CHARACTERIZING CORTICAL VISUAL RESPONSES NEAR THE PERCEPTUAL THRESHOLD

by

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At any given moment, our brain is processing a large amount of sensory information, yet we are only consciously aware of a small portion of it. Information that we perceive must reach a perceptual threshold, which is defined as the point at which a subject can consciously recognize a presented stimulus 50% of the time. However, perceptual thresholds are not static - they vary from day to day and over the course of experimental tasks. Previous research at the single-cell level has suggested that our sensory perception strongly depends on the brain's internal dynamics, often referred to as behavioral state, which changes based on factors like locomotion, arousal, and attention. Yet, whether behavioral states can account for fluctuations within perceptual thresholds is not known. The goal of my project was to characterize the dynamic range of population level neural responses to visual stimuli that varied in contrast and duration. Using wide field calcium imaging of transgenic mice, I identified maximum and minimum neural responses, quantified the population-level neural threshold, compared these values across cortical visual areas, and identified stimulus parameter values that likely lie near the perceptual threshold. In future work, pupil diameter and running speed will be tracked alongside neural activity in response to the near-threshold stimulus parameters I identified to further our understanding of how behavioral state influences conscious awareness.

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Introduction

A fundamental function of the brain is to generate subjective, reportable experiences, otherwise known as conscious awareness (Dehaene and Changeux, 2011). At any given moment, our brain is processing a large amount of sensory information, yet we are only consciously aware of a small portion of it. Although conscious perception is an experience we are deeply familiar with, our scientific understanding of its underlying neural mechanism is still in the early stages.

The visual system is the most used modality within consciousness research, in part because of our reliance on vision to navigate our world and also due to our extensive knowledge about the neuronal pathway that underlies it (LeDoux et al., 2020). For us to visually perceive a given stimulus, photons of light are first received and transformed into neural signals by retinal cells. These signals leave the retina via the optic nerve and are conveyed to the lateral geniculate nucleus (LGN) in the thalamus, then on to the primary visual cortex or V1, which can detect certain features of a stimulus such as orientation and direction. From there, neural activity is conveyed to higher order visual areas (HVAs) which spatially surround V1 within the cortex. The HVAs integrate more complex qualities of an image, like its color, brightness, form, and motion, in addition to incorporating other sensory information from other brain regions carrying out different functions.

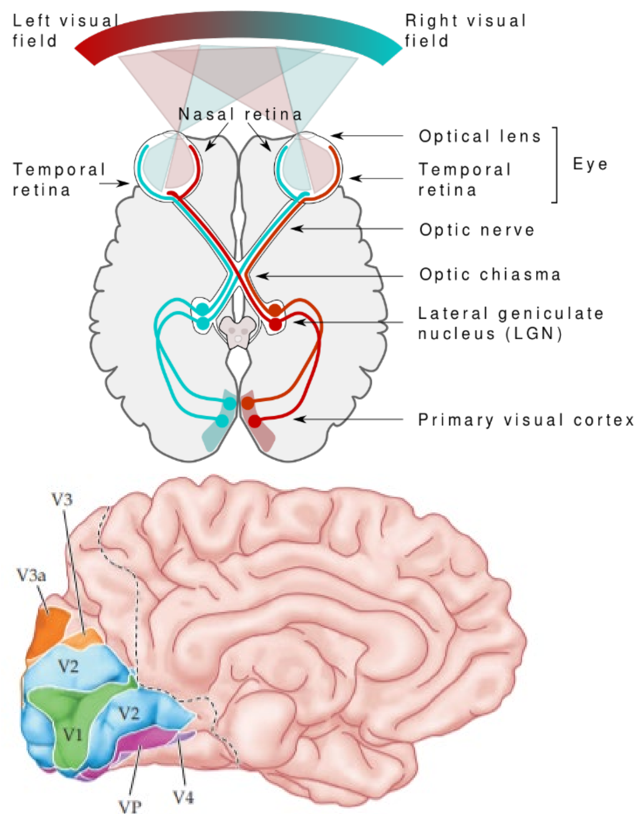

Figure 1: Basic visual system pathway and anatomy

Top: Schematic of primary visual pathway from the retina to primary visual cortex. Image by Miquel Perello Nieto, distributed under a CC BY-SA 4.0 license. Bottom: Medial view diagram of primary visual cortex (V1) and higher order visual areas (HVAs). Image taken from Purves et al., 2012.

How can we study consciousness? Visual consciousness is often studied using subjects who participate in tasks that require them to report whether they see or do not see a presented image. Since information that we perceive must reach a certain threshold of neural activity, the subjects' brain activity during the task is recorded and can be used to associate specific neural responses with conscious awareness. There is both a neural threshold, based on how neural activity changes in response to stimulus parameters, and a perceptual threshold which is based on a behavioral report. In visual consciousness research, the perceptual threshold is defined as the point at which a

subject can report seeing a presented stimulus 50% of the time it is presented (Kalloniatis and Luu, 2011).

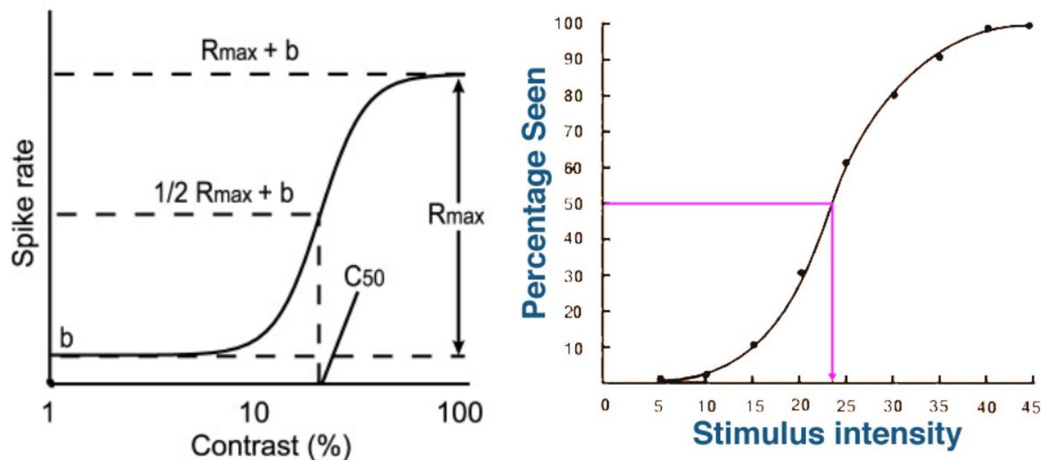

Figure 2. Diagram of a neural and perceptual threshold

Left: A contrast-response function showing the neural threshold of a single neuron, where Rmax is the maximal neuronal response and C50 is the contrast which evokes half of the maximal neuronal response (taken from Soma et al., 2013). Right: General definition of a perceptual threshold, a stimulus parameter value where the subject can report seeing a presented stimulus 50% of the time it is presented (indicated by the pink arrow). Figure taken from Kalloniatis and Luu, 2011.

Recent investigations into the neuroscience of consciousness using humans and primates have suggested that conscious perception is associated with greater neuronal activity in HVAs (Dehaene et al., 2001; Sergent and Dehaene, 2004; Van Vught et al., 2018). However, the perceptual threshold at which this transition occurs is not static – it can vary from day to day and over the course of experimental tasks (Busse et al., 2011). One possible explanation for this observation concerns the brain’s internal dynamics, often referred to as behavioral state, which is known to greatly affect our sensory perception (McCormick et al., 2020). A behavioral state which we are all familiar with

is the state of sleep, in which our ability to perceive sensory information dramatically decreases, but the definition also encompasses factors like locomotion, arousal, and attention (McCormick et al., 2020; Niell and Stryker, 2010). Visual detection tasks have been used to investigate behavioral states' effect on sensory perception using stimuli at either low, medium, or high parameter values, however, these studies have not yet incorporated a range of parameters around the perceptual threshold. Thus, whether behavioral states can account for fluctuations within perceptual thresholds is not known.

The goal of my project was to characterize the dynamic range of population level neural responses to near-threshold visual stimuli and compare across visual areas in a mouse model. I achieved that by displaying stimuli that varied in contrast and duration during simultaneous wide-field calcium imaging of cortical visual activity. In future work, pupil diameter and running speed will be tracked alongside neural activity in response to parameters I identified to further our understanding of how behavioral state influences conscious awareness.

Mice in particular present a promising model for future consciousness research as there is a vast toolbox of methods for precise neural manipulation which can be used to overcome the technical and ethical barriers typically seen in humans and primates (Dehaene and Changeux, 2011). Further, the mouse visual system resembles primates in its organization and functional complexity and mice rely on vision to perform natural behaviors (Huberman and Niell, 2011; Hoy et al., 2016). Notably, wide-field calcium imaging can capture neural population activity across the mouse cortex, and thus provides a comparable technique but at a higher resolution and greater spatial coverage to functional magnetic resonance imaging (fMRI) and electroencephalogram (EEG)

methods used in past human and primate studies (Dehaene et al., 2001; Wekselblatt et al., 2016).

Research that has attempted to characterize the neural mechanisms of consciousness is especially relevant for patients with disorders of consciousness, such as people in comas, minimally conscious states, or vegetative states. In some studies, signs of conscious perception have been detected in a small proportion of people who are non-responsive, suggesting the possibility of future therapeutics directed at the recovery and restoration of consciousness if we are able to understand and manipulate the underlying mechanism (Sohn, 2019). Additionally, understanding the effects of behavioral state on consciousness has potential applications to optimizing our sensory perception and aiding with disorders of attention, such as attention deficit hyperactivity disorder (ADHD).

Literature Review

Behavioral state originated in humans with techniques such as fMRI and electroencephalogy (EEG), where researchers found that global brain activity followed distinct electrical patterns that corresponded to specific behavioral contexts (McCormick et al., 2020). The state of sleep versus wake and selective attention were extensively studied at first within humans, however, with the use of mice, studies looking into arousal and motor activity have become more relevant.

Several studies in the mouse visual cortex have found that locomotion corresponds with enhanced visual responses to subthreshold stimuli through means of increasing the neural response amplitude and decreasing the membrane potential variability (Bennett et al., 2013; Niell and Stryker, 2010). Additionally, arousal, as

measured by pupil diameter, has been found to follow an inverted-U shape trend shown in Figure 3 (McCormick et al., 2020). At intermediate levels of arousal, neural responses and behavioral performance have a maximal peak, whereas at low or high levels of arousal both responses decrease (McCormick et al., 2020).

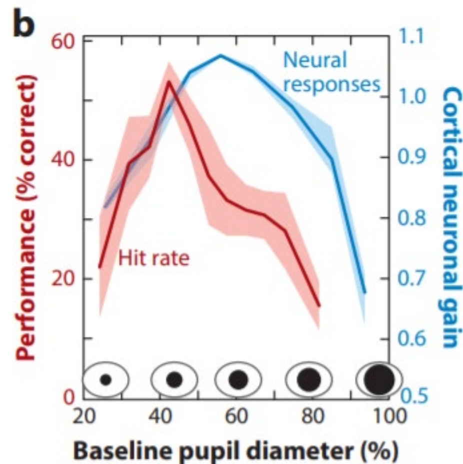

Figure 3: Effect of arousal on neuronal responses and behavioral performance

This figure illustrates the inverted-U shaped trend of arousal on neural activity and task performance. Figure taken from McCormick et al., 2020.

Most studies have been conducted at the single-cell or synaptic level, but recent studies have suggested that neural population activity could underlie observed behavioral state effects (Reimer et al., 2014). Specifically, it is believed that neuromodulation by neurotransmitters such as norepinephrine and acetylcholine could function to shift the balance of excitation and inhibition to alter neuronal responsiveness to sensory stimuli (McGinley et al., 2015). My research will build on past behavioral state and consciousness studies by recording population-level neural activity while using a range of stimulus parameters near the perceptual threshold.

Research Questions and Hypotheses

There are three research questions guiding my investigation:

1. What is the dynamic range of cortical visual activity during viewing of visual stimuli of varying contrast and duration?
2. How does the dynamic range vary across cortical visual areas?
3. How does behavioral state, such as arousal and locomotion, affect mouse visual cortex neural responses to near threshold visual stimuli?

The first question is narrow but will provide valuable information for our specific project model since characterizing the dynamic range will allow for further precision when selecting stimuli parameters for future experiments. Further, this information has not been categorized at population level, or compared across visual areas, thus motivating my second research question. The third question is broader and addresses the goals of the long-term, subsequent projects that will build from my own research.

I hypothesize that the neural threshold for contrast will be around 6.25% which is similar to what has been found in single neuron studies (Niell and Stryker, 2010). I also predict that the neural threshold for duration will be less than 250 ms as that is within the range of response latency on behavioral tasks. I am uncertain how different visual areas will respond to near-threshold stimuli of varying contrasts and durations as this has not been characterized at the population level before. One possible outcome is that higher order visual areas that are more sensitive to contrast and duration might have a lower neural threshold.

Methods

Animal Care

All experimental procedures were carried out under protocols approved by the University of Oregon Institutional Animal Care and Use Committee. Two adult tetO-GCaMP6s transgenic mice, both male and female, were used in this experiment. Animals were maintained in the animal facility at the University of Oregon on a 12h light/12h dark reverse light cycle. Imaging occurred during the dark phase of the cycle.

TetO-GCaMP6s Mice

Our mice are transgenically engineered to express the fluorescent calcium indicator GCaMP6s in cortical excitatory neurons under the control of a tetracycline-controlled transactivator (tTA) driver line. When calcium binds, such as at the end of a neuronal action potential, and the cortex is illuminated with blue light from the wide-field calcium imaging set-up, active neurons brightly fluoresce allowing us to record global neuronal activity dynamics.

Surgical procedures

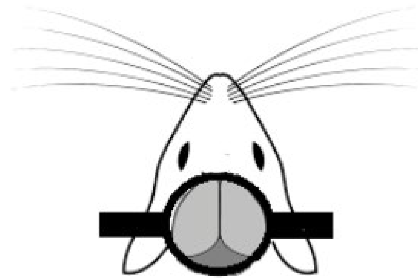

Figure 4. Top-down diagram of cranial window headplate

Image modified from Van Rheede, 2020.

Mice were surgically altered with a cranial window implant and coverslip, following procedures based on Wekselblatt et al. (2016). Animals were anesthetized using isoflurane (4% induction; 1.1-2% maintenance) in 100% O2 (1.1 L/min). Body temperature was maintained at 37.5°C by a feedback-controlled heating pad. The animal's breathing and level of anesthesia was monitored throughout the procedure. Sterilized instruments and aseptic techniques were used throughout the procedure. The animal was positioned in a stereotax with their head stabilized by earbars. Using cotton-tip applicators, scalp hair was removed with Nair and the surgical site was cleaned using three alternating applications of betadine and isopropanol.

The animal's scalp was incised and the skull was cleared of connective tissue. VetBond was used to readhere the edges of the scalp to a lower position on the skull. An 8mm headplate was then attached to the skull using liquid superglue and the opening in the headplate was filled with superglue. A clear plastic coverslip was added on top of the superglue layer so that it covers the entire visual cortex and was left to dry.

Near the end of the procedure, the animals were given subcutaneous injections of 0.5 ml Carprofen (5 mg/ml) and 0.25 ml saline for post-operative pain and dehydration. Animals were then transferred to a clean, 37°C heated cage and provided a petri dish of dissolved Nutri-Cal. The mice were allowed to recover for a week before being extensively handled.

Spherical Treadmill and Wide-field Calcium Imaging

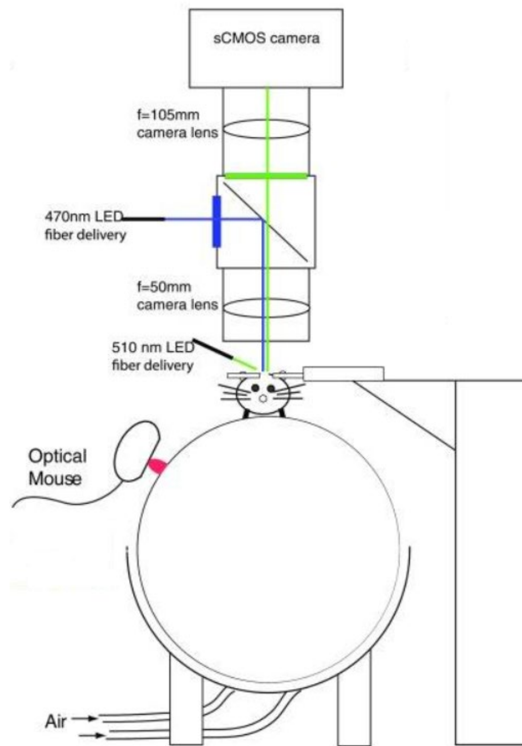

Figure 5. Spherical treadmill and wide-field calcium imaging set-up

Figure taken from Wekselblatt et al., 2016.

We conducted wide-field calcium imaging using a custom-built macroscope positioned directly overhead the mouse's headplate. This technique allowed us to monitor cortical dynamics across the entire dorsal surface at 50 μm and 10 Hz resolution throughout our experiments. During imaging, mice were set-up on a spherical treadmill with the mouse's headplate attached to a fixed crossbar that hung above a freely rotating Styrofoam ball. A computer monitor was placed in front to cover most of the mouse's visual field. A custom MATLAB script generated and displayed visual stimuli (shown in Figure 6) on the computer screen and recorded the mouse's corresponding neural activity.

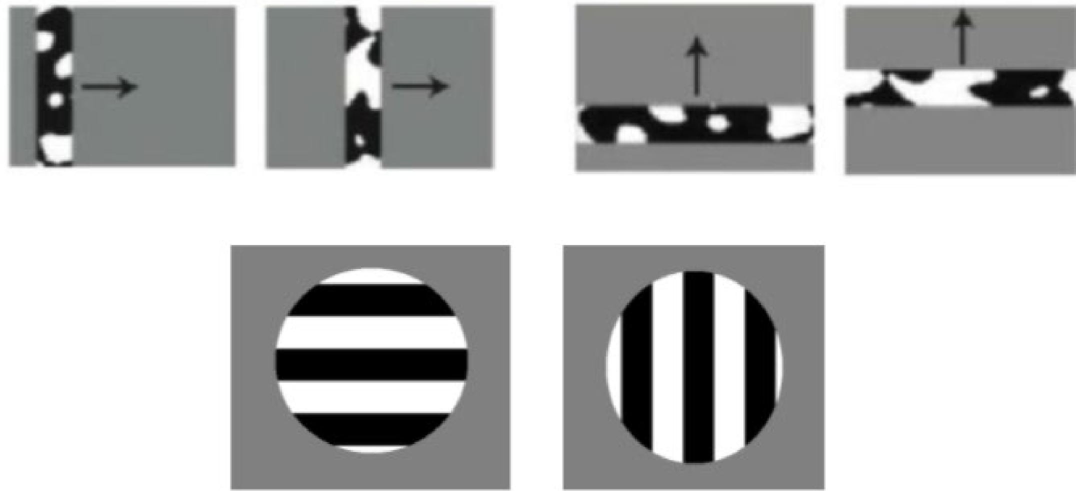

Figure 6. Examples of presented stimuli

Top: Representation of TopoX (Left) and TopoY (Right) stimuli (Wekselblatt et al., 2016). Bottom: Representation of circular grating stimuli that varied in contrast and duration.

MATLAB Data Analysis

Using custom MATLAB scripts, fluorescence values were calculated for each pixel within each image frame as dF/F, or the fluorescence change relative to baseline activity (the mean fluorescence over the recording period). For further analysis, specific points were selected in different visual areas and compared across duration and contrast, generating Figures 11-15.

Results

Retinotopic Mapping of Primary Visual Cortex

To evaluate and ensure proper headplate fixation and visualization of V1, we performed wide field calcium imaging to generate a retinotopic map of the visual cortex prior to imaging with any stimulus. Using a moving window of periodic topographic noise shown in Figure 6, we generated maps of the preferred locations in visual space of the entire visual cortex at the population level. This allowed us to estimate the locations of visual cortical regions for each mouse by using an overlay of landmarks.

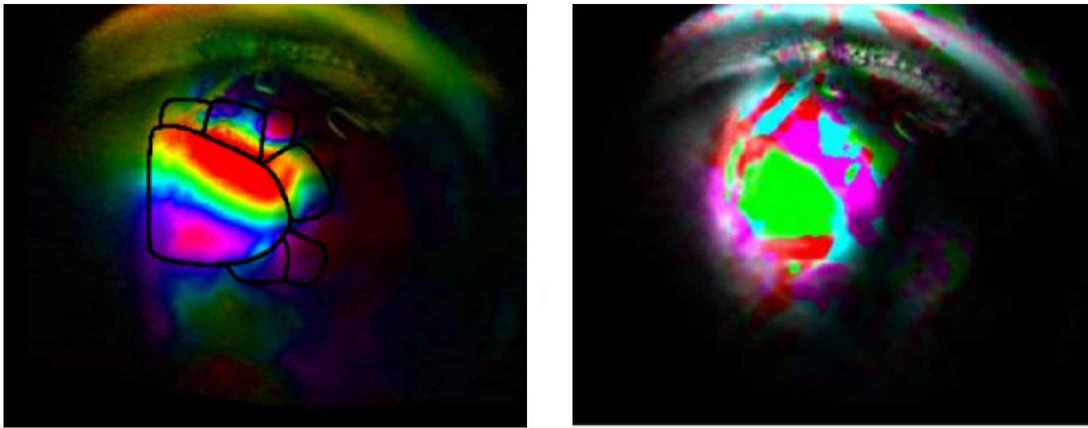

Figure 7. Retinotopic mapping of the mouse visual cortex

Left: Retinotopic map overlay shows estimated location of primary visual cortex and higher order visual areas from a topoX task. Right: Estimated visual cortex architecture based on both topoX and topoY data.

Pixelwise Neural Response to Stimuli of Varying Contrast and Duration

We next measured neural activity while mice passively viewed a random order of circular grating stimuli at seven contrast levels (0, 3, 6, 12, 25, 50, 100%) and five durations (16, 33, 66, 133, 266 ms). Both contrast and duration values were based on a uniformly spaced log scale. Duration values were selected to be less than 250 ms because that is within the range of response latency on behavioral tasks.

For Figure 8 and Figure 9, the brain activity for a given contrast or duration value, respectively, was averaged across all trials of that value. Each row shows the time course of recorded neurons throughout the stimulus presentation, including a short period before the stimulus was presented, when the stimulus was on the screen, and after it was off the screen.

From these results, we determined that there was a contrast and duration dependent increase in overall neural activity in response to visual stimuli, which is the general trend we expected to see. Notably, the duration pixel wise graphs show less maximal activity than the contrast pixel wise graphs because we chose a shorter range of durations.

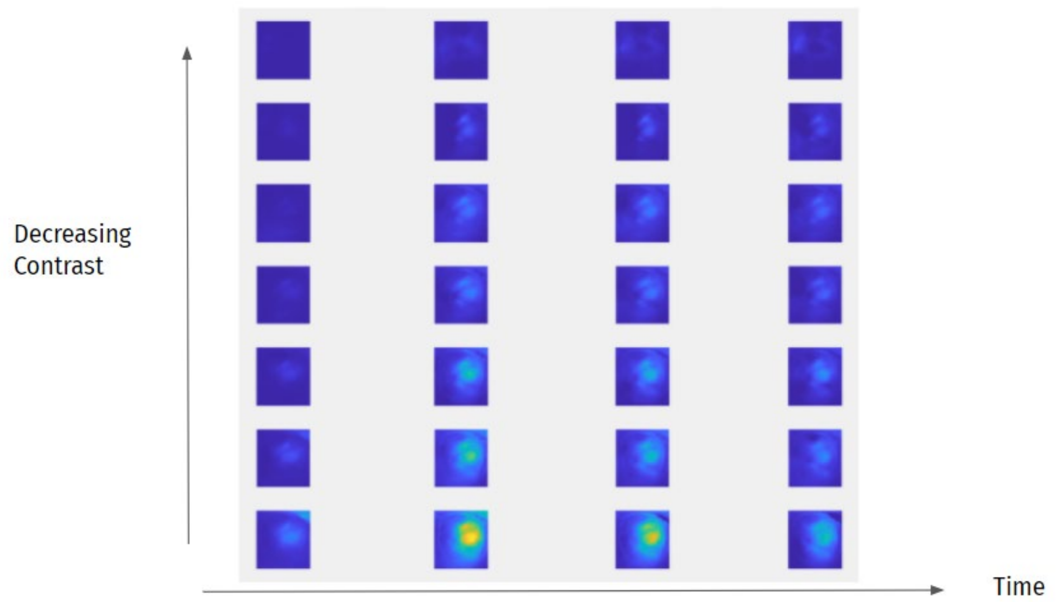

Figure 8: Pixelwise graphs based on contrast

Average visual cortex fluorescence at stimulus onset across all trials of different contrast values over time.

Figure 9. Pixelwise graphs based on duration

Average visual cortex fluorescence at stimulus onset across all trials of different duration values over time.

Comparing Fluorescence Across Visual Areas by Contrast

In Figure 10, five points were selected for further analysis, using a pixel-wise image of peak fluorescence, or the maximal neural response, averaged across all trials. The selected points targeted the primary visual cortex (V1), three higher order visual areas (LM, AL, AM), and a control point which should not fluoresce. The higher order visual area points were selected based on their ease of identification and to test for differences between HVAs that are at different stages within visual processing hierarchy.

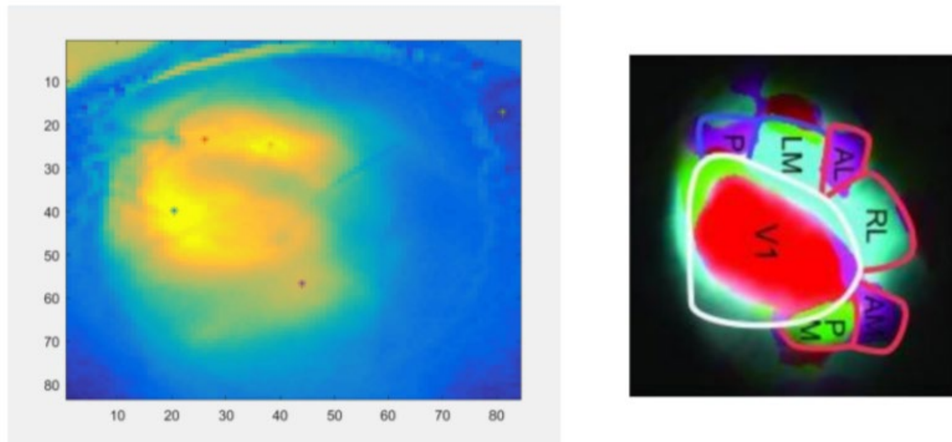

Figure 10: Selected reference points and labeled visual cortex architecture.

Left: Selected reference points chosen from a pixel-wise image showing peak fluorescence averaged across all trials. Right: Figure taken from Wekselblatt et al., 2016 and rotated 90 degrees for ease of comparison.

Interestingly, there are higher order visual areas which appear to not be active in any significant capacity during stimulus presentation. Since the visual cortex contains a retinotopic map of visual space, we note that this result could be due to our experimental set-up, as the monitor which displays the stimuli covers most, but not all,

of the mouse's visual field. Thus, the HVAs which are not represented could correspond to visual space that is not associated with the presented stimuli.

From these selected points, change in fluorescence from the baseline average (dF/F) across the entire recording session was compared across contrasts for each visual area, creating Figure 11.

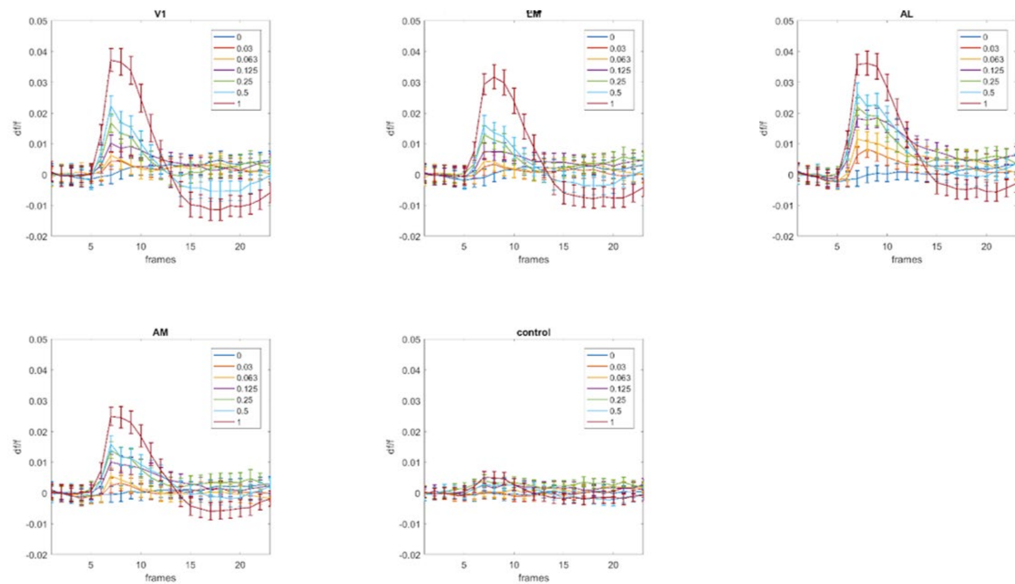

Figure 11: Fluorescence values (dF/F) compared across contrasts for each visual area

Contrast response functions (CRFs), where the maximal df/F value for each point at a given contrast value were plotted for each visual area as shown in Figure 10. For the first plot which looks at V1, we found that the maximal neural response occurs at 100% contrast and the minimal neural response occurs at 0% contrast. The inflection point, or the neural threshold, appears to be somewhere between 6-25% contrast. This trend is consistent across all visual areas, showing that all selected areas have a similar contrast-dependent sensitivity. In preliminary trials of varying parameter values where we used much longer durations (results not shown), we had peak fluorescence values of about 0.08 dF/F at 100% contrast. The peak value of the CRFs shown here appears to be

around 0.03-0.04 dF/F which is much lower and likely a consequence of the shorter duration range that we chose.

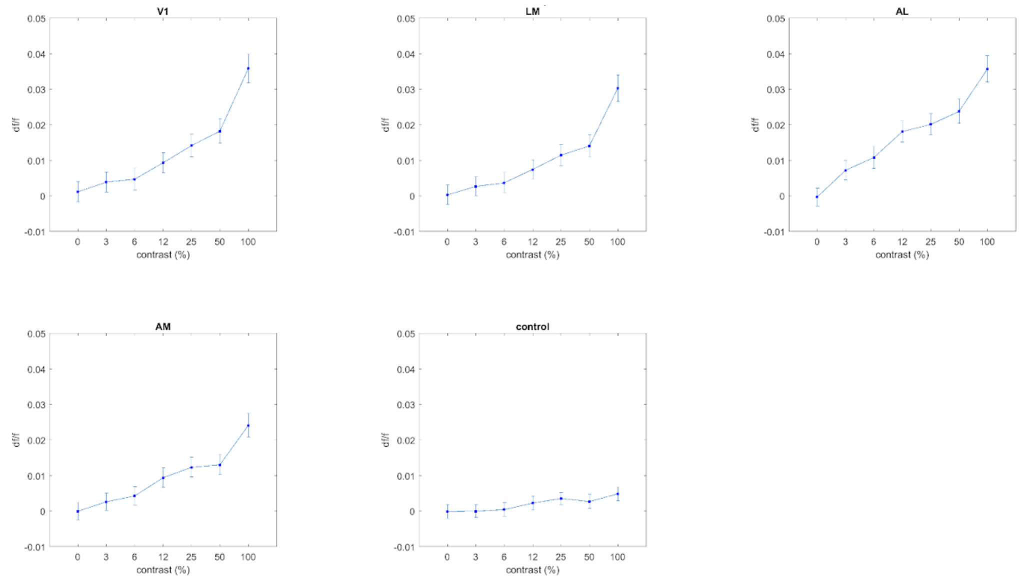

Figure 12: Contrast response function across visual areas

Comparing Fluorescence Across Visual Areas by Duration

Using the same selected points as in Figure 10, change in fluorescence from the baseline average (dF/F) across the entire recording session was compared across durations for each visual area, creating Figure 13. The duration response function is presented in Figure 14. For V1, we determined the maximal neural response occurs at 133 ms and the minimal neural response around 16 ms, with the perceptual threshold likely between 66-133 ms. Similar to contrast, these duration trends are consistent across visual areas, indicating that all selected areas exhibit sensitivity to these parameter values.

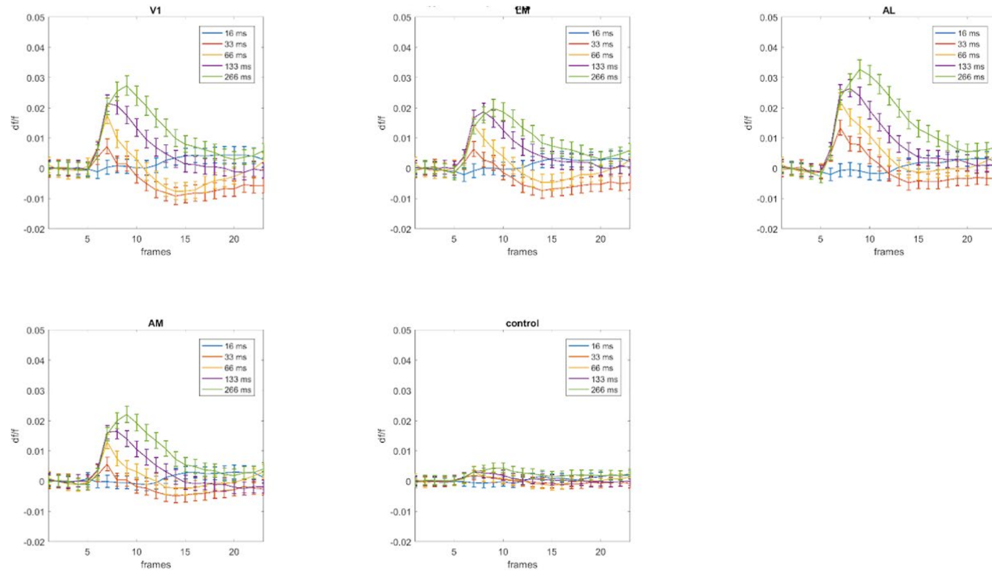

Figure 13: Fluorescence values (dF/F) compared across durations for each visual area

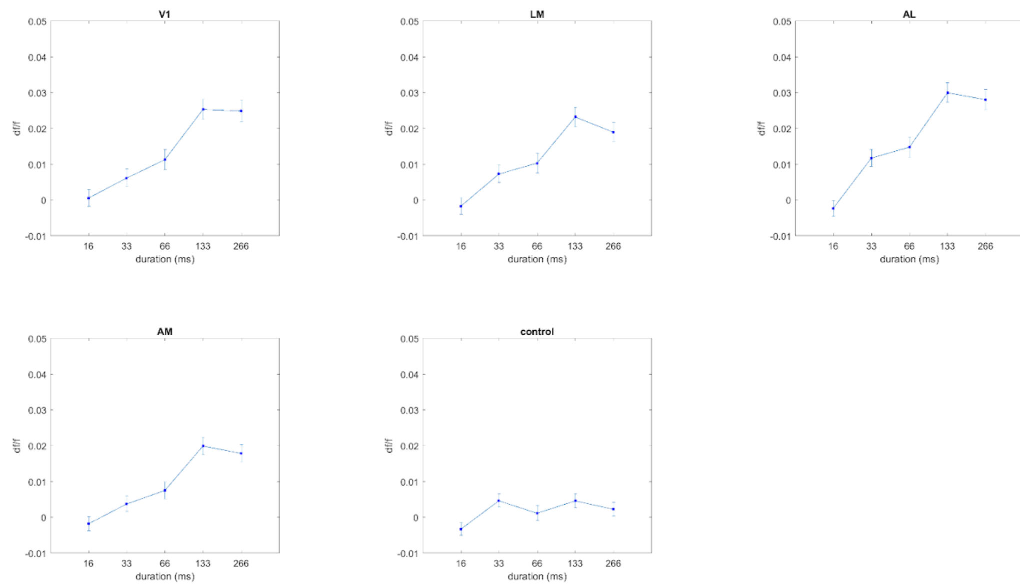

Figure 14: Duration response function across visual areas

Characterizing the Dynamic Range of Contrast and Duration

Lastly, we graphed the contrast response function for each duration and compared across visual areas as shown in Figure 15. Each colored line corresponds to a different duration and the dF/F values are plotted on the y-axis for each contrast value. In this figure we found that a higher contrast is not sufficient for compensating for very short durations as evidenced by the large difference in neural activity between 33, 66, and 133 ms duration at 100% contrast. This result is important because we wanted to find a short enough duration that gives us a good response curve over the different contrasts to optimize selected parameters for future testing. Based on our results presented here, we believe this range may lie between 66-133 ms.

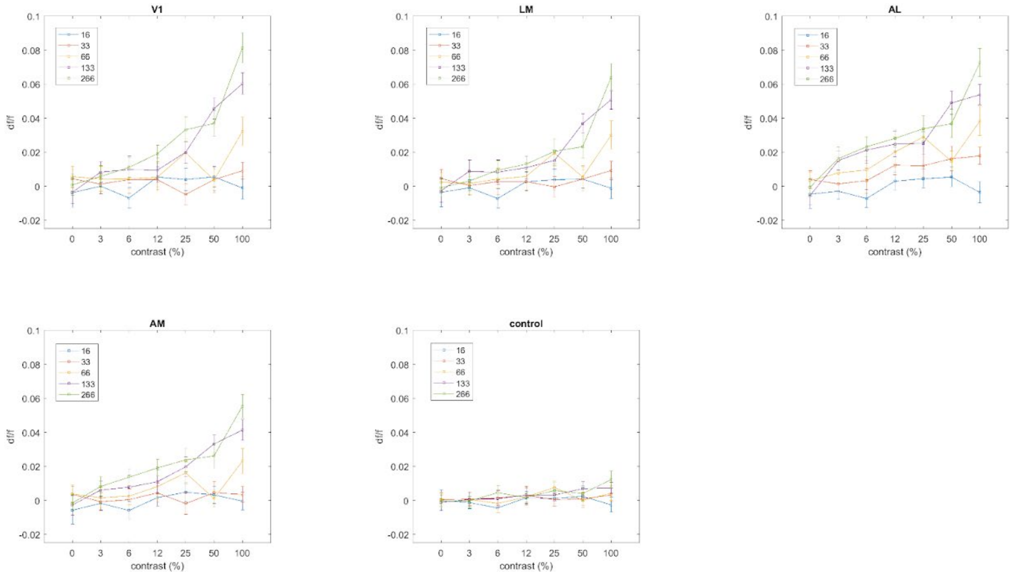

Figure 15. Contrast response function for each duration compared across visual areas

Discussion

Summary

Through wide-field calcium imaging of the mouse visual cortex, I characterized the dynamic range of cortical visual activity for visual stimuli varying in contrast and duration across visual areas. We estimated the neural threshold to be between 6-25% contrast and 66-133 ms duration. We also found similar trends across all chosen HVAs, suggesting that the selected areas all exhibit sensitivity to the range of parameters.

Since the neural threshold overlaps the perceptual threshold, these results serve to optimize future work of choosing stimulus parameters. Although our spherical treadmill set-up vastly increases the amount of trials a given mouse can undergo, having a solid understanding of near-threshold values of contrast and duration will allow us to maximize experimental efficiency later on and limit the chances of the mouse becoming disengaged with the task as a result from running too many preliminary trials and being on the ball for too long. Specifically, looking at contrast response functions by duration was important as we were able to determine the shortest duration we could use that still gives us a good response curve across the different contrasts.

Future Directions

In future work, pupil diameter and running speed will be tracked alongside neural activity in response to parameters I identified to further our understanding of how behavioral state influences conscious awareness. Preliminary pupil-tracking data during a topoX/topoY task is shown in Figure 16, illustrating the feasibility of the next steps of this project.

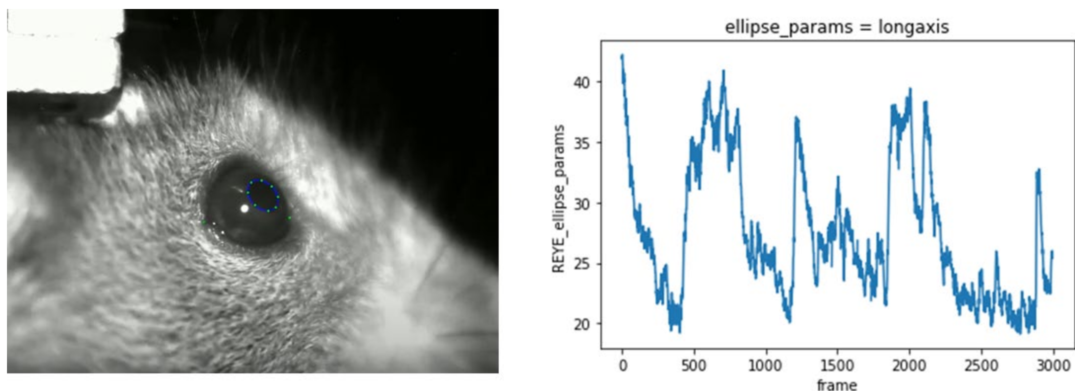

Figure 16: Preliminary pupil-tracking data

Left: Analysis by a neural network to identify pupil diameter (outlined by the blue circle) within a given camera frame. Right: Tracking of pupil diameter across a topoX/topoY recording session.

We expect that these future studies at the population level will follow previous behavioral state experiment trends that were found at the single-cell level, including an inverted-U shaped dependency on arousal and an overall increase in perception sensitivity of below-threshold stimuli while actively moving (McCormick et al., 2020; McGinley et al., 2015; Niell and Stryker, 2010). Understanding population-level dynamics of behavioral state may be especially important in illuminating the role of neuroregulatory agents which have been previously implicated as a potential underlying mechanism behind different behavioral states.

In addition, the results of this work motivate future studies of consciousness in a mouse model. Wide-field calcium imaging not only provides a comparable method to past consciousness research conducted in humans and primates, but the mouse model itself is an avenue to overcome past technical and ethical barriers. Vast experimental manipulations within mice, such as optogenetics, which allows for temporary inactivation of targeted brain regions, make the completion of functional studies testing the causal roles of specific brain regions easier.

Significance

Lastly, these results hold significance in translating to human neurological disorders. Characterizing the neural basis of consciousness may one day provide insight on how we can therapeutically treat patients with disorders of consciousness. By understanding what brain regions or neural circuits are essential to conscious perception, we might then be able to manipulate them to restore normal function.

Further, investigating how behavioral state ties into consciousness is relevant for attention disorders. Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder associated with symptoms of inattention, impulsivity, and hyperactivity and it is believed to stem from an imbalanced regulation of cortical neural circuits (Russell et al., 2005). If we can identify the optimal behavioral state that enhances sensory perception, it could potentially serve as a way to compensate for pre-existing neural dysregulation that hinders perception.

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