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BINOCULAR INTEGRATION USING STEREO MOTION CUES TO DRIVE BEHAVIOR IN MICE

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BINOCULAR INTEGRATION USING STEREO MOTION CUES TO DRIVE BEHAVIOR IN MICE

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Dedication

To my friends and family

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Abstract

Binocular Integration Using Stereo Motion Cues to Drive Behavior in Mice

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The visual system presents an opportunity to study how two signals converge to generate a novel representation of the world: depth. The slight difference in positions between the two eyes means that different images are encoded by the left and right eyes by generating disparity signals. Another way to generate depth signals is by presenting different motion signals to the two eyes. Even though the binocular visual system has been studied for a long time, the mechanisms behind binocular integration when objects move in depth are largely unknown. In this dissertation, I demonstrate a new model for studying motion-in-depth signals using mice.

Mice are an attractive animal to study the binocular visual system not only because they share common visual pathway as primates and other mammals, but also because there are genetic tools that can be used to study the underlying circuitry for binocular integration during motion-in-depth cues. Thus far there have been very few studies regarding binocularity in mice. This dissertation will focus on the behavioral

output during stereoscopic motion-in-depth signals in mice and investigate visual areas involved in these behaviors.

In the first section, I investigate whether mice discriminate motion-in-depth signals like primates, using disparity and motion signals presented to each eye. I find that mice are able to discriminate towards and away stimuli and that the binocular neurons in the visual cortex were critical for the computation of this signal. In the second section we measured optokinetic eye movement generated by motion-in-depth stimulus. I found that vergence eye movement in mice is driven primarily by the motion signals presented in each eye. This phenomenon can be explained largely by the summation of monocular motor signals of the two eyes that happens subcortically.

These two experiments both show clear behavioral output that can be only generated when presented with binocular motion-in-depth signals. I find both cortical and subcortical components of binocular integration that are responsible for the generation of these behavior outputs which demonstrates the complicated nature of binocular integration associated with motion-in-depth signals. My work in this dissertation provides the foundation for studying binocular integration in rodents.

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Chapter 1: Introduction

Sensory systems integrate multiple signals coming from the environment for organisms to respond to their surroundings appropriately. The visual system is an excellent circuit to study how neurons integrate multiple inputs. Mammals have two separate eyes that are offset horizontally. Even though the images from the two eyes are mismatched, humans do not perceive the images as separate images. Instead, we view the world with a cyclopean perception; i.e. a single snapshot image of the world. This merging of left and right eye image creates a particular signal that is used for perceiving the world in three dimensions.

Binocular integration can generate signals that reflect static depth as well as motion-in-depth. Unlike static depth signals, which can be generated using disparity cues, motion-in-depth signals can be generated using both disparity cues (change in disparity signal: CDOT) and/or motion cues (interocular velocity difference: IOVD). The critical component that generates depth signals during motion-in-depth for CDOT is the disparity signal while the critical component of the IOVD is the integration of the direction and speed components between the two eyes. Although numerous studies have investigated how we as humans perceive motion-in-depth, it remains unclear how this binocular integration is occurring.

The main goal of this dissertation is to introduce a new animal model to study binocular computations during motion-in-depth signals. To achieve this goal, I first trained mice to discriminate motion signals moving in depth by combining disparity and motion signals in the two eyes (chapter 2). I then investigated areas that might be involved in binocular integration (chapter 3). Next, I investigated eye movements evoked by motion-in-depth cues. Based on these results, I discuss the possible computations that could explain these eye movements (chapter 4). Finally, I propose future studies that could identify

regions in the brain where potential binocular computations that drive binocularly-driven eye movements could occur when presented with for motion-in-depth signals (chapter 5).

In this first chapter, I provide the background and significance of my work for binocular integration in mice. In the second chapter, I will review the basic computation and cues that are required for the two known signals (CDOT and IOVD) that give rise to motion-in-depth perception. I will go over the basic model that can explain the computation behind disparity and some of the shortcomings of this model. I will also explain some of the important properties required for IOVD computation. And finally, I will compare the CDOT and IOVD signals together and discuss the similarities and differences between the two signals.

In the third chapter, I discuss behavioral evidence for motion-in-depth cues. I will briefly discuss previous studies involving humans and non-human primates and how the perception of depth can be altered with the alteration of CDOT and IOVD signals. Next, I will introduce mice, a new model, to study motion-in-depth discrimination. I will describe my experiments in which I trained mice to discriminate motion-in-depth signals and demonstrate successful motion-in-depth discrimination. I will also investigate the circuitry behind binocular integration during motion-in-depth stimulus.

In the fourth chapter, I will discuss vergence eye movements that occur during 3-dimensional motion. I will briefly discuss previous work on humans and non-human primates and discuss signals that drive vergence eye movements in primates. Next, I will introduce mice as a model through which to study the computation that occurs during vergence generated by optokinetic eye movements. The goal of this experiment was to determine whether mice can make vergence eye movements when presented with motion-in-depth signals and to investigate the computations underlying left and right eye signal integration.

In the final chapter, I will discuss subcortical brain areas that might be involved in this binocular integration that drives OKR vergence eye movement during motion-in-depth cues.

Chapter 2: Motion-in-depth signals

2.1. Overview

In this second chapter, I discuss the basic computations and cues that are involved in the computation of motion-in-depth cues. I go over the disparity energy model that can explain the computation behind disparity signals and some of the shortcomings of this model. I also go over important properties required for IOVD computation and compare the CDOT and IOVD signals together and discuss the similarities and difference between the two signals.

2.2. CDOT signal

Binocular integration gives rise to depth perception in humans. This depth signal can be divided into two categories: static depth and motion-in-depth. Static depth is computed using only disparity signal while motion-in-depth can be created using both disparity signal (CDOT) and motion signal (IOVD) presented in each eyes. The CDOT signal can be extracted using the temporal derivative of binocular disparity signal which means that the CDOT signal is generated by integrating time and disparity signals together. Therefore, to understand the underlying mechanism behind CDOT, it is essential to understand how the disparity signal is computed between the two eyes.

2.2a. Disparity signals

Disparity signals arise when there is a mismatch in the images between the two eyes. In humans, the two eyes are positioned in a horizontal offset that generates distinct images between the two eyes. The mismatch of images between the two eyes can be easily seen when a person alternates viewing from one eye while closing the other eye. One can see the image from the left eye is not exactly the same as the image from the right eye. This shift in the left and right eye images creates disparity signal.

To calculate the disparity, first, it is essential to identify which image corresponds to which eye (correspondence problem) and second, it is critical to match the polarity between neurons within similar receptive fields to know how much the position of the images are shifting between left and right eyes. I will discuss the binocular energy model which explains how different types of cells in the visual cortex might compute disparity selectivity and also discuss theories for how the correspondence problem is solved in the visual system.

2.2b. Binocular energy model

In primates and carnivores, disparity selective cells exist within the primary visual cortex (Hubel & Wiesel 1973; Pettigrew et al., 1968; Nikara et al., 1968; Joshua & Bishop 1970; Barlow et al., 1967; Poggio & Fischer, 1977). One of the early findings on binocular neurons in the visual cortex was that disparity selective neurons are classified into four types: tuned excitatory, tuned inhibitory, near, and far. Some of these neurons (tuned inhibitory, near, and far) have unbalanced monocular inputs while others (tuned excitatory) received balanced binocular input that responded to a range of depth (Poggio & Fischer, 1977). Many binocular neurons could be stimulated either with receptive fields superimposed or field offset in various degrees (Pettigrew et al., 1968). This gave rise to the idea that the emergence of disparity selectivity is due to the combination of signals from similar monocular respective fields and neurons are tuned to different shifts of receptive field positions (Hubel & Wiesel, 1962; Pettigrew et al., 1968; Maske et al., 1984) or tuned to interocular phase shifts (Ohzawa et al., 1990).

The visual cortex (V1) mainly consists of two types of neurons. Simple cells, which are sensitive to black and white polarity of gratings or bars, and complex cells which are not sensitive to the polarity of the grating or bar stimulus (insensitive to on and off regions).

Simple cells are derived from multiple inputs from the LGN neurons while complex cells are made of multiple simple cells (Hubel & Wiesel, 1962). There are several ways in which disparity selectivity can arise from simple and complex cells in V1. Simple cells are commonly understood as linear neurons because of their distinct separation of on and off receptive field domain (Hubel & Wiesel, 1962; Fleet et al., 1996). This makes modeling disparity selectivity in simple cells relatively straightforward. For the binocular simple cells, the disparity selectivity can be calculated by the weighted sum of the response from left and right eye (Fig. 2.1B). But cortical neurons have a relatively low firing rate, and this model doesn't fit well when the weight becomes negative. To solve this problem, simple cells are modeled as half-wave-rectified linear neurons (Movshon et al., 1978a).

Because simple cells have clear on and off regions, disparity selectivity in these neurons can be characterized by summing simple cell inputs from left and right eye with same retinotopic location (zero disparity), two different retinotopic location with the same on and off polarity (position shift), or two same retinotopic location with different on and off polarity (phase shift) (Fleer et al., 1996). On the other hand, complex cells do not have a distinct separation of on and off receptive field domain and instead respond to visual stimulus to both on and off regions. For this reason, disparity selectivity in complex neurons has been modeled as energy neurons (Adelson & Bergen, 1985) (Fig. 2.1D). The disparity energy model (also known as the binocular energy model) has been one of the key theories for understanding how simple and complex cells use both phase and position shifts to generate disparity selectivity. Ohzawa and his colleagues in 1990 first proposed the idea. The model proposes that complex cells are modeled by adding the squared responses of four pair of simple linear neurons (halfwave-rectified) that are 90

degrees out of phase since complex cells receive multiple inputs from the simple cells. (Ohzawa et al., 1990).

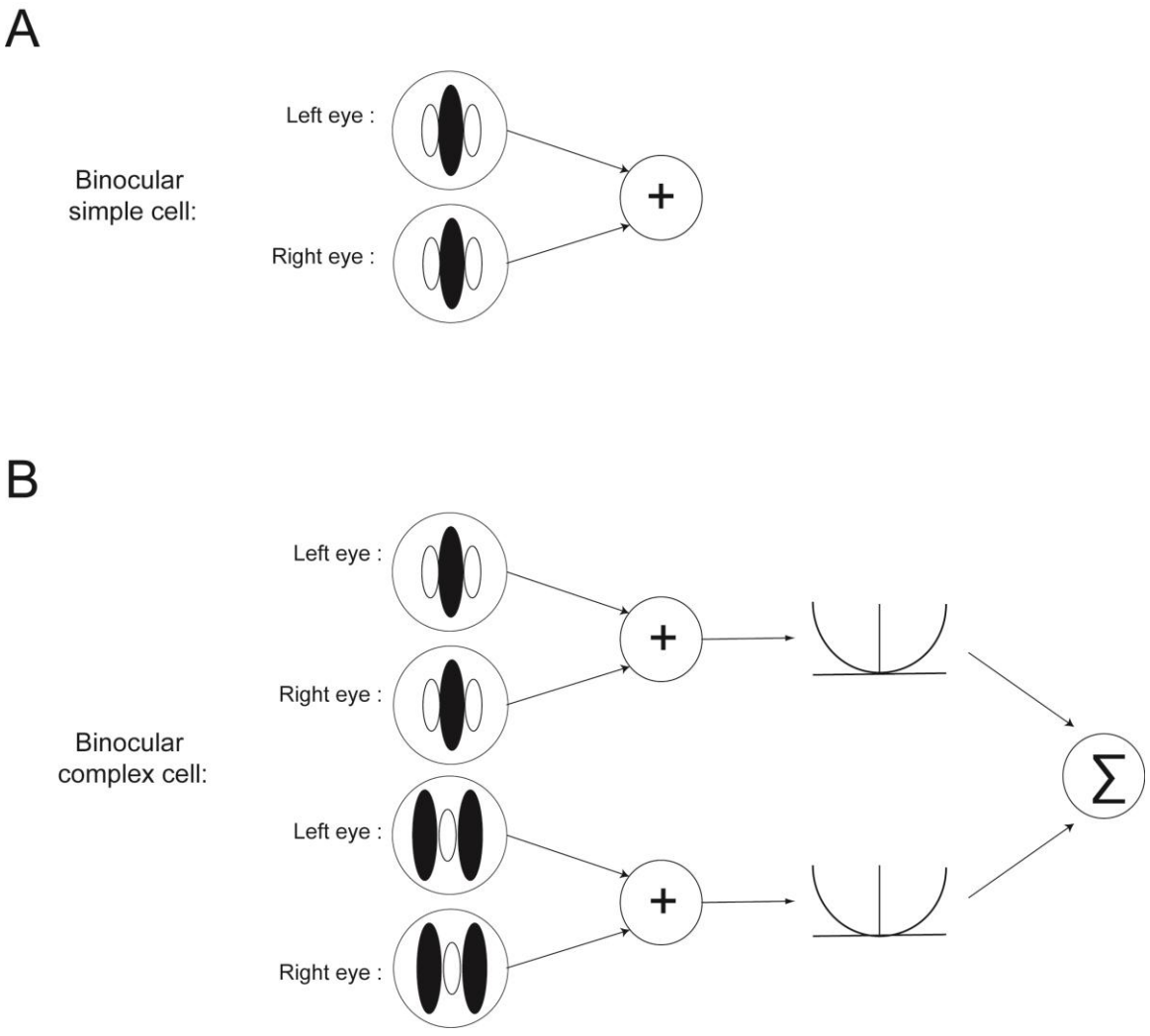

Figure 2.1. Disparity model for simple and complex cells
(A) Model for simple cell where the input from two cells are summed linearly. (B) binocular energy model for complex neurons (adapted from Fleet et al., 1996)

2.2c. Correspondence problem

Disparity selectivity requires integration of two different retinal inputs (left and right eye) and to compute disparity correctly, it is critical to identify which signal from the

right eye correspond to signals on the left eye. This is known as the correspondence problem. Although the binocular energy model can explain how disparity selectivity emerges from different types of cells in the primary visual cortex, it needs additional computation to detect false matches.

One way to solve the stereo correspondence problem is to reduce the signals from false matches and to amplify the correct matches. By taking the mean responses of neurons that have similar disparity tuning but have different orientation tuning, one can filter out and lower signals created by false matches (Qian & Zhu, 1997).

Another way to lower false matches is to compute the disparity using a coarse-to-fine sequence. This method utilizes high spatial frequencies to maximize the accuracy of disparity estimates and low spatial frequencies to maximize the range of the estimates (Marr et al., 1979). Applying this method in disparity energy model that use position and phase shift, Chen and Qian discovered that neurons with position shift disparity tuning are good for a coarse estimate of disparity while phase shifts are good for finer estimates and combining this with orientation and spatial pooling improves the disparity estimate (Chen & Qian 2004).

Although these simulations work well to explain how disparity signals are computed, it is not always the case that the neurons behave according to the model. Read and Cumming used natural images to investigate the difference in phase and position tuning in disparity selectivity and found that phase shift tuning does not occur in natural images. This raises the question of how during experimental settings with controlled spatial frequency, stimulus size, and orientation there are phase shifting and position shift binocular neurons but not during a natural scene. If the phase shift binocular neurons are not used in natural images, what are they being used for? Read and Cumming showed that the phase shift neurons are activated when there is a false match and might act as a detector

to help with the correspondence problem (Read & Cumming, 2007). Later Tanabe and Cumming provided neurophysiological data showing suppression of neuronal responses to false matches supporting this idea of a system (false match detection) in place to solve the correspondence problem. (Tanabe & Cumming. 2008).

2.2d. Disruption of disparity neurons

As mentioned before, disparity selectivity is computed by using signals from both left and right eyes, and thus, any disruption of signals from one or both eyes can lead to disruption on disparity selectivity. Neurons in the primary visual cortex have a specific time window, called the critical period, when the neurons are plastic and can change their tuning properties depending on the input they received during this time window during their development. After the critical period is over, the neuronal tuning property becomes permanently "fixed" to the immature state before the critical period. Monocular deprivation during critical period is one way to disrupt the visual input from one that results in weakening of binocular properties in V1. When one eye is closed shut during this critical period, there is a big shift in ocular dominance and cells in the visual cortex are more selective for the eye that was not disturbed. Also when an animal goes through monocular deprivation during the critical period, the binocular neurons show poor disparity tuning even after the deprived eye is restored (Hubel et al. 1977; Shatz & Stryker 1978; LeVay et al. 1980; Scholl et al., 2017).

2.3. IOVD signal

2.3a. Overview

The second signal that is crucial for detecting motion-in-depth cues is the motion signal presented to the two eyes. Interocular velocity difference (IOVD) arises when there

is a discrepancy in motion direction and/or velocity between the two eyes. In 2-dimensional motion, the speed and direction of moving scene or an object would be equal between the two eyes, but when an object moves in depth, the motion direction and speed varies between the two eyes. For example, when an object is moving directly towards a person, the left eye will be presented with an object moving in the rightward direction, and the right eye will see an object moving in the leftward direction. If the object is moving towards the center between the eyes, the speed of the object would be equal, but if the direction changes, the speed in which the object is presented in each eyes will change.

Unlike disparity, IOVD signals do not rely on the exact position of the images between the two eyes; instead, the speed and direction of the motion presented in each eye is the critical component in IOVD signal. IOVD signal doesn't utilize polarity signal from the simple cells since it only requires the speed of the motion presented in each eye and therefore the specific retinotopic position and shift of an object is irrelevant. For this reason, the computation of IOVD signal does not require computations involving polarity sensitivity of simple and complex cells as in disparity computation. In this section, I will explain how direction and speed, the two important component of IOVD signal, are computed in the nervous system.

2.3b. Direction selectivity

In most mammals (primates and cats), direction selective cells originate in the primary visual cortex (V1). Neurons in V1 respond not only to the specific orientation of bars but also respond to the specific direction of moving bars (Hubel &Wiesel, 1962; Hawken et al., 1988; Gur et al., 2005). This is different from the LGN or retinal ganglion cells where the cells do not respond to a specific orientation nor direction due to a circular receptive field (Cleland & Levick 1974). To calculate the direction of motion, neurons

must integrate the time and location information from multiple sources and compare them with neurons with slightly different retinotopy.

So how are the direction selective neurons integrating spatiotemporal information? There are three possible models on how direction selectivity can emerge in V1. The first model is based on intracortical integration; The second model is based on thalamocortical interaction; and finally the third model is the case where direction selectivity emerges from the retina.

For the intracortical model, direction selectivity is predicted to rise from integration between excitatory inputs with different latency (Suarez et al., 1995; DeAngelis et al., 1993; Movshon et al, 1978) or interaction between excitation and inhibition input with different spatiotemporal response (Torre & Poggio 1978; Barlow & Levick 1965).

The second model for direction selectivity is based on thalamocortical integration. It has been reported that there are different (fast and slow) latencies in cells of the LGN (Saul & Humphery, 1990; Saul & Humphery, 1992) that support this model. There have been numerous studies that support the thalamocortical model by both direct and indirect measurements (Priebe et al., 2010; Lein & Scanziani 2018).

Lastly, in rodents, there is evidence for direction selective cells in the retina (Cruz-Martin et al., 2014; Hillier et al., 2017). However, eliminating direction selective cells in the retina does not completely abolish direction selectivity in the cortex (Hillier et al., 2017), which is consistent with the idea that the visual cortex retains the mechanism in which to compute direction selectivity separate from the retinal direction selectivity even in rodents.

2.3c. Speed tuning

The second key component of IOVD signal is speed. To achieve IOVD computation, it is important to have a system that detect the speed of the motion presented and successfully compute the difference in speed between the left and right eye. Similar to direction tuning, speed tuning can be computed by using spatial location and time component. Traditionally it has been thought that speed can be calculated by computing the ratio of temporal frequency and spatial frequency and there are neurons tuned to different spatial and temporal frequencies in V1 (Movshon et al., 1978; Movshon, 1975). Simple cell and complex cell in the visual cortex have slightly different tuning for speed in that the V1 simple cells show tuning for spatial and temporal frequency, but complex cells show similar tuning property as neurons in MT; showing preference to speed in all spatial frequencies (Priebe et al., 2003; Priebe et al., 2006). Because MT neurons share similar speed tuning properties as V1 complex cells, it is thought that the MT neurons inherit this property from the complex cells in V1.

Both direction selectivity and speed tuning share similar computations in that they require integration of space and time. Retinal ganglion cells and neurons in the LGN do not possess the same spatiotemporal frequency tuning as seen in the visual cortex or MT neurons (Hicks et al., 1983; Derrington and Lennie, 1984). V1 is a computationally crucial area as neurons in the V1 are known to integrate various signals from the LGN which lacks orientation, direction, or speed tuning.

2.4. Conclusions

In this chapter, I discussed two components known to contribute in the computation of motion-in-depth cues. The first signal, change in disparity over time (CDOT), is generated by integrating disparity signal and time component together. The second signal, interocular velocity difference (IOVD), is based on the motion and velocity signal

comparted between the two eyes. In the real world, the two signals are naturally occurring simultaneously, such that when an object is moving towards you, it will have both CDOT signals from the mismatch of an image from the two eyes as well as opposite IOVD motion in the two eyes. Because of this, it used to be viewed that these two signals were interchangeable but later it was proposed and proven that CDOT and IOVD both have independent mechanisms. As discussed above, when computing the disparity between the two eyes, it is essential to know phase and position of the image as well as the specificity of the eyes. Unlike disparity, the IOVD signals don't rely on specific phase or position tuning of individual neurons in the visual cortex but rather the direction and speed of motion play a crucial part in the computation for motion-in-depth signal. The effect that cortical manipulations, such as monocular deprivation, has on disparity signal is robust and we see drastic changes in binocularity of V1 neurons due to cortical manipulations, yet little is known about the changes that occur during IOVD stimulus. Further studies involving separation of CDOT and IOVD signal needs to be conducted to see how changes in the cortical neurons impact IOVD only conditions. Next, I provide perceptual and behavioral evidence for motion-in-depth discrimination as well as the neuronal signals associated with this signal.

Section 1
Chapter 3
Behavioral evidence of motion-in-depth discrimination

3.1 Overview

The two signals that allows us to perceive motion-in-depth cues are change in disparity over time (CDOT) and interocular velocity difference (IOVD) presented in each eyes. Chapter 2 describes some of the basic components and computations behind CDOT and IOVD signals. In this chapter, I will present previous behavioral studies on motion-in-depth discrimination in primates as well as new behavioral studies on motion-in-depth signals in mice.

3.2. Human and monkeys performing motion-in-depth discrimination tasks

There are several ways for humans to perceive motion-in-depth cues using monocular signals. Looming (object will get bigger as it moves closer to you), motion parallax (object that is closer to you move faster when you are in motion), and shadows can offer information about objects moving in depth without using any binocular information. But in this chapter, I will be talking about true binocular depth perception that requires the integration of left and right eye signals.

CDOT is one of the cues that drive motion-in-depth perception in primates. The CDOT signal can be further divided into disparity and time components. Unlike IOVD cues, which requires direct comparison of motion direction and speed between the two eyes, CDOT is generated by computing the shift in binocular disparity over time. This requires first, the computation of disparity signals and second, comparison between previous binocular disparities. Therefore, to study the CDOT signal it is useful to understand how disparity signal plays a role in human depth perception.

In this section, I will be talking about behavior evidence for static depth discrimination using pure disparity signal as well as motion-in-depth discrimination using CDOT and IOVD stimulus.

3.2a. Perceptual experiments using disparity signals

Traditionally, stereo-vision (binocular vision) was studied using disparity signals. There are two types of disparity signals that humans can use to detect depth; absolute disparity and relative disparity. When we fixate on a single point, an object placed behind or in front will create a shift in the image within each eye. For example, if an object is placed behind the fixation point, the object will shift left for the left eye and shift right for the right eye. The difference of shift in the angle due to the horizontal shift in the image between the two eyes is defined as absolute disparity (Fig. 3.1). In this example, we would see an increase in the absolute disparity when the object is placed behind the fixation point. The relative disparity is generated when a second object is placed. The relative disparity is defined by the difference in monocular angle between the two objects (Fig. 3.1). Because relative disparity explores the relationship between two objects, it is independent of fixation point while the absolute disparity is defined by the fixation point.

Humans are better at discriminating relative disparity compared to absolute disparity (Andrews et al., 2001; McKee et al., 1990), but neurons in the early visual areas are quite insensitive to relative disparity but primarily sensitive to absolute disparity (Neri et al., 2004; Cumming & Parker 1999). There is evidence in human fMRI where the ventral pathway is more involved in relative disparity computation while the dorsal pathway is more involved in absolute disparity computation (Neri et al., 2004) and some evidence suggests neurons in V2 being sensitive to relative disparity (Thomas et al., 2002).

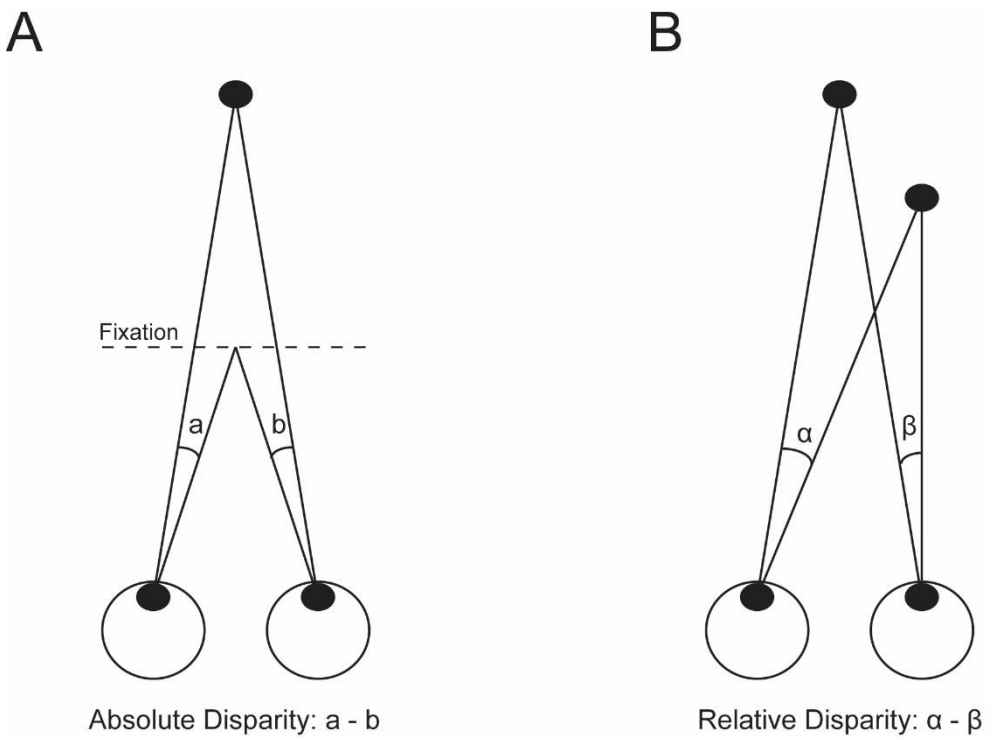

Figure 3.1. Absolute and Relative Disparity
(A) Model showing how absolute disparity is computed. (B) Model showing how relative disparity is computed.

Mismatch images between the two eyes create disparity signals but not all discrepancy between the left and right eyes create depth perception. To perceive depth using disparity requires an exact match of the images between the two eyes. Cumming and Parker conducted experiments in which a subject was introduced to anticorrelated stereogram in which one eye was presented with black dots and the other eye was presented with white dots. The only difference between the two images was the color of the dots, and the subjects were unable to perceive depth from the anticorrelated stereogram (Cumming & Parker 1997). Even though perceptually irrelevant, binocular neurons in MT, V1, and MST respond to anticorrelated stimuli in an inverted tuning curve for disparity (Cumming

& Parker 1997; Krug et al., 2004; Takemura et al., 2001). Cumming and Parker also conducted an experiment in which vertical disparity was introduced to the subjects. Unlike horizontal disparities, subjects were unable to perceive depth through vertical disparities (Cumming et al., 1991) which implies that the horizontal shift is a critical component in generation of depth signal. These studies hint that there are additional computations occurring in the higher visual areas that drives the behavioral discrimination for motion-in-depth signals as lower visual area seems to be responding indiscriminately regarding if the signal is behaviorally relevant or not.

3.2b. Perceptual experiment using CDOT

Disparity signals and their contribution to depth perception in humans have been studied for a long time. Because of the robust depth perception created from disparity signals, it has long been hypothesized that motion-in-depth signals were largely driven by the CDOT (Cumming & Parker 1994; Gray & Regan 1996) and it is possible to create motion-in-depth signals using a pure CDOT stimulus. Previous studies have created pure CDOT stimulus by showing random dot stereogram with changing disparity between the left and right eye and re-drawing the dots every frame (Julesz, 1971) and found pure CDOT stimulus does indeed create motion-in-depth signals. In humans and non-human primates visual area MT has been one of the primary target to study motion-in-depth signals due to its critical role in two dimensional motion processing along with presence of disparity selectivity in the area (Joo et al., 2016; DeAngelis & Newsome, 1999; Huk et al., 2002; Albright 1984; DeAngelis & Newsome, 2004; Smith & Wall, 2008; Smith et al., 2006; Rokers et al., 2009) and not surprisingly, studies have found neurons in area MT to be selective for motion-in-depth signals in monkeys (Czuba et al., 2014; Sanada &

DeAngelis., 2014). These evidence suggests that area MT could be an important area for binocular computation behind motion-in-depth signals.

3.2c. Perceptual and behavioral experiments using IOVD signals

Unlike change in disparity signals, there have been relatively few studies involving IOVD signal for motion-in-depth perception. There has been some debate on the relevance of IOVD signal when it comes to motion-in-depth perceptions. Some studies show little to no IOVD involvement in motion-in-depth (Cumming & Parker 1994; Gray & Regan 1996) while others present with some strong evidence showing evidence for IOVD involvement in motion-in-depth discrimination separate from disparity (Shioiri et al., 2000; Fernandez & Farell 1005; Brooks., 2002; Rokers et al., 2008; Czuba et al., 2010). Czuba et al. showed strong evidence for CDOT being used in a slow stimulus close to the fixation point while IOVD stimulus being used during high speed and more peripheral positioned stimulus (Czuba et al., 2010).

There are also neuronal evidence for CDOT and IOVD having separate and independent responses from one another, suggesting a separate neuronal pathway for these two signals involved in motion-in-depth signals. There evidence in area MT where a population of neurons is selective for the direction of motion-in-depth and there is even some evidence towards stronger selectivity for IOVD signal than disparity (Sanada & DeAngelis 2014; Czuba et al., 2014).

These studies suggest different pathways for CDOT and IOVD computations and further experiments need to be conducted to assess the specific mechanism behind CDOT and IOVD contributions to the perception of motion-in-depth.

3.3. Motion-in-depth discrimination in mice

3.3a. Overview

Unlike work in primates and carnivores, there are few studies on binocularity in rodent models, despite it being a useful model to study neural circuitry. Our lab demonstrated disparity tuning in mouse V1 similar to those of cat and primate (Scholl et al., 2013), but there has been little behavioral evidence supporting the usage of neurons coding for depth information. The only depth discriminating behavior that was used in the previous study was gap detection study in which free moving rats were given a task to discriminate gap on a track (Legg & Lambert, 1990; Wallace et al., 2013). However, this behavior paradigm does not allow the animal to utilize pure binocular signal since there are various monocular signals from which depth information can be extracted from the environment, such as shadows, motion parallax, and size of the object.

In this section, I will present a new behavior paradigm in rodents in which the animal has to utilize pure binocular signals, controlled by different stimulus presented to the left and right eyes, a task similar to those in primate studies (Czuba et al., 2014; Rokers et al., 2009; Sanada & DeAngelis, 2014). Studying motion-in-depth signals in rodent model allows us to study and manipulate the circuitry behind IOVD and CDOT computations in a way that is not possible in primate studies.

3.3b. Introduction

Organisms construct a three-dimensional (3D) representation of the world by integrating the distinct information available to the two eyes. The offset perspectives of the two eyes also provide critical information about the motion of objects through depth: each eye sees opposite directions of motion for an object moving either directly towards or away from an observer. In humans and non-human primates, such inter-ocular velocity

differences (IOVDs) are known to be an important cue for 3D motion perception (Czuba et al., 2014; Rokers et al., 2009; Sanada & DeAngelis, 2014).

The neuronal basis for binocularity has been extensively studied in cats and monkeys (Barlow et al., 1967; Pettigrew et al., 1968), but other mammals, such as mice, share similar functional pathways. In contrast to cats and monkeys, mice have laterally-oriented eyes but still possess a 40-degree binocular visual field. The binocular zone of primary visual cortex (V1) contains neurons with a variety of disparity selectivities (Scholl et al., 2013) and ocular dominance (Drager, 1978). It is not known whether those signals are used for visually-guided behavior. Previous work has demonstrated that rodents can estimate the size of a gap on a track (Legg & Lambert, 1990; Wallace et al., 2013), but it is unclear from these studies whether the visual cues employed are binocular or monocular.

We found that mice are able to distinguish 3D motion direction – responding differently to a binocular presentation of towards versus away motion. This behavior depended critically on the visual cortex, as optogenetic inactivation of cortex disrupted their ability to distinguish directions of motion through depth. The successful discrimination of binocular stimuli demonstrates that mice are able to appropriately integrate eye-specific motion signals to discriminate motion-in-depth, akin to that by humans and non-human primates.

3.3c. Results

To test whether mice are able to integrate signals from the two eyes to guide behavior, I trained mice expressing ChR2 in PV+ neurons (Methods) to perform a go/no-go task on the basis of the stereoscopic visual motion-in-depth. I implanted a head plate to fix the animal's head during behavior and placed glass windows over V1 to allow photostimulation of ChR2-expressing neurons. Animals were rewarded when they walked or stopped to binocularly-distinct visual stimuli (see Methods for training paradigm). I

presented four visual motion conditions that in humans are perceived as: “away” (left eye receives leftward motion and right eye receives rightward motion), “towards” (left eye receives rightward motion and right eye receives leftward motion), and two frontoparallel motion conditions, corresponding to matched leftward or rightward motion for both eyes (Fig. 3.2A). Animals were first trained to walk when the leftward motion was presented to both eyes; after they learned that association, animals were trained to stop when a “towards” stimulus was presented, and to walk in all other conditions.

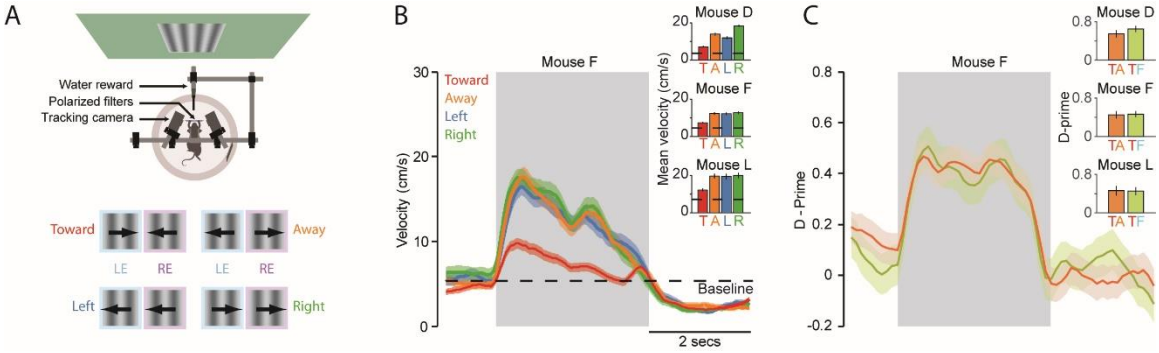

Figure 3.2. Binocular integration for behavior in mice.
A. Mice were trained to walk on a floating ball while images were presented using a stereo projector and polarized filters (top). Four visual conditions were presented corresponding to all combinations of rightward and leftward motion to both eyes (bottom). Conditions of opposite direction movement evoke a perception of motion-in-depth. *B.* Walking speed depends on the visual stimulus. Traces and shading show the mean and standard error of walking speed for the four stimulus conditions of a single animal (mouse F). The shaded grey region indicates when a visual stimulus was presented. Mice were trained to stop for the toward stimulus condition. Water reward was given at the end of the visual stimulus for correct trials (arrow). Inset bar graphs show the mean walking speed during the visual stimulation for all three mice. The dash black line indicates the baseline second before visual stimulus onset. *C.* Discriminability between stimulus conditions measured by D-prime. D-prime was calculated between toward and away conditions (orange trace), and between toward and frontoparallel conditions (green trace) for mouse F. Inset bar graphs show mean D-prime value of the three mice.

After training, we assayed how well their walking speed distinguished the towards stimulus condition from other conditions. Walking speed was slower for the towards stimulus than the other 3 stimuli. Walking speed for towards diverged from other conditions at 70 ms ($P < 0.05$, permutation test) (Fig. 3.2B). I estimated the degree that mice were able to discriminate binocular conditions using d-prime. Mice could discriminate between towards and frontoparallel motion (mean d-prime = 0.62, bootstrapped 95% CI = [0.53, 0.76]). Critically, our mice showed differential behavior between towards and away motion stimuli (mean d-prime = 0.48, bootstrapped 95% CI = [0.44, 0.52]) (Fig. 3.2C). Swapping the polarizing filters between eyes resulted in the reversal of behavior (Fig. 3.3A) and removing polarizing filters disrupted the discrimination task (Fig. 3.3B). In summary, mice were able to distinguish towards motion from other conditions— motion information that was only available by integrating right and left eye signals appropriately.

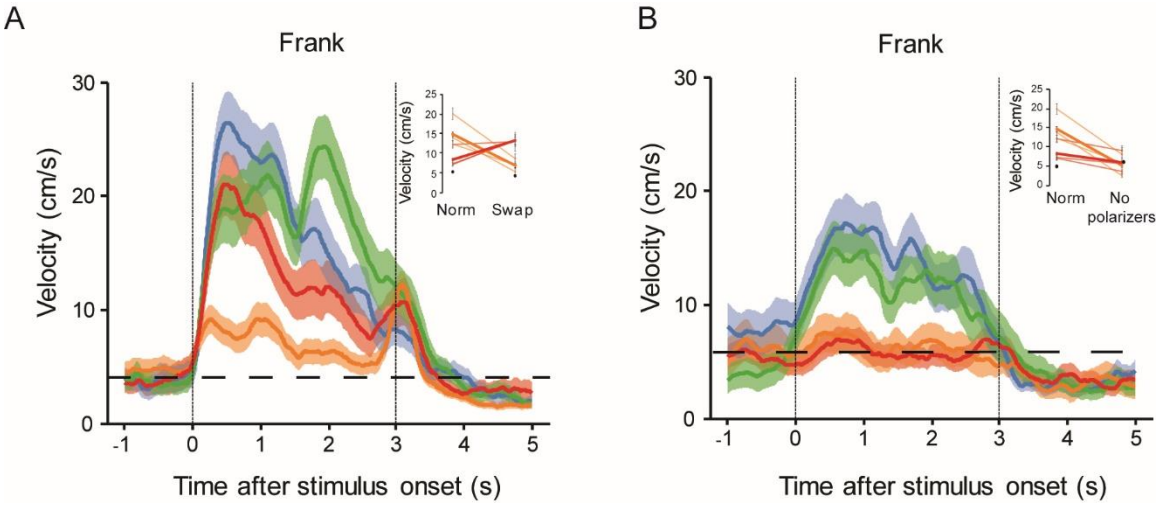

Figure 3.3. Control conditions for swap glass and no glass during motion perception task

(A) Average velocity plot of Frank after stimulus onset under swap condition. Orange: away stimulus, red: Towards stimulus, green: rightward stimulus, and blue: leftward stimulus. Stimulus onset is indicated with shaded gray area. The black dash line indicates the average velocity one second before the stimulus onset. To the right of the figure, I show the average velocity of all the animals during the stimulus between normal and swapped conditions. Orange is with the away stimulus and red is with towards stimulus. We see that there is a reversal in behavior when the polarized lenses are swapped between left and right eye.

(B) Average velocity plot of Frank after stimulus onset under no glass condition. Average velocity of Frank after stimulus onset under no-glass condition. Color code is the same as (A). The dashed line indicates the average velocity one second before the stimulus onset. The graph to the right shows the average velocity of the animal during the stimulus between normal and no glass conditions. Orange is with the away stimulus and red is with towards stimulus. We see that the animals are unable to distinguish towards and away stimulus when polarized lenses are removed.

The binocular integration underlying this behavior could occur in many different brain regions, as left and right eye pathways converge in the LGN (Howarth et al., 2014), superior colliculus (Berman et al., 1975), and V1 (Drager, 1978; Hubel and Wiesel, 1962). Because V1 has been thought to be a primary site for binocular integration (Scholl et al., 2013), we investigated if visual cortex is required for this binocular task. Silencing cortical

neurons optogenetically (Glickfeld et al., 2013) greatly impaired discrimination performance(Methods, Supplementary figure 3): The mean of all animals' walking speed for the towards stimulus remained very low (3.52 cm/s) but the walking speed for the away condition also dropped to 4.28 cm/s indicating that the animals were not able to distinguish between these two stimuli while visual cortex was inactivated (Fig. 3.4). In concert with the change in walking behavior, d' values declined dramatically when comparing the towards and away conditions (inactivated d' mean = 0.17, bootstrapped 95% CI = [0.01, 0.34]). These findings suggest that cortical activity strongly contributes to this visually-guided task, as it does for both orientation and contrast discrimination tasks (Glickfeld et al., 2013).

One interpretation of our optogenetic inactivation experiment is that binocular integration is disrupted because it depends on integrating monocular cues that originate in both hemispheres. Alternatively, binocular integration could depend on interactions between contralateral and ipsilateral eye inputs that converge in the region of binocular overlap in visual cortex. To distinguish between these hypotheses, I unilaterally silenced the visual cortex. For two out of three animals, there was still a significant difference in walking speed between towards and away conditions (mean d' = 0.43, bootstrapped 95% CI = [0.13, 0.67])(Fig. 3.4). Therefore, it appears that the binocular portion of visual cortex is sufficient for animals to distinguish towards and away conditions, and suggests that binocular cells in V1 are integrating inputs from left and right eyes relevant to this task.

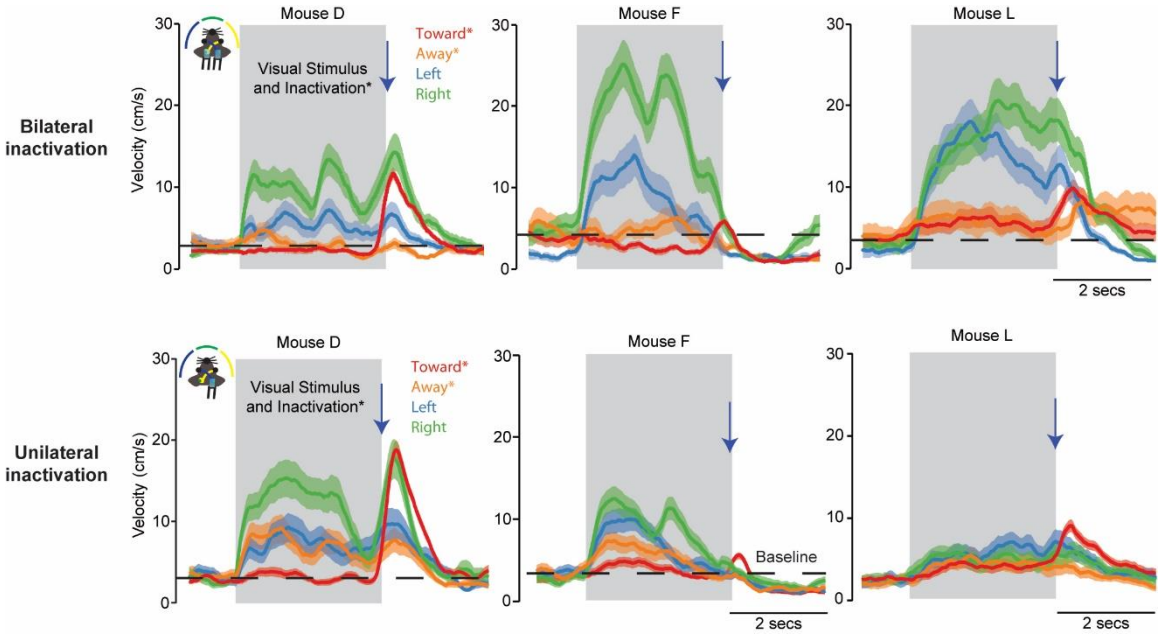

Figure 3.4. Effects of cortical inactivation on discrimination.
A. Walking speed is plotted for the four conditions (as in Fig. 1B) for each animal. For the "towards" and "away" conditions cortex was inactivated bilaterally using optogenetics. The dashed line indicates the baseline walking speed. B. As in A, but for unilateral inactivation.

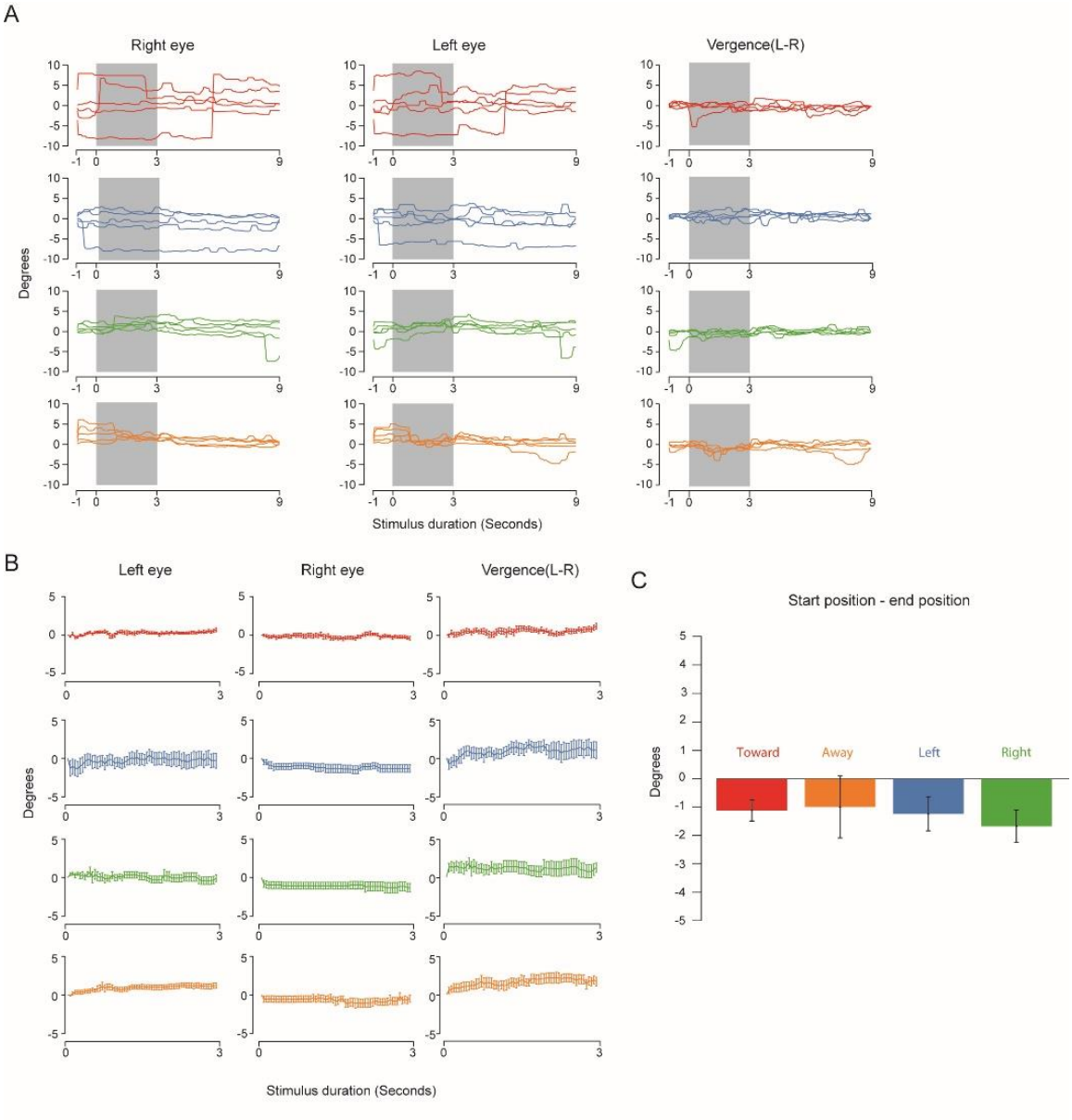

Figure 3.5. Individual eye movement traces show no significant eye movement related to the stimulus conditions.

(A) Five raw traces of eye movement for animal D during toward(red), left(blue), right(green), and away(orange). The grey shaded area indicates stimulus duration. The diagram shows eye traces from the right (left column) and left (middle column) eyes. Right column shows the Vergence degree calculated from subtracting left eye position from the right eye positions.

(B) Average eye movement for animal L during toward(red), left(blue), right(green), and away(orange). The diagram shows eye traces from the right (left column) and left (middle

column) eyes. Right column shows the Vergence degree calculated from subtracting left eye position from the right eye positions.
(C) Bar graph of change in vergence position from data in figure B. I subtracted first and last position during stimulus duration (toward mean:-1.11 [-1.48 -0.74] ; away mean: -0.99 [-2.08 0.11] ;left mean:-1.23[-1.83 -0.64]; right mean: -1.67 [-2.23 -1.11]) and found that they were not significantly different from one condition to another.

To track objects moving in depth, humans and non-human primates often change the relative position of their eyes (Erkelens and Collewijn, 1985; Nefs and Harris, 2008). The IOVD stimulus employed here might evoke eye movements related to their behavior. I, therefore, measured eye position using infrared cameras mounted in front of each eye and computed the change in vergence angle. Left and right eye movements were correlated, but I did not see consistent changes in eye position or vergence angle for our four stimulus conditions (Fig. 3.5). I calculated change in vergence angle between the beginning and end of the stimuli (right mean: 0.32° [95% CI: -0.53, 1.24]; left mean: 0.22° [95% CI: -0.92, 0.92]; towards mean:0.11° [95% CI: -0.60, 0.81]; away mean: 0.18° [95% CI: -0.98, 1.15]) and I saw no significant changes in the vergence angle between the four different stimulus conditions.

3.3d. Discussion

Despite rodents sharing common visual properties with primates and cats, there is a clear gap in binocular information for the rodent model. To investigate behavior evidence for binocular discrimination task, I constructed a paradigm in which the animals have to rely on signals coming from left and right eye to determine the correct stimulus for reward. I found that mice were able to discriminate motion-in-depth signal using stimulus that contained only CDOT and IOVD stimulus. These findings represent the first demonstration that mice can use binocular visual signals to guide behavior. I have shown that mice can integrate left and right eye motion signals to guide their behavior and that this behavior

depends on cortical activity. The binocular integration required to distinguish 3D motion direction may occur within V1 or reflect computations in other visual areas that are routed through V1. Mouse V1 contains neurons with a variety of selectivities which may be necessary for computing motion-in-depth, including neurons with varying degrees in ocular dominance, disparity selectivity, and direction selectivity. These results suggest that the binocular processing of visual information by mice may be similar to that in other mammals (Baker & Bair, 2016), and the tools that can be applied in the mouse brain may allow for a detailed dissection of the circuitry underlying the computations for object motion, depth, and other canonical visual dimensions.

3.3e. Methods

Experimental Procedures

All procedures were approved by The University of Texas at Austin Institutional Animal Care and Use Committee

Transgenic Mouse Construction

To generate experimental animals, PV-Cre knock-in mice17 were crossed to a Cre-dependent ChR2-EYFP strain18. The PV-Cre; Ai32 progeny selectively expressed ChR2 in PV+ interneurons.

Animal preparation and surgery

Adult male mice (4 to 6 months) were used in these experiments. To immobilize the head during training, a titanium bar was placed on the skull and secured with dental cement under isoflurane anesthesia. 3.5mm craniotomies were made over the visual cortex in both hemispheres and covered with glass windows. Kwik-Cast Silicone Elastomer*(World Precision Instruments, Inc.) was placed over the glass windows to prevent light from penetrating the windows.

Training

All animals were water-restricted for a week before training and the weight of the animals were maintained within 30% of the original body weight. The animals were acclimated to the training apparatus during the restriction period. The training apparatus was designed so that the animal would walk on a Styrofoam ball that was floating on the air while head fixed19. Water was delivered to the animal at the end of the stimulus whenever they made the correct behavior to the given visual stimulus. The animals' walking speed was tracked using optical mouse (figure 1A, top). For the first 3 weeks the animals were trained to walk to a right moving grating stimulus to pair them with walking behavior to a visual stimulus. After successfully learning to walk when visual stimuli were presented, I increased the number of stimulus conditions, requiring the animals to walk faster for away, right and left stimuli than for toward stimuli.

Swapping polarizers: After all the animals successfully performed the task above 60% correct, I reversed the left and right polarizer glasses and ran the same protocol as the control on the same day. Animals were rewarded as in the control conditions.

No glass: As in the swapped polarizers paradigm, after all the animals successfully performed the task above 60% on a given day, I removed the left and right polarizer glasses and ran the experiment. Animals were rewarded as in the control conditions.

V1 inactivation through photostimulation: After all the animals successfully performed the task above 60% on a given day, I ran the behavioral protocol as in the control but with blue light (470 nm wavelength) photostimulation over visual cortex during "towards" and "away" stimuli. Animals were rewarded as in the control conditions.

Eye tracking

During all the experimental procedure and training, camera recorded video of the eye movements. The tracking images were analyzed with custom MATLAB software (MathWorks). The center of the pupil was tracked throughout the entire experiment.

Visual Stimulus

We used a DLP LED projector (VPixx Technologies Inc.) that had a refresh rate of 240 Hz at full HD resolution (1920 x 1080), operating in a gray-scale mode (mean luminance = 59.75 cd/m2). One pixel subtended 0.13° at a viewing distance of 18 cm. The left and right images were modulated by a circular polarization alternator in front of the optics of the projector. The onset of each orthogonal polarization was synchronized with the video refresh, enabling interleaved refresh rates of 120 Hz for each eye's image. Customized circular polarization filters were attached to the animal's left and right eye views of the stimuli, which were front-projected onto a polarization-preserving screen (Da-Lite® 3D virtual black rear screen fabric, model #35929).

The grating stimuli were generated using Psychtoolbox20 running on a Mac PC. The spatial frequency of the grating was 0.02 cycles per degree (cpd) and drifting speed was 29 °/s. The full-field grating was displayed in a square (68° x 68°) centered toward upper visual field. For 3D motion, the left and right images were anti-phased (180°) to remove possible disparity information to compute motion-in-depth. For frontoparallel motion, the same image was presented to the left and right eye.

There were 15 experimental blocks in an experimental session (675 s). Five stimulus trials (two towards, one away, one left, and one right) were randomized within a block. A trial consisted of a 3 s visual stimulation period and a 6 s blank period. During the visual stimulation period, the grating stimuli were displayed for 1 s followed by a 0.5 s blank inter-stimulus interval, which was repeated twice.

Data analysis

MATLAB was used to analyzed data and generate figures. I first applied root-mean-square (rms) analysis with 250 ms window on the raw time series of velocity trace of each session. The raw velocity traces included any movement generated by the animal since absolute value of velocity was used to analyze data. From the resulting time series, I extracted each trial's time series between -1 s and 5 s after stimulus onset. The first trial's time series was discarded from further analyses. I concatenated each trial's time series for each condition at the individual level.

The velocity during stimulus presentation (0 ~ 3 s) was averaged at each trial level. Then, I calculated the grand average velocity for each condition at individual level to estimate the averaged running velocity for each condition. The baseline velocity was calculated the velocity before the stimulus onset (-1 ~ 0 s) in the same way. I used bootstrapping analysis to estimate the confidence interval of the mean velocity for each condition. All reported confidence intervals(CIs) were generated as bootstrapped estimates of ± 1SEM (i.e., the central 68.2%).

3.4. Conclusions

In this chapter, I described the behavioral evidence for both IOVD and CDOT signals used in motion-in-depth cues as well as behavior evidence for static disparity in primates. Traditionally disparity signal (CDOT) was thought to be the dominant signal that drives motion-in-depth cues, but more recent studies have shown motion signals (IOVD) to be also involved in extracting motion-in-depth signals (Sanada & DeAngelis 2014; Czuba et al., 2014).

There have been numerous behavioral evidences on humans and non-human primates in response to CDOT and IOVD signal, yet the mechanism behind this binocular

computation is less understood. Here, I introduce a new animal model, mice, that could aid in the investigation of binocular circutiry behind motion-in-depth computations.

Unlike primates, there have been no direct behavioral evidence for binocular integration in rodents. Recently, more experiments involving rodent visual system have been used to study the underlying mechanisms behind circuitry of visual pathways. Rodents are highly trainable with to perform a visual task and they possess genetic tools to be able to target and manipulate specific cell types (Guo et al., 2014; Danskin et al., 2015; Long et al., 2015; Samonds et al., 2018). Rodents also share similar binocular visual properties as primates (Scholl et al., 2013; Gordon & Stryker, 1996). Despite the similarities, there has been no behavior evidence demonstrating the animal utilizing pure binocular signals. In this chapter, I show behavior evidence of mice using stereoscopic stimulus that includes both CDOT and IOVD signals in discrimination task, and the binocular neurons in the visual cortex may play a critical role in this behavior. Unfortunately, the behavior is not as good as those we see in human or primate studies (mean % correct is around 63% for mice), and that hinders our ability to introduce manipulation (such as contrast or spatial frequency) to the visual stimulus to conduct psychophysics. Nevertheless, there is clear behavioral evidence for rodent binocular integration.

Section 2
Chapter 4:
Eye movement associated with motion-in-depth signals

4.1. Overview

In the second portion of this dissertation, I will expand on the existing behavioral evidence for binocular integration by examining the eye movements when viewing motion-in-depth stimulus. Unlike the previous chapters, we examined a behavior that does not require training and is naturally evoked when animals are presented with motion-in-depth signals.

Animals move their eyes in response to external (global) motions in their surroundings or to track objects. Some eye movements are voluntary (saccade or smooth pursuit) while others are reflex (optokinetic reflex response, OKR). The vast majority of the studies involving eye movements have been conducted using primates which are characterized by foveated retinas. The fovea is a region in the retina densely packed with retinal ganglion cells. Because of the densely packed retinal ganglion cells, the acuity in the foveal region is greatly increased and primates move their eye to focus the image into the foveated region of the retina. In primates, the two eyes make conjugate eye movements most of the time which means that they move in the same direction at the same time in a coordinated fashion (version). The second type of eye movement involves the eyes moving in an opposite direction (vergence) and this occurs when viewing stimulus with depth information (static depth and motion-in-depth).

In this chapter, I will discuss vergence eye movements associated with motion-in-depth stimulus. There are two ways to generate vergence eye movement, namely through the smooth pursuit and through OKR. Here, I investigate the mechanism underlying OKR vergence eye movement.

4.2. Optokinetic response (OKR)

Optokinetic reflex response (OKR) is an eye movement that occurs in response to a large motion in the environment. The OKR eye movement follows the direction of the global motion which helps stabilize the image on to the retina. Optokinetic nystagmus is part of OKR in which slow eye movement (in the direction of the global motion) is followed by a rapid saccadic eye movement in the opposite direction to return the eyes close to its original position. OKR is a very robust signal and has been studied in most vertebrates as it is a system that is well conserved among vertebrates.

An interesting feature of OKR is the asymmetry between nasal-to-temporal and temporal-to-nasal motion in most animals. Most vertebrates, including mammals, have higher temporo-nasal motion during OKR eye movement (Fite et al., 1979; Hess et al., 1985; Fritsches et al., 2002; Collewijn, 1975; Katte & Hoffmann 1980), but mammals with fovea and/or large binocular overlap (such as primates, cats, and ferret) don't have this asymmetry (Hein et al., 1990; Evinger & Fuchs, 1978; Distler et al., 1999). The mechanisms behind primates symmetrical OKR eye movement is hypothesized to be due to the projections from the visual cortex to the nucleus of the optic tract (NOT), the dorsal terminal (DT) nucleus, and accessory optic system (AOS). Many studies have shown that this symmetric adjustment of the OKR in primate and cat is mediated by the visual cortex as lesions or disruption of binocular neurons of visual cortex leads to asymmetry in OKR, similar to what we see in rodents (Zee et al., 1987; Wood et al., 1973).

The asymmetry in many vertebrates, other than primates and cats, is due to retinal projection to the AOS being dominated by exclusively contralateral input. In primates and cats, because of the large population of binocular neuron in the visual cortex, it is possible that the binocular neurons are correcting OKR to be symmetrical. OKR in vertebrate involves primarily subcortical structures such as the NOT and AOS. But in the primate,

there have been reports of several neocortical regions involved in OKR (Bucher et al., 1997).

4.2a. Vergence eye movement during OKR

Vergence eye movement occurs when we shift our gaze from a far point to a near point (in depth). It is defined by eyes moving in the opposite direction (vergence) which is different from conjugate eye movement, where the two eyes move in the same direction, during 2-dimensional moving motion (version).

There are several ways to elicit vergence eye movements in primates. We make vergence eye movements during the smooth pursuit when an object is moving in a 3-dimensional space. Vergence eye movements can also occur as part of OKR eye movement if the global motion is moving in a 3-dimensional space. In primates, the main visual signal that drives vergence eye movements is thought to be the binocular disparity signals, but IOVD signals can also elicit robust vergence eye movement (Sheliga et al., 2016). Even though vergence eye movements are commonly associated with visual stimulus moving in 3-D space, the perception of depth is not required to elicit this eye movement. Even in anticorrelated dot stimulus (humans do not perceive depth with anticorrelated dots) vergence eye movements persist (Masson et al., 1997). Another method that creates vergence eye movement without the perception of depth is to use a vertical IOVD stimulus (Sheliga et al., 2016). This is analogous to vertical disparity signals which elicit vergence eye movements in humans (Yang & Miles., 2003).

There are several cortical and subcortical regions involved in the generation and correction of eye movements. Not surprisingly, many of these regions are also involved in vergence eye movement. One of the importation computation behind vergence eye movement that is different from other eye movements is the involvement of binocular

integration. Unlike eye movements generated from 2-D visual stimulus, vergence eye movements require (in primates) disparity and/or IOVD signals. There are several cortical areas that are known to have these binocular properties. Area MT and the frontal cortex is known to contain neurons tuned to 3-dimensional (Czuba et al., 2014; Sanada & DeAngelis, 2014; Gamlin & Yoon, 2000).

Even though binocular signals are critical in making accurate vergence eye movement, there are also subcortical regions known to play a role in vergence eye movement such as the cerebellum (Nitta et al., 2008), superior colliculus (Van Horn et al., 2013), as well as midbrain pretectal and tectal areas that are known to be involved in most eye movements.

There have been numerous studies showing multiple cortical and subcortical structures involved in vergence eye movements but we know less about how binocular integration between left and right eyes to elicit smooth vergence eye movements. Here I introduce a new model that could help investigate the mechanism behind binocular integration during vergence eye movement.

4.3. Vergence eye movement in mice

4.3a. Overview

In this section, I introduce a new animal model to study vergence eye movements. Previous studies have largely focused on disparity signals to create vergence eye movements but recently there has been some evidence for IOVD signal eliciting vergence eye movements (Sheliga et al., 2016). To better understand the computation between the two eyes and specific visual cues driving vergence eye movements I presented a random dot stereogram to mice.

4.3b. Abstract

We stabilize the dynamic visual world on our retina by moving our eyes in response to motion signals we receive. Coordinated movements between the two eyes are characterized by version when both eyes move in the same direction and vergence when the two eye move differently. Vergence eye movements have been proposed to be important for tracking objects in three dimensions and may be elicited in primates by both differences in the spatial signals, or disparity, or by differences in the motion that the two eyes receive. These vergence eye movements require the integration of left and right eye inputs, but it remains unclear which neural circuits are responsible for the integration that leads to these eye movements. To address this issue, we measured vergence eye movements in mice using a stereoscopic stimulus that is known to elicit vergence eye movements in primates. We found that the primary signal for vergence eye movements is the difference in motion presented to each eye, whereas spatial disparity cues had little impact on vergence. We also found that the vergence eye movements we observed in mice were not affected by silencing visual cortex, or by manipulations that disrupt the normal development of binocularity in visual cortex. Instead, we demonstrate that right and left eye motion cues in rodents could be described by a summation of motion signals that occurs in subcortical structures.

4.3c. Introduction

The sensory system integrates multiple signals coming from the environment so the organism can behave appropriately in their surroundings. One example of this process is the integration of visual inputs from the two eyes. Mammalian eyes are offset horizontally, providing distinct perspectives on our visual environment. Even though the images from left and right eyes are distinct, we integrate these perspectives generating a single

perception of the visual world, also known as the cyclopean view. The integration of left and right eye signals provides cues for an object depth in the world and aids in stabilizing gaze on objects in depth.

Mammals use a number of different eye movements to stabilize objects on their retina. One of these stabilizing eye movements, the optokinetic reflex (OKR), is generated when there is a large global motion in the environment. Importantly this eye movement is not only sensitive to two-dimensional shifts in the world, but to changes in depth. In primates, global shifts the visual scene in depth cause the two eyes converge or diverge, depending on whether the scene shift towards or away from the animal. Previous studies have shown that sensory structures, the frontal eye fields and frontal cortex (Gamlin & Yoon, 2000), the cerebellum (Nitta et al., 2008) and midbrain pretectal and tectal areas (Mays, 1984) all play a role in generating OKR eye movements but we do not know which circuits are responsible for coordinating the binocular eye movements that reflect shifts in scene depth.

The coordination of binocular eye movement to motion in three dimenations has not been examined in rodents thus far. Rodents do exhibit OKR movements for two-dimensional motion (Cahill & Nathans, 2008; Tabata et al., 2010; Liu et al., 2016, Samonds et al., 2018) but it is unclear if mice coordinate their eyes to generate the vergence eye movements required to stabilize changes in scene depth. Because their eyes are laterally placed on the head their binocular field of view is limited and they may not require coordination (Wallace et al. 2013). Here, using stereoscopic dots, we demonstrate that mice have vergence eye movements associated with a stimulus moving towards or away from the animal. We demonstrate that these vergence eye movements are driven by motion signals rather than the disparity signals and that they result from a sublinear combination occurring between left and right eye motion signals. Finally, we show that cortical activity

has little impact on these vergence eye movements. Neither monocular deprivation, which disrupts binocular integration in the visual cortex, or optogenetically silencing visual cortex has an impact on these vergence eye movements. Therefore, subcortical structures are primarily responsible for the gaze stabilizing vergence eye movements observed in rodents.

4.3d. Results

Vergence eye movements in mice

We set out to determine whether changes in scene depth would evoke coordinated eye movements in rodents. We are particularly interested in situations in which the left and right eyes move in the same direction (version) relative to cases in which the two eyes move in opposite directions (vergence) that can be evoked by changes in scene depth. We placed awake mice on an air-floated styrofoam ball and measured eye movements while random dot stereograms were presented to the animals in which the right and left eye viewed dots moving in opposite directions (Fig. 4.1A). The dot patterns had sinusoidal trajectories to the left and right for each eye. Humans perceive this stimulus as moving towards and away. We measured the eye movements in 3 animals while these binocular motion stimuli were being presented. In response to this visual stimulation, mice had smooth eye movements which followed the motion of dots presented in each eye (Fig. 4.1A, right). To compute the vergence eye movement elicited by this stimulus, we subtracted the right and left eye position traces. These vergence eye movement traces followed the motion in depth signals that are present in this stimulus. We quantified the vergence eye movement by computing the amplitude of the sinusoidal vergence at the frequency of the motion oscillation and found no significant difference between conditions in which the stimulus moved toward first (TF) and away first (AF) ($P>0.05$, paired t-test), though these stimuli induced vergence movements at the opposite temporal phase (TF:

mean phase = -65 +/- 3.7 degrees; AF: mean phase = 99 +/- 13.8 degrees, Fig. 4.1B). Despite their small binocular visual field mice make vergence eye movements when presented with this stereoscopic stimulus.

Motion signal drives vergence eye movement in mice

There are two major cues primates are known to use for depth perception. Interocular velocity difference (IOVD) and change in disparity (CD) signals. Studies have shown vergence eye movement driven by CD signals (Masson et al., 1997; Rambold & Miles, 2008) and IOVD signals (Erkelens & Collewijn, 1985a, 1985b, Sheliga et al., 2016) in both humans and non-human primates. We initially used a stimulus that included both disparity and motion signals, as naturally occurs in our environment, which elicited vergence eye movements (Fig. 4.2A, TF = 2.12 +/- 0.21, AF = 1.74 +/- 0.18). While the amplitude of these vergence eye movements have a lower gain that found in humans (Schweigart et al., 1997), it is comparable the gain of OKR eye movements elicited by two-dimensional OKR (Liu et al., 2018, Tabata et al. 2010).

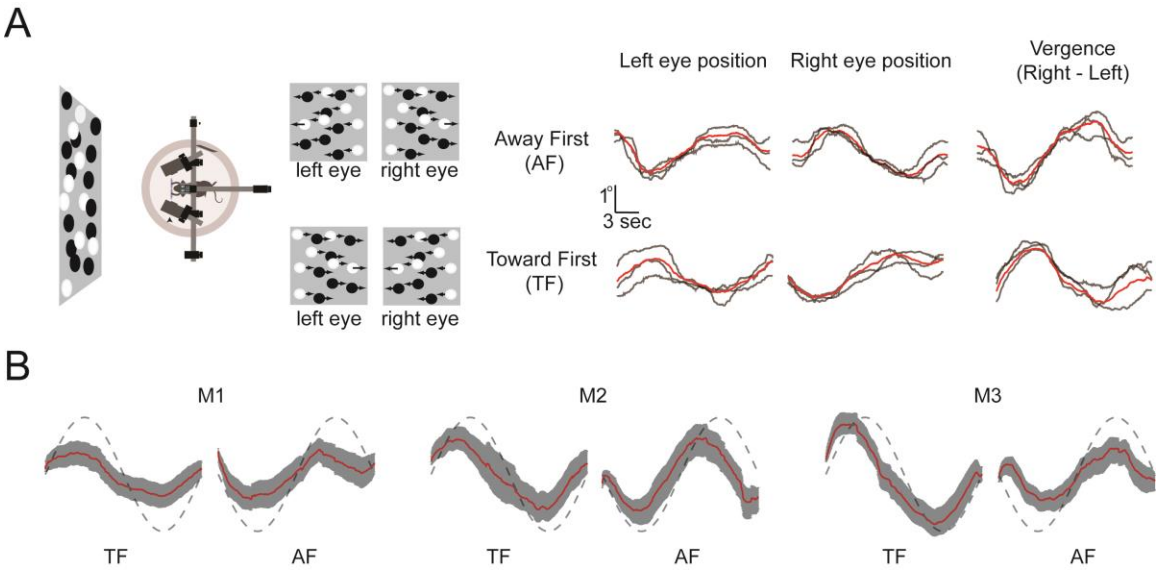

Figure 4.1. Vergence eye movements in mice
A. Diagram of the experimental setup and the stimulus motion presented to each eye is shown on the left. Individual eye movement traces for the left eye, right eye and vergence are shown in the right panel for stimuli in which the stimulus moved away first (AF, top) or toward first (TF, bottom). The vergence eye movement was calculated by subtracting the right eye position from the left eye position. Red lines indicate the mean across all trials. **B.** Average vergence eye movement for 3 animals for TF and AF conditions. Red lines indicate mean of all trials and the grey shaded area is the standard error of the mean. The dashed sinusoidal line is the motion in depth, but note that the actual stimulus motion was max -12 to 12 degrees.

To determine whether IOVD or CD signals are responsible for these vergence eye movements we generated stimuli that isolate these signals. We generated an IOVD only stimulus by presenting different patterns of dots to each eye, but each pattern had the same velocity profile as in our control condition. The vergence eye movements elicited by this stimulus closely matched the control condition (AF: 3.38 +/-0.27, TF: 1.75 +/- 0.28 Fig. 4.2B) but in AF condition we observed a slight increase in vergence amplitude for IOVD only stimulus (AF: Control vs IOVD only t-test, $P < 0.5$). It therefore appears that the IOVD signal alone can elicit for these vergence eye movements. To present a signal that

contained only CD signals we presented matched dots to each eye in which a consistent disparity was enforced, but we changed the location of the dots presented on a frame by frame basis. The disparity increased or decreased as occurred in our control condition, but because the dots were randomly replotted on each frame there was no overall motion signal for each eye (Sanada & DeAngleis. 2014). This condition failed to elicit coherent vergence eye movements. The amplitude of the modulation both towards first and away first stimuli dramatically declined and failed to elicit a significant vergence eye movement with the same timing as the control condition except for in a single animal in the away first condition only (Fig. 4.2D, CD only).

One potential problem with the CD isolating stimulus is that the rapid update of the dots may make generating appropriate disparity signals difficult for the mouse visual system. An additional problem is that the disparities we have employed may be outside the range that may be encoded by the visual systems (Scholl et al. 2013). We therefore first altered the rate at which dots were redrawn (from every frame to every 5th frame). Even when we slowed the refresh rates of the dots, we still did not observe significant vergence eye movements with the same timing as the control condition (Fig 4.2D, CD only, Slow Refresh). Next we decreased the disparity amplitude to ±6 degrees in our stimulus to see if this smaller range of disparity cues could elicit vergence eye movement. This condition also failed to elicit significant vergence eye movements (Fig. 4.2D, CD only, Low Amp). Mouse vergence OKR, therefore, seems to be dominated by motion signals instead of disparity signals.

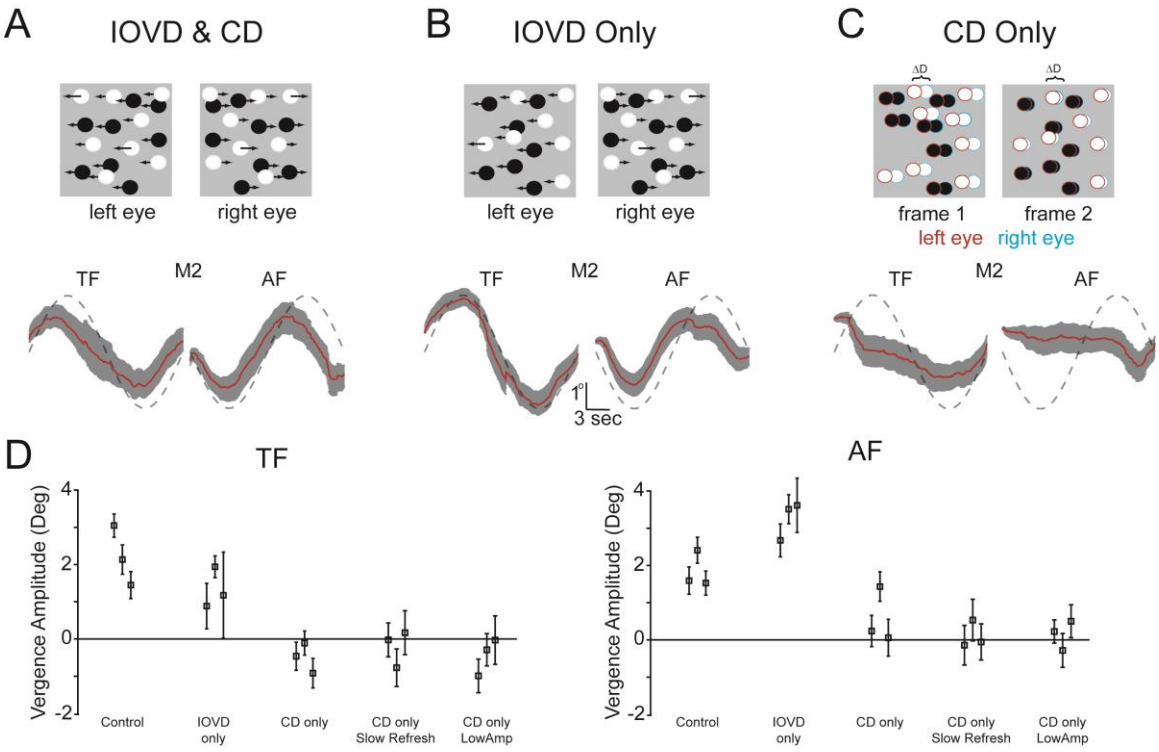

Figure 4.2. Segregating signals that drive vergence eye movements.
A. The IOVD & CD condition present both motion signals and disparity signals that may generate vergence eye movements. The stimulus contains correlated dots that move in opposite directions (top panels). Average vergence eye movements for toward first (TF) and away first (AF) condition of M2 during control condition are plotted in the bottom panels. Red lines indicate mean of all trials and the grey shaded area is the standard error of the mean. **B.** As in A, but for the IOVD only condition in which the dots were uncorrelated to eliminate disparity signals (see methods). **C.** As in A, but for a stimulus in which the two eyes view correlated dots with disparity signals but in every frame, the dots are repositioned to eliminate motion signals (see methods). **D.** Vergence amplitude in each stimulus condition during toward first (TF) and away first (AF) condition for control, IOVD only conditions, change in disparity only (CD), change in disparity only condition where the refresh rate of the dots was reduced to 6 Hz (CD only Slow Refresh), and change in disparity amplitude was reduced to max ±6 ° (CD only Low Amp) for both TF and AF conditions. Each point represents an individual animal. Error bars indicate the standard error of the mean.

Sub-linear combination in vergence eye movement in mice

We have demonstrated that IOVD signals can elicit vergence eye movements in mice. Such IOVD signals require a comparison of motion presented to the left and right eye. This appears to contrast with two-dimensional OKR, which has been characterized as binocular and not relying on the eye in which receives visual stimulation in humans (Quaia et al. 2018). That is, monocular motion information elicits similar eye movements in both eyes. If vergence eye movements relied on a simple linear summation of motion signals received by the two eyes, then opposite motion signals would cancel and no vergence eye movement would be elicited (Fig. 4.3A top). This contradicts our measurements of vergence eye movements, so we examined alternative combinations which might account for the vergence eye movements we observe. A second model which also relies on a simple linear combination of motion signals is that monocular motion signals elicit unequal eye movement resulting in a larger movement for the eye that was stimulated than the other eye (Fig. 4.3A middle). In this model, the difference in amplitude between the left and right eye during monocular viewing predicts that a binocular stimulus will evoke a vergence eye movement. A third linear model that also generates vergence eye movement is based on the idea that monocular motion signals only drive eye movements in the eye that was stimulated (Fig. 4.3A bottom).

To constrain these models for vergence eye movements, we measured eye movements when the stimulus was presented monocularly, and the other eye was occluded. As before, we presented sinusoidally moving dot patterns moving either rightward or leftward moving first stimulus to one eye while occluding the other. We then tested whether the vergence response to our binocular stimuli could be predicted from these responses to monocular stimulation.

We observed that when only one eye was presented with a motion signal both eyes moved in the same direction as the motion pattern. Importantly, however, the amplitude

of the eye movements was distinct: the occluded eye moved less than the eye that was presented the motion stimulus (Fig. 4.3B. TF: t-test, $P < 0.05$ for both right eye blank and left eye blank; AF: t-test, $P < 0.05$ for both right eye blank and left eye blank). Using these eye movements, we then made predictions about the vergence eye movements that would be evoked for the towards condition (Fig. 4.3B). We combined left and right eye movements evoked by left eye stimulation with the left and right eye movements evoked by right eye stimulation. Note that the motion trajectories in each condition are the opposite, as is the case for the IOVD stimulus. We then subtracted the predicted right and left eye positions to generate the predicted vergence eye movement (Fig. 4.2B, right). The predicted vergence eye movement (generated from a linear combination of left and right eye movements) had a larger amplitude than the observed vergence eye movement for the toward first condition but not different in away first condition (AF: 2.54 +/- 0.54, TF: 4.48 +/- 0.48; Fig. 4.2C, t-test, TF: $P < 0.05$; AF: $p = 0.25$), indicating a possible sublinear combination between left and right eye. It is important to note that the asymmetric interaction of the two eyes is required to account for vergence eye movements (Fig. 4.2A middle) and the eye movements do not simply reflect the visual motion that each eye receives (Fig. 4.3A bottom). The vergence eye movements we observe could therefore emerge from a sublinear combination of the eye movements evoked by monocular stimulation alone.

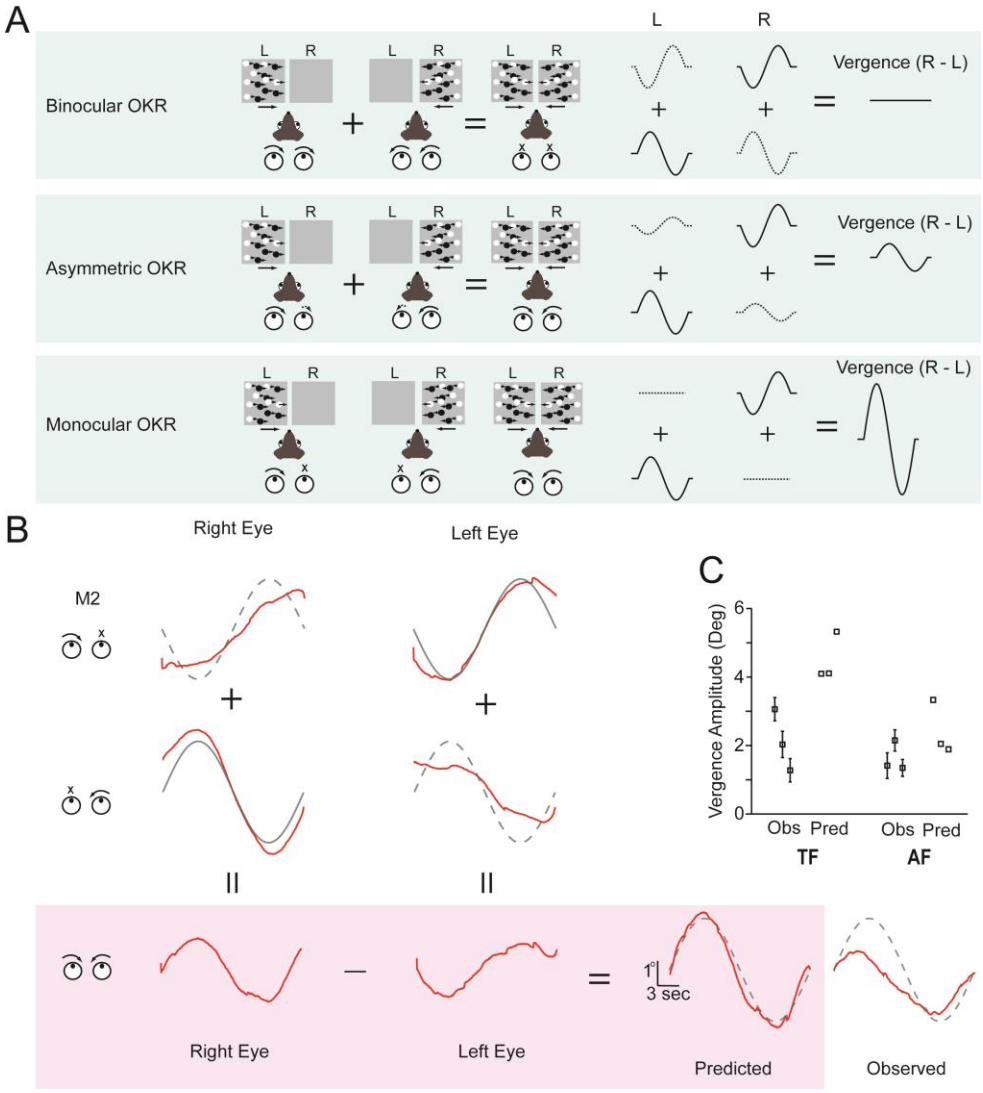

Figure 4.3. Sublinear combination generates vergence eye movement in mice
A. Three eye movement potential models for vergence OKR. In the first model both eyes make an equal motion during monocular viewing, and direct summation of left and right eye movement will generate cancelation of vergence eye movement (top). In the second model, the eyes make unequal eye movements during monocular viewing and summation of monocular eye movements will generate a vergence eye movement (middle). In the third model the eye presented with the stimulus moves and the non-stimulated eye does not make an eye movement (bottom). This condition will generate bigger vergence eye movement than the asymmetric condition. **B.** Left and right eye movements during monocular stimulation of either the left eye (top) or right eye (middle). We then compute the predicted eye movements to binocular stimulation for each eye (bottom, left panels)

and the resulting predicted and actual vergence eye movements (right panel). **C.** Comparison between the predicted condition and observed condition in both toward first stimulus and away first stimulus. Each point represents an individual animal. Error bars indicate the standard error of the mean.

Circuits for OKR vergence eye movement in mice

Previous studies in primates have implicated circuits in the visual cortex (Gamlin & Yoon, 2000), cerebellum (Nitta et al., 2008) and subcortical regions (Freedman & Sparks, 1997; Mays 1984) in generating OKR vergence eye movements. Left and right eye visual signals are known to converge along the primate thalomocortical visual pathway: V1 neurons are known to be disparity selective (Poggio and Fischer 1977; Pettigrew et al. 1968) and MT neurons are selective for motion-in-depth (Czuba et al; 2013). In mice, binocular responses have been observed in the thalamus (Howarth et al., 2014) and disparity selectivity has been measured in visual cortex (Scholl et al., 2013). We hypothesized that the integration of left and right eye motion signals to generate vergence eye movements could stem from interactions that rely on activity in the visual cortex.

It is well known that disrupting visual input to one or both eyes in a young animal has an impact on how the binocular visual system develops throughout adulthood. Monocular deprivation in an animal during the critical period is known to shift the ocular dominance, alter visual acuity in the deprived eye, and alter the disparity selectivity in V1 neurons throughout the adulthood of the animal (Hubel & Wiesel 1963; Gordon & Stryker 1996; Scholl et al., 2017). To see if altering binocularity of neurons in the visual cortex could alter OKR vergence eye movement, we performed monocular deprivation (MD) in young mice during the developmental critical period. All animals went through for 10 days (P23-P33) of MD and we measured the eye movements to motion in depth signals 1-2 days after we opened the deprived eye (Fig. 4.4A). We observed large vergence eye movements and found no changes in vergence eye movement in MD animals when compared to that

of the control animals for the AF condition (MDAF: 1.71 +/- 0.18) although we observed slight decreased vergence eye movement for the TF condition (MDTF: 1.22 +/- 0.14. t-test, $p = 0.04$; t-test, $P < 0.05$. Fig. 4.3B). In sum these data suggest that the disruption of binocular signals that follows monocular deprivation has little effect on vergence eye movements.

Next, we tested whether a dramatic alteration of cortical signals can alter vergence eye movements in mice. We inactivated the visual cortex using PV-ChR2 transgenic mice, optogenetically silencing the cortex while the animals were viewing the moving dot stereogram (Fig. 4.5A) (Liu et al., 2013). We found that inactivation of visual cortex had little impact on vergence eye movements. The amplitude of the vergence eye movement slightly increased for the TF condition during inactivation but found no difference for the AF condition (TF: t-test, $p = 0.05$, AF: t-test $p = 0.22$. Fig. 4.5B). This finding buttresses the MD results indicating that activity in visual cortex has little influence on the OKR vergence eye movement.

One concern with our inactivation experiment is that the LED light used to activate PV+ neurons may not be sufficiently strong to silence visual cortex. To test if the PV neurons in these transgenic animals are being activated by the LED light, and thus silencing other cortical cells, we recorded neuronal activity from an awake animal using tungsten electrodes. Without the optogenetic silencing, there is a clear response in the LFP at the onset and offset of the visual stimulus (Fig 4.6, top). This visually-evoked response was eliminated when visual cortex was inactivated by the increased activity of PV+ neurons (Fig. 4.6, middle panel). Instead of observing responses to the visual stimulus, there is a clear response to the onset and offset of the LED light that was used to activate PV+ neurons. The response to both optogenetic and visual stimulus matches that observed to the LED light alone (Fig. 4.6, bottom panel). Therefore, our inactivation experiments

silence visual cortex despite the absence of an effect on the vergence eye movements induced by the stereo motion signals.

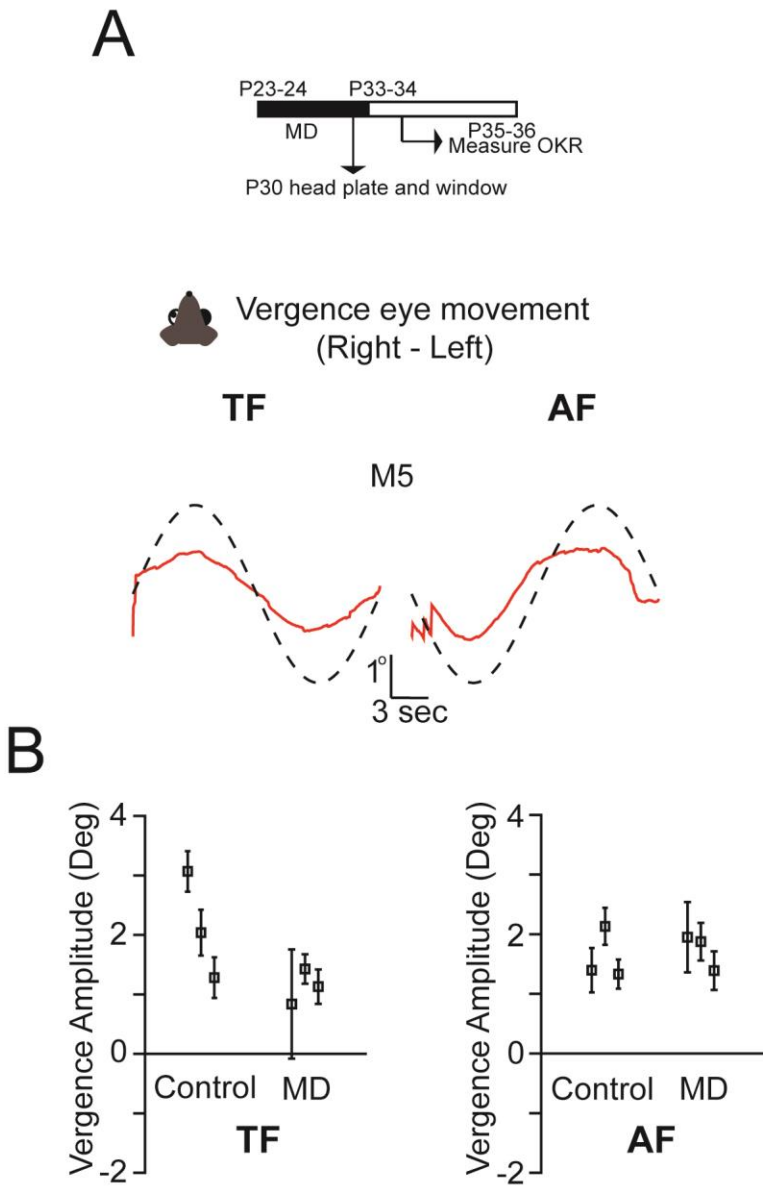

Figure 4.4. Monocular deprivation and vergence eye movements
A. Timeline of monocular deprivation (top). Mean vergence eye movement of animal M5 after MD for the toward first and the away first conditions (bottom). **B.** Vergence amplitude comparison between control animals and monocular-deprived animals for toward first and away first stimuli. Error bars indicate the standard error of the mean.

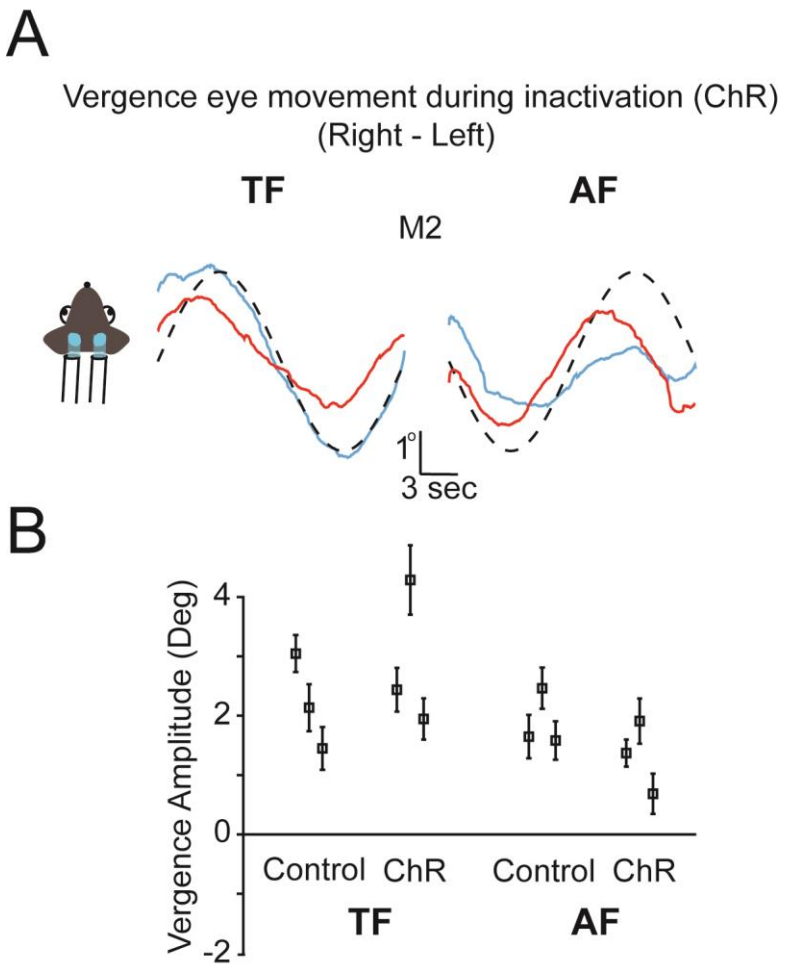

Figure 4.5. Visual cortex inactivation and vergence eye movements
A. Mean vergence eye movements of animal M2 during visual cortex inactivation for the toward first (left) and the away first conditions (right). Red line indicates the mean vergence eye movements during control condition while the blue line indicates when there was inactivation. **B.** Vergence amplitude comparison between control condition and ChR condition for toward first and away first stimulus across animals. Error bars indicate the standard error of the mean.

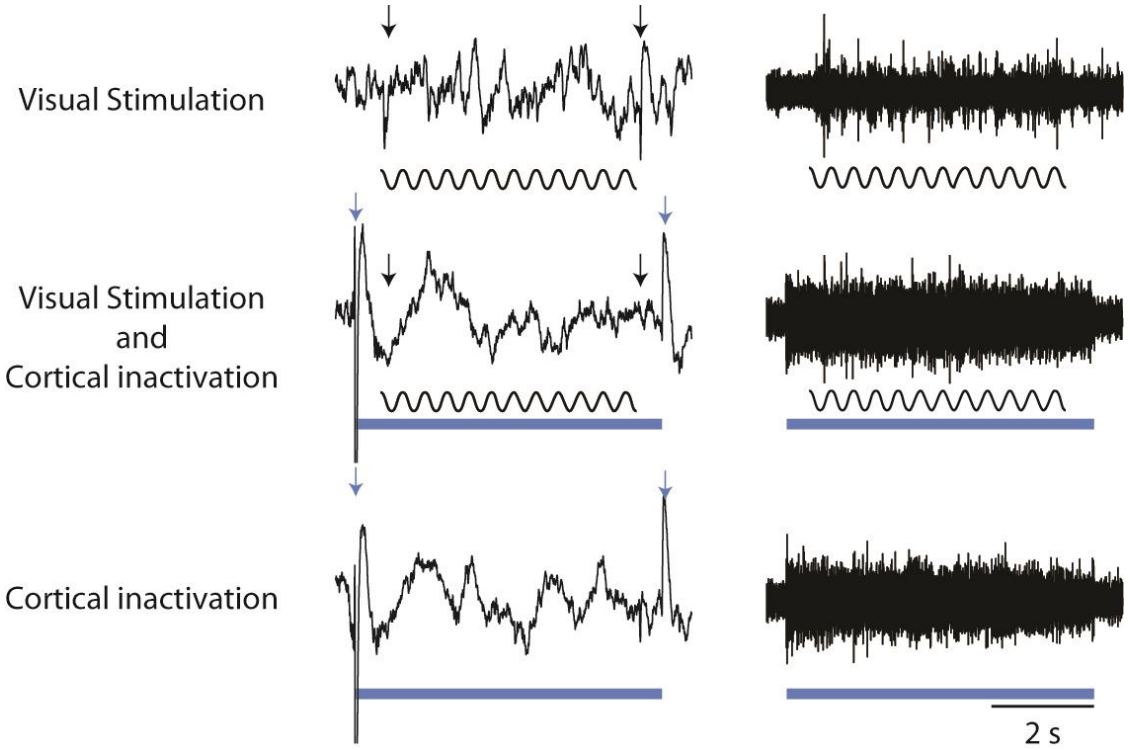

Figure 4.6. Extracellular recording during optogenetic stimulation
LFP and multiunit recordings during optogenetic stimulation. The blue square indicates the duration of optogenetic activation and the sinusoidal wave indicates the visual stimulus. Sinusoidal grating (with duration of 5 seconds) with 100% contrast with 45 degree orientation was used to stimulate the neurons in the visual cortex. Top: Mean LFP during visual stimulation (left) and a single trial of multiunit activity (right). The onset and offset LFP changes are indicated by black arrows. Middle: Mean LFP (left) and single trial multiunit responses (right) during visual and optogenetic stimulation. The optogenetic blue light (470 nm) came on 500 ms before the visual stimulation and lasted until 500ms after the visual stimulation. Black and blue arrows indicate the onset and offset of LFP responses to visual and optogenetic stimulation respectively. Bottom: LFP and multiunit responses during optogenetic stimulation only. Blue arrows indicate the onset and offset LFP response to optogenetic stimulation.

4.3e. Discussion

The visual system is confronted with the challenge of integrating the two retinal images to generate a single cyclopean perspective. We measured this integrative process through the binocular coordination of eye movements. In response to motion in 3-dimensional space, the eyes move in opposite directions (vergence eye movements). This OKR vergence eye movement helps to stabilize images onto the retina when the environment moves in depth. Vergence eye movements have been studied in primates, primarily focusing on those elicited by disparity cues (Masson et al., 1997; Erkelens & Collewijn. 1985) but less is known about the impact of motion in depth cues. To better understand the signals and circuitry that guide vergence eye movements, we developed a paradigm to measure these eye movements in mice where the visual pathways may be dissected.

We found that mice make vergence eye movements when viewing a stereoscopic stimulus that is primarily driven by motion signals (IOVD). We also demonstrate that these vergence OKR eye movements may be predicted by a sublinear combination of the responses elicited by monocular stimuli. While both eyes move in response to a monocularly presented stimulus, the eye that receives the motion signals moves more than the other eye. This asymmetry predicts vergence eye movements on the order of those elicited by binocular stimuli.

Responses in the neocortex have been implicated in the generation of vergence eye movements (Gamlin & Yoon, 2000; Takemura et al., 2007). While we found that disparity signals had little influence on vergence eye movements, visual cortex may nonetheless be an essential node in the visual pathway for these vergence eye movements. Wetherefore used two techniques to determine whether visual cortex plays a role in generating vergence OKR. First, we disrupted the development of binocular circuitry in visual cortex by

performing monocular deprivation during the critical period. This manipulation had little impact on the vergence OKR. Second, we used optogenetics to inactivate visual cortex while the animal viewed the stereoscopic stimulus. This manipulation also did not impact vergence OKR. Surprisingly we found a slight increase in the vergence OKR by this manipulation which may suggest that disparity suppress rather than enhance these eye movements. Both of these experiments suggest that processing along the geniculocortical pathway has little impact on the generation of vergence OKR and ablation of visual cortex has little impact on the ocular motor response. While the neocortex in rodents may not be the primary site to generate the OKR, it may nonetheless regulate the gain of these eye movements (Liu et al., 2016; Harvey et al., 1997; Tusa et al., 1989).

There are two potential models that could explain the vergence eye movements we observe. First, these vergence eye movements could arise from a binocular integration of sensory information from left and right eyes, which is then relayed to appropriate motor areas and converted into eye movements (Fig. 4.7A). Alternatively, the integration necessary for the execution of vergence eye movements may not require sensory integration, but instead be the product of the integration of motor signals resulting from sensory stimulation to each of the eyes alone (Fig. 4.7B). Our monocular experiment, in which we restricted visual signals to one eye, demonstrates that sublinear combination of left and right eye motor signals, instead of sensory signals, can account for OKR vergence eye movements (Fig. 4.3). While our monocular experiment largely agrees with the second model, there are still unknown variables influencing the gain of eye movements, as our predicted eye movements from the monocular condition has significantly larger vergence amplitude than in the control TF condition we observe. Previous studies in primates have hypothesized that various visual areas in the neocortex may exert influence on eye movements via sensory binocular integration (Liu et al., 2016; Harvey et al., 1997; Tusa et

al., 1989; Gamlin & Yoon, 2000; Takemura et al., 2007). Our cortical manipulation experiments demonstrate that the visual cortex does not directly drive OKR vergence eye movements, but leaves open the idea that cortical pathways may influence the gain of OKR vergence eye movement.

It is known that motion signals necessary for 2 dimensional OKR eye movements emanate from retinal processing in rodents. Eliminating starburst amacrine neurons in the mouse retina abolishes OKR in mice (Yoshida et al., 2001). The subcortical nature of the circuitry for vergence eye movements we have uncovered may reflect this difference in where direction selectivity is extracted. For rodents this initially occurs in the retina, whereas in primates, direction selectivity is often ascribed to processing in the visual cortex. Several subcortical structures are known to receive binocular projections and may be key to coordinating these vergence eye movements. The nucleus of the optic tract (NOT) is known to play an important role in OKR eye movement (Yakushin et al. 2000) and contains binocular neurons (Cynader & Hoffmann 1981). The superior colliculus is another subcortical structure that receives binocular input and sends out projections to the ocular premotor neurons. The superior colliculus receives direct retinal input that projects which innervates distinct collicular layers with matched in retinotopy (Drager & Hubel 1975). The superficial layer contains binocular neurons (Economides et al., 2018) and deep layer contains ocular motor neurons that generate saccades and smooth eye movements that can have vergence components (Wurtz & Albano, 1980; Schiller & Stryker, 1972; Robinson 1972; Van Horn et al., 2013). A bilateral lesions of the rostral superior colliculus can result in convergence palsy in humans (Ohtsuka et al., 2002), indicating that the superior colliculus may be essential node for the control of vergence eye movements. The binocular integration required for the OKR vergence eye movements we have measured likely rely on these subcortical structures.

While we have demonstrated that the neocortex does not provide an ongoing signal to evoke this vergence eye movement, the neocortex may nonetheless provide signals that are necessary to change the amplitude of this eye movement. Indeed, experiments that elicit plasticity in the oculomotor system appear require neocortical responses to adjust gain (Liu et al., 2016). Therefore, while we do not observe an impact of neocortical response of OKR vergence eye movements, they may be still essential to adjust eye movement gain.

In summary, we examined the signals underlying OKR vergence eye movements in mice and show that a motion signal (IOVD) is the primary driving signal behind this behavior. We also found the computation behind this vergence eye movement is a sublinear integration between left and right eye movements and surprisingly limited ongoing involvement of the visual cortex during this behavior.

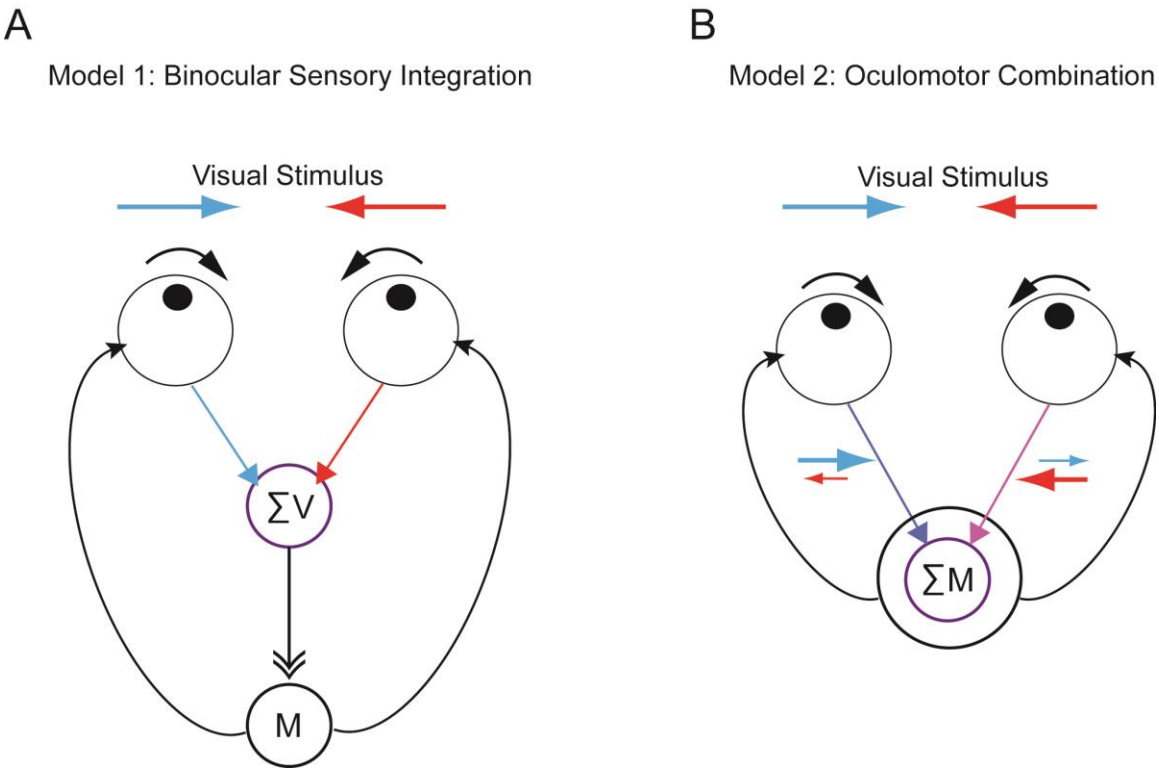

Figure 4.7. Models for OKR vergence eye movement
A. Binocular sensory integration model. The first model illustrates a mechanism in which sensory signals (red and blue) are first integrated and motor signals (black) are generated following that integration. **B.** Oculomotor combination model. The second model illustrates a mechanism in which vergence eye movement is generated by combination of motor signals from the two eyes. The visual signals drive asymmetric motor signals (purple) which are then summed to generate the vergence eye movement (black). Red: Leftward motion in right eye; Blue: Rightward motion in left eye. The motor signal from the two eyes are combined to generate vergence eye movement (black).

4.3f. Methods

Experimental Procedures

All procedures were approved by The University of Texas at Austin Institutional Animal Care and Use Committee and conformed to National Institutes of Health standards.

Animal preparation and surgery

Eight male and female mice were used in these experiments. To generate experimental animals for which visual cortex could be inactivated, PV-Cre knock-in mice (Scholl et al., 2015) were crossed to a Cre-dependent ChR2-EYFP strain (Madisen et al., 2012). These progenies selectively expressed ChR2 in PV+ interneurons.

To immobilize the head during training and our measurements, a titanium bar was placed on the skull and secured with dental acrylic under isoflurane anesthesia (Kuhlman et al. 2011). Craniotomies were made over the visual cortex in both hemispheres and covered with glass windows. Light penetration was blocked by occluding the window during periods in which no inactivation was used.

Awake eye movement recording

The animals were initially acclimated to the training apparatus for 3 days before the experiment. Animals walked and stopped freely on a floating Styrofoam ball while they were head-fixed (Dombeck et al., 2007). Polarizing lenses were mounted in front of each eye of the animals. After 3 days of acclimatization, we began to record eye movements in response to stimuli presented dichoptically. During all the experimental procedures and training, an IR camera recorded video of the eye movements at 30 Hz. An artificial eye with a diameter of 3.1 mm was used to calibrate eye position estimates. Eye positions were extracted (based on the center of the pupil) and analyzed using custom MATLAB software (Samonds et al. 2018).

Visual Stimulus

We used a DepthQ HDs3D2 projector (DepthQ/Lightspeed Design, Inc.) with a refresh rate of 120 Hz at full HD resolution (1920 x 1080), operating in gray-scale mode (mean luminance = 59.75 cd/m2). Stimuli were either rear-projected onto a polarization-

preserving screen (Da-Lite® 3D virtual black rear screen fabric, model #35929) or front-projected onto a silver polarization-preserving screen (Severtson, SeVision 3D GX, 2.2 Silver). The left and right images were modulated by a circular polarization alternator in front of the optics of the projector. One pixel subtended 0.1° at a viewing distance of 22 cm. Black and white dot motion stimuli moving in a sinusoidal motion (±12.4°) was generated using MATLAB (Mathworks, Natick, MA) and Psychtoolbox (Brainard, 1997). Each of 400 dots of 5-degree of the visual field in diameter was displayed within a 108-degree square aperture in front of the mouse and the stimulus lasted for 20 seconds followed by 15 seconds blank period.

The direction of motion of the dots varied between towards first condition (left eye: rightward motion first, right eye: leftward motion first) and away condition (left eye: leftward motion first, right eye: rightward motion first) and was randomly repeated during the trail.

Inactivation

We used a 470 nm fiber-coupled LED light (Thor labs) to activate ChR2. The light covered the entire 3 mm cranial window on both hemispheres and the intensity of the light was between 1-1.3 mW, measured by an optical power meter (ThorLabs, S130VC). The light was turned on 500ms before the stimulus and for the entire stimulus duration (20.5 s). Extracellular recordings were made from awake animals using 2 mega-ohm tungsten-in-glass electrodes (Alpha-Omega, Israel) while presenting visual stimuli (Scholl et al. 2013).

Monocular deprivation

Five male and female mice (P23-36) were used for monocular deprivation experiment. We sutured shut the right eyelid of each animal at age p23-24 under 1.5%

isoflurane anesthesia and checked daily that the sutures were intact. For three animals the monocular deprivation was successful for the period of 10 days and we examined the eye movements in those animals. At P30 we attached the head-plate (see animal preparation and surgery). At P33-34 we took the sutures out under 1.5% isoflurane anesthesia and artificial tear was applied to the opened eye. We waited one or two days before conducting our eye movement measures.

Data Analysis

Vergence was calculated by subtracting right eye position to left eye position. We eliminated eye movement traces that had more than 5 saccades (saccade was defined by motion within 3 frames larger than 5 degrees) in a given trial. Because the motion in depth stimulus was sinusoidal, the vergence amplitude was computed from the fundamental frequency of the motion in depth signal using Fourier analysis. Vergence amplitude was calculated by the peak-to-trough at the frequency of the motion in depth signal. The standard deviation and error of these amplitudes were computed from the projection onto the mean vergence trajectory for toward first and away first conditions.

4.4. Conclusions

In this chapter, I discussed vergence eye movements that are driven by binocular integration. Mammals make coordinated eye movements to 2-dimensional movements around the world (version). Similar eye movement, but in opposite direction, occurs when there are 3-dimensional movements in the environment (vergence). Even though there have been numerous studies on primate visual system and eye movements that occur during various visual tasks, we do not know the binocular computation behind vergence eye movements. Using mice, I discovered a possible sublinear binocular integration that can

account for OKR driven vergence eye movement. I showed that this computation is unlikely occurring in the neocortex as silencing the visual cortex had little impact on the vergence eye movement. In the next chapter, I will propose some possible subcortical areas that could be involved in this binocular computation.

Chapter 5: Future directions

5.1. Overview

The first two chapters in this dissertation discuss various signals involved during motion-in-depth cues. In chapter 3, I presented data suggesting behavioral motion-in-depth discrimination is most likely occurring in the visual cortex in mice. In chapter 4, I showed that unlike behavior discrimination, the binocular integration responsible for OKR vergence eye movements does not depend on the visual cortex. In this chapter, I will go into detail about subcortical regions that are known to possess binocular neurons and areas in which the computation behind OKR vergence eye movement could be occurring.

5.2. Future directions

As briefly mentioned in the previous chapter, there are several areas in the visual pathway that contain binocular neurons. Traditionally, it was believed that signals from the left and right eye are well segregated until they reach the primary visual cortex (V1). It has been well-documented that most neurons in of primate V1 are binocular and show tuning property that arises from the integration of left and right eye (disparity) (Hubel & Wiesel, 1973; Pettigrew et al., 1968; Nikara et al., 1968; Joshua & Bishop, 1970; Barlow et al., 1967; Poggio & Fischer, 1977). Although not prominent, there are studies showing evidence for binocular neurons in the subcortical areas independent of the visual cortex. In this chapter, I discuss some subcortical areas that are known to contain binocular neurons and could have functional implications, such as generating vergence eye movements.

5.2a. Binocular neurons in the lateral geniculate nucleus

The percent of binocular cells are considerably small in the lateral geniculate nucleus (LGN) compared to the primary visual cortex (V1) (Cat: Murphy & Sillito, 1989; Monkey: Zeater et al., 2015). In the LGN of both cats and monkeys even though there are

fewer binocular neurons, there are populations of neurons that are modulated by binocular input. Most reports show binocular modulation primarily reducing the response of neurons in the LGN (Cat: Xue et al., 1987; Monkey: Marrocco & McClurkin, 1979; Rodieck & Dreher, 1979).

The primate LGN is organized through parvocellular (P), magnocellular (M), and Koniocellular (K) layers (Norton et al., 1988; Xu et al., 2001). K neurons constitute for less than 10% of the LGN population and are the least studied neuron in the LGN. Despite their sparseness, recent studies have shown a portion of K neurons responding to binocular stimulation (Cheong et al., 2013; Zeater et al., 2015) and M neurons are known to carry information about motion which makes it an attractive neuron to study binocular integration for motion-in-depth cues (Andrews & Blakemore, 2002). Similar to primates, mice LGN also contains neurons that respond to binocular stimulation. And it has been shown that cortical feedback to the LGN does not account for the response of the binocular cell in the LGN (Howarth et al., 2014). This evidence suggests that in both primate and mice, binocular neurons in the LGN might carry important role to assist behavior that requires binocular integration (such as vergence eye movement).

5.2b. Binocular neurons in the superior colliculus

The superior colliculus (SC) is one of two major areas that receive direct input from the retina, the other being the LGN. The superficial layers of the SC receive visual inputs from the retina as well as the visual cortex and the pretectum. (Interestingly in rodents, the retinal projection to the SC is greater than the projection to the LGN). The superior colliculus receives direct retinal input which innervates the superficial collicular layers in a retinotopic fashion (Drager & Hubel, 1975). The superficial layers of the SC project to deeper motor area where it is shown to have neurons topographically organized to the

direction and amplitude of saccade eye movement (Sparks et al., 1976). The SC also integrates information from multiple modalities.

Traditionally, it was viewed that there is a segregation within the superficial SC by ocular input, but recent studies have shown evidence for binocular neurons present in the stratum griseum superficial of the SC and that binocularity persisted in strabismus animals (Economides et al., 2018). Also there is evidence for neurons in the SC responding to vergence eye movements (Van Horn et al., 2013) and bilateral lesions of the rostral superior colliculus can result in convergence palsy in humans (Ohtsuka et al., 2002) which indicates that the superior colliculus may be essential node for the control of vergence eye movements. These studies strengthen the argument for binocular integration occurring in the SC.

Even though there has been some evidence for binocular responses in the SC, these binocular responses may reflect the influence of binocular inputs from the visual cortex or LGN. Nonetheless, because of the heavy influence of the SC in eye movements, the SC is a good area to investigate binocular integration required for vergence eye movements.

5.2c. Binocular neurons in the cerebellum

The cerebellum is another major area within the vertebrate hindbrain that is well known for its role in the control of movements. Therefore, it is not surprising that the cerebellum plays a major role in generating accurate and smooth eye movements. The cerebellum is known to be involved in most voluntary eye movements such as saccades and smooth pursuit. Lesions of the oculomotor vermis results in inaccurate saccadic eye movements (Barash et al., 1999) and bilateral ablation of the flocculus reduces the gain in smooth eye pursuit (Zee et al., 1981). Neurons in various parts of the cerebellum (such as the caudal part of the fastigial nucleus, cerebellar vermis and flocculus) are known to

discharge in response to saccadic eye movements as well as smooth eye pursuit. (Ohtsuka & Noda 1991; Fuchs et al., 1993; Ohtsuka & Noda 1995; Miles et al., 1980). Although cerebellum plays a big role in eye movements, it is not thought to be responsible for the initiation of the movement; rather, it is responsible for finely tuning the movement. For this reason, the cerebellum has to receive information about the position and the eye movement that was initiated. The cerebellum receives a projection from the nucleus reticularis tegmenti pontis (NRTP) and dorsolateral pontine nucleus (Leigh & Zee, 2006) and those areas receive signals from the frontal eye field (Ono et al., 2004).

Even though we have a good understanding of the role that the cerebellum has on these voluntary 2-dimensional eye movements, there have been fewer studies on eye movement generated by 3-dimensional movement. More importantly, there has been lack of evidence suggesting binocular neurons in the cerebellum that could integration depth signal generated from left and right eyes. Even so, people with damage to the cerebellum have lower gain in their vergence eye movement (vergence during pursuit) (Sander et al., 2009). And studies have shown neurons in the cerebellar dorsal vermis are tuned to vergence eye movement. Silencing these neurons results in a reduction of vergence velocity (Nitta et al., 2008; Zhang & Gamlin.1998). Several studies show the cerebellum plays a role in vergence eye movements (especially the smooth pursuit vergence eye movements) but it is unclear if the signals we observe in the cerebellum are derived from other areas of the brain (cortical or subcortical) or if the binocular integration is occurring in the cerebellum itself. Further studies need to be conducted to determine if there are true binocular neurons in the cerebellum.

5.2d. Binocular neurons in the nucleus of the optic tract

The nucleus of the optic tract (NOT) and dorsal terminal nucleus (DTN) are another possible areas where binocular information from the two eyes could be integrated to generate vergence eye movement. As shown from my experiments with mice vergence eye movements, a critical computation in generating the OKR vergence eye movement is the integration of motion signals from the two eyes. Neurons in the NOT are direction-selective and send signals to ocular motor areas (Yakushin et al. 2000). Also in primates, the NOT receives bilateral projections from the retina which makes the NOT neurons binocular (Kourouyan & Horton 1997; Telkes et al., 2000; Cynader & Hoffmann, 1981). But similar to the cerebellum, it is unclear if the binocularity that we observe in the NOT or DTN is due to binocular integration within the NOT or reflects upstream integration as these areas receive inputs from several visual cortical areas (MT, STS, V1) (Monkey: Hoffmann et al., 1991; Lui et al., 1995; Distler & Hoffmann, 2001; Rat: Schmidt et al., 1993; Cat: Schoppmann, 1981).

Some studies in cats have shown strong evidence for cortical binocular integration impacting the NOT. It has been shown that infant kittens lack binocular neurons in the NOT and only after cortical projection to the NOT has been established, the neurons in the NOT response to both contra and ipsilateral stimulation (Distler et al., 1999). Monocular deprivation and strabismus, which are both known conditions that alter binocular neurons in the visual cortex, weaken the binocular signals in the NOT (Cynader & Hoffmann, 1981; Grasse et al., 1984) and lesions of the visual cortex in cats severely deprive binocular convergence on accessory optic system (AOS) (Grasse et al., 1984).

Even though there is some evidence suggesting cortical influence for binocularity in NOT in cats, it not known if primates and rodent follow the same pattern. Further studies are required to rule out NOT as a possible area for binocular integration responsible for OKR vergence eye movement.

Chapter 6. Conclusions

The sensory system allows us to interpret signals in our surroundings which help guide us in making appropriate behavioral decisions fit for the environment. The visual system integrates signals from the left and right eyes to generate a representation of the world in depth and primates use images and motion from the two eyes to compute depth signal in the environment. Motion-in-depth signals can be generated by comparing the difference in the image in the left and right eye (CDOT) and by comparing the speed and direction of motion in each eye (IOVD). Even though there have been numerous studies in humans and non-human primates on signals that generate depth cues, it is still unclear what the computation behind binocular integration is that generates motion-in-depth signals. In this dissertation, I introduced mice as a new animal model to study the computation behind depth signals which has 40 degree of binocular visual field and is known to possess binocular neurons that are disparity selective in the primary visual cortex (Scholl et al., 2013). Here, I investigated two different behavior evidence for binocular integrations that occur in mice during motion-in-depth signals and attempt to dissect the circuitry behind binocular integration during this depth signals.

In this dissertation, I briefly explained two signals (disparity (CDOT) and motion (IOVD)) that are known to create motion-in-depth cues in primate (chapter 2). The CDOT signal is generated from computing the disparity signals (generated by comparing images on the left and right eyes) and integrating the disparity signals over time. In chapter 2, I discuss binocular energy model that is widely used to explain how disparity selectivity could arise in the primary visual cortex. I also discussed speed and direction tuning that is critical in IOVD signals. Next, I discussed behavior evidence of motion-in-depth discrimination in primates and rodents (chapter 3). In this chapter I also discussed thalamocortical pathway where the visual cortex is one of the key areas involved during motion-in-depth discrimination task. In primates and cats, the visual cortex is a well-known

area that integrates left and right eye inputs and V1 contains disparity-selective and direction-selective cells which makes it an attractive area to study the computation behind depth signals (Hubel & Wiesel 1973; Pettigrew et al., 1968; Nikara et al., 1968; Joshua 1970; Barlow et al., 1967; Poggio & Fischer, 1977). Higher order visual area such as MT receives projections from the visual cortex and area MT is known to contain neurons tuned for 3-dimensional space (Czuba et al., 2014; Sanada & DeAngelis, 2014). Given the evidence from previous studies in primates and the similarities primates and rodent share in their visual pathways, I speculated that rodents might be able to conduct motion-in-depth discrimination similar to primates. Mice are now commonly used to study vision as genetic tools to manipulate and target specific cells and areas of the brain have made the circuitry more accessible. Identifying if mice can perform motion-in-depth discrimination task is a crucial step is studying binocular integration as it is the first proof that mice can utilize integrated signals from left and right eyes.

I designed a behavioral paradigm in which mice had to make a decision (stop or go) based on motion-in-depth signals presented to them. These motion-in-depth signals were generated by combining opposite moving grating presented in each eye which gives the animal both disparity cues as well as motion cues. This stimulus generates grating moving towards and away in human perception. I conducted multiple control experiments to assure that the motion signal presented to the animals was the cue that drove the behavior (see chapter 3). I also discovered that the visual cortex is required for the mice to discriminate motion-in-depth signals as silencing the visual cortex abolished the behavior.

These results suggest that mice, similar to primates, can utilize disparity and motion signals from each eye to discriminate motion-in-depth signal and the visual cortex is the area that is responsible for this computation. Even though our experiment showed clear behavioral discrimination in our task, the performance was not high enough to perform

psychophysical experiments. I understand that this is a difficult task for the animals and the training took longer than other behavior training conducted in mice. Nonetheless, mice can use integrated information from the left and right eye and would be a great model to study the mechanism behind binocular integration further.

In the second part of this dissertation, I investigated a natural eye movement behavior that occurs when presented with motion-in-depth signals (chapter 4). Most eye movement studies have been conducted using primate model and most evidence from the studies suggest large cortical influence to the eye movements. However, there are fewer studies on eye movement on rodent models. To study the binocular integration required during vergence eye movement, I presented motion-in-depth signal to mice and measured their OKR vergence eye movement. Mice retina are not foveated so we decided to use OKR signal which is known to generate eye movement in non-foveated animals (Fite et al., 1979; Hess et al., 1985; Fritsches et al., 2002; Collewijn, 1975; Katte & Hoffmann 1980).

I found that mice make vergence eye movement when opposite moving full-field random dots are presented in each eye. I found that the vergence eye movements are motion driven and disparity alone could not elicit vergence eye movements. This is different from primate studies as humans are very good at using disparity signals to generate vergence eye movement. I also discovered that the computation that occurs between left and right eye during vergence eye movements could be explained through sublinear combination and the eyes are not simply following the stimulus presented in each eye. The unbalanced movement between left and right eye when presented with monocular signals drives the OKR vergence eye movement in mice.

For many years, the cortical influence on eye movements have been well documented and studied in primates. Surprisingly in our experiment, I found no cortical contribution in the generation of OKR vergence eye movement as monocular deprivation

and ontogenetic silencing of the visual cortex had little impact on these eye movements. This suggests that the binocular integration responsible for vergence eye movements is occurring someplace in the subcortical area of the brain.

In chapter 5, I discussed possible subcortical areas that could be important for OKR vergence eye movement. There are couple subcortical areas (superior colliculus, NOT, and the cerebellum) known to have binocular neurons that could be involved in vergence eye movements. Even though the visual cortex might not be the area involved in OKR vergence eye movement, it is still involved in the interpretation of motion-in-depth signal as silencing V1 abolishes mice ability to discrimination motion-in-depth signals (chapter 3).

In this dissertation, I provide a basic foundation for how mice can be used to study the binocular integration. Rodents have become a popular animal model to study the visual system in recent years as the genetic advantages of using mice allow us to target, manipulate, and tag specific cell types while being minimally invasive to the animal. This allows us to study the visual system in a way that was not possible in primates. Even though mice don't have foveated vision and have a small binocular visual field, mice share many commonalities with the primate visual system. Mice have simple and complex cells in the visual cortex and those cells are tuned to orientation and disparity. The details of the composition and organization may be slightly different from primates, but overall the signals conveyed by the visual system seem to be similar to primates.

I demonstrate that mice can discriminate motion-in-depth signals and the binocular neurons in the visual cortex are critical for this computation. Future work is needed to investigate the specific computation on these binocular neurons during depth stimulus. I also show that that mice make vergence eye movements when there is a large global motion presented in both eyes moving in depth and that the computation is occurring subcortically. These two experiments provide behavior evidence of binocular integration in mice and

provide groundwork on investigating the mechanism behind mammalian binocular integration.

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