Motor Learning of Optokinetic Response

Report Author

Marcelo Beramendi Caballero

Project Partner

Daniel Popp

04/24/2023

1. Background

1.1. Introduction

In order to survive in the natural world, animals have to be able to rapidly adapt to changing situations. This requires them to possess senses that allow them to successfully detect visual stimuli from potentially harmful targets and to maintain a stable visual field, even during self-motion. For example, predators need to keep their prey on sight while they are running to catch it, and birds need to maintain visual stability while flying at very high speeds. The optokinetic response (OKR) plays an essential role, because it allows for the maintenance of a clear image of a rapidly changing environment.

OKR consists of a series of rapid eye movements that occurs when the environment around us changes quickly, either due to objects moving very fast, or due to self-movement. For example, we use OKR when we see a fast car going by, or when we are driving and see our surroundings change very quickly. Without OKR, we would not be able to keep track of our surroundings during movement.

Studying the OKR reflex is immensely useful for several reasons. First, it provides us with a much deeper understanding of how the eyes work in coordination with the brain to process visual information. Studying visual processing is crucial because our senses provide the base information that allow more complicated cognitive processes to take place, so figuring out how our perception works is a first step towards studying higher-order cognition (Fogarty & Stern, 1989; O'Reagan, 1987). Secondly, it can provide insight into treatments for amblyopia, a condition that leads to monocular vision loss (Holmes & Clarke, 2006). It has been found that videogames can "induce plasticity in the visual system of adults with amblyopia" (Li et al., 2011). Since videogames often involve moving targets, studying the optokinetic response could help develop more effective treatments. Finally, it can also be useful for people whose professions require them to work with very fast speeds, like aviation. Understanding how OKR can be improved could help prevent accidents caused by human error.

The effectiveness of OKR can be studied in controlled settings by providing participants with simple visual stimuli, like colored stripes moving across a screen. Then, eye movements of participants can be tracked and compared to the movement of the stimuli. We call this measurement the OKR gain. If eye movement distance is the same as the distance moved by the stimuli, then a score of one is provided. This is very important, because having a way of scoring OKR gain allows us to research how it can improve with training.

A particular area of interest in the study of OKR are the brain processes that lead to its memory consolidation. That is, studying the underlying physiological mechanisms behind our ability to improve our OKR gain. The reason for this is that repeated exposure to experimental trials where the match between eye movement and the changes in the environment is measured can improve the optokinetic response, so understanding how this happens could provide with insights regarding long-term memory consolidation.

In "Modeling Memory Consolidation During Post training Periods in Cerebellovestibular Learning", Yamazaki et al. develop a simple model of the cerebellar network, where OKR gain is predicted by modeling the synaptic weights of the two main synapses responsible of its effectiveness: the parallel fiber-Purkinje cell (PF-PC) synapses, and the mossy fiber-vestibular nuclear neurons (MF-VN) synapses (Yamazaki et al., 2015). In our paper, we aim to verify the results obtained by Yamazaki et al. by re-implementing their model in MATLAB.

More specifically, we will be testing the following central hypotheses. First, we hypothesize that during training, short-term increases in OKR gain will be observed in short-term memory formation in PC cells. Secondly, we hypothesize that repeated training should lead to the formation of long-term memory, represented by the MF-VN synaptic weight. Third, we hypothesize that formation of long-

term memory should occur after training rather than during training. Fourth, we hypothesize that several short training periods should be more effective in increasing OKR gain than fewer and longer training periods. Fifth, we hypothesize that simulating selective depletion of $GABA_A$ receptors, and deficiencies of PF-LTD and PF-LTP based on genetic modification, should impair memory consolidation. More specifically, we hypothesize that impairing PF-LTP should prevent any kind of learning, while PF-LTP and selective depletion of $GABA_A$ receptor should impair long-term memory consolidation, but not short-term memory formation.

We will also be extending the model in several ways. First, we will test the effect of different training paradigms in short-term memory consolidation for PF-LTD deficient mice. We hypothesize that having more short periods of training should be better than having less but longer periods of training. However, we also hypothesize that this difference will be minimal, because of how quickly PF-LTD deficient mice decrease their OKR-gain after training. Secondly, we will explore that the time constants, which were fitted to experimental results in the paper, have in the evolution of the system. In particular, we hypothesize that increasing tau_{learn} and tau_v should decrease long-term OKR gain, while increasing $t_{recovery}$ should increase long-term OKR gain. Finally, we will test the effect of combining PF-LTD deficiency with selective depletion of $GABA_A$ receptors. We hypothesize that this combination will prevent both short-term memory increases and long-term memory consolidation.

1.2 . Background: Describing the Cerebellar Network

Before describing the equations, it is important to understand the basic physiology of the system. Yamazaki et al. provides a very useful visualization of the model.

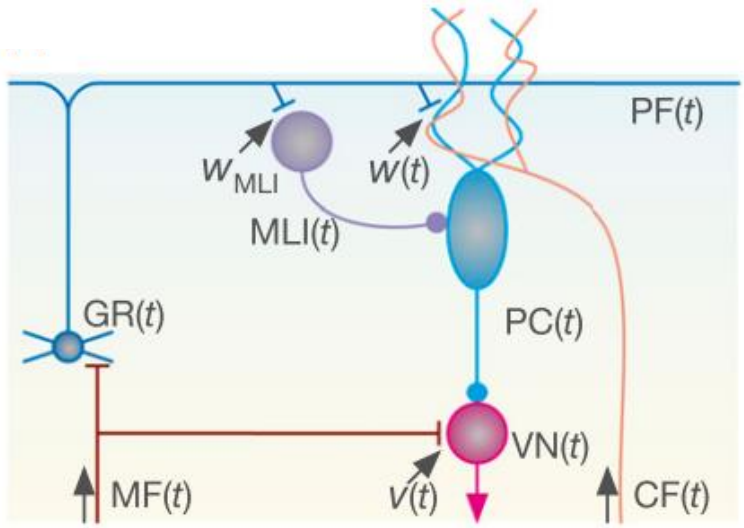

Figure 1. Cerebellar circuit visualization (Yamazaki et al., 2015). Variables are defined in the text.

The figure illustrates a model of the cerebellum. As we can see, it receives two inputs: signals from Climbing Fibers (CF) and Mossy Fibers (MF). The output of the system is the signal sent by the Vestibular Nuclear neurons (VN), which are in charge of maintaining stable vision of the target being followed. It also plays an important role in maintaining body posture and head position (Hernandez & M Das, 2023).

Climbing Fibers (CF) provide graded error signals to the cerebellum, which allow it to make corrective adjustments to the performed movements (Streng et al., 2017; Zang & De Schutter, 2019). Mossy Fibers convey sensory information about the environment, body position, and body movements (Knierim, 2014). In the case of the optokinetic response, MF convey information about the target being followed by the eyes, plus the position and movement of the eyes. They do this by providing an excitatory input

(Sillitoe et al., 2012, p. 11) to both Granule Cells (GR) and the Vestibular Nuclear neurons (VN). Granule Cells (GR) are in charge of processing the visual and motor information (McMurray, 2020) provided by the Mossy Fibers (MF).

The axonal extensions of Granule Cells (GR) are called Parallel Fibers (PF) (Taylor & Ivry, 2014, p. 9), and they carry out the encoded sensory and movement information to Purkinje Cells (PC) in the form of excitatory synapses. This is what we will refer to as the PF-PC synapses, and their synaptic weight will be represented with variable $w(t)$. PF-PC synapses carry out Purkinje Cell Long Term Depression (PF-LTD).

While GR directly excite Purkinje Cells (PC), they also indirectly inhibit them by exciting Molecular Layer Interneurons (MLI), which "control PC activity via inhibitory synaptic transmission" (Kim & Augustine, 2021). Finally, after integrating the inputs from both PF and MLI, Purkinje Cells (PC) provide an inhibitory input to the Vestibular Nuclear neurons (VN).

VN also receives direct excitatory input from Mossy Fibers (MF), forming what we will refer to as the MF-VN synapses. The synaptic weight of the MF-VN synapse will be represented with variable v(t). This synapse is responsible for MF-LTP in the system. In summary, the Vestibular Nuclear neurons (VN), which is in charge of modulating the movements performed by the eye and therefore of generating optokinetic response, receives excitatory input from Mossy Fibers (MF) and inhibitory input from Purkinje Cells (PC).

2. Numerical Methods

Now that we understand how the different parts of the system interact, we can derive the necessary equations for modeling OKR gain. All of the following derivations were explained by the authors in a Supporting Information document, which they published with the paper for those seeking to understand how the model was derived. In the following section, I will provide a summary of the most important steps of the derivation.

2.1. Deriving the Equation for Optokinetic Response Gain

As stated in the description of the system, the Vestibular Nuclear neurons (VN) are responsible of modulating OKR. Therefore, to derive the equation for OKR gain, we need to model the output produced by VN. Since VN receive input from Purkinje Cells (PC), it is useful to start deriving the equation governing the behavior of PCs. All the derived equations consider the population activity of each neuron type.

2.1.1. Purkinje Cells

As it was previously mentioned, PCs are excited by PFs (the axonal extensions of GRs) and inhibited by MLIs. Therefore, the equation for the activation of PCs looks as follows.

$$PC(t) = w(t)GR(t) - MLI(t) + PC_0 \quad (1)$$

Recall that w(t) represents the PF-PC synaptic weight. Since Purkinje Cells can fire spontaneously, a PC_0 term was added to account for this.

Also remember that MLIs are excited by GR. The conversion is not direct, so we add a w_{MLI} term.

$$MLI(t) = w_{MLI}GR(t) \quad (2)$$

Yamazaki et al. assume that GRs simply transmit the same information from MFs. This is not entirely true, but it is a reasonable assumption to build a first, simple model that can be used as a starting point for later improvements.

$$GR(t) = MF(t) \quad (3)$$

When plugging equations 1 and 2 into equation 3, we obtain the following.

$$PC(t) = w(t)MF(t) - w_{MLI}GR(t) + PC_0 \quad (4)$$

$$PC(t) = w(t)MF(t) - w_{MLI}MF(t) + PC_0 \quad (5)$$

Finally, by factorizing MF, we obtain the final equation for Purkinje Cells (PC) activation.

$$PC(t) = MF(t)(w(t) - w_{MLI}) + PC_0 \quad (6)$$

2.1.2. Vestibular Nuclear Neurons

From the description of the cerebellar circuit, recall that MFs excite VN through the MF-VN synapse, which has synaptic weight v(t). Therefore, MF activity is included in the equation with a positive sign. Additionally, PCs inhibit VN, so PC activity is represented in the equation with a negative sign. Just like for the PC equation, a term VN_0 is included to represent the spontaneous activation of the Vestibular Nuclear neurons.

$$VN(t) = v(t)MF(t) - PC(t) + VN_0 \quad (7)$$

Since we already know the expression for PC(t) (equation 5), we can plug it into the equation for VN(t) to obtain the following.

$$VN(t) = v(t)MF(t) - (MF(t)(w(t) - w_{MLI}) + PC_0) + VN_0 \quad (8)$$

Expanding equation 8, we obtain the following.

$$VN(t) = v(t)MF(t) - MF(t)w(t) + MF(t)w_{MLI} - PC_0 + VN_0 \quad (9)$$

We then factorize MF(t).

$$VN(t) = MF(t)(v(t) - w(t) + w_{MLI}) - PC_0 + VN_0 \quad (10)$$

To understand the next step, we have to remember that we are dealing with a population of neurons, and not with single cells. Therefore, it is possible to decompose the activity of term MF(t) in terms of its mean activity ($\overline{MF}$) plus its fluctuation around the mean at every point in time (δMF(t)).

$$MF(t) = \overline{MF} + \delta MF(t) \quad (11)$$

Substituting equation 11 into equation 10 produces the following equation.

$$VN(t) = \overline{MF}(v(t) - w(t) + w_{MLI}) + \delta MF(t)(v(t) - w(t) + w_{MLI}) - PC_0 + VN_0 \quad (12)$$

We can see that in this equation, the left and right terms are constant, so we can combine them together into a simple term K.

$$VN(t) = \delta MF(t)(v(t) - w(t) + w_{MLI}) + K \quad (13)$$

2.1.3. Equation for Optokinetic Response Gain

As it was previously mentioned, VN is in charge of modulating the optokinetic response. In other words, eye movement is proportional to VN activity. Keep in mind that we can ignore the constant part K from the $VN(t)$ equation, because constant activity does not have a role in modulating eye movement. Since only the changing part of $VN(t)$ regulates eye movement, we can define the following equation.

$$EYE(t) = g_{EYE}\ \delta MF(t)(v(t) - w(t) + w_{MLI}) \quad (14)$$

According to the authors, g_{EYE} is a constant that converts neural activity into eye movements. Keep in mind that this eye movement is defined in proportion to the movement of the given stimuli.

Finally, OKR gain can be defined as the maximum amplitude of the eye movement. By setting a constant $g_{OKR} = 2\ \max(\delta MF(t))$, we can obtain the final equation for describing OKR gain.

$$OKR(t) = g_{OKR}(v(t) - w(t) + w_{MLI}) \quad (15)$$

We can see that this equation is compatible with our knowledge of the system. On one hand, the larger v(t) (MF-VN synaptic weight), the more excitation VN receives, so eye movements are expected to be larger. On the other hand, the larger w(t) (PF-PC synaptic weight), the more inhibition VN receives, because PCs inhibit VN. As we will see later in the paper, the difference between these two variables is what will drive the development of OKR gain.

2.2. Deriving the Equations for the Synaptic Weights v(t) and w(t)

So far, we know that the equation describing OKR gain involves the synaptic weights of the MF-VN and PF-PC synapses, $v(t)$ and $w(t)$, respectively. Therefore, the natural next step is to derive the equations that govern the behavior of these two variables.

2.2.1. PF-PC Synaptic Weight, w(t)

Let us first start with the equation for w(t). The most important factor driving the change in w(t) is PF-LTD. When Parallel Fibers (PF), the axonal extensions of Granule Cells (GR), fire at the same time as Climbing Fibers (CF), PF-LTD is triggered, which weakens the PF-PC synapse. Because of this, we include a $-\langle GR(t)CF(t)\rangle$ term.

In addition to this, w(t) also undergoes LTP triggered by the sole activation of GRs. While the exact mechanisms behind PF-LTP are still not entirely known, we do know that when Parallel Fibers (PF) fire, there is a downstream release of Calcium, which strengthens the PF-PC synapse (Wang et al., 2014). Therefore, we include a $\langle GR(t)\rangle$ term, where $\langle\rangle$ is just notation for the average. All averages are taken over a small timespan such that $\delta X(t) = 0$. This will be useful later for canceling terms.

Finally, PF-PC synapses also undergo spontaneous decay, so the more PF-PC synapses there are, the more likely they are to decay, so we include a $-w(t)$ term. This leads us to the following equation.

$$tau_w \frac{dw}{dt} = -\langle GR(t)CF(t)\rangle + \langle GR(t)\rangle - w(t) \quad (16)$$

Recall that $GR(t) = MF(t)$. Replacing in 16, we get the following.

$$tau_w \frac{dw}{dt} = -\langle MF(t)CF(t)\rangle + \langle MF(t)\rangle - w(t) \quad (17)$$

Also recall that $MF(t) = \overline{MF} + \delta MF(t)$. Similarly, $CF(t) = \overline{CF} + \delta CF(t)$. Replacing in 17, we get the following.

$$tau_w \frac{dw}{dt} = -\langle(\overline{MF} + \delta MF(t))(\overline{CF} + \delta CF(t))(t)\rangle + \langle\overline{MF} + \delta MF(t)\rangle - w(t) \quad (18)$$

Solving, we get the following.

$$tau_w \frac{dw}{dt} = (\overline{MF} - \overline{MF}\ \overline{CF}) - \langle\delta MF(t)\delta CF(t)\rangle - w(t) \quad (19)$$

Here, we need to remember that there are two different stages for which this equation can apply. During training periods, $\delta MF(t)\ and\ \delta CF(t)$ are not independent. However, after training (during recovery), they are independent, which means we can state the following.

$$\langle\delta MF(t)\delta CF(t)\rangle = 0\ (at\ rest) \quad (20)$$

We can also define the following simplifying terms:

$$c_{OKR} \equiv \langle \delta MF(t) \delta CF(t) \rangle \quad (21)$$

$$w_0 \equiv \overline{MF} - \overline{MF}\,\overline{CF} \quad (22)$$

Replacing equations 20, 21 and 21 in equation 19, we obtain the following final equation for the rate of change of $w(t)$.

$$\frac{dw}{dt} = \begin{cases} \frac{1}{tau_{learn}}(-w(t) + w_0 - c_{OKR}), & during\ training \\ \frac{1}{tau_{recovery}}(-w(t) + w_0), & after\ training \end{cases} \quad (23)$$

In equation 23, tau_{learn} and $tau_{recovery}$ are the time constants for the training and resting periods. tau_{learn} is much smaller than $tau_{recovery}$.

2.2.2. MF-VN Synaptic Weight, v(t)

The MF-VN synaptic weight undergoes MF-induced LTD. We represent this with a $-\langle \mathrm{MF(t)v(t)} \rangle$ term.

Additionally, when MF and VN fire together, they go through Hebbian Learning, permanently strengthening the synapse. This is represented with a $\langle MF(t)(V\,N(t) - \langle V\,N(t) \rangle) \rangle$ term. Here, $-\langle V\,N(t) \rangle$ represents the postsynaptic activity.

With all of that said, we can derive an equation for $v(t)$.

$$tau_v \frac{dv}{dt} = -\langle \mathrm{MF(t)v(t)} \rangle + \langle MF(t)(V\,N(t) - \langle V\,N(t) \rangle) \rangle \quad (24)$$

We previously derived an expression for $VN(t)$. Therefore, we can substitute equation 12 into equation 23, and also replace $MF(t) = \overline{MF} + \delta MF(t)$ to obtain the following equation.

$$tau_v \frac{dv}{dt} = -\overline{MF} v(t) + \langle \delta MF(t) \delta MF(t) \rangle (v(t) - w(t) + w_{MLI}) \quad (25)$$

Here, Yamazaki et al. make the assumption that MF spiking exhibits a Poisson distribution. This is very convenient, because Poisson distributions have $mean = variance$. Therefore, from the assumption, it follows that

$$\langle \delta MF(t) \delta MF(t) \rangle = \overline{MF} \quad (26)$$

Assuming $\overline{MF} = 1$ and replacing equation 26 into equation 25, we can obtain the final differential equation for v(t).

$$\frac{dv}{dt} = \frac{1}{tau_v}(-w(t) + w_{MLI}) \quad (27)$$

Just to make them easier to find, the following are the final equations that govern the behavior of the system.

$$OKR(t) = g_{OKR}(v(t) - w(t) + w_{MLI}) \quad (28)$$

$$\begin{cases} \frac{1}{tau_{learn}}(-w(t) + w_0 - c_{OKR}), & during\ training \\ \frac{1}{tau_{recovery}}(-w(t) + w_0, & after\ training \end{cases} \quad (29)$$

$$\frac{dv}{dt} = \frac{1}{tau_v}(-w(t) + w_{MLI}) \quad (30)$$

3. Simulations and Results

3.1. Analyzing the dynamics of OKR gain under normal conditions

The first thing we tested was whether our model produced the same dynamics as those from the original paper. To do this, we run a simulation where training happened for one hour at the start of five consecutive days, followed by four days of recovery.

The following time constants were used.

$$tau_{learn} = 20\ minutes$$

$$tau_{recovery} = 2.5\ hours$$

$$tau_v = 5.5\ hours$$

From this experiment forward, these time constants will always be used, unless specified otherwise. The figure below shows the obtained results.

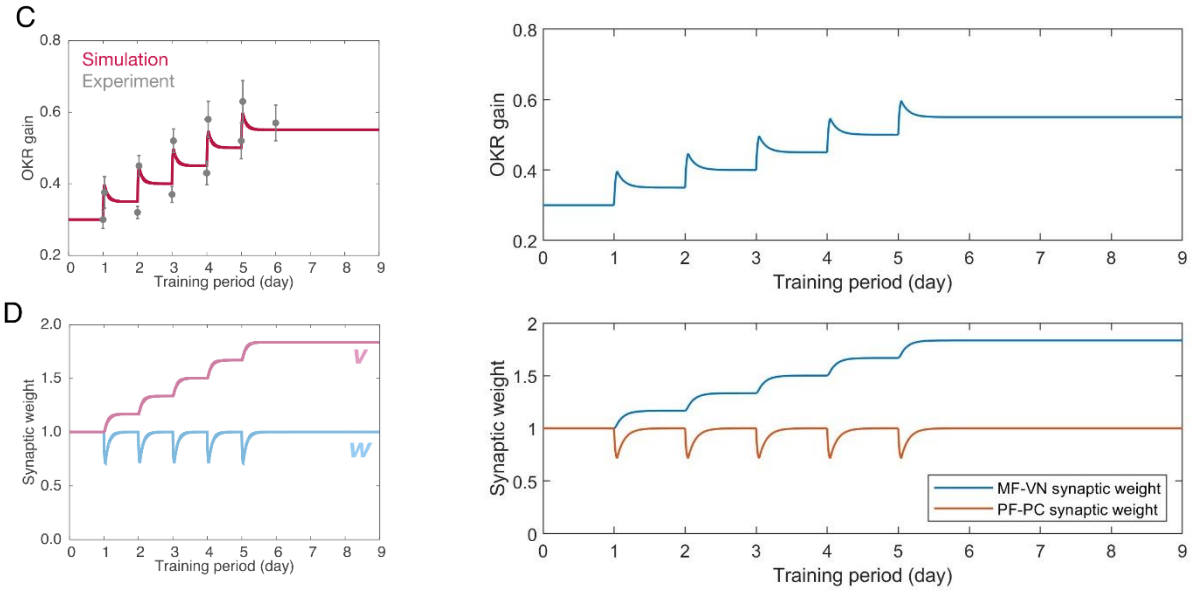

Figure 2. Five one-hour training sessions. Top figures shows OKR gain through days. Bottom figures show the dynamics of the synaptic weights. (Left) Results from the original paper. (Right) Our results.

Results show that our implementation matched that of Yamazaki et al., both for the behavior of OKR gain and of synaptic weights $v(t)$ and $w(t)$. This figures show the role of each synaptic weight in contributing to both short-term and long-term memory formation. During training, w(t) rapidly decreases, and slowly rises back to its original value after training. In contrast, v(t) rises during training, and keeps increasing after training until it reaches a plateau. OKR behavior combines the properties of both v(t) and w(t), since it quickly increases during training, followed by a stable decrease after training. However, since v(t) does not decrease after training, OKR stabilizes at a value higher than its initial one.

3.2. Effect of different training paradigms in long-term memory consolidation

The second thing we tested was how distinct training paradigms had an effect in the consolidation of long-term memory. Yamazaki et al. compared this results to previously obtained experimental data, but

we will just compared our results to those of the Yamazaki et al. paper, since we do not have access to the experimental data.

We tested four different training paradigms, all with a total training time of one hour. The first training paradigm consisted of one training session of 1 hour. The second consisted on 4 training sessions of 15 minutes, all of which happened in a single block of 4 hours. The third consisted of 4 training periods, which were spread across 4 days. The last consisted of 8 training periods of 7.5 minutes, which happened during the course of 8 days. As we can see, all training paradigms have the same total amount of training. Therefore, any differences found in OKR gain will be due to the structure of the training paradigm. The picture below compares our results from those of Yamazaki et al.

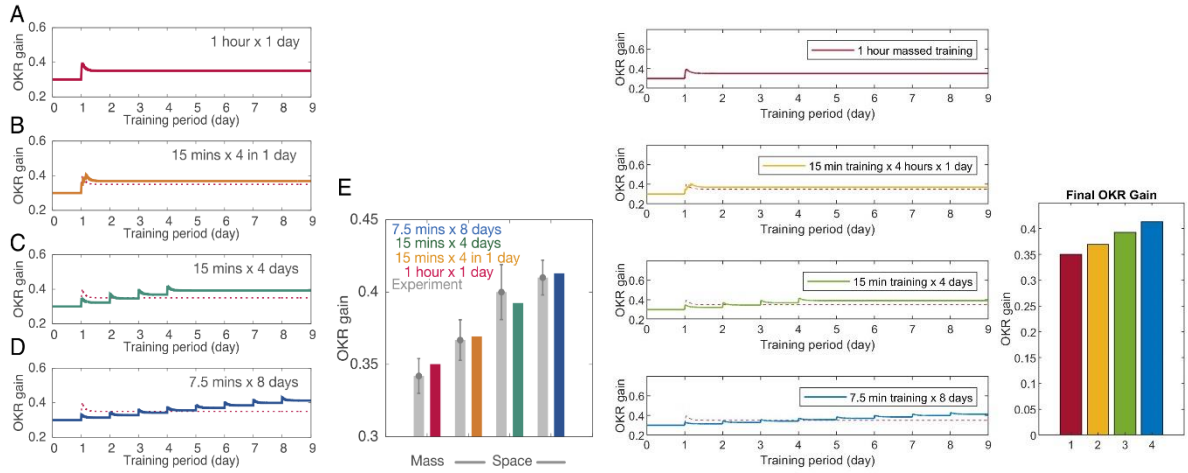

Figure 3. Long-term memory consolidation under different training paradigms. (Left) Original figure from Yamazaki et al. (Right) Our results.

As we can see, our results both qualitatively and quantitatively match those from the original paper. We can see that training for a single one-hour block produced the worst long-term memory consolidation. Even more, comparing the results of training paradigms 2 and 3, it seems that for an identical number of training sessions of the same length, it is better to leave more space between trainings, instead of

putting them one right after the other. It also appears that the best way to maximize OKR gain is to train for a short time in several training sessions. The reason for this will be explained in the Discussion.

3.3. Harmful Genetic Mutations

We will study how three different genetic mutations can affect both short-term and long-term memory consolidation.

3.3.1. PF-LTP Deficiency

The genetic mutation we will study is PF-LTP deficiency. As stated in the Methods section, PF-LTP is responsible for strengthening the PF-PC synapse. When PF-LTP is impaired by a genetic mutation, PF-PC have no mechanism for increasing its strength, so it is bound to reach a steady state of 0. We will consider that steady state has already been reached by the start of the simulation.

Additionally, since the PF-PC synapse is no longer present, Purkinje Cells (PC) can only receive inhibitory input from MLIs, which means that PCs will no longer inhibit VN. Since VN is never inhibited, the MF and VN continue to fire together, and as it was explained previously, this leads to their synaptic weight, v(t), continually increasing. v(t) will eventually reach stability at a value higher than usual. Again, we will consider that v(t) has already stabilized at the start of the simulation, as expressed in the equation below.

Both of these effects can be seen in the equations below.

$$w(0) = 0 = w(t)\ (steady\ state)\ \ (31)$$

$$v(t) = v(0) > 0 \text{ (steady state)}\ \ (32)$$

It is then easy to see how OKR will not be able to increase in the absence of PF-LTP. Since OKR gain depends on both v(t) and w(t), but they are now both constants, OKR gain will always remain at its starting value, as shown in the equation below.

$$OKR(t) = Constant\ \ (33)$$

3.3.2. PF-LTD Deficiency

As it has been explained, PF-LTD happens when Parallel Fibers (PF) fire together with Climbing Fibers (CF), and it is one of the core mechanisms driving change in $w(t)$. Recall that this was expressed in the term -$\overline{MF}\ \overline{CF}$, which also appeared in equation 22. If $\overline{MF}\ \overline{CF} = 0$, then we would get the following.

$$w_0 \equiv\ \overline{MF} > \overline{MF} - \overline{MF}\ \overline{CF}\ \ (34)$$

Since this new term is larger, the synaptic weight for PF-PC, $w(t)$, will also become larger, so Purkinje Cells (PC) will become more active, since they will receive more excitation from Parallel Fibers (PF). This leads to PCs more strongly inhibiting the VN, so at rest, we would have the following.

$$VN(t) = 0\ \ (35) \text{ (at rest)}$$

This means that there is now a threshold for the activation of VN neurons and OKR, because if VN does not activate, there cannot be OKR. This threshold is the following.

$$v(t) - w(t) + w_{MLI} \geq 0\ \ (36)$$

Adding this new threshold to the equations of OKR gain and v(t) results in the following new set of equations.

$$OKR = \begin{cases} g_{OKR}(v(t) - w(t) + w_{MLI}), if\ v(t) - w(t) + w_{MLI} \geq 0 \\ 0, \quad if\ v(t) - w(t) + w_{MLI} < 0 \end{cases} \quad (37)$$

$$v(t) = \begin{cases} \frac{1}{tau_v}(-w(t) + w_{MLI}),\ if\ \ v(t) - w(t) + w_{MLI} \geq 0 \\ 0, \qquad\qquad\qquad\qquad\qquad if\ v(t) - w(t) + w_{MLI} < 0 \end{cases} \quad (38)$$

Finally, for this simulation, $w_0 = 1.1$ and $c_{OKR} = 1$. The only reason the authors provided for this was that they assume some sort of compensation mechanism exists to still allow learning to happen. However, they did not go in-depth regarding what they thought this mechanism looked like.

3.3.3. Selective Depletion of $GABA_A$ Receptors

In PCs, $GABA_A$ receptors capture the inhibitory input from MLIs. Therefore, when they are blocked, MLIs can no longer inhibit PCs. This leads to PCs transmitting a much stronger inhibition to the Vestibular Nuclear neurons (VN).

Authors represented this deficiency by setting $w_{MLI} = 0$. However, this would mean that the OKR value could go negative, so a compensation constant $c_{compensate} = 1$ was added. Again, no explanation was provided regarding what this compensation mechanism could be.

After this change, the differential equation for $w(t)$ remained unchanged, but the one for $v(t)$ changed to the one below.

$$\frac{dv}{dt} = \frac{1}{tau_v}(-w(t)) \quad (39)$$

3.3.4. Results for all Genetic Deficiencies

Figure 4 shows our results for all of the mentioned genetic mutations. First of all, we can see that PF-LTP deficiency had the expected effect, because OKR gain never increased. Secondly, Row B shows that PF-LTD deficiency did impair long-term memory formation, since it appears that OKR gain constantly decreases during training. Even more, it shows that short-term memory was left untouched, in contrast with PF-LTP deficiency. Finally, Row C shows that, similarly to PF-LTD deficiency, selective depletion of $GABA_A$ receptors also affected only long-term memory formation. However, it had an effect on short-term memory that PF-LTD deficiency did not have, since the duration of the OKR gain peaks induced by the fast decreases in the PF-PC synaptic weight $w(t)$ are much smaller than those that happened under PF-LTD depletion.

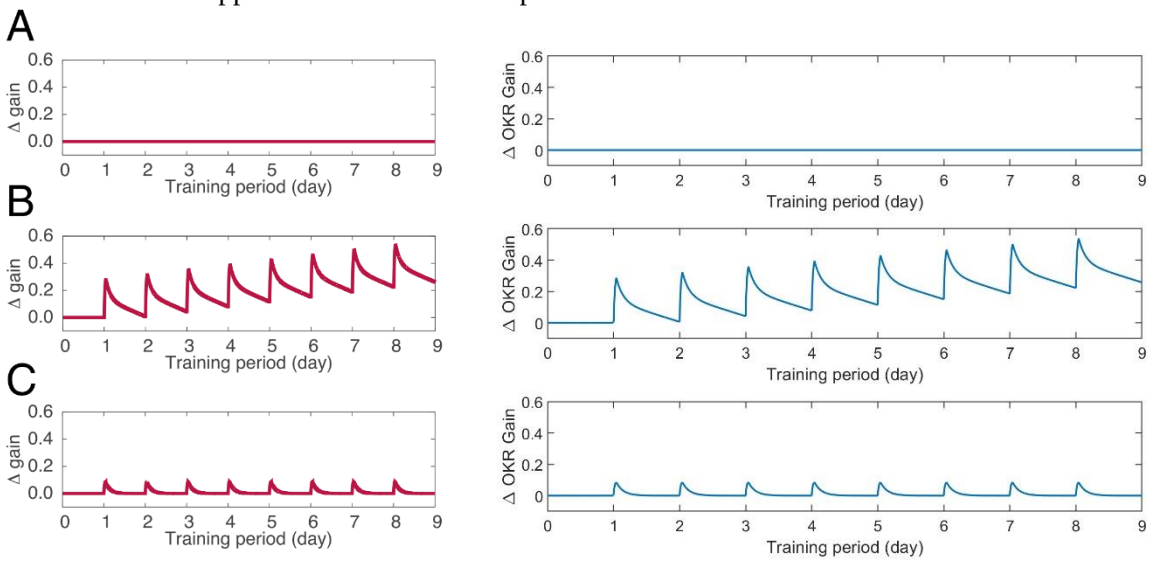

Figure 4. Left column are the original paper results. Right column are our results. Row A shows the effect of PF-LTP deficiency. Row B shows the effect of PF-LTD deficiency. Row C shows the effect of selectively depleting GABA receptors.

3.4. Extensions

3.4.1. Testing Different Training Paradigms for PF-LTD Deficient Mice

Yamazaki et al. tested how different training paradigms lead to different levels of long-term memory consolidation. However, we want to know what happens if long-term memory consolidation is impaired via PF-LTD deficiency. Since mice with deficient PF-LTD are unable to form long-term memories, it makes no sense to test them days after training. Therefore, different training paradigms were designed.

The total training time for all paradigms was of one hour, and they were all tested an hour before the last training session. The first training paradigm consisted of 1 block of 1 hour. The second consisted on 20-minute training sessions evenly distributed among 8 hours. The third consisted of 15 minutes of training through 6 hours. The final training paradigm consisted on 10-minute training sessions every 4 hours. As it can be seen, all training paradigms were designed such that training evenly spread across the entire day.

Figure 5 shows the results from running these simulations. We can see that, just like for the results of section 3.2., several shorter training sessions are better than fewer longer training sessions. These results will be discussed further in the Discussion section.

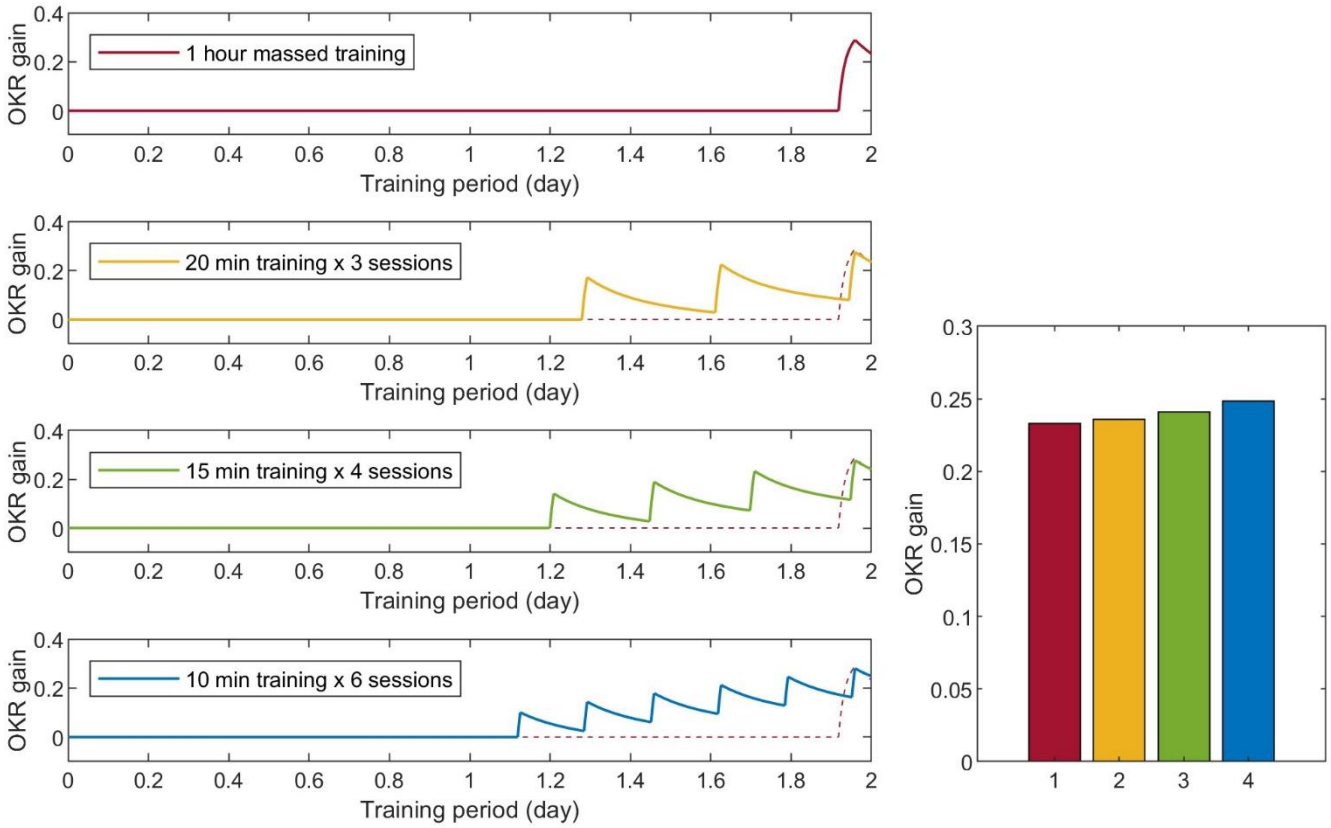

Figure 5. The effect of different training paradigms in short-term memory formation.

3.4.2. Exploring the effect of changing time constants.

As described previously, the model has three time constants: $\text{tau}_{\text{learn}}$, $\text{tau}_{\text{recovery}}$, and tau_{v}. These were set to static values of 20 minutes, 2.5 hours, and 5.5 hours, respectively. Since each time constant plays a role in modulating a different part of the system it is of our interest to study how lower and higher values of time constants influence long-term memory consolidation.

This is particularly the case because while Yamazaki et al. explored the effect of completely shutting down different synapses, they did not try to only partially try to weaken or strengthen them. Exploring partial weakening and strengthening of synapses may provide us with an insight regarding how genetic mutations that affect the time constants might look like. Therefore, for the same conditions of the simulation in parts 3.1, we varied the value of the time constants and measured the final OKR gain at the end of the 8th day. Results are provided in Figure 6.

The middle plot shows that increasing tau_{recov} increases long-term memory consolidation, while increasing tau_{learn} and tau_v decreases long-term memory consolidation. These results will be further explained in the discussion section.

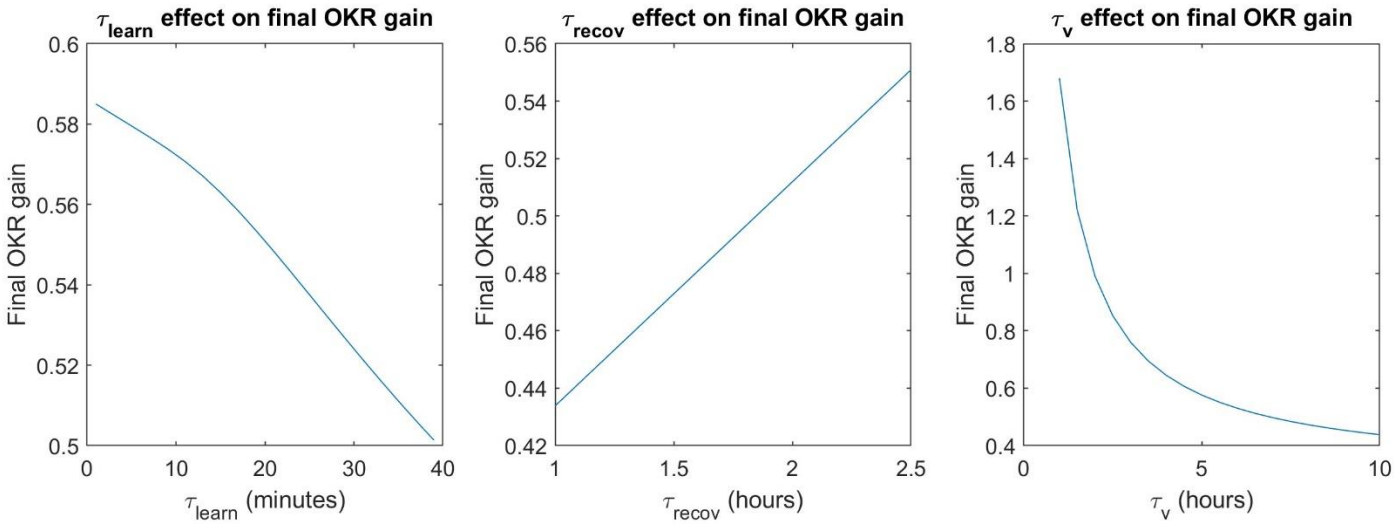

Figure 6. Effect in final OKR gain of varying OKR constants. (Left) tau_learn was varied from 1 to 40 minutes. (Middle) tau_recov was changed from 1 to 2.5 hours. (Right) tau_v was changed from 0 to 10 hours.

3.4.3. Combining PF-LTD Deficiency with Selective Depletion of $GABA_A$ Receptors

We wanted to explore the effect of combining two different ways in which the cerebellar circuit can be disrupted. We already know that both PF-LTD and depletion of $GABA_A$ receptors target long-term memory consolidation, but still allow for short-term memory formation to occur. To do this, we simply took the resulting equations from Section 3.3.2, which correspond to the simulation of PF-LTD deficiency, and set $w_{MLI} = 0$, as for the simulation of $GABA_A$ receptor depletion. The resulting equations were the following.

$$OKR(t) = \begin{cases} g_{OKR}\big(v(t) - w(t)\big), if\ v(t) - w(t) \geq 0 \\ 0, \quad if\ v(t) - w(t) < 0 \end{cases} \tag{40}$$

$$v(t) = \begin{cases} \frac{1}{tau_v}\big(-w(t)\big), & if\ \ v(t) - w(t) \geq 0 \\ 0, & if\ v(t) - w(t) < 0 \end{cases} \tag{41}$$

Results are shown in Figure 7. We can see that OKR remained at 0 all the time, even though the PF-PC synaptic weight was undergoing its regular oscillations. The reason for this will be explained in the Discussion section.

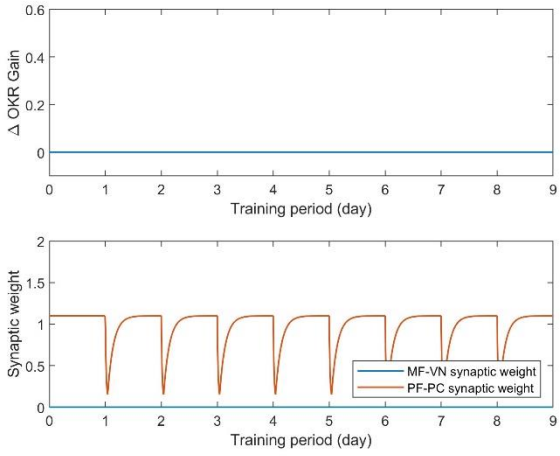

Figure 7. Training under PF-LTD deficiency, combined with depletion of GABAA receptors.

4. Conclusions and Discussion

The results obtained allow us to draw several conclusions regarding our hypotheses. Firstly, we can conclude that the hypothesis proposing that short-term increases in OKR gain should manifest in the formation of short-term memory in Purkinje Cells (PC) is correct. This can be observed in Figure 2, which clearly shows that $w(t)$, which represents the synaptic weight of the PF-PC synapses, decreases during training, but rises back to its original value after training. Since the expression for OKR gain is proportional to the difference between $v(t)$ and $w(t)$ (Equation 28), decreasing $w(t)$ while increasing $v(t)$ leads to a short peak in OKR(t). However, since the changes in $w(t)$ only remain for shortly after training, we can conclude that its effect on OKR gain are only present short-term (during training), and do not last in the long-term (after training).

This matches our current understanding of the cerebellar circuit. During training, Mossy Fibers (MF) provide the sensory input to the system in the form of excitatory synapses to Granule Cells (GR). This leads to PF exciting both the Molecular Layer Interneurons (MLI) and Purkinje Cells (PC). This means that PF and Climbing Fibers (CF) are shooting at the same time, which triggers the CF-mediated PF-LTD. Once the training input is no longer provided, MF won't transmit the sensory information of the task (because the task is no longer present), so GR won't activate. As a result, PF and CF will not be firing at the same time, which stops the PF-LTD effect. Once PF-LTD is not present the $-c_{OKR}$ term is no longer present in the equation ruling the behavior of $w(t)$, allowing the PF-PC synaptic weight to go back up to its original value.

Secondly, we can conclude that our hypothesis stating that repeated training should lead to long-term memory formation by increasing the synaptic weight of the MF-VN synapse, v(t), was correct. This is also observed in Figure 2**,** which shows that, in contrast with the short-term changes in the PF-PC synaptic weight, changes in v(t) remain stable even after training has ended. During each training session, v(t) increases. After increasing during training, it keeps increasing until it reaches a plateau, and does not decline in the long-term. Figure 2 also shows that OKR(t) peaks at the end of training, followed by a stable decrease. However, this decreases in OKR(t) does not take it back to its starting value, but only to a higher one. This is precisely because the increase in $v(t)$ is permanent. Therefore, we can conclude that the mechanism behind long-term memory formation after repeated training sessions is the permanent increase in the MF-VN synaptic weight.

This result is significant because it is compatible with our knowledge of the cerebellar circuit. During training, MF excites VN, so they start firing together. As it was previously stated, when MF and VN fire together, they undergo Hebbian Learning. This Hebbian Learning process is responsible for the permanent strengthening of the MF-VN synapse. Therefore, $v(t)$ does not decrease to its original value.

The described results from Figure 2 also allow us to conclude that our third hypothesis, which stated that long-term memory formation occurred after training and not during training, was correct. OKR(t) becomes stable after decreasing from the peak that corresponds to the end of training sessions. The obtained stability happens because $v(t)$ remains stable after increasing, $and\ w(t)$ rises back to its original value after decreasing. Once $w(t)$ reaches its initial value again, and $v(t)$ stops increasing and reaches its plateau, OKR(t) increase becomes stable, representing long-term memory formation.

We can also conclude that our fourth hypothesis stating that a larger number of short training sessions should be more effective than fewer but longer training sessions is correct. Figure 3 shows that this is the case. The reason this happens is that there appear to be diminishing returns: the longer the training session, the slowest OKR gain increases. Paying close attention to the start of the training sessions in Figure 1, we can see that $v(t)$ increases faster at the start of the training session. Therefore, having shorter training sessions allows $v(t)$ to spend more time at its fastest increasing rate. Since $v(t)$ is responsible for long-term OKR gain, this adds up after several training sessions, resulting in a higher final OKR gain, meaning better long-term memory consolidation.

Additionally, our simulation of deficiencies in PF-LTD and PF-LTP resulting from genetic mutations in mice supports our fifth hypothesis that memory formation would be impaired as a result of this deficiencies. In particular, Figure 3A shows that PF-LTP deficiency does not allow for either short-term or long-term memory formation of optokinetic response. Figures 3B and 3C indicate that PF-LTD and selective depletion of $GABA_A$ receptors only target long-term memory, but still allow for short-term memory formation. However, Figures 3B and 3C also show that PF-LTD deficiency has a much smaller effect on long-term memory formation than selective depletion of $GABA_A$ receptors on PCs. This is likely due to the compensation constants that were added in Section 3.3.2., when deriving the equations for PF-LTD deficiency.

In addition to recreating the results and conclusions from Yamazaki et al., we were also able to arrive at several new insights about the role of the cerebellar circuit in improving the optokinetic reflex. The first insight we added to the existing results was the confirmation of our first extension hypothesis, which stated that under PF-LTD deficiency, having more short periods of training should be better at increasing OKR gain than having less but longer periods of training (just like under normal conditions). Figure 5 shows that this was in fact the case. Even more, we were also right about the fact that this improvement would be minimal.

The reason having more short trials is better is the same as for the regular simulations without PF-LTD deficiency. This might be a little counter intuitive, because PF-LTD deficiency affects long-term memory consolidation, so OKR improvements should not add up and the results for all training paradigms should be the same. However, this does not happen because in contrast with selective depletion of $GABA_A$ receptors, PF-LTD deficiency allows for the short-term increase in OKR to last for a longer amount of time. Therefore, if training sessions happen during the same day, like in our simulation, it is still possible for OKR improvements to add on top of each other.

While it is true that they will all go back down to 0 in the long term, this result is very significant because it shows that it is possible to schedule training sessions in a way that still allows individuals to have permanent improvements in their optokinetic response, as long as they follow an appropriate training schedule. This means that even individuals who have impaired long-term memory formation of OKR can increase their OKR gain in the long-term if they undergo constant training and do not allow their OKR gain to go back to its starting point.

The second additional insight we provided was to explore the effect of the time constants in the system. In particular, we tested the effect of decreasing and increasing time constants tau_{learn}, $tau_{recovery}$, and tau_v. We did this because Yamazaki et al. explored the consequences of completely shutting down different parts of the cerebellar circuit, but it is also valuable to understand how partially weakening or strengthening different parts of the system could influence long-term memory formation.

Our simulations allowed us to confirm our second extension hypothesis, which stated that increasing tau_{learn} and tau_v should decrease long-term OKR gain, while increasing $t_{recovery}$ should increase long-term OKR gain. These results can be observed in Figure 6. This stands in accordance with their role in the differential equations. On one hand, $tau_{recovery}$ slows down the rate of increase of $w(t)$ after training, meaning that when it is increased, $w(t)$ takes longer to go back up to its initial value. Since the differential equation of $v(t)$ depends on $wMLI - w(t)$ (with $w_{MLI} = 1$ and $w(0) = 1$), and $w(t)$ is remaining more time at lower values, $v(t)$ is allowed to increase at faster speeds, which accelerates long-term memory consolidation.

On the other hand, tau_{learn} has the role of slowing down the decrease of $w(t)$ during training, so the larger tau_{learn} is, the more time $w(t)$ will stay at higher values. This means that $v(t)$ will increase at a lower increase rate, slowing down long-term memory consolidation. Similarly, tau_v directly slows down the rate of change of $v(t)$, so the larger it is, the slower long-term memory consolidation will be. All of these are valuable insights, because they let us get a deeper understanding of how potential

diseases could harm OKR gain by partially affecting different parts of the cerebellar circuit, instead of by completely shutting down synapses.

The last part of our extension tested the effect of combining PF-LTD deficiency with selective depletion of $GABA_A$ receptors, both of which have been found to disrupt long-term memory consolidation while still allowing for short-term memory. As explained previously, this simulation was carried out using the same equations used for the PF-LTD deficiency simulation, but setting $w_{MLI} = 0$ like in the $GABA_A$ depletion simulation. As Figure 7 shows, $v(t)$ is never allowed to increase, because $w(t)$ is always larger. For the same reason, OKR gain stays at 0 during the entire simulation. All of this happens despite the fact that $w(t)$ does go under its normal cycle of decreasing and increasing throughout the simulation.

This provides us valuable insight with the importance of the PF-MLI synapses in short-term learning under PF-LTD deficiency. When PF cannot communicate with MLI, MLI cannot inhibit the activity of PC. Therefore, PC just continually keeps inhibiting VN, contributing to the complete shutdown of the optokinetic response. This stands in contrast with the results provided by Yamazaki et al., where only simulating PF-LTD deficiency still allowed for short-term OKR improvement. When the PF-MLI synapse does not work properly, this becomes impossible. Therefore, our hypothesis that combining PF-LTD deficiency with selective depletion of $GABA_A$ receptors would prevent both short-term memory formation and long-term memory consolidation was found to be correct.

While the model has proven to be useful in describing data from previous experiments, there are several ways in which it could be improved. One of its main limitations is the fact that OKR gain is always lower than the movement of the target. However, this does not match the real world, where our eye movements often get ahead of the target being observed when we are not following it properly. This overshooting of the optokinetic response cannot be described by the model, so steps could be taken to account for it. In particular, the input from Climbing Fibers, which encode the difference between our intended movements, our eye movements, and the movement of the target, could be used to derive an expression representing the OKR error. That way, the system would be able to represent cases where our optokinetic response is imprecise not by being slower, but faster than the target.

Another clear limitation of the model is the fact that OKR gain could theoretically increase infinitely. This is not realistic because of the physical constrains of the human eye. However, it would be a good idea to use the model as a basis for a neuromechanical model that more precisely combines the output of the cerebellar circuit with a model of the muscles responsible for executing eye movements. Both of these improvements could lead to a better model that allows us to test several much more specific, quantitative hypotheses about how short-term and long-term memory formation of the optokinetic response lead to the modulation of eye movements in coordination with muscles.

Works Cited

Fogarty, C., & Stern, J. A. (1989). Eye movements and blinks: Their relationship to higher cognitive processes. *International Journal of Psychophysiology: Official Journal of the International Organization of Psychophysiology*, *8*(1), 35–42. https://doi.org/10.1016/0167-8760(89)90017-2

Hernandez, E., & M Das, J. (2023). Neuroanatomy, Nucleus Vestibular. In *StatPearls*. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK562261/

Holmes, J. M., & Clarke, M. P. (2006). Amblyopia. *The Lancet*, *367*(9519), 1343–1351. https://doi.org/10.1016/S0140-6736(06)68581-4

Kim, J., & Augustine, G. J. (2021). Molecular Layer Interneurons: Key Elements of Cerebellar Network Computation and Behavior. *Neuroscience*, *462*, 22–35. https://doi.org/10.1016/j.neuroscience.2020.10.008

Knierim, J. J. (2014). Chapter 19—Information Processing in Neural Networks. In J. H. Byrne, R. Heidelberger, & M. N. Waxham (Eds.), *From Molecules to Networks (Third Edition)* (pp. 563–589). Academic Press. https://doi.org/10.1016/B978-0-12-397179-1.00019-1

Li, R. W., Ngo, C., Nguyen, J., & Levi, D. M. (2011). Video-game play induces plasticity in the visual system of adults with amblyopia. *PLoS Biology*, *9*(8), e1001135. https://doi.org/10.1371/journal.pbio.1001135

McMurray, C. (2020). *Granule Cells*. https://www.brainfacts.org:443/brain-anatomy-and-function/cells-and-circuits/2020/granule-cells-103020

O'Reagan, J. K. (1987). *Eye Movements from Physiology to Cognition*. https://www.goodreads.com/book/show/23083377-eye-movements-from-physiology-to-cognition

Sillitoe, R. V., Fu, Y., & Watson, C. (2012). Chapter 11—Cerebellum. In C. Watson, G. Paxinos, & L. Puelles (Eds.), *The Mouse Nervous System* (pp. 360–397). Academic Press. https://doi.org/10.1016/B978-0-12-369497-3.10011-1

Streng, M. L., Popa, L. S., & Ebner, T. J. (2017). Climbing fibers predict movement kinematics and performance errors. *Journal of Neurophysiology*, *118*(3), 1888–1902. https://doi.org/10.1152/jn.00266.2017

Taylor, J. A., & Ivry, R. B. (2014). Chapter 9—Cerebellar and Prefrontal Cortex Contributions to Adaptation, Strategies, and Reinforcement Learning. In N. Ramnani (Ed.), *Progress in Brain Research* (Vol. 210, pp. 217–253). Elsevier. https://doi.org/10.1016/B978-0-444-63356-9.00009-1

Wang, D.-J., Su, L.-D., Wang, Y.-N., Yang, D., Sun, C.-L., Zhou, L., Wang, X.-X., & Shen, Y. (2014). Long-Term Potentiation at Cerebellar Parallel Fiber–Purkinje Cell Synapses Requires Presynaptic and Postsynaptic Signaling Cascades. *Journal of Neuroscience*, *34*(6), 2355–2364. https://doi.org/10.1523/JNEUROSCI.4064-13.2014

Yamazaki, T., Nagao, S., Lennon, W., & Tanaka, S. (2015). Modeling memory consolidation during posttraining periods in cerebellovestibular learning. *Proceedings of the National Academy of Sciences of the United States of America*, *112*(11), 3541–3546. https://doi.org/10.1073/pnas.1413798112

Zang, Y., & De Schutter, E. (2019). Climbing Fibers Provide Graded Error Signals in Cerebellar Learning. *Frontiers in Systems Neuroscience*, *13*. https://www.frontiersin.org/articles/10.3389/fnsys.2019.00046