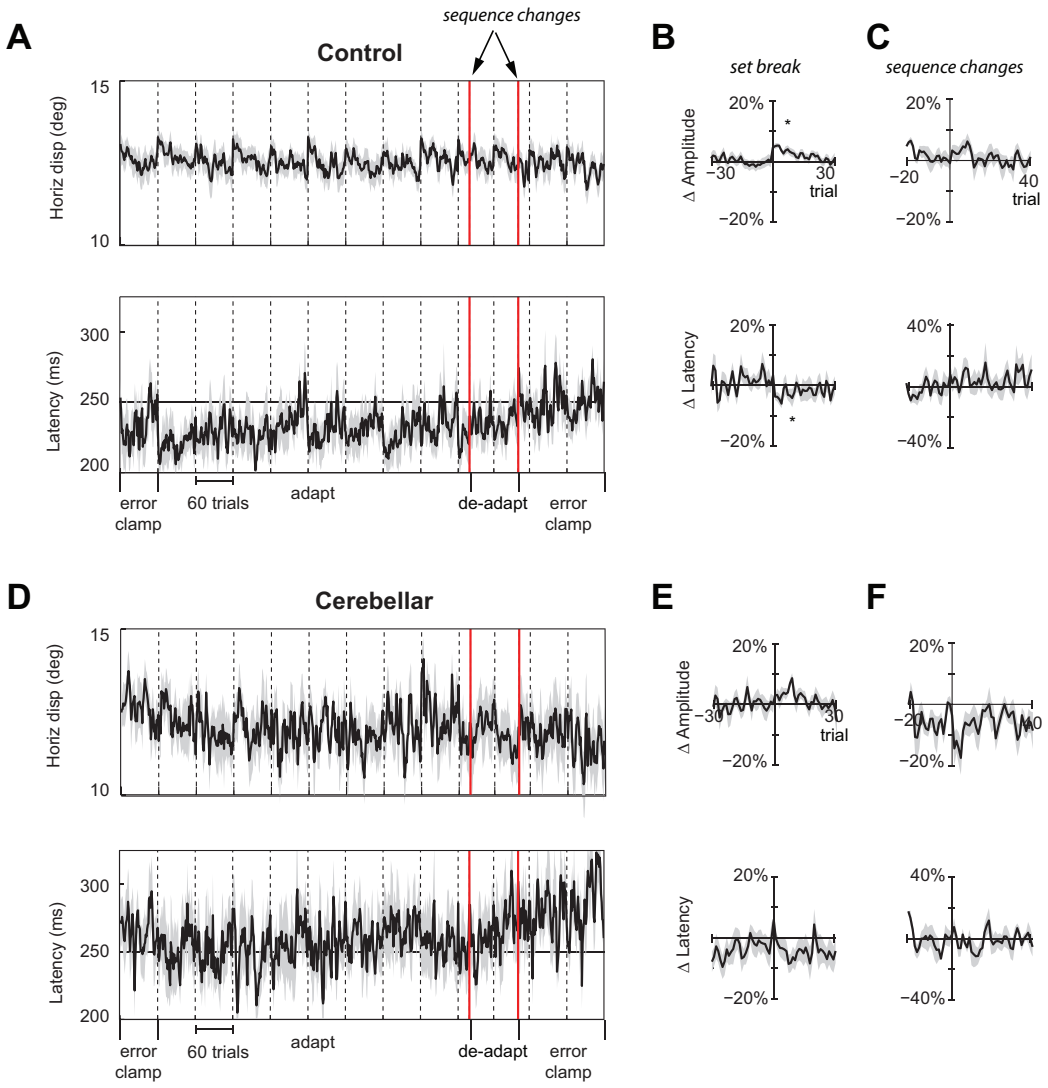


Figure 3.4: Horizontal amplitude and saccade latency (A,D) Set to set changes in horizontal amplitude and saccade latency. Dotted vertical lines mark set boundaries. Each set consisted of 60 trials. Red lines mark trial type transitions that occur within sets without breaks. (B,E) To show the effect of set recovery more clearly, we calculated percent change with respect to the first bin of each set and aligned on the start of each set. The amount of recovery is calculated as the difference between the last and first bins. Paired t-tests are used to test within subject changes ($*p < 0.05$). Shading indicates across subject SEM. (C,F) show trials aligned on switch from CCW to CW cross-axis target jumps in the middle of 9th set of cross-axis target jumps.

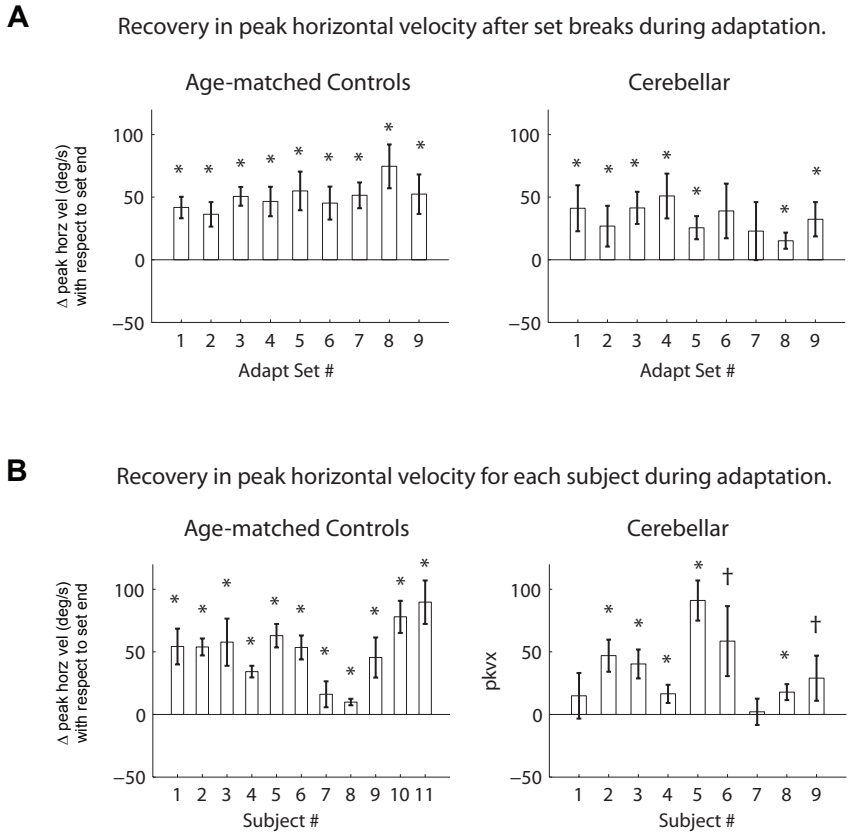


Figure 3.5: Closer look at recovery following breaks for peak horizontal velocity. (A) Recovery of peak horizontal velocity with respect to the end of the previous set. All set boundaries showed recovery in peak velocity in controls. In cerebellar patients, seven out of 9 set boundaries (1-5, 8-9) showed significant recoveries ($p < 0.05$). (B) Recovery of peak horizontal velocity for single subjects. All control subjects showed significant recovery of peak horizontal velocity after set breaks. Seven out of 9 cerebellar patients either showed significant recovery ($p < 0.05$, subjects P2-5, P8) or trend toward significance ($p < 0.1$, subjects P6 and P9).

In summary, motor commands that accelerated the eyes along the horizontal dimension were affected by two forms of variability: set breaks produced a sharp increase, while target repetition produced a gradual decrease. In healthy people, this variability appeared to be corrected within the same saccade, whereas in the cerebellar subjects, the variability produced dysmetria.

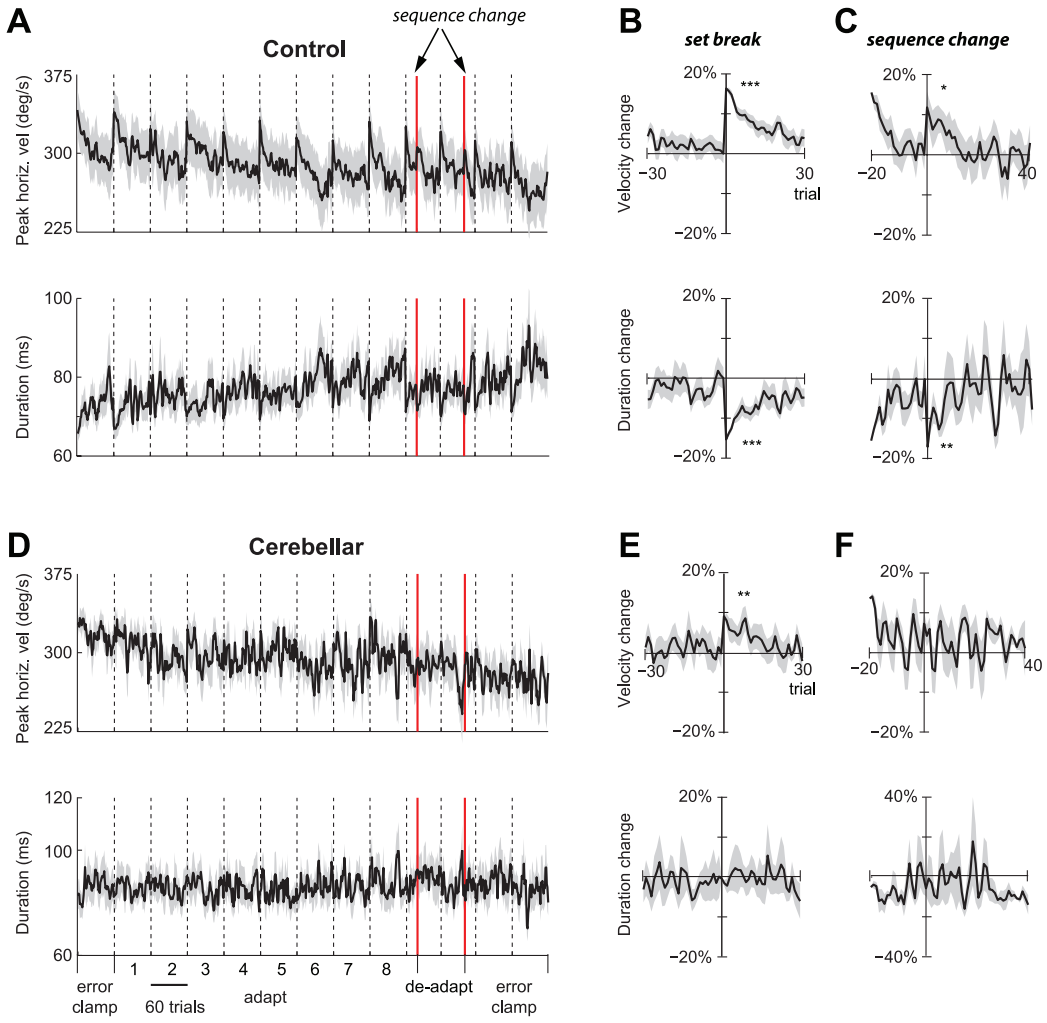


Figure 3.6: Effect of set breaks on saccade horizontal velocities and durations. (A, D) Peak vertical velocity and duration, averaged across each group. Dotted vertical lines mark set boundaries. Each set consisted of 60 trials. Red lines mark sudden changes in target sequence that occurred within sets without breaks. (B, E) Within subject changes in peak velocity and duration, aligned to set re-start. The plots show percent change with respect to the last bin of each set. The amount of recovery is calculated as the difference between the last and first bins (t-test, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$). Shading indicates across subject SEM. (C, F) Within subject changes in peak velocity and duration, aligned to the sudden change in sequence of targets from CCW to CW cross-axis target jumps. Parts A, B, and C are control data, and D, E, and F are cerebellar data.

### 3.3.2 What caused the variability in the motor commands that initiated the saccades?

It is possible that the experiment induced use-dependent fatigue in the neuronal or muscular structures of the oculomotor system, and the set breaks allowed recovery from this fatigue. However, data from a crucial component of our experiment argues against this possibility: after 20 trials in the final adaptation set, the target sequence unexpectedly switched from a counter-clockwise to a clockwise sequence (start of de-adaptation, first red line in Figure 3.6A). If fatigue is a form of habituation in the sensory neurons that convey target information to the motor system, then the transition from adaptation to de-adaptation should not produce a recovery because the stimuli that elicited horizontal saccades activated precisely the same retinal location as before. Similarly, if fatigue is a form of use-dependent reduction in the response of the extra-ocular muscles, then there should be no recovery because the transition from adaptation to de-adaptation did not include a rest period. However, if the fatigue is due to a top-down factor, for example, a decline in an attentional state, then the surprising event should produce recovery.

The unexpected change in the position of a vertical target produced an immediate and robust recovery of velocities in response to the subsequent horizontal target. In Figure 3.6C and 3.6F, the saccade parameters are aligned to the first trial after the target sequence changed from counterclockwise to clockwise target jumps. Changes in percentage are calculated with respect to the trial before the sequence change. In controls, we found an increased velocity of 32.9°/s or 11.8% ($p < 0.05$) and decreased duration of 12.5ms or 16.9% ($p < 0.01$). Horizontal displacement ($p = 0.64$) and reaction time ($p = 0.20$) did not change significantly (Figure 3.4C). Importantly, this recovery was smaller the second time the target sequence changed (at the end of the de-adaptation block, second red line in Figure 3.6A): controls showed a 20.4°/s or 7.7% increase in peak velocity ($p = 0.15$). That is, the change in the target sequence

produced a sharp increase in velocities when it first occurred, but a smaller one when it repeated.

In cerebellar patients, the unexpected change in target sequence produced a 24.9°/s or 7.3% increase in peak velocities, but these changes did not reach significance ($p = 0.22$). There were no significant changes in duration ($p = 0.57$), horizontal amplitude ($p = 0.51$), or reaction time ($p = 0.53$). Therefore, the data from the control subjects suggested that the changes in the commands that initiated the saccades were probably not due to a neuronal or muscular fatigue process that required passage of time for recovery. Rather, the fact that an unexpected change in the stimulus restored peak velocities suggests that the decline in velocity was due to reduced motivation, boredom, or a similar top-down effect.

### 3.3.3 Adaptation and the multiple timescales of memory

Our experiment was designed to not only quantify adaptation capabilities of healthy and cerebellar patients, but also to potentially unmask the multiple timescales that underlie this adaptation. We considered a common paradigm in which a long period of adaptation was followed by a brief period of de-adaptation [62, 65, 66]. If there are multiple timescales that support adaptation, then behavior should exhibit signatures of these timescales [67, 68]. For example, a fast timescale of adaptation should produce forgetting with passage of time (during set breaks), and forgetting with removal of the adaptation-driving errors (during error-clamp trials). This fast timescale should also produce rapid learning in the presence of error. A slow timescale of adaptation should resist de-adaptation (when errors reverse direction, termed "extinction") and produce spontaneous recovery toward the previously adapted state in the post-adaptation error-clamp period. In the cerebellar patients, is the damage predominantly affecting one timescale of adaptation?

During the adaptation block, as the saccade was initiated, the target at the horizontal meridian jumped vertically (in a counter-clockwise direction), resulting in an endpoint error which was corrected with a second saccade. In response to this endpoint error, both the control and the cerebellar groups learned to produce primary saccades that had increasing vertical motor commands, but the learning was significantly smaller in the cerebellar patients (Figure 3.7A). For example, the change in vertical endpoint from the pre-adapt error clamp trials to the last set of adaptation was $+2.01^\circ$ in control subjects ($p < 10^{-4}$), and $+0.56^\circ$ in cerebellar patients ($p < 0.05$), with the change being significantly smaller in the cerebellar patients (Figure 3.7B). Despite the significant amount of adaptation in the saccades made by the cerebellar patients, their adapted response was missing a fundamental characteristic. The control subjects exhibited robust forgetting during each set break: the vertical endpoint of control saccades suddenly decreased (first arrow, Figure 3.7A). This set structure was prominent when we plotted the changes in saccade parameters with respect to the last bin (last two saccades) of each set (Figure 3.7C). On average, the vertical endpoint declined by $0.43^\circ$ or 26% at set start ($p < 0.005$, set start vs. previous set end) and the peak vertical velocity declined by $5.8^\circ$/s or 14.3% ($p < 0.05$). By the sixth saccade after set start the vertical endpoints and velocities had recovered to the magnitude of the previous set (Figure 3.7C). That is, the short break produced forgetting, and the set re-start produced rapid relearning. When viewed as a group, both the forgetting and the rapid relearning were absent in the saccades of the cerebellar patients.

When we analyzed the data in terms of individual subjects, we found a strong correlation between a subject's tendency to forget at set breaks and the ability to learn rapidly after set start. For example, Figure 3.7E shows the change in vertical endpoint position during the first 6 trials after the set start (re-learning) as a function of change in the same index during the set break (forgetting). These two measures were strongly correlated in the control subjects ($r = 0.79$, $p < 0.004$), and marginally

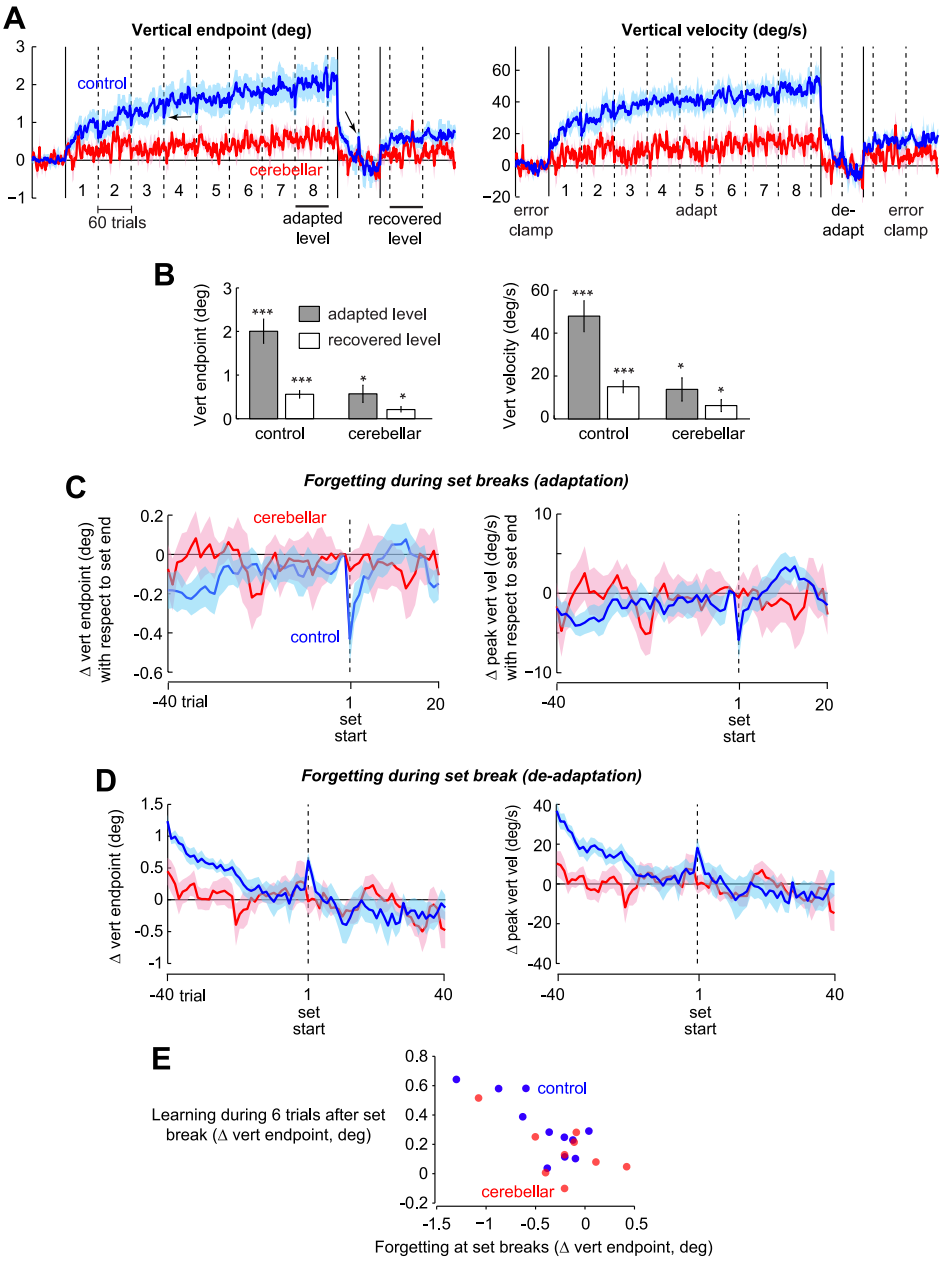
A
Vertical endpoint (deg)
control
cerebellar
60 trials
adapted level
recovered level
Vertical velocity (deg/s)
error clamp
adapt
de-adapt
error clamp
B
Vert endpoint (deg)
adapted level
recovered level
control
cerebellar
Vert velocity (deg/s)
control
cerebellar
C
Forgetting during set breaks (adaptation)
Δ vert endpoint (deg) with respect to set end
cerebellar
control
-40 trial
set start
Δ peak vert vel (deg/s) with respect to set end
set start
D
Forgetting during set break (de-adaptation)
Δ vert endpoint (deg)
-40 trial
set start
Δ peak vert vel (deg/s)
set start
E
Learning during 6 trials after set break (Δ vert endpoint, deg)
control
cerebellar
Forgetting at set breaks (Δ vert endpoint, deg)

Figure 3.7: The multiple timescales of adaptation. (A) The plots show the vertical endpoint of the primary saccade and its peak vertical velocity. Cerebellar patients (red) are impaired in adapting to cross-axis target jumps as compared to controls, but nevertheless show significant adaptation. In the de-adapt period, the behavior of both groups returned to baseline, but in the following error-clamp trials, there was partial recovery. Dashed vertical lines denote set breaks. Solid vertical lines denote changes of trial types. Note that in the control group, there is forgetting (first arrow) at each set break followed by rapid re-learning. Also note that forgetting reverses direction (second arrow) in the de-adaptation period. (B) Summary of the performance at the final set of adaptation and during the first 60 trials of error-clamp II in controls and patients ($*p < 0.05$, $**p < 0.01$, $***p < 0.001$). Error bars indicate SEM. (C) Vertical endpoint and velocity aligned on set start, as in Figure 3.6B. The forgetting followed by rapid re-learning is present in controls but absent in patients. (D) Vertical endpoint and velocity at the set break in the de-adaptation block. Only the controls exhibit reverse-forgetting. Error bars indicate SEM. (E) Rapid learning within the first 6 trials of each adaptation set and forgetting at set breaks for individual subjects. The control group showed a strong correlation of $r^2 = 0.62$ with $p < 0.004$. The cerebellar subjects showed a marginally significant correlation of r2 = 0.40 with p = 0.067.

significant in the cerebellar subjects ($r = 0.63$, $p = 0.068$). The one cerebellar subject who showed forgetting at set break also showed rapid relearning at set start.

It is possible that the rapid changes in performance after set start are not due to rapid relearning, but a contextual effect in which there is re-manifestation of a previously learned state. There is a simple way to check for this. If the forgetting and rapid relearning are both due to a fast adaptive process, then the same fast learning should be present at the very first adaptation set as well as after each set break. On the other hand, if the rapid change after set start was due to revisiting a previous context, then it should be absent in the first set as that context had not been repeated before. In the control group, we found rapid learning in the very first set: the change in vertical velocity by trial 6 was 12.56°/s ($p < 0.05$), which was no different from the average change observed after set breaks (within subject t-test, $p = 0.33$). Similarly, the vertical endpoint changed by 0.34° ($p < 0.05$) in the first 6 trials of the first set, which was no different than changes seen after set breaks (within subject t-test, $p = 0.57$). This is consistent with the idea that set breaks induced

forgetting, and set re-start induced relearning; both of which are signatures of a fast adaptive process.

We were concerned that for the cerebellar subjects we could not detect forgetting during the set-breaks because they had learned only a small amount. Therefore, we focused on the last three adaptation sets as during these sets the response showed significant adaptation. Despite this, we could not detect a robust change in the cerebellar saccades at set start in our measures of adaptation ($p = 0.13$ for vertical endpoints and $p = 0.12$ for vertical velocity).

An interesting prediction of the idea that learning in healthy people is supported by two timescales is that when adaptation is followed by de-adaptation, the direction of forgetting should reverse [62]. To explain this, consider that during the de-adaptation period a competition may be formed between a fast adaptive mechanism that learns the CW perturbation, and the slow adaptive mechanism that previously has learned the CCW perturbation. During the set break in the de-adaptation block the fast mechanism should forget, and the behavior should revert to what the slow mechanism had learned. Whereas during the adaptation period forgetting during set breaks was toward baseline, now in the de-adaptation period forgetting should be away from baseline toward the CCW value stored by the slow system.

Indeed, for the control subjects the set break in the de-adaptation period produced reverse-forgetting (recovery of 0.45° in vertical endpoint and 12.3°/s in vertical velocity, $p < 0.05$, second arrow in Figure 3.7A and close-up of the de-adapt period in Figure 3.7D), but this pattern was missing in the cerebellar subjects ($p = 0.25$). This result further confirms that the fast timescale of adaptation was present in the control subjects but missing in the patients.

Our simple two-timescale model could not account for one aspect of the data. If the return of performance to baseline (i.e., washout or extinction) during de-adaptation was solely due to a competition between two timescales of adaptation, and if cerebellar subjects were impaired in the fast timescale, these subjects should show a slower than

normal rate of de-adaptation. This was not the case. In the de-adaptation period, vertical endpoint and velocity of saccades in cerebellar subjects returned to baseline even faster than controls (Figure 3.7A). This possibly indicates that de-adaptation in cerebellar subjects benefited from the ability to inhibit a previously learned pattern, rather than set up a competition between a fast and a slow adaptive process.

The de-adaptation block was followed by an error-clamp block. In this block, both groups exhibited spontaneous recovery of their previously adapted behavior. In controls, vertical endpoints and velocities were significantly greater than baseline ($p < 0.001$, Figure 3.7B). Similarly, in the cerebellar patients vertical endpoints and velocities were significantly greater in the final error-clamp block than baseline ($p < 0.05$). Spontaneous recovery is a signature of the slow adaptive system that resists unlearning during the de-adaptation period [62]. On average, the magnitude of the spontaneous recovery in controls was 28% of the state achieved during the adaptation block. In the cerebellar patients, the magnitude of the spontaneous recovery was 33% of the state achieved during the adaptation block. Importantly, there were no significant differences in the magnitude of percent spontaneous recovery in the two groups.

### 3.3.4 Saccade curvature

A prominent feature of saccades in cross-axis adaptation is curvature [29], i.e., motor commands that initiate the saccade appear to adapt by a smaller amount than those that terminate the saccade. A proxy for curvature is the difference in the slopes of the saccade near its start and finish. We divided each saccade into four equal horizontal segments and measured the slope of each segment. Figure 3.8A shows the slope at saccade start (termed S1) and the slope at saccade end (termed S4). In both groups S1 increased significantly during the adaptation block (+0.12, $p < 10^{-4}$ in controls, +0.028, $p < 0.05$ in cerebellar patients), with the changes

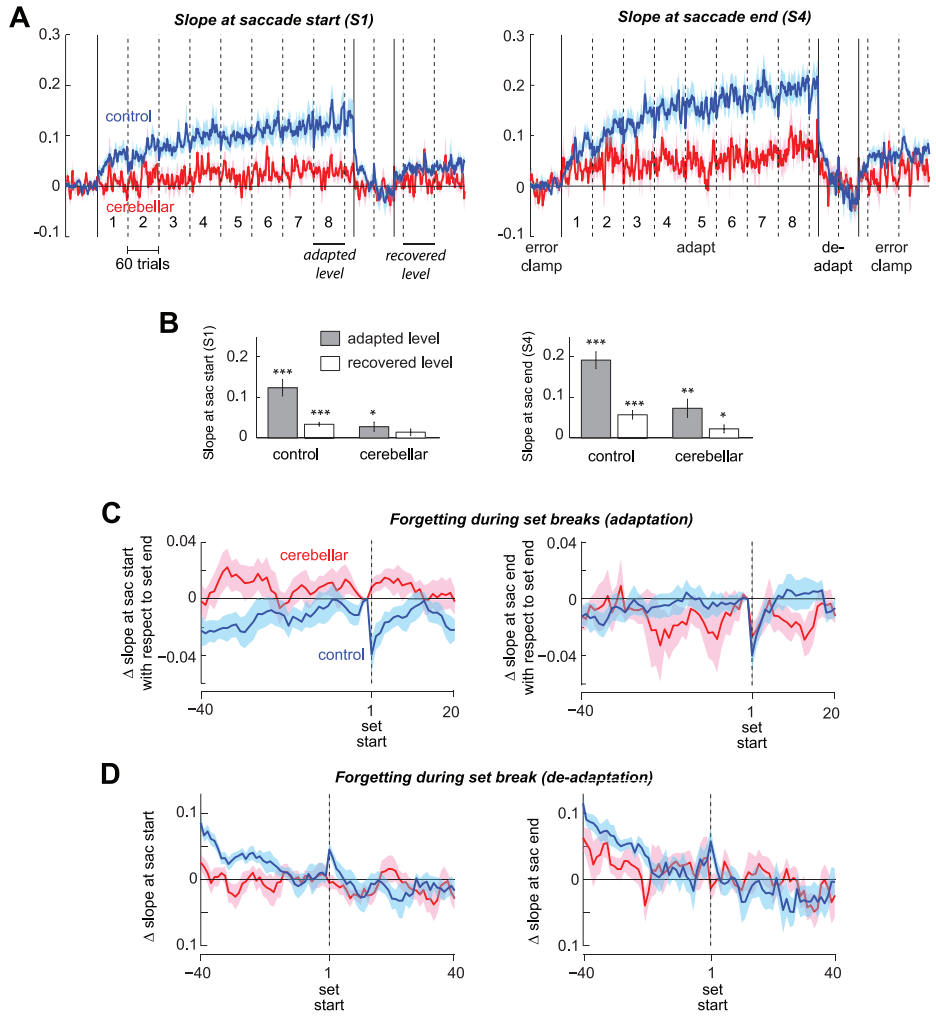


Figure 3.8: Early vs. late part of single saccades. We divided each saccade into four equal horizontal segments and measured the slope of each segment. (A) The slope at saccade start, termed S1. (B) Within subject change in S1 with respect to the end of the previous set (C) The slope at saccade end, termed S4. (D) Within subject change in S4 with respect to the end of the previous set. Error bars indicate SEM.

being significantly smaller in cerebellar patients ($p < 0.001$). In both groups, S4 was larger than S1, resulting in saccades that curved toward the target (within group comparison, last set of adaptation, +0.19, $p < 10^{-5}$ in controls, +0.073, $p < 0.01$, in cerebellar patients). When the trial-to-trial changes in slope were aligned on set starts, we once again observed the fast timescales of learning in the healthy controls (S1 dropped by 0.039 or 35%, $p = 0.01$, S4 dropped by 0.041 or 26%, $p = 0.01$), but

not clearly in the cerebellar group: S1 showed no drop at set break ($p = 0.3$), and while S4 dropped by 0.026, 42% at set break, it showed similar drops both before the set break and after the set break. Similarly, Figure 3.8D illustrates that the set-break during de-adaptation produced reverse-forgetting in the control subjects (recovery of 0.34 for S1, $p < 0.05$, recovery of 0.028 for S4, $p < 0.05$), but not in the cerebellar group ($p = 0.4$ for S1 and $p = 0.15$ for S4).

### 3.3.5 Ability to compensate for variability predicts ability to learn from endpoint errors

Finally, we asked whether a subject's ability to control endpoint accuracy during the pre-adaptation control trials was a predictor of their ability to learn from endpoint errors during adaptation trials. Our proxy for the ability to control accuracy was endpoint variability (standard deviation, SD) and endpoint bias in the oblique control trials, before the adaptation trials began. Our proxy for the ability to adapt was the vertical endpoint achieved in the final set of the adaptation block. As a group, the cerebellar patients had larger vertical bias (negative value means undershooting, $p < 0.001$, Figure 3.9A), more horizontal endpoint variability ($p < 0.01$, Fig 7B), and more vertical endpoint variability ($p < 0.05$, Figure 3.9C) than controls. Inclusion of the cerebellar group with healthy controls in a regression analysis would, of course, produce a significant correlation between control of saccade accuracy and adaptation. However, a more interesting question is whether within the control subjects, the ability to control endpoint variability was a predictor of the ability to adapt. Indeed, in healthy subjects the ability to control saccades during the oblique trials was a predictor of the ability to adapt to errors during the adaptation trials (blue circles, Figure 3.9A-C, vertical bias: $r^2 = 0.43$, $p < 0.05$; horizontal variability: $r^2 = 0.50$, $p < 0.05$; vertical variability was close to significance: $r^2 = 0.32$, $p = 0.06$). (In comparison, we found no correlation between horizontal bias and amount of learning.)

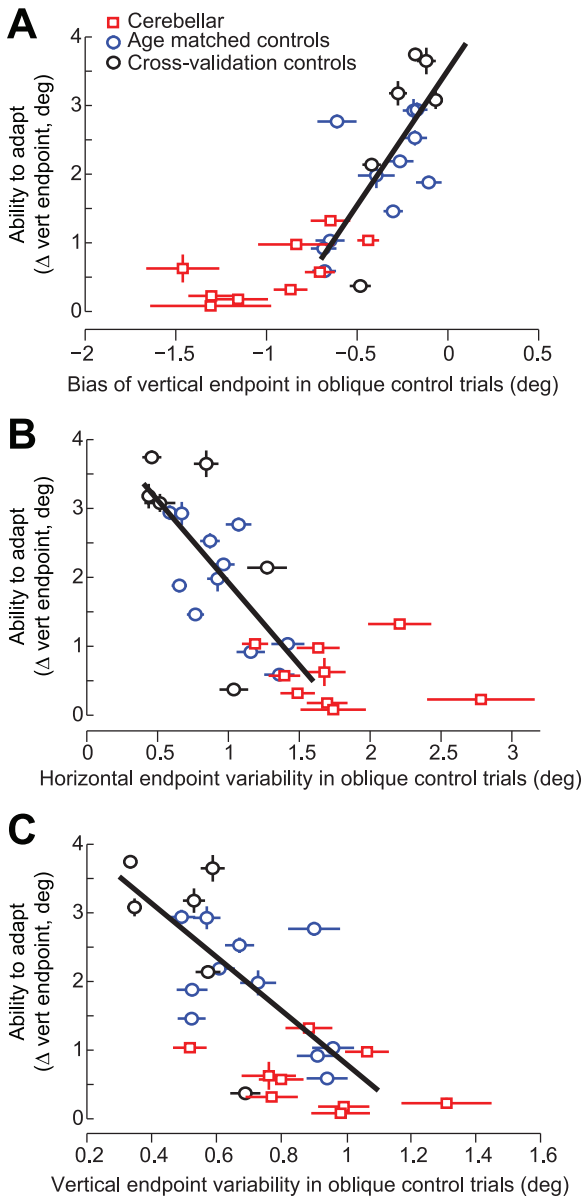


Figure 3.9: The ability to compensate for internal sources of variability correlates with the ability to compensate for external sources of error. (A) Correlation between bias in the vertical direction for oblique trials and learning along the vertical direction during adaptation. The best fit line is for control subjects. Error bars are SEM. (B-C) Horizontal (or vertical) endpoint variability before adaptation is plotted on the x-axis and the ability to adapt to endpoint errors during adaptation trials is plotted on the y-axis. The best fit line is for all control subjects. Error bars for horizontal and vertical variability are standard errors of the standard deviation estimate.

To test the strength of the correlation between endpoint variability and learning, we considered a cross-validation procedure. We added to our analysis six additional control subjects (black circles, Figure 3.9) who were not age-matched to the patients. Within this larger control group, we found an even stronger relationship between the trial to trial control of saccade accuracy and vertical adaptation (vertical bias: $r^2 = 0.51$, $p < 0.005$; vertical variability: $r^2 = 0.42$, $p < 0.005$; horizontal variability: $r^2 = 0.50$, $p = 0.001$).

To further test the idea that the ability to control endpoint variability predicts the ability to adapt, we considered other measures of within trial saccadic control. For example, as saccade horizontal velocity decreases, durations should increase to maintain horizontal amplitude. This implies that for a given subject, a negative correlation between peak horizontal velocity and duration is indicative of better endpoint control. Indeed, this measure was also a predictor of the ability to learn from endpoint errors: the more negative the correlation between peak horizontal velocity and duration, the better the ability of that subject to learn from vertical endpoint errors ($r^2 = 0.27$, $p < 0.05$ for all controls). In another example of within saccade control, consider that as saccade horizontal velocity changes, the more positive the correlation with horizontal amplitude, the less perfect the compensation (e.g., if a decrease in velocity is not compensated, the result is a decrease in amplitude). Indeed, people who exhibited a positive correlation between horizontal velocity and amplitude were generally the subjects who also learned the least from the vertical endpoint errors ($r^2 = 0.30$, $p < 0.05$ for all controls).

In summary, we found that a healthy subjects ability to control endpoint accuracy during the pre-adaptation control trials predicted their ability to learn from endpoint errors during adaptation trials.

## 3.4 Discussion

Some three decades ago, David Robinson proposed that saccadic motor commands are monitored and corrected to steer the eyes to the target [11]. Later work suggested the cerebellum was central to this monitoring process [14]. In the current computational view of motor control (e.g. Shadmehr and Krakauer, 2008 [50]) the cerebellum may implement a forward model [69] that uses efferent copy to predict consequences of motor commands and contributes to the online correction of movement. Presumably, the forward model learns from endpoint errors to maintain accuracy. Saccades (as compared to reaching movements) are particularly useful for testing the theory of forward models because these eye movements are completed too quickly for visual or proprioceptive feedback to play a role in control. Here, we wished to quantify the influence of the cerebellum on both the within saccade compensation of the commands that initiated the movement, and the longer-term learning that compensated for persistent errors.

Our subjects were healthy people and patients with a neuro-degenerative disorder (SCA-6) that affected the Purkinje cells of the cerebellum. As noted before [29], repetition of a target on the horizontal meridian gradually reduced horizontal saccade velocities, and short breaks rapidly increased these velocities. In healthy people, this variability was generally compensated via corrective motor commands that arrived later in the same saccade. However, the compensation was missing in cerebellar subjects. In healthy people, the within saccade ability to compensate for the variability in the horizontal velocity was a predictor of the ability to adapt to errors in the vertical direction. The adaptation relied on a memory that exhibited multiple timescales: a fast process that learned quickly from endpoint errors but showed forgetting during the short set breaks, and a slow process that learned gradually, resisted unlearning, and became latent during a brief period of de-adaptation but re-emerged after cessation of the de-adapting stimulus. Despite significant adaptation in the cerebellar

subjects, their adapted saccades were missing the forgetting and the rapid-relearning, suggesting that the damage to the cerebellar cortex had produced a deficit that mostly affected the fast timescale of adaptation.

### 3.4.1 A source of internal variability in the motor commands that initiate a saccade

In this study only healthy controls were able to compensate for variability due to repetition (gradual decline of saccade horizontal velocity and its rapid recovery after set breaks). This compensation was via a change in the time course of the deceleration phase, late in the saccade. Therefore, while the source of the variability appeared to be outside the cerebellar cortex (as it was present in both the patients and the controls), only subjects with a healthy cerebellum corrected for the variability.

Saccade slowing could be due to fatigue of the oculomotor plant or cognitive factors. Here, we gained new insights into the source of this repetition attenuation of saccade velocities: we found that an unexpected change in the repeating target produced immediate recovery of the horizontal velocities. This suggests that the slowing of the saccades and its recovery at set breaks were unrelated to neuromuscular fatigue in the oculomotor plant, as recovery would require passage of time. Sensory neurons that encode some particular attribute of a stimulus usually show progressively smaller responses when that attribute is repeated [70,71]. This repetition suppression has been observed in area V1 of the occipital cortex [72] and in the superficial layer of the superior colliculus [73]. Because the receptive field of these cells is retinotopic and the unexpected change in the repeating stimuli did not alter its positions in retinotopic coordinates, the recovery of velocity cannot be explained by recruitment of new sensory neurons with different receptive fields. That is, the repetition attenuation is probably not a bottom-up phenomenon. However, it is known that the brain directs attention to a visual stimulus that has behaved differently than expected [74]. It

seems likely that the repetition attenuation in saccade velocities was due to top-down cognitive factors like attention.

Our observation agrees well with the data from Golla et al. [19] who also noted a drop in saccade velocities that went uncompensated in cerebellar patients. A possible explanation is that the cerebellum receives a copy of the motor commands and then makes adjustments to steer the eyes to the target [14]. Indeed, cells in the cerebellar vermis and caudal fastigial nucleus show discharges with timing that could be used to adjust motor commands during the deceleration phase of the saccade [75–77].

### 3.4.2 The multiple timescales of adaptation

In healthy people, adaptation appeared to consist of two distinct processes: a fast process that exhibited forgetting and re-learning at set breaks, and a slow process that exhibited little forgetting and strong resistance to unlearning when the endpoint errors suddenly reversed direction (the de-adaptation period). We had earlier observed a similar two-state process in a gain adaptation paradigm [62], and in a reaching paradigm [66, 67]. In cerebellar patients, the fast adaptation process appeared to be impaired as the learned vertical component did not exhibit forgetting during rest periods. In contrast, the slow process was at least partially spared in the patients as the learned vertical component exhibited recovery during the error clamp period that followed the brief de-adaptation stimulus.

Is the lack of evidence for a fast adaptive process in cerebellar patients due to increased noise in these subjects? Indeed, it is possible that our inability to observe a component of adaptation in our subject group was due to sample size and increased variability in that group. However, note that we found significant changes in horizontal velocities in the saccades of the same patients at set breaks, but no forgetting in the vertical velocities (Figure 3.6C). Changes in horizontal velocities are unrelated to adaptation [29], and are examples of fast cognitive or attentional processes that

affected saccades of both patients and healthy controls.

There are experimental results which support the idea that the cerebellar cortex may be specialized for fast processes that underlie motor memory, whereas the deep cerebellar nuclei may specialize in the slow processes. For example, in classical conditioning of the eye blink reflex, washout of the previous learning still results in a more rapid re-acquisition than when the subject is naïve, a phenomenon termed savings. Medina et al. [78] have attributed this to different timescales of learning in the cerebellar cortex and nuclei. Barash et al. [16] suggested that there are two processes that adjust the saccade gain (eye displacement/target amplitude): the rapid gain adjustment mechanism depends on the cerebellar cortex while the slower adjustment takes place outside of the cerebellar cortex. Similar suggestions have been made for the role of the cerebellum in other types of oculomotor learning [79–81].

### 3.4.3 Are the changes in the vertical motor commands an adaptive response related to deficits in the horizontal motor commands?

At set starts, we found that the internal/cognitive perturbation is effectively absent since horizontal saccade velocity recovered. At the same time, vertical motor commands showed a large reduction in control subjects. That is, when there was little need to correct for deficits in the motor commands that initiated the saccade, there was also a reduced ability to express learning, i.e., an apparent forgetting. The cerebellar subjects, however, displayed neither the ability to correct for changes in the horizontal motor commands nor the forgetting. One hypothesis to explain this observation is that the cerebellum learns a compensatory response in the vertical direction, but this response can only be expressed when there is a deficit in the horizontal motor commands that initiate the saccade. In this view, the term forgetting is unjustified

because the changes in set breaks are not due to decay or loss of a previously learned response, but simply a lack of necessity to express it.

Although this is an attractive hypothesis, there are a number of patterns in our data that are inconsistent with it. First, the rapid learning that follows set breaks has a much faster rate (achieving previously learned level within 6 trials) than the repetition induced drop in the horizontal velocity which slows over the course of many more trials. That is, changes in the horizontal velocities alone could not explain the forgetting and rapid relearning in the vertical direction. Second, at set start we found robust reductions in not just the vertical commands that terminated the saccade, but also the vertical commands that initiated it (Figure 3.8C). Therefore, forgetting in the vertical motor commands occurred too early into a saccade to have been a response to changes in horizontal motor commands. Finally, if set breaks did not produce forgetting, then the rapid relearning after set start is a re-manifestation of a previously learned state, which should not be present in the first adaptation set. In fact, rapid learning was present in the first adaptation set. Taken together, the data is more consistent with the idea that the time passage during set breaks induced forgetting, the large errors at set re-start induced relearning, and damage to the cerebellar cortex primarily influenced these fast timescales of adaptation.

### 3.4.4 The ability to compensate for internal sources of variability correlates with the ability to compensate for external sources of error

In our experiment, there were two potential sources of movement error: one due to internal variability in the motor commands that initiated the saccade, and the other due to external perturbations of the target. We found that a subject's ability to control endpoint accuracy during the pre-adaptation control trials predicted their ability

to learn from endpoint errors during adaptation. The relationship is consistent with other studies [82], suggesting that maintenance of saccade accuracy in daily life and short-term saccade adaptation have shared neural mechanisms, perhaps dependent on the cerebellum [15, 16]. Alternatively, greater endpoint variability causes lack of adaptation by providing inconsistent errors to drive learning. It is also possible that subjects with greater inherent variability attribute more error to their own motor output which does not warrant updating of the internal representation of the visual environment [83, 84]. If increased variability indeed causes lack of adaptation, one could test this idea by inducing adaptation by clamping the error with respect to the saccade endpoint. This way control subjects and patients would perceive the same motor performance and receive the same error information.

In summary, we found that there is variability in motor commands that accelerate the eyes, but this variability is partially corrected within a saccade via the cerebellum. In healthy people, the ability to compensate for variability is correlated with the ability to learn from endpoint errors. While damage to the cerebellar cortex significantly impairs the ability to learn from endpoint errors, the impairment is focused on a fast adaptive process that learns rapidly from error but also exhibits significant forgetting with passage of time.

# Chapter 4

# Feedback control of saccades perturbed by TMS

## 4.1 Introduction

Transcranial magnetic stimulation (TMS) is an increasingly popular tool in neuroscience. However, its effects on the brain are not well understood. In this chapter, we report a nonspecific effect of TMS: when applied immediately before and during a saccade, TMS can slow or even pause a saccade midflight. The perturbation to the saccade is similar to that seen with direct electrical stimulation of omnipause neurons [85] or rostral superior colliculus [86]. Sensory stimulation, stimulation of the supraorbital nerve and noise bursts also induce pauses in saccades [87, 88]. Despite the strong perturbation of TMS on eye trajectories, these saccades usually end close to the target. This correction is present even when we blank the target so that no visual information is available. Therefore, compensation of this perturbation is likely dependent on a feedback control process and an estimate of the ongoing state of the eye during a saccade. In this work, we seek to characterize the effects of TMS in perturbing saccades and to model the underlying neural mechanisms mediating the

perturbation and its correction.

The TMS induced perturbation to the saccades was nonspecific to the brain region, as similar perturbations occurred for saccades in all directions and regardless of where we applied the TMS: top of the head, the cerebellum, or the parietal cortex. The sound of TMS alone (i.e. coil discharged at least 0.3 meters away from the head) could also induce pauses, although very rarely. TMS is known to have startling effects on the brain, and we believe that this nonspecific effect is likely acting through the startle circuits of the brain rather than by altering function of a specific part of the brain. In fact, a few studies on acoustic startle created their startling sound stimuli by discharging a magnetic device on a metal plate [89]. In addition to the sound, TMS on the head can stimulate the facial nerves, which is another way of engaging the startle circuits. Siebner et al. [90] reported that TMS can induce nonspecific and pervasive inhibition of the motor system. They applied TMS on different regions of the brain and observed inhibition of hand EMG activity. This effect shows up 40ms after TMS which is on the same timescale as the pauses we observe in saccades with TMS. Studies involving TMS should take into consideration this effect when interpreting effects of TMS on the brain.

## 4.2 Materials and Methods

### 4.2.1 Subjects

We tested five healthy control subjects (average age 42) as they performed visually guided saccades. All subjects gave written consent to protocols approved by the Johns Hopkins Institution Review Board.

### 4.2.2 Experimental setup and design

Subjects sat in a dark room with their head restrained using a dental bite-bar. We used a scleral search coil system to record horizontal and vertical eye movements at 1000 Hz from either the right or the left eye (Robinson, 1963). Raw eye position information from the coils was filtered in hardware (90-Hz low-pass Butterworth), digitized (1,000Hz), and saved on a computer for later analysis. A 0.2° red laser beam was rear-projected onto a translucent screen located 1 meter in front of the subject. Target position was varied by a galvo-controlled mirror.

While all data presented here are recorded from the magnetic search coil system, we also recorded eye movements using infrared video tracking (Eyelink 1000) in a few additional subjects and confirmed the perturbing effects of TMS. Furthermore, we recorded high resolution (500Hz frame rate) video images of the eye in one subject, again showing clearly the pauses in the saccadic eye movements.

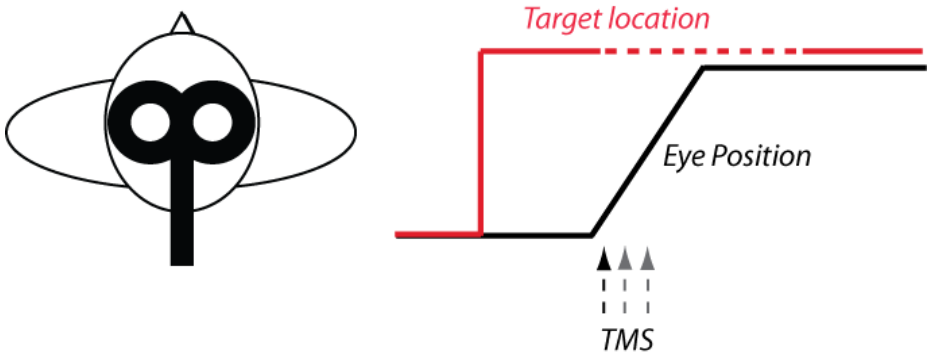


Figure 4.1: TMS methods. TMS was placed at the vertex for most experiments. TMS was triggered with respect to saccade onset for Experiments 1 and 2 and with respect to target onset for Experiment 3. The target was turned off (dotted line) for Experiment 1.

#### 4.2.2.1 TMS setup

. Transcranial magnetic stimulation was performed with a Magstim 200 stimulator with a maximum output of 2.2 Tesla, connected to a figure of eight magnetic coil,

each loop having a diameter of 7cm. The stimulation strength varied from 50% to 60% . The TMS coil was placed near the vertex, or Cz according to the EEG 10-20 system (Figure 4.1).

### 4.2.3 Data Analysis

The duration of saccades was determined by a 16°/s speed threshold. Abnormal saccades were excluded from analysis using global criteria that were applied to all subjects: 1) Saccade amplitude less than 67% of the target displacement, ranging from 15-30°. 2) Saccade reaction time less than 100ms or greater than 500ms. 3) Abnormal saccade trajectories due to large blinks.

Saccades perturbed by TMS show a variety of velocity profiles, some only decelerate briefly while others come to a complete stop. Pauses were labeled as such only when the velocity profile had two clear peaks as in Fig. 4.2. "Pause velocity" was the time when the eyes slowed down the most from the effect of TMS. The pause duration was then determined based on a velocity threshold of 16°/s above the "pause velocity". The end of the pause is also the beginning of the resumed movement. The end of the resumed movement was determined using a fixed velocity threshold (16°/s). To be considered a pause rather than just a transient slow down, we only considered pause velocity of less than 50°/s.

### 4.2.4 Experiment 1: Pauses in oblique, horizontal, and vertical saccades

We used 15° saccades in cardinal directions as well as oblique directions. TMS was triggered with respect to saccade onset at a 30°/s velocity threshold. Later analysis shows that the earliest time we can trigger TMS is around 5ms into the saccade. This delay is due to online filtering of the velocity signal. The TMS coil was placed

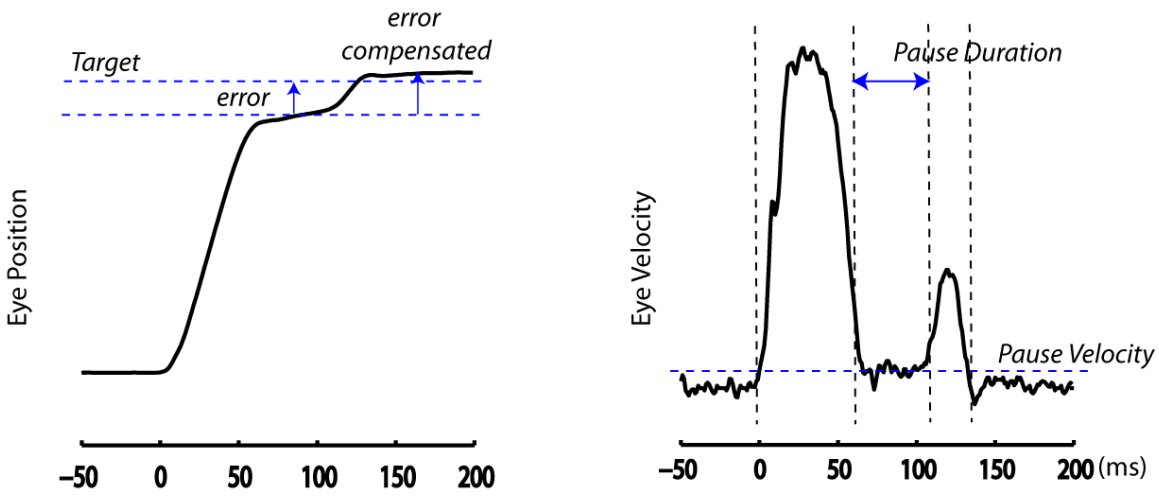


Figure 4.2: Pause data analysis. (A) Compensation of perturbation to saccade. Error is the distance from the paused location to the target. Error compensated is the distance traveled in the resumed movement. (B) Pause characteristics. Pause duration calculated by first finding the minimum velocity during the pause and then looking forward and backward until to the points in time when the velocity exceed the minimum pause velocity by 16°/s

at the top of the head, near the vertex, or Cz according to EEG 10-20 system. We applied TMS at other locations such as the cerebellum and parietal cortex to show the nonspecificity of this effect. We also test if the sound of TMS is enough to elicit saccades, by discharging the TMS coil at least 30cm above the head.

On each trial, subjects had to fixate the target for a random period of 1500-2300 ms, after which time the target stepped 15° or 30° away. Horizontal, vertical, and oblique saccades were tested in separate blocks. TMS was triggered near saccade onset randomly in 67% of the trials. In some of the experiments (such as reported in Figure 4.4), we blanked the target as soon as saccade onset was detected. This ensured that the resumed movement was not visually guided. We also did control experiments in two subjects to measure lid movements during saccades.

### 4.2.5 Experiment 2: TMS during saccades

We applied TMS during oblique saccades of 30° (21.2° in the horizontal and vertical components). A larger saccade was chosen here to provide a larger window of time when TMS would affect saccade execution. The TMS coil was always placed at the top of the head. TMS was randomly delivered near saccade onset (5ms after saccade start) or 15, 25, 35, 45, or 55ms into the saccade. TMS was delivered on a randomly chosen 70% of the trials. Since the TMS takes around 4 seconds to charge, the smallest intertrial interval was about 4 seconds. The average time between TMS pulses was 6.4 seconds.

### 4.2.6 Experiment 3: TMS before saccades

We applied TMS at various times before a saccade. To do this, we used 15° oblique saccades symmetric about the midline (10.6° in horizontal and vertical component). We triggered TMS with respect to target onset randomly at 40, 60, 80 ms before saccade onset, assuming an average saccade latency of 180ms. We made minor adjustments to this assumption during the experiment to ensure a good distribution of TMS times before saccade onset. For analysis post-experiment, we grouped trials into bins according to the time of TMS before saccade onset. The TMS coil was always placed at the top of the head. TMS was applied randomly on 75% of the trials with an average time between TMS pulses of 5.5 seconds.

## 4.3 Results

### 4.3.1 Nature of the pauses (Experiment 1)

Pauses occurred for saccades in all directions. Figure 4.3 shows examples of pauses in horizontal and vertical saccades and Figure 4.4 shows pauses in oblique saccades.

The pauses in saccades are a nonspecific effect of TMS, that is, we observed similar pauses whether we applied TMS to the top of the head, cerebellum, or parietal cortex. The time from TMS to a complete pause in saccades was around 65ms and the pauses in saccades lasted on average 29 ms. Even though pauses in saccades occurred 65ms after the time of TMS, the effect of TMS in perturbing the eyes likely started earlier. A closer look at the velocity profiles show that interrupted saccades may start to deviate from control profile as early as 40ms. This is in agreement with when Siebner saw inhibition of hand EMG after TMS. The pause duration is too short for visual feedback to play a role in feedback control of the saccade. In oblique saccades, the horizontal and vertical components show interruptions around the same time.

Sound alone (i.e. TMS coil discharged at least 0.3 meters away from the head) also induced pauses, although very rarely. Some subjects showed a few trials with pauses with sound alone while other subjects' saccades were not perturbed at all by sound. The much diminished effect of sound agrees with the result of Becker [87] and Siebner [90]. Siebner found almost no reflex blinks with just the sound of TMS, while Becker reported that in order of efficacy in pausing saccades, electrical stimulation of the supraorbital nerve was the best, followed by noise bursts, and then flashes of light. Becker, however, did not report the sound or light level used. It is possible that a sufficiently loud sound could produce the same effect as TMS in pausing saccades. The robust effect of TMS in engaging startle circuits is mostly due to stimulation of the facial afferents, but could be potentiated by other modalities, namely tactile and acoustic. In fact, multimodal stimuli are more robust in eliciting startle reflex with summation of tactile, acoustic, and vestibular systems shown to be the most effective [91].

We found no clear habituation of pausing behavior in response to TMS: pauses occurred just as frequently early in the experiment as late in the experiment. This is surprising especially when the subjects who participated in this study were tested repeatedly on different days. The intertrial interval was at least 4 seconds (the time

it takes to recharge the TMS coil). Even at such short intertrial interval, we did not observe habituation of the pausing behavior. This maybe be because we are directly exciting the trigeminal system rather than indirectly affecting it with acoustic noise or light flashes. Domingo et al. [92] found that reflex blinks easily habituate to sound and light flash, whereas reflex blinks are more robustly seen in response to air puffs. Therefore, the type of stimulus can alter the blink reflex. TMS appears to be a very robust way of inducing pauses and is not painful like surface electrical stimulation of the supraorbital nerves.

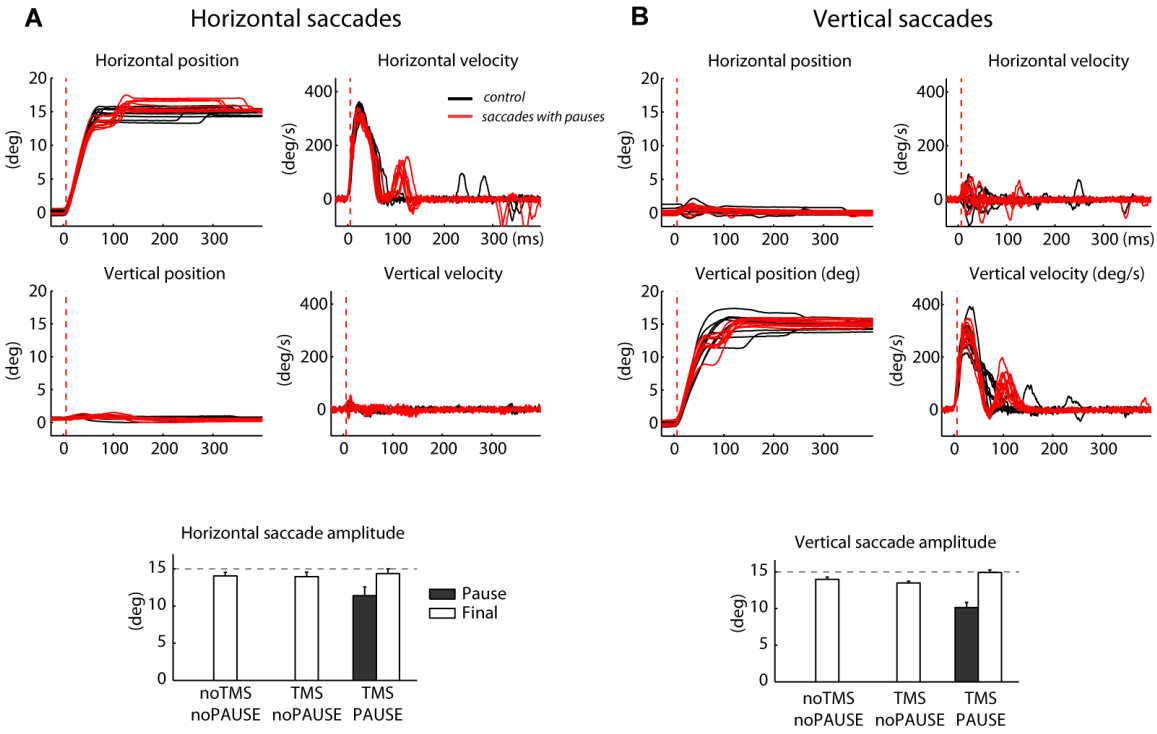


Figure 4.3: Pauses occur in horizontal and vertical saccades. (A)Pauses in horizontal saccades. (B) pauses in Vertical saccades. Notice that actual corrective saccades come much later in the saccade. The top panels are from a single subject while the bar plots show group data from 4 subjects. Dotted red line denotes time of TMS.

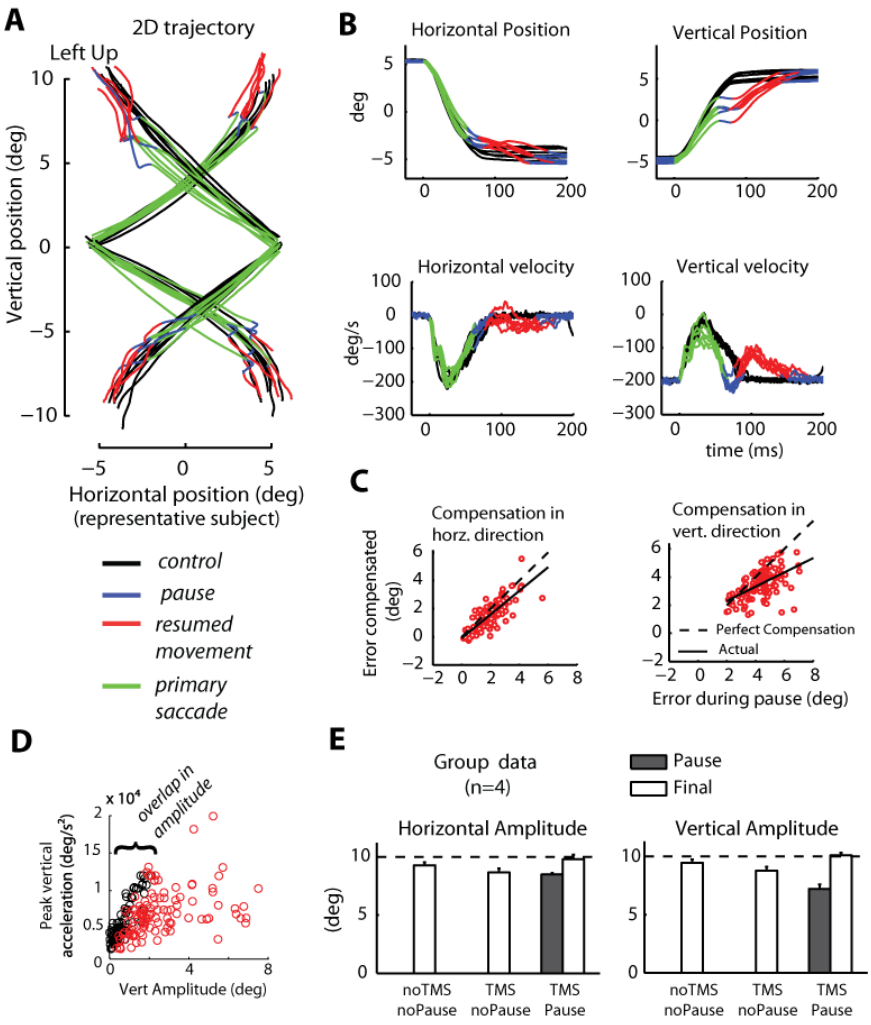


Figure 4.4: Pauses in oblique saccades. (A)Two-dimensional trajectories of oblique saccades which pause and which do not pause. (B) Horizontal and vertical position and velocity traces of the same saccades as in A. (C) Compensation in the horizontal and vertical components for paused saccades. The size of the resumed movement is highly correlated with the amount of positional error during the pause. (D) The resumed movements (red) are often slower than saccades of comparable amplitude (black), see region of overlapped amplitude. These control saccades are taken from visually guided corrective saccades during the same experiment. (E) Paused saccades' final ending positions after the resumed movement are larger than control saccades which did not have TMS and did not pause. There are some trials which had TMS but did not show clear resumed movement (middle bar). These saccades were likely also interrupted by were close enough to the goal so that no corrective movement took place.

#### 4.3.1.1 Compensation for the perturbation

The perturbed saccades landed very close to the target, even when the target was extinguished upon saccade onset so that no visual information is available during the pause. Analyzing the saccades that paused and had clear resumed movements, we found that the size of the resumed movement is highly correlated to the distance to the goal during the pause (Figure 4.4C). Therefore, the resumed movement always had the appropriate size and direction to take the eyes to target from the paused location. Despite this clear compensation, the final amplitudes of the paused and resumed saccades were often larger than control saccades which did not have TMS (see Figures 4.3 and 4.4E). For example, the perturbed oblique saccades were on average 0.53° greater in the horizontal amplitude and 0.64° greater in the vertical amplitude than control saccades. Saccades that did not resume moving (center bar: "TMS,noPause" in Figures 4.3 and 4.4E) were likely still perturbed, since they had smaller amplitudes than control saccades. Perhaps these saccades ended close enough to the goal (less than 1.35° away) so that they did not require a correction.

#### 4.3.1.2 Resumed movement after pause

The resumed movements are on average slower and more variable than visually guided saccades of the same amplitude (taken from corrective saccades in the same experiment). Figure 4.4D shows that peak acceleration of the resumed movements are lower than normal saccades of the same amplitude. Peak velocity of resumed movements are also slower than that of normal saccades. We chose corrective saccades because they overlap in amplitude with the resumed movement post-interruption. They also started at similar eye positions. There are a few possible reasons for slower resumed movements. The crisp initiation of normal saccades depends on the inhibition of omnipause neurons (OPN) on the excitatory burst neurons (EBNs). The EBN membranes exhibit post-inhibitory rebound (PIR) and fire most rigorously just

after removal of OPN inhibition. The transient inhibition caused by TMS is perhaps too short to cause PIR; therefore the resumed movements are slower compared to control saccades. Another possibility is that the resumed movements are memory guided in contrast to corrective saccades, which are visually guided.

#### 4.3.1.3 Lid movement during saccades

Blinks often accompanied saccades on TMS trials. Blinks habituated within the first 10 trials of the experiment from a modest reflex blink to very small movements in the lid. Figure 4.5A shows horizontal saccades of one subject with and without pauses. For this subject, the amount of lid movement accompanying saccades with TMS was not very different from trials without TMS. Furthermore, compared with a voluntary blink where the lids completely closed, the TMS induced lid movement were very small. Therefore the pauses in saccades and measurable lid movement are not tightly related. During vertical saccades (Figure 4.5B), lid movement was coordinated with the eyes and showed clear "lid saccades". When we applied TMS during vertical saccades, we saw pauses in the lid saccade as well as the eye saccade.

The small amount of lid movement in horizontal saccades and conjugate eye-lid movements in vertical saccades suggest that the lids are under central control and that the eyes are not being paused due to mechanical perturbations of the lid on the globe. In one experiment where we recorded from both eyes, we observed that the pauses were conjugate in the two eyes, further supporting the idea that pauses are central in nature. Therefore, we would like to suggest that the perturbation in the eye trajectory is not dependent on having a reflex blink. Rather the effect of TMS may be engaging startle circuits which in turn induces many behavioral responses, two of which are reflex blinks and pauses in saccades. However it is still possible for blinks (when they do occur) and saccades to interact at the level of the colliculus as suggested by Goossens [93].

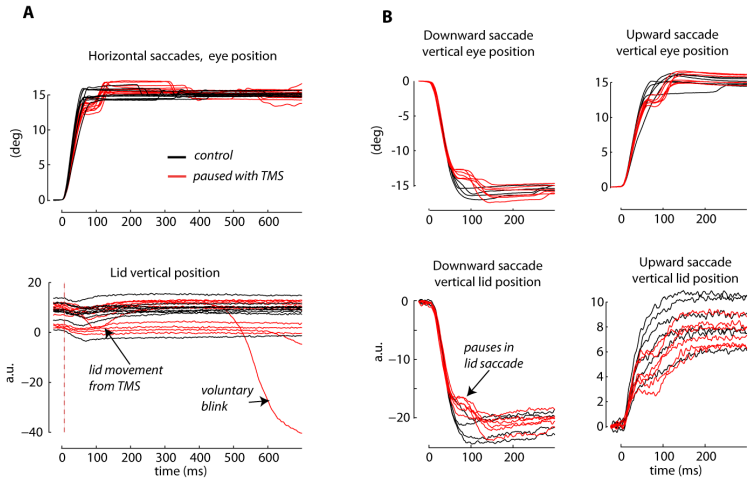


Figure 4.5: Lid during TMS and saccades for one subject. (A)Horizontal saccades. Amount of lid motion caused by TMS is very small compared to voluntary full-closure blinks. (B) During vertical saccades, the lid also moves like a saccade, complete with the pauses when the eyes pause. Black:control trials. Red: trials with TMS and pauses in saccades.

### 4.3.2 TMS timing during saccades (Experiment 2)

Given that the pauses occurred at a potentially long delay of 65ms after TMS, the saccade had to be of sufficient duration to observe clear effect from TMS. For saccades of long duration (30° oblique saccades had duration $>$ 100 ms), we observed that TMS applied early in the saccade transiently slowed the eyes, creating double peaked velocity profiles, whereas TMS late in the saccade could pause the eyes (Figure 4.6B). It appears that saccades are easier to stop when TMS is given later in the saccade.

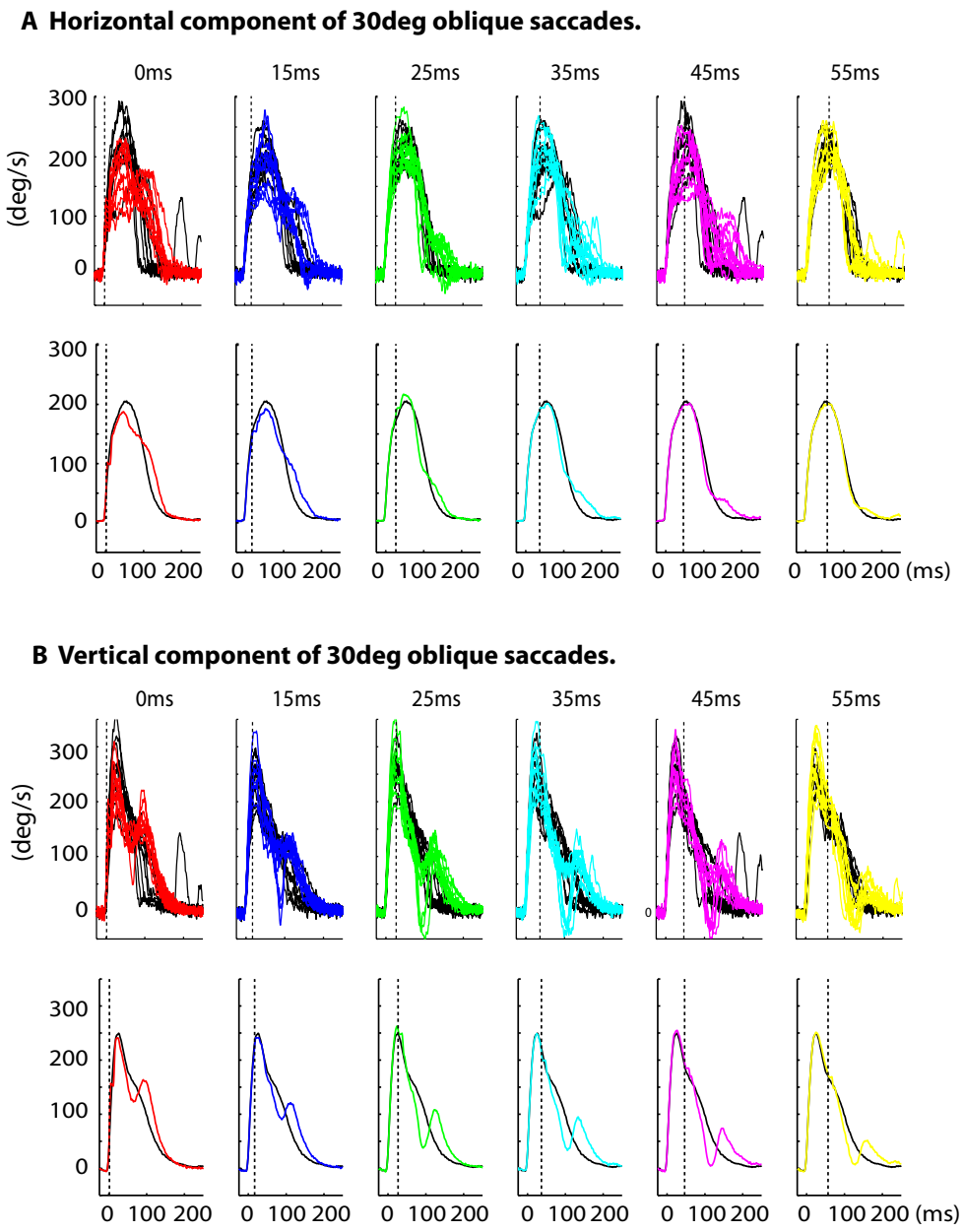


Figure 4.6: TMS applied at various times during saccades (Experiment 2). TMS applied early in the saccade slowed the eyes. TMS applied late in the saccade could completely stop the eyes. Maximum perturbation from TMS occurred 65ms after the time of TMS. Dashed vertical line indicates time of TMS. (A) Horizontal component. (B) Vertical component shows stronger perturbation. The plots are from one of 3 subject who performed this task.

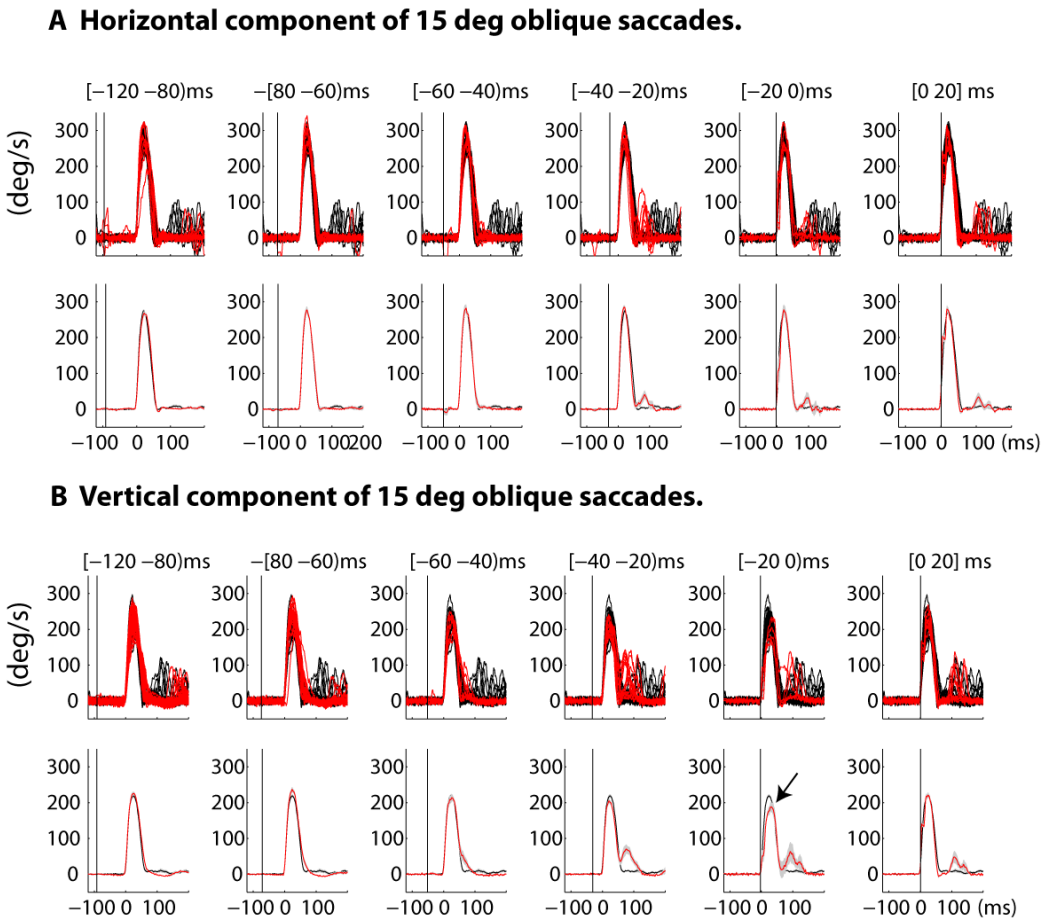


Figure 4.7: TMS before saccades (Experiment 3), subject 1. (A) Each subplot bins trials with TMS which occurred within a time window specified in the title of each subplot. Black traces are control trials and red traces are from TMS trials.(B) Vertical traces.

### 4.3.3 TMS timing before saccade (Experiment 3)

TMS applied during a saccade can slow or completely stop the eyes. We wondered what would happen if TMS is applied right before a saccade. Could saccade initiation be altered? Subjects made 15° oblique saccades while TMS was triggered with respect to target onset but in time to take place at -80, -60, and -40 ms with respect to the estimated saccade onset time. Out of the 4 subjects tested, no drastic effect on saccade initiation and no saccade was prevented from taking place.

Figure 4.7 shows the horizontal and vertical components of one subject whose saccades showed no appreciable changes when TMS was applied before saccade onset. TMS applied near saccade onset produced similar perturbation as TMS applied immediately after saccade onset. Figure 4.8 shows saccades of another subject, some of which were altered by pre-saccade TMS (see arrows). It appears that saccade initiation can be altered, but no drastic changes were seen.

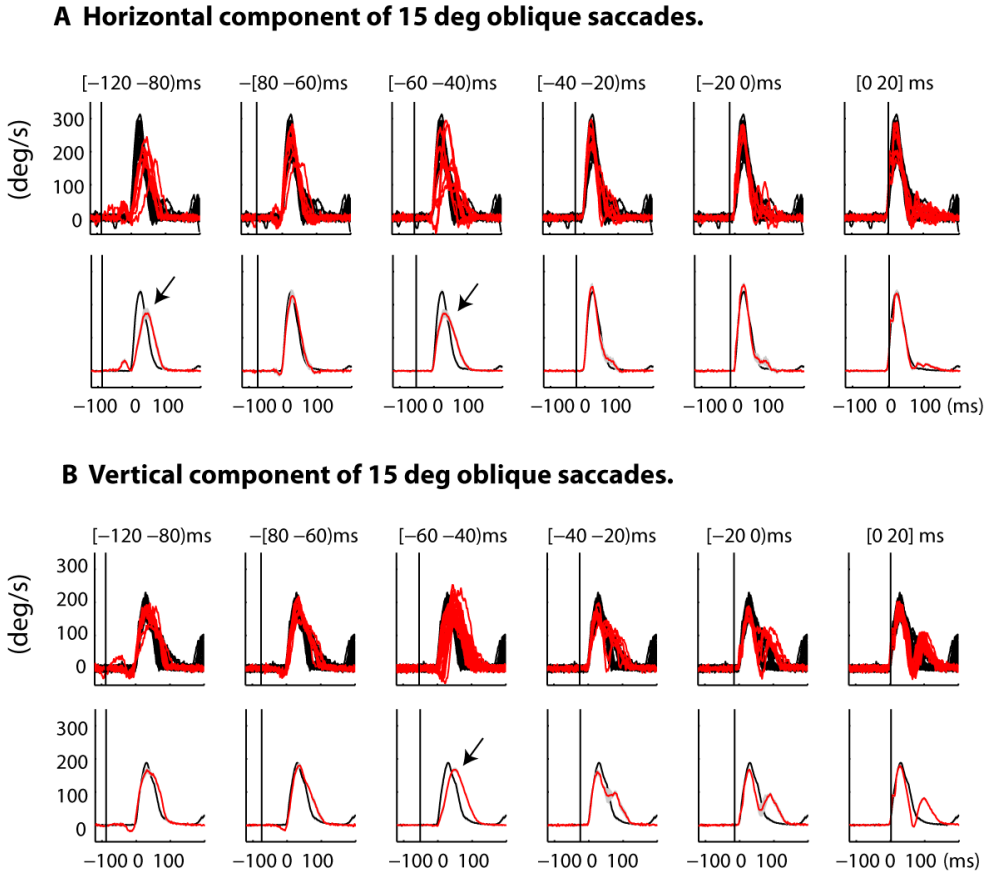


Figure 4.8: TMS before saccades (Experiment 3), subject 2. (A) Each subplot bins trials with TMS which occurred within a time window specified in the title of each subplot. Black traces are control trials and red traces are from TMS trials.(B) Vertical traces.

## 4.4 Model and Simulations

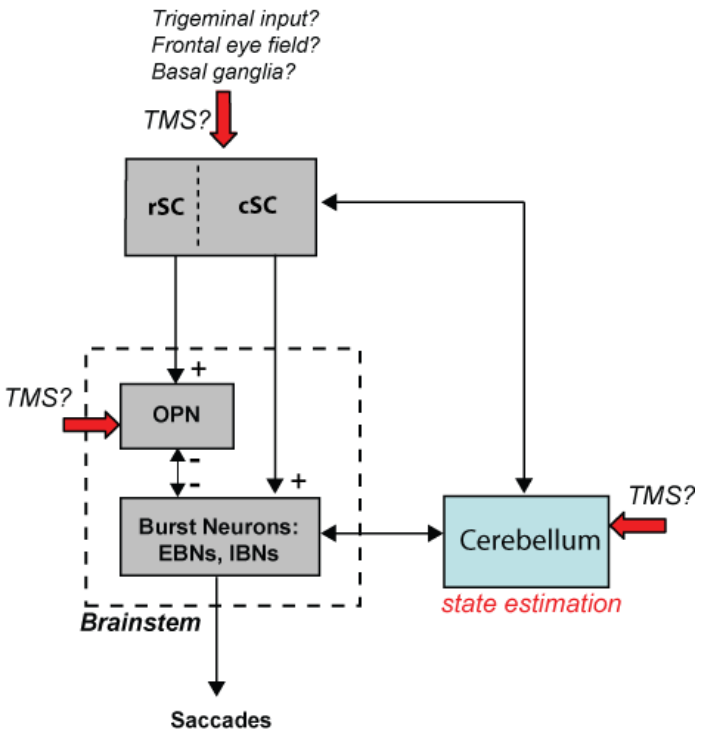


Figure 4.9: TMS could be influencing the OPNs directly, the Superior colliculus, or the cerebellum. OPN:omnipause neurons, EBN:excitatory burst neurons, IBN:inhibitory burst neurons

The effect of TMS on pausing saccades provides an intriguing way to study saccade initiation and feedback control process for saccade accuracy. To simulate the effects seen in this study, one has to consider the interactions among the superior colliculus, the cerebellum, and the saccade burst generator (Figure 4.9). TMS could cause pauses through trigeminal inhibition of the superior colliculus (SC) as suggested by Goossens et al. [88], directly reactivating the omnipause neurons (OPN), or even affecting the cerebellum. We sought to use modeling to differentiate these possibilities. Other effects we sought to describe with our model are that saccades are easier to pause later in a saccade, resumed saccades are typically slower than normal saccades of comparable amplitude, and that interrupted saccades with resumed movement often

land further than uninterrupted saccades. In this model, I have included some of the recent neurophysiological findings on feedback control of saccades and saccade triggering [94, 95].

This model is based on the one presented by Ramat et al. [96] and is simulated in Simulink/Matlab. The model is based on classic control and has a few key components: 1) two coupled EBN/IBN pairs. 2) The burst neurons fire at a rate dependent on the size of the motor error.

$$B(e) = \begin{cases} B_m(1 - e^{(err - err_0)/b}), & \text{if } err > err_0 \\ 0, & \text{if } err \leq err_0 \end{cases}$$

3) The motor error ($err$) is calculated by integrating the velocity output from the burst neurons and then subtracting this estimate of current eye position from the desired goal of the movement. 4) The burst neurons membranes are modeled as high pass filters with adaptation. This design simulates the post-inhibitory rebound of burst neuron membranes and allows the burst neurons to fire right away when inhibition from the OPNs are removed. This aspect of the model already predicts that resumed movements would be slower than normal saccades. The OPN of this model is simply a gate that is open when the motor error is higher than a threshold of 1.3°.

I expanded this model by making more detailed implementations of the superior colliculus and the OPNs. Instead of being a simple gate that is controlled by motor error, the OPNs now has two inputs, one from the rostral superior colliculus and the second from bilateral IBNs. These two inputs serve as trigger signals to turn off the OPNs and release the burst neurons to move the eyes. After the initial trigger to turn off the OPNs, the OPNs' inhibition is maintained by the IBNs until the end of the saccade. This agrees with the work of Yoshida et al. [94] which showed that OPN membrane potential follows the velocity output form the burst neurons. The OPNs will spike again once the membrane potential returns to a certain threshold.

The superior colliculus now has one rostral region and two caudal regions (left

and right). The colliculus has two inputs: spatial target location and the motor error provided by the neural integrator. When the motor error is small, the rostral SC is active and in turn keeps the OPNs to maintain fixation and inhibiting any saccades. When a visual signal activates a location on the spatial map of the SC, this target position information is relayed to the comparator which calculates the motor error. The caudal SCs project to the contralateral EBNs and IBNs.

### 4.4.1 Omnipause neurons and paused saccades

Omnipause neurons (OPNs) are usually on during fixation and turn off right before a saccade, thereby releasing its inhibition on the saccade burst neurons to accelerate the eyes quickly. Electrical stimulation of the OPNs [85] pauses saccades midflight much like what we observe with TMS. Therefore, a simple explanation of our observations could be that the OPNs turn on prematurely during a saccade due to the effects of TMS. Figure 4.10 shows that saccades can indeed pause midflight if the OPNs are turned back on transiently during the saccades. This simple model would explain why saccades in all directions are paused by TMS.

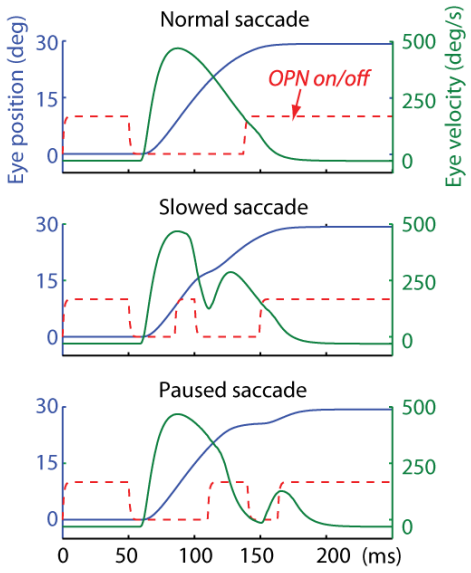


Figure 4.10: Pauses can occur if OPNs are turned on during a saccade.

### 4.4.2 Inhibition of the superior colliculus

Electrical stimulation of the rostral part of the superior colliculus (SC) can also pause saccades midflight [86, 98]. Therefore, the effects of TMS could be on the superior colliculus. Goossens et al [93] reported that reflex blinks elicited by airpuffs resulted in short latency (10ms) transient suppression of saccade related burst neurons in the SC. Within 10-30ms all neurons resumed their activity, and their burst discharge continued until the perturbed saccade ended near the extinguished target. It is conceivable, but has not been shown, that stimulation of the supraorbital nerve (closer to the effects of TMS) would also cause transient inhibition of the colliculus.

If TMS activates startle circuits leading to general inhibition of the superior colliculus, then the EBNs and IBNs would be disfacilitated during a saccade, thereby slowing the eyes. With enough disfacilitation of the IBNs, the OPNs would turn back on. Once the effect of TMS is over, the remaining motor error will once increase the firing rate of the EBNs and IBNs until the eyes reach the target. It would be

easier to inhibit the EBNs and IBNs later in the saccade when they are less active, and consequently increasing the likelihood of the OPNs turning back on. This may explain why saccades are easier to pause when TMS is delivered later in the saccade.

### 4.4.3 Cerebellum and paused saccades

Another possible mechanism to saccades is premature activation of the contralateral IBNs. This can occur if the cerebellum or the superior colliculus preferentially inhibits the contralateral IBNs. For example, to model interrupted saccades observed in patients with Tay-Sachs disease, Optican [97] favors a premature activation of the caudal fastigial nucleus which chokes off the saccade rather than reactivation of the OPNs. Premature activation of the caudal fastigial nucleus could also underlie the TMS induced pauses in saccades.

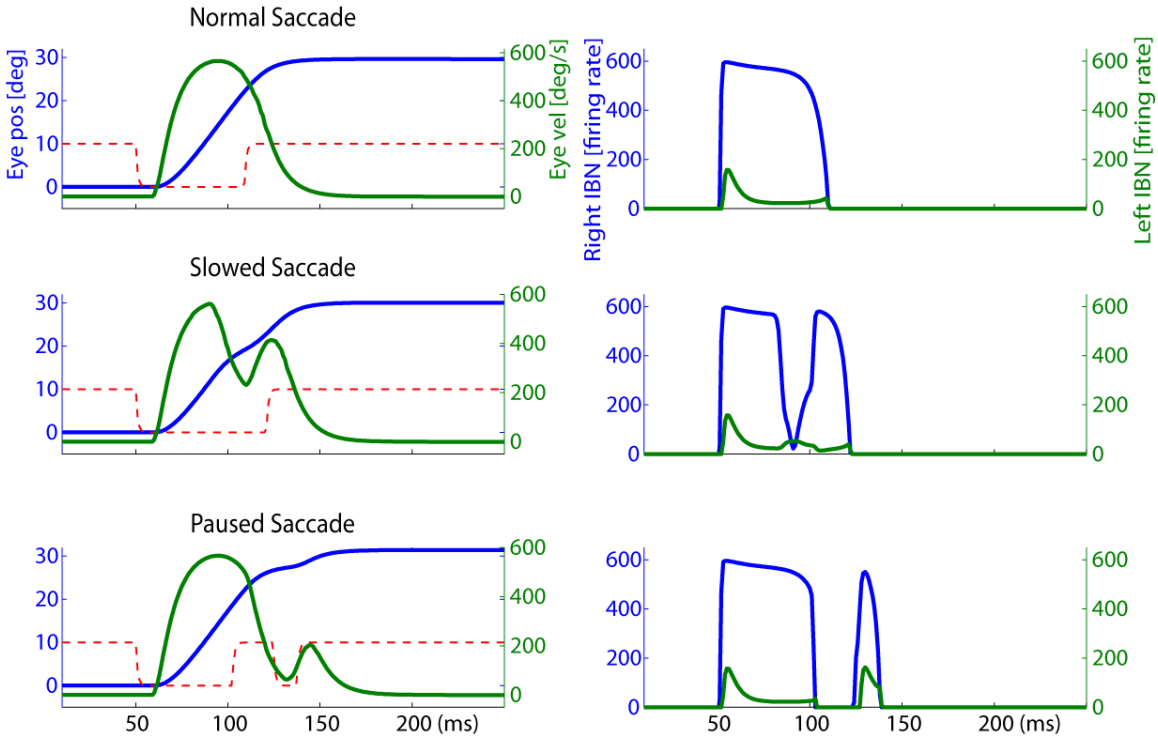


Figure 4.11: Pauses can be mediated by general inhibition of the superior colliculus which leads to disfacilitation of EBNs and IBNs during saccades. The OPNs do not need to resume activity to pause the eyes. However, the OPNs can come on if the IBNs are silent enough, which is more likely to occur near the end of saccades. Red dashed line denote OPN on/off.

## 4.5 Discussion

### 4.5.1 TMS, saccades, and the brain

TMS, when applied during saccades, had the nonspecific effect of pausing saccades midflight. Pauses occurred for saccades in all directions. The location of TMS was not critical: We observed similar pauses with TMS applied at the top of the head, cerebellum, parietal cortex, and with sound alone. We think that TMS is engaging "startle" circuits of the brain. But why should startle have the effect of pausing saccades? Perhaps startle has a system wide effect on the brain. Indeed, Siebner's

study [90] demonstrates that TMS mediated effects go beyond just the facial area. He showed that TMS applied on various parts of the head can pause EMG activity in the hand. Perhaps startle causes inhibition of many motor pathways. The nonspecific effect of TMS should be taken into consideration when interpreting brain function in TMS studies.

One study that needs reinterpretation is that of Hashimoto et al. [99]. They reported that TMS of the right cerebellar vermis produced hypometric ipsilateral saccades and hypermetric contralateral saccades. Our work and that of Siebner [90] clearly demonstrates that TMS of the cerebellum can induce strong perturbations on saccades. It is conceivable that their observation is due to misinterpretation of TMS-associated perturbation to saccades. For example, to observe hypometric saccades, TMS during saccades of appropriate durations can truncate these saccades to a position near the goal, but not far enough to warrant any resumed movements. To observe hypermetric saccades, a slightly perturbed saccade (one that does not stop completely midflight) can compensate but overshoot a little. This overshooting would be due to correction of perturbed saccades, and not due to disruption of cerebellar function. Hashimoto et al. did not report any pause-like behaviors in saccades. They did report that sometimes saccades seem to reverse direction briefly, which is possible with large blinks.

When we applied TMS to the cerebellum, we did not observe any effects to suggest that cerebellar function had been altered. The only difference in applying TMS to the cerebellum versus other brain areas was that the pauses might occur more frequently. This is perhaps because TMS on the cerebellum engages the startle pathway more strongly. To study the function of the cerebellum with TMS, it would be difficult to remove the confounding effect of startle. One possibility is to use paired stimulus paradigm. Inter stimulus interval of 100ms can suppress most of the R2 component of the blink reflex [100]. Or it might be possible to find orientations of the TMS coil to minimize excitation of the trigeminal system.

### 4.5.2 Feedback control of perturbed saccades

Perturbed saccades typically resumed and ended near the target even without visual guidance, potentially relying on a local feedback loop and estimate of the current state of the eyes. Robinson proposed such a local feedback loop [11] and Quaia suggested that the cerebellum may be important for this feedback loop [14]. One way to answer this question is to test patients with cerebellar degeneration and look for differences in how they respond to TMS.

Saccades are often thought of as ballistic movements since they are too short in duration to be influenced by sensory feedback during the movement. Here we show a kind of perturbation to the saccade that can alter the saccade command. If the saccadic system was purely open loop, then the saccades perturbed by TMS would not be accurate. The type of perturbation here is very artificial: we do not naturally receive magnetic stimulation of our trigeminal system. However, other more natural kinds of perturbation do exist and need compensation. For example, voluntary blinks can also perturb saccades [101]. Top-down effects of attention and motivation are all "disturbances" to saccades that require compensation in order for saccades to be accurate.

However, this internal compensation process is not perfect. We see from the results of the fatigue study (Chapter 3) that even healthy controls do not fully compensate for the effects of fatigue. Here, not all interrupted saccades resume, possibly because the size of the error is too small. Or, if compensation does take place, resumed movement often takes the eyes further than unperturbed saccades. It appears that the feedback process, although very important, only partially compensates for inaccuracies in saccades [10].

### 4.5.3 Likely mechanism of pauses in saccades

The effect of TMS in slowing or pausing saccades completely could be mediated via several brain regions. TMS could cause the OPNs to turn on briefly during a saccade which then causes the eyes to slow or pause. TMS could also be influencing activity of the superior colliculus, the brainstem burst generator, or the cerebellum. While a simple explanation would be that OPNs are turned on briefly by TMS somehow to induce the pauses, we think this is unlikely to be the only mechanism. It is more likely that multiple pathways are involved with inhibition of the superior colliculus being the primary mechanism. Inhibition of the SC disfacilitates the EBNs and IBNs which then slows the eyes. If IBN activity is low enough, which is more likely to occur later in a saccade, the OPNs can turn back on and more effectively stop the eyes.

The OPNs are unlikely to be the only mechanism to pause saccades because their role in terminating saccades is still under debate. In saccade generation, the role of OPN is to provide a synchronized go signal to the burst neurons to mediate fast accelerations of the eyes. After the saccade has started, OPN activity does not signal the ends of saccades. Instead, OPNs are under inhibition from the inhibitory burst neurons. Yoshida et al. [94] showed that OPN membrane hyperpolarization follows saccade velocity. When saccade velocity shows transient slowing like the perturbations from TMS that we observe (see Figure 8 of Yoshida's paper), the OPN membrane becomes less hyperpolarized, but not enough to generate action potentials. This result shows clearly that OPN reactivation is not necessary for saccades to slow down. This result makes it unlikely that the OPNs reactivate to slow the saccades in our work. Schultz et al. [102] showed that OPN activity follows blinks and does not cause blinks. Together, the works of Yoshida and Schultz suggest an important role of OPNs in saccade initiation but not saccade termination.

Many questions remain concerning the pauses in saccades. If the primary site of TMS effect is inhibition of the superior colliculus as Goossens et al. [88] suggested. Then by what path/circuit does the inhibition arrive at the superior colliculus? The

inhibition could come from the basal ganglia, frontal lobe, or even the cerebellum. Other unanswered questions are why paused saccades typically end further than control saccades and why vertical saccades seem easier to pause. Although both the horizontal and vertical components of saccades paused, we find that vertical and oblique saccades show more incidences of pausing than purely horizontal saccades. This maybe due to the vertical burst neurons have smaller gain than horizontal burst neurons. This fits with the observations that most saccadic oscillations are horizontal or multidirectional but never pure vertical.

In summary, we found that a single pulse of TMS during a saccade perturbed the eye's trajectory, causing a reduction in velocity or an outright pause. This perturbation was corrected within the same saccade by motor commands that compensated and brought the eyes near the target. As this correction occurred even without visual input (in conditions where the target was removed), it appears that the correction to the perturbation is due to an internal feedback process that has an estimate of the current state of the eye. Furthermore our findings emphasize that TMS can have non specific, presumably startle effects on motor behavior, and these effects should be taken into account when interpreting the effects of TMS on brain function.

# Chapter 5

# Conclusions

We make graceful and accurate movements by relying on sensory feedback and internal predictions to tell us the state of our body. Without these two sources of information, our movements would reveal more of the underlying variability of our motor commands. I showed in Chapters 2 and 3 that even simple eye movements can be influenced by our attentional and motivational state, which then must rely on feedback processes to ensure accuracy. The cerebellum appears to be critical for this internal predictive process as cerebellar patients are impaired in compensating for these internal sources of variability.

Chapter 4 examined the unexpected finding that transcranial magnetic stimulation can perturb saccades. I hope that this finding benefits the scientific community in two ways. One, TMS, through its effects on the startle circuits of the brain, is a novel tool and potentially a powerful one for studying feedback control of saccades and control of movements in general. Two, I hope that this work will alert other researchers to the nonspecific effects of TMS which can confound interpretations of studies involving TMS.

My work focuses on one specific type of movement we make: saccades. However, the principles learned here apply to other movements. Patients with cerebellar degeneration do not only have trouble making accurate saccades, they also have difficulty

making many other movements more critical to their daily life such as walking and talking. A better understanding of the mechanisms and brain areas involved in motor control will hopefully help us design better rehabilitation strategies for these patients.

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Ph.D. Biomedical Engineering, Johns Hopkins University, 2003-2010

M.Eng. Electrical Engineering and Computer Science, Massachusetts Institute of Technology, 2001-2002

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## EMPLOYMENT

**Motorola Electronics Ltd.** Beijing, China

*July 2002 - January 2003* Ported Microsoft's Windows Media Video Decoder to Digital Signal Processing board.

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*Summer and Fall 2001* Designed and implemented a fast and easy way to measure arterial stiffness by using Doppler Ultrasound. (Master's thesis)

*Summer, 2000* Explored adaptive signal processing of ultrasound data for the segmentation of tissue and blood pool in cardiac images.

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**Boston Heart Foundation** Cambridge, MA

*Fall, 2000—June 2001* Implemented 2D active surface to extract arterial volume from ultrasound data to differentiate normal and abnormal arterial function.

**MIT, Spoken Languages Group** Cambridge, MA

*June 1998 to June 1999* Implemented concatenated speech synthesis techniques to create more natural sounding speech in Pegasus, a conversational information retrieval system.

## TEACHING

**Johns Hopkins University** Baltimore, MD

*Spring 2007* Teaching assistant for undergraduate course on signal processing. Organized weekly tutorial to clarify course material.

*Spring 2006* Head teaching assistant for Medical Imaging Systems which covered the physics and signal processing of CT, Ultrasound, MRI, and PET. Lectured 4 times. Wrote exams and organized review sessions.

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*Spring 2003* Taught design labs for a class on biomedical signal processing at Shanghai Jiaotong University.

**Massachussetts Institute of Technology** Cambridge, MA

*Spring Term 2002* Teaching assistant for graduate course on Biomedical Signal and Image Processing. Organized weekly lab sessions.

## HONORS

Ruth L. Kirschstein National Research Service Awards from National Institute of Health, 2008-2010.

Macklin Fellow for Ataxia Research, Johns Hopkins Ataxia Center, 2007-2008.

Neuroengineering Training Initiative Fellow, Johns Hopkins, funded by NIH, 2006-2007.

# PUBLICATIONS

**A cost for time in control of voluntary movements,** Reza Shadmehr, Jean-Jacques Orban de Xivry, Minnan Xu-Wilson, Ting-yu Shih (2010) Journal of Neuroscience (submitted).

**Staircase and square-wave jerks in early Parkinson's disease** Aasef Shaikh, Minnan Xu-Wilson, Stephen Grill, David S. Zee (2010) British Journal of Ophthalmology (accepted).

**Cerebellar contributions to adaptive control of saccades in humans,** Minnan Xu-Wilson, H Chen-Harris, DS Zee, R Shadmehr (2009) Journal of Neuroscience 29: 12930-12939.

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**Real-Time Magnetic Resonance Imaging-Guided Endovascular Recanalization of Chronic Total Arterial Occlusion in a Swine Model,** AN. Raval, PV. Karmarkar, MA Guttman, C Ozturk, S Sampath, R DeSilva, RJ Aviles, Minnan Xu, VJ Wright, WH Schenke, O Kocaturk, AJ Dick, VK Raman, E Atalar, ER McVeigh, RJ Lederman, Circulation 2006 Feb 28; 113(8): 1101-7