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State-Dependence is State-Dependent: Local and Global Influences of Spatial Selection
and Locomotion in Mouse Primary Visual Cortex

A dissertation submitted in partial satisfaction of the requirements of the degree of
Doctor of Philosophy

in

Neurosciences with a Specialization in Computational Neurosciences

by

Ethan Gregory McBride

Committee in charge:

Professor Edward Callaway, Chair
Professor Takaki Komiyama, Co-chair
Professor Timothy Gentner
Professor John Reynolds
Professor John Serences

2018

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University of California San Diego

2018

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LIST OF ABBREVIATIONS

50-50	Mice trained with symmetric change probabilities; 50% for each side
80-20	Mice trained with asymmetric change probabilities; 80% on one side
AAV	Adeno-associated virus
ChR2	Channelrhodopsin-2
CSD	Current source density
LFP	Local field potential
MLR	Mesencephalic locomotor region
PV	Parvalbumin, protein expressed by a particular type of inhibitory neuron
r_{sc}	Spike count correlations
V1	Primary visual cortex

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Chapter 2 is currently being prepared for submission for publication of the material. McBride EG, Lee SJ, Callaway EM. “Local and global influences of spatial selection and locomotion in mouse primary visual cortex.” The dissertation author was the primary investigator and author of this material.

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ABSTRACT OF THE DISSERTATION

State-Dependence is State-Dependent: Local and Global Influences of Spatial Selection
and Locomotion in Mouse Primary Visual Cortex

by

Ethan Gregory McBride

Doctor of Philosophy in Neurosciences with a Specialization in Computational
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University of California San Diego, 2018

Professor Edward Callaway, Chair
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Over the past decade, mice have emerged as a useful model for studying vision, owing in large part to their genetic tractability. Such studies have also yielded the unexpected and fascinating finding that movement, particularly locomotion, has a striking effect on cortical visual activity in mice. The discovery of so-called state-dependent visual processing suggested that the role of even primary sensory areas is not as simple as previously thought. Many studies showed that locomotion enhances visual neural

activity, but few directly examined whether it actually improved sensory perception in a behavioral task. For my dissertation project I addressed this by examining the interactions between locomotion-dependent modulation of brain state and different goal-directed sensory selection brain states. Two groups of mice were trained to visually monitor either one of two locations (selective) or both (non-selective) for a contrast change, and this simple difference produced a spatially selective and non-selective brain state in primary visual cortex (V1), respectively. Locomotion affected the two groups of mice differently, impairing performance and neural representations of visual information of selective mice, while having no effect on non-selective mice. These and other results suggest that these two groups of mice use local versus global mechanisms to perform their respective tasks, and in the case of selective mice, the global influence of locomotion disrupts their locally modulated brain state and impairs performance. Locomotion influences brain state differently, depending on whether the animal employs a spatially selective state to perform its task. Thus, state-dependence is state-dependent. These findings demonstrate the importance of studying complex interactions, and argue for reducing reductionism in neuroscience as we gain the necessary technology to carry out such studies. Moving forward, this mouse model will do just that, and enable investigation into the cell type and circuit mechanisms underlying these phenomena. Wading into the enormous complexity of the brain may ultimately be the only way to understand how it works as a whole.

Chapter 1. Introduction

Using mice to study visual cortical circuits

Vision literally defines how we see the world, and as such draws the interest of humans in general and neuroscientists in particular for a number of reasons. Since it is the primary sense we humans use to navigate our environment, studying vision is both intuitive and vitally important for understanding our own brains. In practical terms, visual stimuli are relatively easy to control, as it is easy to probe the basic visual parameter space. In the earlier days of neuroscience, it made the most sense to study the neurobiology of visual processing using animal species similar to us, such as other primates or other predator species with large binocular overlap like cats.

A great deal of progress has been made with these experiments, but genetic tools for neural circuit dissection have not and may never fully catch up to these animal models. This limits the ability to identify and manipulate specific cell types, a set of techniques that have become essential for asking questions about the neural basis of perception (Luo et al., 2008, 2018). Interactions between different cell types play a huge role in sensory information processing, along with every other function the brain performs, so understanding them will be essential for understanding brain function.

Enter mouse models of vision. The genetic tractability of mice has made them an attractive model organism for investigating neural circuitry and cell types in the hopes that fundamental mammalian organizational principles of the brain can be elucidated (Huberman and Niell, 2011). As such, mice have become increasingly used in studies of the visual system (Carandini and Churchland, 2013; Seabrook et al., 2017).

While mouse visual acuity is lacking when compared to primates, mice primarily use vision for navigation (Chen et al., 2013) and their visual systems share hierarchical properties with the primate visual system. Up to 11 extrastriate visual cortical areas exist in the mouse, each of which has its own map of retinotopic space, and these areas have distinct functional properties (Garrett et al., 2014; Glickfeld et al., 2013, 2014; Marshel et al., 2011; Wang and Burkhalter, 2007), suggesting hierarchical visual information processing similar to that found in primates (Felleman and Van Essen, 1991). Some important differences exist between visual areas of mice and primates, including differences in cortical layers, proportion of retinal projections directly to superior colliculus versus thalamus, and that mice have a “salt-and-pepper” organization of feature representation in primary visual cortex rather than functionally similar cortical columns (Huberman and Niell, 2011; Seabrook et al., 2017). However, these differences could be explained simply by differences in wiring efficiency according to brain size (Koulakov and Chklovskii, 2001), as orientation selectivity in individual neurons (Niell and Stryker, 2008) and connectivity between similarly-tuned neurons is present in both mice and primates. Overall, basic visual response properties of neurons in the mouse visual cortex are strikingly similar to those in primates (Niell and Stryker, 2008). Importantly, humans are closer evolutionarily to mice than to cats (Krubitzer, 2007), a traditional model visual system that earned visual neuroscientists Hubel and Wiesel the Nobel Prize (Hubel and Wiesel, 1962). The common ancestor of mice and humans is 10 millions years more recent than the common ancestor of cats and humans (Krubitzer, 2007). Thus not only are they genetically tractable, but findings from mouse visual neuroscience have potential to be genetically translatable to humans.

Where mice show increasing promise is in their ability to perform complex behaviors, and thus allow scientists to study neural mechanisms underlying those behaviors (Carandini and Churchland, 2013; Huberman and Niell, 2011; Seabrook et al., 2017). It is important to carefully choose a behavior based on the research question (Juavinett et al., 2018), as more highly controlled perceptual behaviors can address what the mouse brain *can* do, while more ethologically relevant behaviors can address what the mouse brain *naturally* does, and these behaviors may be learned more quickly. Many studies have already established that mice readily learn visual perceptual tasks (Carandini and Churchland, 2013), and they also use vision for ethological escape (Yilmaz and Meister, 2013) and cricket-hunting behavior (Hoy et al., 2016). Mouse behavioral tasks continue to push their perceptual and cognitive limits, and these advances combined with improved genetic tools and cell-type targeting methods, the ability to record from more and more simultaneous neurons, and selectively perturb activity in those neurons will lead to exciting findings in the years to come.

Optimal brain states and their relation to perception

For a long time it has been appreciated that different brain states lead to different perceptual abilities. At the coarsest level, being asleep versus awake produce drastically different abilities to detect sensory stimuli. In finer detail, we know both subjectively and experimentally that gradations in motivation within the waking state have effects on behavioral performance in a variety of tasks. Yerkes and Dodson performed a classic study in which they trained mice to perform what may be the first two-alternative forced

choice task for rodents (Yerkes and Dodson, 1908). Mice had to walk through either a white or black doorway, and in one room they would receive an electric shock. To encourage a choice in a timely fashion, experimenters “placed a piece of cardboard between [the mouse] and the doorway ... and gradually narrowed the space in which the animal could move about freely by moving the cardboard toward the electric boxes.” Mice learned to reliably choose the non-shocking box more quickly if the shock was mild, but more slowly if the shock was too strong or too weak. Thus the “Yerkes-Dodson law” or inverted-U curve was born. An optimal level of motivation produces optimal behavioral performance. Less talked about was their finding that changing the difficulty of discrimination, in terms of the difference in the color of the boxes, also shifted the inverted-U curve.

Unfortunately, that initial study has a few issues, summed up nicely in this literally poetic abstract from an article published in *Psychological Reports* (Brown, 1965):

There is a flaw

In the evidence for the Yerkes-Dodson Law.

To call it "ubiquitous"

Is pretty iniquitous.

Put in prose, the main gripes of W. P. Brown were that the sample size was not large enough (2-3 mice for each condition) and the criterion for learning was somewhat arbitrary and altering it would significantly change their results. These are important

criticisms of the generality of the Yerkes and Dodson study. Regardless, several studies in the 110 years since have corroborated the inverted-U relationship between some measure of motivation or arousal versus behavioral performance (Aston-Jones and Cohen, 2005; Cools and D'Esposito, 2011; McGinley et al., 2015b, 2015a; Vijayraghavan et al., 2007).

One important recent study showed an inverted-U relationship in mice between performance in a more tightly-controlled task and neurophysiological measures of arousal (McGinley et al., 2015b). The mice had to detect a tone embedded in noise, and performed best at an intermediate level of arousal, which corresponded to stable hyperpolarization of auditory membrane potential, while low arousal corresponded to rhythmic slow oscillations and hyper-arousal to depolarization. This and other studies also showed pupil diameter in mice to be closely linked to arousal, both of which are themselves closely linked to neuromodulatory activity (McGinley et al., 2015b; Reimer et al., 2014, 2016).

Fluctuations in arousal due to neuromodulatory activity are clearly very important for task performance. However, as our subjective experience with different levels of task difficulty suggests, different tasks likely have different optimal levels of arousal. For example, writing a dissertation requires a very specific level of engagement, certainly not too low but also not too high. Too much general arousal, induced by a large dose of coffee, can make the mind race and make writing nearly impossible. On the other hand, different tasks may benefit from hyper-arousal, particularly physical tasks like running. Even lower-level mental tasks, such as spike sorting, operate on a different inverted-U curve. Thus it is important to consider that an inverted-U curve only exists for each

particular task. The true optimal state curve likely lies in a high-dimensional task-space intersecting an arousal-space, where different measures and definitions of arousal interact with task parameters to produce a particular brain state. The findings of my thesis research support this idea, as do the findings of Yerkes and Dodson, and will be discussed further in Chapter 2. Put another way, the oft-reported state-dependence of cortical neural activity is itself state-dependent.

Locomotor modulation of mouse primary visual cortex and its relation to attention

Over the last decade, several studies have demonstrated that the mouse primary visual cortex contains more than just visual signals, including reward (Shuler and Bear, 2006) and motion signals (Niell and Stryker, 2010). In particular, visual responses in mouse V1 are strongly modulated by locomotion (Maimon, 2011; Niell and Stryker, 2010), and some V1 neurons are even tuned for visual flow speed (Saleem et al., 2013). Effects of locomotion include increased stimulus-evoked firing rates in V1 (Ayaz et al., 2013; Erisken et al., 2014; Niell and Stryker, 2010; Polack et al., 2013; Vinck et al., 2015), visual thalamus (Erisken et al., 2014; Williamson et al., 2015), and superior colliculus (Ito et al., 2017), decreased spike count correlations (Erisken et al., 2014; Vinck et al., 2015), fano factor (Erisken et al., 2014), and low frequency oscillations in V1 (Niell and Stryker, 2010; Vinck et al., 2015). These effects amount to an increase in signal-to-noise ratio of visual responses, which is also increased with arousal alone (Vinck et al., 2015). These effects resemble those of attention in primates (Chalk et al., 2010; Cohen and Maunsell, 2009; Desimone and Duncan, 1995; Fries et al., 2001; Harris

and Thiele, 2011; Maimon, 2011; Mitchell et al., 2007, 2009; Reynolds and Chelazzi, 2004; Treue, 2003; Vinck et al., 2013), although few studies have directly measured whether locomotion improves behavioral performance, perhaps the most important property of attention.

Much is known about the mechanisms of how locomotion modulates visual cortex. Stimulation of the mesencephalic locomotor region (MLR) in the brainstem induces locomotion (Lee et al., 2014) and MLR sends projections to the basal forebrain, which contains cholinergic neurons that project across the brain that are thought to play an important role in the effects of locomotion and arousal on primary visual cortex activity (Fu et al., 2014). Stimulation of MLR projections to the basal forebrain caused changes in response properties in V1 resembling those of locomotion, even when the MLR was stimulated subthreshold of locomotor activation (Lee et al., 2014). These studies show an important role of subcortical areas in cortical modulation of sensory processing due to locomotion, but we still do not understand how the local cortical circuitry in V1 supports these changes. The effect may be due in part to differential modulation of inhibitory neuron subtypes leading to disinhibitory mechanisms (Fu et al., 2014), though this has been recently disputed with findings that all inhibitory neuron subtypes increase firing rate during locomotion (Dipoppa et al., 2018; Pakan et al., 2016).

More recently, a wide range of movements in addition to running were shown to be correlated with visual cortex activity, including whisking, jaw movements, limb movements, and licking (Musall et al., 2018; Stringer et al., 2018). Facial movements in particular were highly correlated with spontaneous cortical activity (Stringer et al., 2018). In one study, cortical activity was dominated by the movement-related activity – the

authors artificially removed this movement-related activity to best isolate task-related activity (Musall et al., 2018). Why would the brain represent motor information so strongly and ubiquitously across the cortex? Perhaps by broadcasting motor efference copies all over the brain, cortical areas are more able to make associations between movements and sensory outcomes. This could be an important substrate of sensorimotor learning, but more work needs to be done. These studies demonstrate the need to record from many behavioral variables, because it is possible that even task-aligned changes in sensory cortical activity result in part from this widespread motor-related activity rather than just sensory information processing. In addition, they show that movement-related activity in sensory cortex, including locomotion-induced modulation of visual cortical activity, could have a previously unknown important role in brain function.

However, locomotion does not affect all brain areas equally. A study of Allen Institute data showed that firing rates in the extrastriate visual areas decreased (Christensen and Pillow, 2017). In addition, in auditory areas locomotion suppresses stimulus-evoked responses in cortex and thalamus (McGinley et al., 2015b; Schneider et al., 2014; Williamson et al., 2015). This relative specificity of locomotor effects suggests it produces a brain state that supports the act of locomotion – enhancing vision would be useful because it is important for navigation (Chen et al., 2013). Suppression of auditory cortex could suppress irrelevant self-induced sounds, which likely increase with running speed. This could correspond to selection of particular visual features that are most important for visual navigation of the environment. However, while these effects of locomotion certainly amount to a form of sensory selection, to claim locomotion causes visual attention in mice would be somewhat overzealous.

Definitions of attention

Though the observed effects of locomotion in mouse V1 in many ways resemble the effects of attention on visual cortex, using mouse locomotion as an analogue of visual attention is simplistic. To consider this comparison, we must examine what exactly is meant by the word attention, and recognize that it is a multi-faceted and complex brain process, contrary to our subjective experience of it. In William James' 1890 textbook on psychology he famously wrote, "Everyone knows what attention is," but that broad definition is in part responsible, I believe, for differing definitions of attention within the field. Conflicting internalized definitions of attention were at the root of many misunderstandings during my attempts to communicate the results contained within this thesis. James goes on to elaborate, "It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalization, concentration, of consciousness are of its essence." While this is an eloquent description of our experience of attention as humans, it does not address the separable parts of attention that may or may not be governed by similar neural mechanisms. There are several aspects of spatial attention that are to some extent distinguishable: arousal, spatial selection, feature selection, and orienting or switching.

William James describes selective attention, "taking possession by the mind...of one out of seem several simultaneously possible objects," which is distinct from more generalized attentiveness or what we might call arousal. Arousal, as discussed in depth earlier in this chapter, interacts with selective attention in an inverted-U curve, where too

much or too little impairs performance, but an intermediate level is “just right,” thus obeying the ubiquitous Goldilocks principle (Aston-Jones and Cohen, 2005; Cools and D’Esposito, 2011; McGinley et al., 2015b, 2015a; Vijayraghavan et al., 2007).

Importantly, selective attention differs depending on what exactly is being selected, broadly divided into spatial or feature-based selection. Spatial selection, as the name implies, involves selecting a particular location in space to attend to and enhancing perception of that location. In other words, knowledge of *where* a target stimulus is likely to appear improves detection if it indeed appears there, but impairs detection at other locations (Posner, 1980; Posner et al., 1980). Feature selection is complementary to spatial selection, and involves selecting a particular feature, such as a color, pattern, or shape, and monitoring that feature above all others. Stated another way, knowledge of *what* stimulus is going to change, or *how* it will change, similarly improves detection of those specific changes (Rossi and Paradiso, 1995). However, in contrast to spatial selection, feature selection can improve detection of the chosen feature globally across the visual field (Sàenz et al., 2003), which is likely very helpful for visual search (Maunsell and Treue, 2006). Given the difference in the scope of their effects, these two types of selective attention may be governed by different mechanisms (Maunsell and Treue, 2006). Of course, spatial and feature attention themselves are not mutually exclusive. When selecting a location, one is usually expecting a particular feature to change, and when selecting a feature, one must often search through a visual space filled with distracters, such as in the famous picture books featuring a character in an iconic red and white striped outfit.

Finally, there is attentional orienting or switching. In humans and other primates, switching is often considered a fundamental part of most attention tasks, and also helps the experiment to be better balanced and controlled by allowing comparisons of neural responses between attend-in and attend-out conditions. However, the switching of attention itself does not necessarily have anything to do with the selective brain states themselves. A recent opinion article (Krauzlis et al., 2014) puts forth the theory that attention itself is not a causative agent, rather it is an effect of value-based learning mediated through subcortical regions, in particular the basal ganglia and superior colliculus. The theory posits that specific modulations in sensory processing are independently learned, and switching between each state is mediated through these subcortical pathways. This paradigm would be consistent with our finding that a selective, goal-directed brain state conflicts with the non-selective, bottom-up brain state produced by locomotion (discussed further in chapter 2). It also argues for switching between brain states to be separable from the actual selective (or non-selective) brain states themselves.

In our mouse task (discussed in more detail below), we largely focused on the spatial selection aspect of attention, so instead of referring to the task as an attention task, we decided to simply call it spatial selection (although it is not completely separable from feature selection – see discussion in final chapter). This is both more accurate and it has provoked far less controversy. On occasion, people have become very argumentative about the definition of attention, often assuming that what we meant by attention was the same as their internal definition of attention, ultimately obscuring the communication of the actual results. Rather than argue whether our task was in fact attention, we decided to

sidestep the issue of this broad term and focus on the aspect we were actually able to investigate directly: the spatially selective brain state. In addition, another group has recently developed a switching spatial attention task for mice, which, by its very existence, should increase acceptance of our findings and other reports of complex mouse perceptual behavior.

Estimating sensory information modulation

Every moment, the brain solves the fundamental puzzle of perception by interpreting spiking activity from different sensory areas and creating an image of the environment. A fundamental puzzle of neuroscience is to understand how the brain makes sense of these billions of simultaneously incoming spikes. Many studies have been done towards this goal, largely using the framework of information theory (Pouget et al., 2000). The majority of work on neural information coding has been done on primate vision or in rodent place coding (Pouget et al., 2000), but increasing work is being done in mouse sensory areas (Dadarlat and Stryker, 2017; Froudarakis et al., 2014). As discussed above, the mouse has the main advantage of allowing specific manipulations of cell types and circuits, thus allowing investigation of how these specific manipulations affect information processing in the brain.

Attention and locomotion, owing to their apparent similarities, have both been subject of studies on how different behavioral states affect sensory information processing in the brain. In general, studies find increased information in the brain due to both attention and locomotion. However, no study has yet described effects of

locomotion on both information and behavior in mice. In contrast, attention in primates has well-established effects on behavior, and is consistently associated with improved information (Moore and Zirnsak, 2017). When we talk about effects of attention or locomotion or any brain state on neural activity, a change in information is most relevant if it is also linked to a change in subsequent behavior. Some studies report consistent changes associated with behavior, but do not directly address population information. On the other hand, many studies report changes in information processing due to a behavioral condition, such as locomotion, but do not assess whether that information is also associated with an improvement in behavior. For example, one study reported that locomotion improved neural information about the orientation of a stimulus presented to the mouse (Dadarlat and Stryker, 2017). One could argue that this improved information could enable better edge detection during navigation, but without showing an actual associated change in behavior, we just don't know. There could easily be a change in information in primary visual cortex, but the animal may not use it or even have access to it.

Calculating information in neural population activity is complex and depends heavily on the interests of the experimenter, whether or not those interests align with the interests of the animal whose neural population activity was recorded. Several types of neural activity changes have been associated with improved information, from simple increased firing rates to preferred stimuli to changes in correlations between neurons (Averbeck et al., 2006; Cohen and Kohn, 2011; Kohn et al., 2016; Pouget et al., 2000). Correlated variability is the amount of trial-to-trial variability shared between neurons, often calculated between each pair of simultaneously recorded neurons, and is frequently

associated with changes in behavioral performance (Cohen and Maunsell, 2009; Mitchell et al., 2009). Too much correlated variability could in theory constrain the ability of a population to encode information, such that adding neurons to the population no longer helps information coding ability because a certain amount of this correlated variability cannot be averaged out of the population. Several studies have found that decreases in correlated variability are indeed associated with behavioral improvement (Cohen and Maunsell, 2009; Mitchell et al., 2009). In addition, these and other studies have used modeling to show how correlated variability can limit population information.

However, more recently, carefully designed studies and sophisticated modeling have shown that correlated variability does not necessarily limit information (Kanitscheider et al., 2015; Moreno-Bote et al., 2014; Seriès et al., 2004). Depending on the task specifics, attention can increase or decrease correlations (Ruff and Cohen, 2014). Whether or not correlated variability limits information depends on whether the variability occurs in a dimension where fluctuations in sensory neuron population activity could be conflated with actual changes in the sensory signal (Kohn et al., 2016). These are termed “differential correlations” and the extent to which they limit information can be directly calculated with a formula or estimated by evaluating the performance of a linear classifier trained on the population data (Kohn et al., 2016). The second method is more broadly applicable and more straightforward to implement, though it often produces an underestimate of population information. Many studies have used a similar approach to assess population information and how it changes in different conditions. We chose to use this approach to assess information content in the neural population for its simplicity and interpretability, and because of the aforementioned studies demonstrating that

calculation of correlated variability alone was insufficient to estimate the information content in a neural population and how it changes across conditions (Averbeck et al., 2006; Cohen and Kohn, 2011; Kohn et al., 2016).

Developing a mouse visual spatial selection task

For the foundation of this thesis work, I developed a mouse visual spatial selection task. We chose to do this for many of the reasons stated above. The incentive to develop such a difficult task for mice was the genetic tools available in the animal, which would enable investigations of the cell types and neural circuit mechanisms underlying sensory selection, a fundamental component of perception. We also believed training mice in a difficult task would be possible because of the increasing numbers of studies published describing mice learning difficult perceptual tasks. Such a task in mice would also allow us to investigate interactions between local and global mechanisms of sensory modulation in a way that had previously not been possible. We also would be able to use new technologies such as high-density laminar microprobes and two-photon calcium imaging to record from large numbers of neurons and multiple brain areas simultaneously. Recording from large numbers of neurons is vital for studying information processing, while recording from multiple areas simultaneously is important for understanding how sensory information is processed and transmitted throughout the brain.

Our task design was as follows: head-fixed mice had to lick to report a contrast change in a drifting-grating stimulus to either its left or right side that could occur at a

random time. If they withheld licking until the change and then licked shortly thereafter, they would receive a water reward. We slightly altered training for two groups of mice. One group was trained with equal change probabilities, that is, the contrast was equally likely to occur on the left or right side of the animal. For the other group, we trained with asymmetric change probabilities: on 80% of trials the change would occur on one side. Mice were allowed to walk or run at will on a wheel, but that movement was not linked to task contingencies in any way. We were of course aware of studies showing striking effects of locomotion on primary visual cortex, so we knew it would be important to track running behavior, and interesting to examine how it interacted with the spatial selection task, especially since only one study we knew of directly examined the effect of running on perceptual behavior.

We chose this design for several reasons. We wanted to examine how sensory selection modulated neural responses to a stimulus, so a stimulus had to be present while the mouse was selecting one side versus another. This was important for our findings (discussed in the following chapter) that many neurophysiological measures were selectively modulated prior to the contrast change, including spike count correlations, fano factor, and firing rates. Unfortunately, it came with a drawback of making the task more difficult to learn. Mice learned the association between the contrast change and reward relatively quickly, but they had trouble withholding licking during the initial low-contrast stimulus.

It was also important for the change to occur at a random time so that the mice could not use timing to predict when to lick – since this was a detection task without a forced choice, mice could potentially learn to perform the task without even using the

visual stimulus (which I believe some did in very early task iterations). In addition, our choice of having a single type of response for either change was both for simplicity and to ensure that no lateralized choice signals would complicate interpretations of recordings from sensory areas.

For the first two years developing and troubleshooting the task, we aimed to train the mice to switch their attention between the two sides. However, attempts continually failed. I believed that mice could do this (a recent study has shown just that), but figuring out exactly how to train them to do so could have taken more years. We instead decided to train mice with differing change probabilities to simplify training, and to use the two different groups to compare selection versus global arousal mechanisms and to what extent they differed.

Ultimately, this choice was advantageous because if we had figured out how to get mice to switch their attention between sides, we likely would not have discovered the interesting differences between the two groups of mice and complex interactions between local and global sensory mechanisms. The non-selective group appears to recruit global arousal mechanisms to perform the task while the selective group is impaired by the global mechanisms that are recruited by locomotion. In addition, this task design meant that to best compare conditions, we had to perform bilateral recordings, which also ended up being vital to our ability to compare global versus local mechanisms. In particular, we could directly show how locomotion had a global effect across hemispheres of V1, while selection had specific, local effects.

Conclusion

With a combination of planning, hard work, and serendipity, my thesis project has yielded unique results that will hopefully be built upon in the years to come. The effect of locomotion on brain state depends on the current sensory selection state of the animal. Thus, state-dependence is state-dependent. The spatial selection task and variants that I developed will be useful to anyone who wants to study local and global mechanisms of sensory selection and how they interact. Unfortunately, I did not have time during my thesis work to fully take advantage of the genetic tools in mice. Future work should be done in that direction to uncover the roles of different cell types and different brain areas in this behavior.

In every task, and in our everyday lives, global arousal mechanisms are constantly interacting with local selection mechanisms to guide us through the environment. Now that better technologies are emerging for recording up to thousands of neurons simultaneously across many brain areas, neuroscience needs to transition away from reductionism previously necessitated by technological limitations. We should embrace the richness of neural mechanisms and study the interactions of several factors; most probably do not interact in the way we expect. Learning how multiple areas and actions affect and are affected by the brain will bring us closer to understanding how the brain functions as a whole.

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Chapter 2. Local and global influences of visual spatial selection and locomotion in mouse primary visual cortex

Summary:

Sensory selection and movement locally and globally enhance neural responses, but how they interact to affect behavior remains largely unknown. Here we describe a novel mouse visual spatial selection task in which animals either monitor one of two locations for a contrast change, or monitor both. Selective mice perform well only when their selected stimulus changes, corresponding to local electrophysiological changes in that hemisphere of V1 including decreased spike count correlations (r_{sc}) and increased visual information. Non-selective mice perform well when either stimulus changes, corresponding to global changes. During locomotion, selective mice perform worse, have increased r_{sc} in V1, and decreased visual information, while non-selective mice are unaffected. Our findings demonstrate that mice can selectively enhance visual information, and the global effect of locomotion impairs local selection. Moving forward, this will be a useful, genetically tractable model for studying neural mechanisms of local and global modulation of sensory information.

Introduction

Perception relies on a combination of local and global neural mechanisms, but the interactions between them remain poorly understood. Local neural effects of attention are well-established in primates, but transgenic methods are unavailable and cell type contributions remain unknown. Global effects are often studied in genetically tractable model species, but until recently, suitable local selection tasks did not exist for these animals. Here we describe a novel spatial selection task for mice that enables us to examine the effects of and interactions between local selection and global movement-related arousal in the same animals. We find that these interactions are complex; the effects of local and global sensory modulations have important differences not predicted by current models, and for any particular task, a different level of global arousal may provide optimal behavioral performance.

Diverting perceptual resources to a particular location or feature improves perception, with the trade-off of impairing perception at other locations or features (Desimone and Duncan, 1995; Posner et al., 1980; Reynolds and Chelazzi, 2004). This trade-off is largely between the amount of detail perceived and the size or number of locations being monitored (Eriksen and St James, 1986; Ester et al., 2014). Visual spatial attention is a particularly well studied type of local selection, primarily in primates. Consistent effects of spatial attention on neural activity include increased stimulus-evoked responses (Desimone and Duncan, 1995; Reynolds and Chelazzi, 2004; Treue, 2003), reduced spike count correlations (Cohen and Maunsell, 2009; Mitchell et al.,

2009), reduced low-frequency (<10Hz) and changes in gamma (30-80Hz) local field potential (LFP) power (Chalk et al., 2010; Fries et al., 2001; Vinck et al., 2013), and reduced trial-to-trial variability (Mitchell et al., 2007). Reduced spike count correlations (r_{sc}) are generally associated with improved performance and reduced low frequency oscillations, consistent with the potential to increase the information coding capacity of a neural population, though lower r_{sc} alone does not necessarily increase information capacity (Averbeck et al., 2006; Cohen and Kohn, 2011; Kohn et al., 2016; Moreno-Bote et al., 2014). Most studies go to great lengths to exclude global effects like arousal, so we know little about how global mechanisms affect the local, neural mechanisms associated with sensory selection.

Global factors are also important for perception and behavior. In a variety of tasks and conditions, an inverted-U relationship exists between arousal and behavioral performance, also known as the Yerkes-Dodson law (Aston-Jones and Cohen, 2005; Cools and D'Esposito, 2011; McGinley et al., 2015; Vijayraghavan et al., 2007; Yerkes and Dodson, 1908). That is, an intermediate level of arousal produces the best behavioral performance, often referred to as the "optimal state." Too little arousal results in an inattentive state, while too much arousal results in a distractible state. Pupil diameter is an effective readout of global arousal across species, and as such shares an inverted-U relationship with performance (de Gee et al., 2017; Larsen and Waters, 2018). Global arousal and pupil diameter are closely linked with neuromodulatory activity (Aston-Jones and Cohen, 2005; Lee and Dan, 2012; Reimer et al., 2014, 2016).

In rodent studies, global arousal and its correlates are strongly associated with movement, including locomotion and active whisking, and these locomotion effects

resemble those of attention (Harris and Thiele, 2011; Khan and Hofer, 2018; Maimon, 2011), though the effects are more complex than simply increasing gain everywhere in the brain. Locomotion increases stimulus-evoked responses in V1 (Erisken et al., 2014; Niell and Stryker, 2010; Polack et al., 2013; Saleem et al., 2013; Vinck et al., 2015), visual thalamus (Erisken et al., 2014; Williamson et al., 2015), and superior colliculus (Ito et al., 2017) and reduces spike count correlations (Erisken et al., 2014; Vinck et al., 2015), fano factor (Erisken et al., 2014), and low frequency (<10Hz) LFP power in V1 (Niell and Stryker, 2010; Vinck et al., 2015). In contrast, locomotion decreases firing rates in mouse higher visual areas (Christensen and Pillow, 2017). In auditory areas, locomotion suppresses stimulus-evoked responses in auditory thalamus (Williamson et al., 2015) and auditory cortex (McGinley et al., 2015; Schneider et al., 2014; Williamson et al., 2015). While an increase in global arousal can occur in the absence of locomotion, the act of locomotion appears to obligate an increase in global visual arousal, at least in V1, that persists up to seconds after the cessation of locomotion (Vinck et al., 2015). Subthreshold activation of the midbrain locomotor region produced similar effects in V1 (Lee et al., 2014), demonstrating the involvement of brainstem and neuromodulatory regions in producing these effects.

What are the behavioral effects of these changes? In one study, locomotion improved the behavioral performance of mice (Bennett et al., 2013). Locomotion was also shown to improve visual information outside the context of a task (Christensen and Pillow, 2017; Dadarlat and Stryker, 2017). More recent studies have shown that a great deal of cortical activity in awake mice can be explained solely by many aspects of the animals' movements, beyond just pupil diameter and locomotion (Musall et al., 2018;

Stringer et al., 2018), and that movement-related activity dominates task-related activity (Musall et al., 2018). However, effects of this broad movement-related activity on behavioral performance have not been directly examined. In addition, mouse attention behaviors including audio-visual attention and visual spatial attention have been recently reported (Schmitt et al., 2017; Wang and Krauzlis, 2018; Wang et al., 2018; Wimmer et al., 2015), demonstrating that mice are capable of more complex tasks than previously thought. These studies investigated sub-cortical or pre-frontal cortical effects, so local effects of spatial attention on mouse sensory cortex and interactions with global movement-related activity remain unknown.

We sought to develop a mouse model for spatial selection and to use it to investigate interactions between local and global mechanisms of sensory modulation, the effects of locomotion on task performance and sensory representations in V1, and whether and how local and global mechanisms affect neural representations of visual information in V1. In our spatial selection task, mice are trained to either selectively monitor one of two visual stimuli, or to monitor both for a change in contrast. We show that spatial selection locally modulates neural responses in ways consistent with selective attention, while dividing perceptual resources globally modulates neural responses in ways that resemble locomotion or global arousal. Locomotion has a global effect on neural responses in both groups, and impairs the behavioral performance of selective mice, while not significantly affecting the behavior of non-selective mice. Consistently, visual information, as measured by linear classifier performance, was highest on correct trials in the selected hemisphere, and decreased during locomotion for selective mice. In non-selective mice, visual information was lower overall and was not modulated by

locomotion. These results show that on a trial-to-trial basis mice can selectively enhance cortical representations of visual information in a particular location, and the global effect of locomotion disrupts that information.

Results:

A mouse spatial selection task

We developed a spatial selection task for mice in which one group of mice selectively monitors one of two locations for a contrast change, and a separate group of mice monitors both locations for a contrast change. Water-restricted mice are head-fixed and able to run freely on a wheel, with a computer monitor centered in each visual hemifield (Figure 2.1a). At the start of each trial, the screens are gray, and then randomly-oriented drifting square gratings appear simultaneously on both sides (see Methods for detailed grating parameters). After a random time determined by a flat hazard function (minimum 2 seconds), the contrast of one of the two stimuli changes. We chose the flat hazard function to ensure a constant change probability and attentional demand (Ghose and Maunsell, 2002), preventing mice from using timing strategies to perform the task. To receive a sucrose water reward, the mouse must withhold licking prior to the contrast change and then lick within a short time window after the change. This is classified as a correct trial (Figure 2.1b). Early licks prevent water delivery and initiate a timeout by increasing the inter-trial interval even if the mouse subsequently licks in the correct window. Trials on which the mouse licked too late or not at all are classified as miss trials, and are neither rewarded nor punished. The only difference

between the training regiments of the two groups of mice is the probability of the contrast change occurring in each hemifield (for more details see Methods). Selective (80-20) mice are trained with asymmetric change probabilities, 80% and 20% so that one side is always more likely to change. Non-selective (50-50) mice are trained with symmetric change probabilities so that each side changes 50% of the time. Importantly, both groups of mice are rewarded when correctly responding to a contrast change on either side. As we will show, this simple difference in the probability of target appearance is enough to produce dramatic differences in behavior and neural activity. Due to individual variability and the structure of the task not conforming to typical signal detection theory analysis, we developed a measure of performance called detection index that compares each animal's performance each day to its chance performance. We calculated chance performance by shuffling first lick times with respect to the random stimulus times and re-classifying correct, early, and miss trials. Thus, detection index represents the number of standard deviations away from chance performance (for more detail see methods and Figure 2.7). Most mice in both groups learned to perform the task well above chance within 60 training sessions (Figure 2.8).

80-20 and 50-50 mice performed differently

Mice trained with 80-20 change probabilities performed well above chance on trials when the more likely change occurred (9.74 standard deviations above chance on stationary trials, $p < 0.0001$, sign-rank test; Figure 2.1c), and performed no better than chance when the unlikely change occurred (0.22, $p = 0.90$, sign-rank test, Figure 2.1c). In

contrast, mice trained with 50-50 change probabilities performed well when the change occurred on either side (7.52, 6.89, $p < 0.02$, sign-rank test, Figure 2.1c). 80-20 mice were also more likely to respond to likely changes than unlikely changes, while 50-50 mice were equally likely to respond to either change (Figure 2.8). Some 50-50 mice performed slightly better when one particular side changed. If we aligned all mice to their best side, there was a slight but significant difference in performance between the two sides, though only on stationary trials ($p = 0.0156$, sign-rank test; Figure 2.1c). Mean reaction times were not significantly different between the two groups (80-20: 475 ± 39 ms; 50-50: 435 ± 81 ms; $p = 0.479$, rank-sum test; Figure 2.8).

We also found that behavior was dependent on the magnitude of the contrast change. 80-20 mice were able to outperform 50-50 mice, particularly at larger contrast changes, but did not perform above chance when the unlikely stimulus changed, even at large contrast changes (Figure 2.8). That 50-50 mice were outperformed suggests that dividing perceptual resources limits their maximum performance.

Interestingly, 80-20 mice performed 55% worse during locomotion (detection index of 4.39 versus 9.74), defined as > 0.5 cm/sec in the one second prior to the contrast change ($p < 0.001$, sign-rank test, Figure 2.1c), while locomotion did not significantly affect the performance of 50-50 mice (Figure 2.1c). Higher speeds were less common (Figure 2.8) and associated with increasingly worse performance by 80-20 mice, but no change in performance by 50-50 mice (Figure 2.8). We chose 0.5 cm/sec as the running threshold to ensure adequate running trials for further analysis, since 80-20 mice ran on fewer trials than 50-50 mice (80-20: 30.8% of trials, 50-50: 45.3% of trials; $p = 0.0346$, rank-sum test, Figure 2.8). Because neural mechanisms of locomotion-induced

modulation are well established and not lateralized, this difference in the effect of locomotion suggests that the 80-20 and 50-50 use different brain states to perform the task. Global neural effects of locomotion may disrupt the brain state supporting local selection, but not the brain state supporting global selection or arousal. These possibilities are explored further, below.

Pupil diameter increases on correct trials for 50-50 but not 80-20 mice

Pupil diameter and global arousal measures are closely linked. In mice, pupil diameter increases dramatically with locomotion, though it has been correlated with arousal and task performance separately from locomotion (McGinley et al., 2015; Reimer et al., 2014, 2016; Vinck et al., 2015). We measured pupil diameter and found that, consistent with previous studies, pupil diameter increased reliably with locomotion in both groups. Due to variability in camera zoom and mouse eye size, we normalized pupil diameter to the average diameter during locomotion (see Figure 2.1d; pupil diameter while running is always close to 1). If we restricted our analysis only to trials when the mouse was stationary, we found a curious difference between the two groups. 50-50 mice had larger pupil diameter on correct trials than on miss trials surrounding both the initial stimulus onset ($p < 0.05$, rank-sum test) and the contrast change ($p < 0.01$, rank-sum test; Figure 2.1d), consistent with previous studies linking larger pupil diameter to task engagement and arousal. However, in 80-20 mice there was no difference in pupil diameter between correct and miss trials (Figure 2.1d). This suggests that 50-50 mice recruit global arousal mechanisms to perform the task, but 80-20 mice do not, perhaps

because increased global arousal disrupts their optimal brain state, as evidenced by their impaired task performance during locomotion.

Optogenetic inactivation of V1 impairs performance

To test the involvement of V1 in the task, we expressed ChR2 in primary visual cortex (V1) parvalbumin-positive (PV) inhibitory neurons and optogenetically activated them to silence V1. Previous studies have demonstrated the effectiveness of this strategy for inactivating cortex (Glickfeld et al., 2013). We injected Cre-dependent AAV1-DIO-ChR2 bilaterally into V1 of PV-Cre mice. Expression of the ChR2 protein selectively in PV+ neurons was confirmed either electrophysiologically or histologically. We found that optogenetic activation of PV neurons effectively silenced V1 and impaired detection of the contralateral contrast change in both groups of mice (80-20: detection index decrease of 7.21, $p < 1e-9$, 45 sessions; 50-50: decrease of 3.90, $p < 1e-11$, 34 sessions; sign-rank test, Figure 2.1e). This shows that V1 is necessary for optimal performance of the task. Interestingly, inactivation of V1 also somewhat impaired detection of the ipsilateral contrast change (80-20: decrease of 2.87; 50-50: decrease of 1.23) Figure 2.1e), which could be explained by light leakage across hemispheres but may also suggest a role for V1 in detection of a stimulus it does not represent.

Local and global effects of spatial selection and locomotion on spike count correlations

To investigate how neural activity relates to the behavior of these animals, we performed simultaneous bilateral recordings in the monocular region of primary visual cortex (V1) using high density silicon laminar microprobes. We recorded simultaneously from up to 70 isolated single units in each hemisphere and identified cortical layers using current source density analysis (CSD; see detailed Methods). Spikes were extracted using Kilosort and phy (Pachitariu et al., 2016; Rossant et al., 2016) and data were analyzed using custom MATLAB software (more details in methods). Only single units that responded significantly ($p < 0.01$, sign-rank test) to either the initial stimulus onset or the contrast change were included in further analysis (77.05% of 2218 recorded single units). We compared neural activity between recordings from the two hemispheres, likely and unlikely, which represent the likely and unlikely changes, respectively (Figure 2.2a). We also performed within-unit comparisons by comparing activity on correct versus miss trials and running versus stationary trials. We performed analyses at four distinct time points: before the initial stimulus onset (prestim), after the initial stimulus onset (stim), prior to the contrast change (prechange), and after the contrast change (postchange) (Figure 2.2b).

Many previous studies show a strong association between decreased pairwise spike count correlations (r_{sc}) and increased behavioral performance. We calculated Pearson's correlations for each pair of simultaneously recorded single units at different trial time points across different trial types. We found that in 80-20 mice, r_{sc} decreased selectively on correct trials in the hemisphere representing the likely change just prior to

the time the change occurred ($r_{\text{correct}}=0.056$, $r_{\text{miss}}=0.078$, $p<1e-13$, sign-rank test, Figure 2.2c). In the unlikely hemisphere, r_{sc} slightly increased on correct trials prior to the contrast change ($r_{\text{correct}}=0.091$, $r_{\text{miss}}=0.083$, $p<0.005$, sign-rank test, Figure 2.2c). The spatially and temporally selective changes in r_{sc} in 80-20 mice are consistent with their selective behavior and suggest a local brain state that follows the task structure. In contrast, the 50-50 mice had reduced r_{sc} on correct trials in both hemispheres and at all time points, consistent with their non-selective behavior ($p<1e-15$, sign-rank test, Figure 2.2d). When aligned to their behavioral bias, r_{sc} was slightly lower in the contralateral hemisphere (pre-change: contra: $r_{\text{correct}}=0.048$, $r_{\text{miss}}=0.106$; ipsi: $r_{\text{correct}}=0.071$, $r_{\text{miss}}=0.151$; contra versus ipsi correct $p<0.01$, miss $p<1e-8$; rank-sum test; Figure 2.2d), again consistent with the association of higher behavioral performance and lower correlations. Despite the slight bias, the largely non-spatially and non-temporally selective nature of modulation in 50-50 mice is consistent with our finding that pupil diameter in these animals is larger across all time points on correct trials (Figure 2.1d), suggesting they use a global mechanism to improve sensory representations. Performance-related differences were not affected by the time window used to calculate r_{sc} , although increasing the time window did generally increase r_{sc} (Figure 2.9).

We then examined the effect of locomotion on r_{sc} . Previous studies have shown that locomotion *decreases* correlations in V1 (Erisken et al., 2014; Vinck et al., 2015). Our data from 50-50 mice were consistent with the literature, as locomotion globally decreases correlations (contra: $r_{\text{running}}=0.048$, $r_{\text{stationary}}=0.057$, $p<1e-12$; ipsi: $r_{\text{running}}=0.060$, $r_{\text{stationary}}=0.096$, $p<1e-90$; sign-rank test, Figure 2.2f), though it did not necessarily correspond to an improvement in behavior. In contrast, we found that in 80-20 mice,

locomotion globally *increases* correlations prior to the contrast change, which is consistent with their impaired performance during locomotion (likely: $r_{\text{running}}=0.068$, $r_{\text{stationary}}=0.048$, $p<1e-15$; unlikely: $r_{\text{running}}=0.091$, $r_{\text{stationary}}=0.053$, $p<1e-45$; sign-rank test; Figure 2.2c). This shows that while selection and locomotion alone each decrease r_{sc} , these effects do not simply combine; instead they appear to interfere with each other.

Even among well-trained mice, performance was variable from day to day. We tested whether these global changes in performance were associated with r_{sc} by plotting behavioral performance for each session versus r_{sc} among simultaneously recorded neurons across all trials from that session. A similar association has been shown over the course of learning in primates (Ni et al., 2018). We found a significant negative correlation between r_{sc} and performance in both the hemispheres contralateral and ipsilateral to the contrast change, even in 80-20 mice, indicating that globally decreased pairwise correlations are associated with improved performance in general, not just at a particular location (contra: $r=-0.333$, $p<0.05$; ipsi $r=-0.465$, $p<0.01$; Figure 2.2g). This could be explained simply by a higher proportion of correct trials, though that would not explain why the r_{sc} in the unlikely hemisphere of 80-20 mice is also negatively correlated with performance. More likely, global decreases in noise correlations reflect a more aroused state, as has been reported previously (Vinck et al., 2015), and this increased arousal supports task performance in both groups, but the optimal level of arousal appears to differ between 80-20 and 50-50 mice.

Local and global effects of selection and locomotion on firing rates

Studies of attention, arousal, and locomotion have all reported changes in firing rates. To investigate changes in firing rates in our data, we z-scored the firing rates of each recorded single unit across 50ms bins to its baseline firing rate during a gray screen. We compared correct versus miss and running versus stationary conditions by subtraction to capture changes associated with each condition (Figure 2.3a, 2.11). To differentiate recorded cortical layers, we used the current source density method (CSD; see detailed methods). In addition, we compared neural responses to their preferred versus non-preferred orientations to examine whether locomotion and selection affected gain differently.

In both 80-20 and 50-50 groups, across all layers, locomotion increased the stimulus-evoked response ($p < 1e-6$, sign rank test, Figure 2.3b-d, S5). The difference peaked at z-scored firing rates of 0.5 for 80-20 mice and 1 for 50-50 mice. This is consistent with previous findings that locomotion increases stimulus-evoked firing rates in V1 (Erisken et al., 2014; Niell and Stryker, 2010; Polack et al., 2013; Vinck et al., 2015).

In deep layers (infragranular, below layer 4) of 80-20 mice and across all layers of 50-50 mice, the firing rate response to the contrast change was larger on correct versus miss trials, with differences peaking at z-scored firing rates of approximately 0.5 ($p < 1e-13$, sign rank test, Figure 2.3e-g, S5). When spikes were aligned to lick onset, the increase in firing rate largely preceded licks (Figure 2.11). This could represent the detection signal the mouse uses to perform the task. Interestingly, in 80-20 mice this

signal is present even in the unlikely hemisphere, which does not directly represent the likely contrast change. However, stimulus onset responses were different between the two groups of mice. While in 50-50 mice the onset responses were enhanced across all layers on correct versus miss trials ($p < 1e-5$, sign-rank test, Figure 2.3g, 2.11), in 80-20 mice the onset responses were only enhanced slightly in deep layers of cortex ($p < 0.01$, sign rank test, Figure 2.3e, 2.11). Furthermore, in the unlikely hemisphere of 80-20 mice, responses to the onset of the stimulus in superficial and granular layers were decreased on correct versus miss trials (mean value -0.21 ; $p < 1e-7$, sign rank test, Figure 2.3f, 2.11), reflecting a suppression of the representation of the stimulus that is unlikely to change. Stimulus onset responses in the likely hemisphere were also somewhat suppressed ($p < 0.01$, sign rank test, Figure 2.3e, 2.11).

We then compared effects of locomotion and selection on changes in neural responses to preferred versus non-preferred orientations. If the response to the preferred stimulus changes more than the response to the non-preferred stimulus, the gain is more multiplicative and selective, whereas if they are equal, the gain is more additive and broad. By subtracting $|\Delta_{\text{preferred}}| - |\Delta_{\text{orthogonal}}|$ we found that in both hemispheres of 80-20 mice, the gain due to selection is more multiplicative than that of locomotion. In contrast, gain in 50-50 mice was not different between selection and locomotion (Figure 2.10). This indicates that in 80-20 mice, the effect of selection is more specific to neurons' preferences, while the effect of locomotion is less specific, suggesting selection and locomotion employ different gain mechanisms in these mice. On the other hand, in 50-50 mice locomotion and task performance are not significantly different, consistent with these mice recruiting global mechanisms to perform the task.

These results indicate that 80-20 and 50-50 mice create distinct brain states for task performance, in part by modulating V1 firing rates differently. 80-20 mice selectively and asymmetrically modulate firing rates while 50-50 mice globally increase stimulus-evoked firing rates, similar to the broad effect of locomotion and consistent with a recruitment of global arousal mechanisms.

Task performance is associated with decreased trial-to-trial variability

Another reported effect of both local selection and locomotion is a decrease in trial-to-trial variability (Erisken et al., 2014; Mitchell et al., 2007). For each unit across different trial types, we calculated fano factor, which is the variability across trials divided by the mean. We found that in 80-20 mice, fano factor decreased selectively in the likely hemisphere on correct versus miss trials (pre change: $\text{fano}_{\text{correct}}=1.175$, $\text{fano}_{\text{miss}}=1.252$, $p<0.002$, sign-rank test, Figure 2.4a). In 50-50 mice, the fano factor decreased in both hemispheres on correct versus miss trials (prechange, $p<0.02$; post change, $p<0.05$, sign rank test, Figure 2.4b). Similar to our correlated variability findings, the hemisphere corresponding to slightly better behavioral performance also had slightly lower fano factor, though this difference was not significant ($p=0.065$, sign-rank test). Locomotion slightly increased fano factor in the likely hemisphere of 80-20 mice at the stimulus onset but not at the contrast change (Figure 2.4c), and locomotion slightly decreased fano factor in 50-50 mice after the contrast change (Figure 2.4d), but overall effects of locomotion on fano factor were not nearly as striking as its effects on other measures, in contrast to a previous study that showed locomotion decreased fano factor

(Erisken et al., 2014). These results provide further evidence that 80-20 mice produce a spatially selective brain state.

Locomotion and selection reduce low-frequency LFP power in both groups

Previous studies report decreases in low-frequency and changes in high-frequency oscillations with both attention in primates and locomotion in rodents (Chalk et al., 2010; Fries et al., 2001; Niell and Stryker, 2010; Vinck et al., 2015). We found consistent decreased low-frequency oscillations with locomotion, but increases in high-frequency oscillations only in 50-50 mice. In both 80-20 and 50-50 mice, delta-band (1-5Hz) local field potential (LFP) power significantly decreased on running versus stationary trials (80-20: $p < 0.03$, 50-50: $p < 0.01$, sign rank test, Figure 2.5), while alpha-band (6-15Hz) power decreased in 80-20 but not 50-50 mice ($p < 0.05$, sign rank test). Locomotion also increased gamma (30-80Hz) power, consistent with previous studies (Niell and Stryker, 2010; Vinck et al., 2015), but only in 50-50 mice ($p < 0.05$, sign rank test). The effect of task performance on LFP power was restricted to low frequencies. On correct versus miss trials, delta-band LFP power decreased significantly in 50-50 mice ($p < 0.01$, sign rank test), and decreased in 80-20 mice but only when mice were also running ($p < 0.05$, sign-rank test). This shows a more consistent effect of locomotion on oscillations, perhaps because locomotion induced modulation can drive synchronization at high frequencies. An intriguing finding is that while locomotion decreases low-frequency LFP power in 80-20 mice, it also increases r_{sc} . In all previous studies known to us, low-frequency LFP

power and r_{sc} change in the same direction, but our findings suggest that these effects are not always linked.

Selection improves, locomotion decreases visual information in 80-20 mice

All of these findings show interesting correlations between behavior and neural activity, but the question remains, is the amount of relevant sensory information in the brain selectively modified in 80-20 mice, and is it altered by locomotion? To assess how changes in neural responses affected task-relevant information in the brain, we trained a linear classifier for each recording in each hemisphere to distinguish between V1 population activity 400ms before and after the contrast change (for other time windows see Figure 2.12). This is similar to what the mouse must do – use activity in its brain to predict whether the contrast changed (Figure 2.6a). We also trained classifiers on trial-shuffled neural activity to assess the contribution of trial-to-trial correlated variability, and on summed neural activity to assess the contribution of total firing rates alone. We then assessed the performance of each classifier on different trial types, and averaged across recordings. A similar approach has been used to decode visual stimuli from neural activity in both primates (Berens et al., 2012; Graf et al., 2011; Seriès et al., 2004) and mice (Christensen and Pillow, 2017; Dadarlat and Stryker, 2017).

Not surprisingly, the classifier performed best at distinguishing pre-change versus post-change when using the full population activity from the likely hemisphere of 80-20 mice (67.2% accuracy, Figure 2.6b). It performed worse both when using the shuffled and when using summed activity (shuffled: 62.4%; summed: 60.2%; $p < 0.005$, sign-rank

test), but still above chance (Figure 2.6b). This shows that, while firing rates alone contain information about the contrast change, the correlated variability of the population activity also contains information about the visual stimulus. Interestingly, the classifier performed above chance at distinguishing unlikely side changes when using population activity from the unlikely hemisphere of 80-20 mice (59.0%, $p < 0.001$, sign rank test, Figure 2.6b), suggesting that it encodes task-relevant information that the mouse does not use, even though the mouse suppresses activity in that hemisphere (Figure 2.3f).

In 50-50 mice, there was a significant difference between the performance of the linear classifier on the full population activity and the shuffled activity ($p < 0.005$, sign-rank test, Figure 2.6b) but not the sums. In the 80-20 unlikely hemisphere, there was not a significant difference. This suggests that the correlated variability structure contains information in 50-50 mice, but not the 80-20 unlikely hemisphere.

When separating trial types, we found that with 80-20 likely hemisphere data, the classifier performed far better on correct trials than miss trials (72.6% versus 64.0%, $p < 0.001$, sign-rank test) and worse on locomotion trials than stationary trials (65.4% versus 69.1%, $p < 0.05$, sign-rank test), just like the mice (Figure 2.6c). This suggests that on correct trials, the mice selectively enhance visual information in V1 about a particular location, but locomotion decreases that information. However, in the unlikely hemisphere there was no difference in performance between trial types (Figure 2.6c), suggesting that while the hemisphere does contain potentially relevant information, it is not modulated on a trial-to-trial basis according to task demands, perhaps due in part to firing rates there

being suppressed (Figure 2.3f). In 50-50 mice, the classifier also performed best on correct trials, but it did not perform significantly differently between running and stationary trials, suggesting that locomotion does not affect overall visual information in 50-50 mice, despite decreased noise correlations (see above Figure 2.2e).

Discussion:

Our results reveal novel interactions between the seemingly similar local and global modulatory mechanisms of sensory selection and locomotion. We show that the effects of locomotion on behavior and visual information representation vary with context. Importantly we find a consistent relationship between correlated neural variability, behavioral performance, and representation of visual information. Our development of a mouse model of spatial selection will facilitate future studies into the roles of different cell types in the neural circuitry supporting both selective and non-selective brain states and the extent to which they differ.

How this spatial selection task relates to previous attention tasks

A simple difference in contrast change probability at different locations was enough to produce striking differences in behavior and brain states between our two groups of mice. Interpreting our results requires examining how this spatial selection task relates to previously described attention tasks. We demonstrated a spatially specific behavior in the 80-20 mice, though unexpectedly, the 80-20 mice did not perform above

chance on unlikely change trials, even with very large contrast changes (Figure 2.8). In a typical attention task, one would expect detection of the unattended stimulus to be decreased, but not completely nonexistent. This asymmetric behavior of the 80-20 group of mice could potentially be explained by asymmetric learning, perhaps not representing spatial attention in the traditional, dynamic sense. These two possibilities would be difficult to distinguish, given evidence that learning and attention cause similar electrophysiological changes (Ni et al., 2018). Despite the possibility of asymmetric learning, our data demonstrate spatially-selective dynamic changes. We trained one group of mice to filter their sensory input by selecting one visual location over another. Our behavioral and electrophysiological results of spatially specific neural activity modulation support that these mice actively select a visual location. Finally, the different effects of locomotion on 80-20 and 50-50 mice show that they employ different brain states to perform the task. The 80-20 brain state may not be a perfect analogue of spatial attention, but our findings demonstrate that it selectively enhances representations of one hemifield and actively suppresses the other.

Correlated variability and behavioral performance

Our findings are consistent with recent studies of correlated variability, and offer some new insights. Decreases in spike count correlations (r_{sc}) were associated with improved performance (except for locomotion-induced decreases in 50-50 mice), and increases in r_{sc} were associated with impaired performance. Importantly, in 80-20 mice task-related decreases were selective to the likely hemisphere, and locomotion-related

increases occurred in both hemispheres, showing how selection has a local effect while locomotion has a global effect (at least in V1). While consistent with previous studies linking r_{sc} and behavioral performance, our results demonstrate that different mechanisms that alone decrease r_{sc} do not necessarily combine additively; rather their interactions are complex.

As further evidence of complex interactions, we also show both a global and local component of r_{sc} associated with behavioral performance. On a session-to-session basis, mean spike count correlations were negatively correlated with performance, even in the hemisphere of V1 that did not represent those changes (Figure 2.2g). This suggests that a component of the r_{sc} decrease is attributable to changes in global arousal from session to session, consistent with a recent study (Ni et al., 2018). However, there is also clearly a local, trial-to-trial component of correlations, as evidenced by the local decrease in 80-20 mice (Figure 2.2c). Further complexity is evidenced by the surprising observation that locomotion decreases low frequency LFP activity in 80-20 mice, but increases r_{sc} .

Neural population information

Previous studies have shown that changes in r_{sc} do not necessarily change population information (Averbeck et al., 2006; Cohen and Kohn, 2011; Kohn et al., 2016; Moreno-Bote et al., 2014). To address this, we more directly assessed changes in population information by using a linear classifier to decode pre- versus post-change population activity. Better performance of the classifier meant that pre and post change activity were more distinguishable, and thus that more information was present in the

population activity. Our finding that the classifier performed best on 80-20 likely hemisphere correct trials, but worse on running trials, shows that those mice can dynamically improve information in V1, and locomotion decreases that information.

To determine the contribution of different aspects of neural activity to population information, we also trained the classifier on summed firing rates and on trial-shuffled population activity, which removes correlated variability. Summed activity did not perform as well as the full population activity, showing that summed firing rates alone do not account for all the information in the population. Trial-shuffled activity also did not perform as well, demonstrating that in this task and experimental setup, spike count correlations contribute to information encoding in mouse V1. However, the contribution of correlated variability to information is not as substantial as previous studies have suggested (Cohen and Maunsell, 2009; Mitchell et al., 2009). Firing rate appears to contain more information, perhaps due to the task specifics.

Most neurons in V1 respond to changes in contrast, so simply summing or averaging across the firing rates of many neurons could be an effective strategy for this change detection task. Perhaps this is why the effect of locomotion can have such a negative effect on behavioral performance in this task – the firing rate increase due to locomotion could be confused with an actual stimulus-related increase. If this were a different task, such as an orientation change detection task, population activity may have been more important for encoding a more complicated feature like orientation. Regardless, r_{sc} still contributed significantly to classifier performance, indicating that it does improve information in this task.

Locomotion reliably influences oscillations

Reduced r_{sc} is typically associated with specific changes in brain oscillations, but we found these oscillations to be more reliably associated with locomotion. Task performance, particularly in attention tasks, is often linked with decreases in low-frequency oscillations and sometimes increases in high-frequency or gamma oscillations (Chalk et al., 2010; Fries et al., 2001). In 80-20 mice, we did find a significant decrease in delta-band local field potential (LFP) power between correct and miss trials, but only when the mouse was also running (Figure 2.5). This was surprising; since 80-20 mice perform better on stationary trials, we would have expected a larger difference in LFP on those trials. We did find that in 50-50 mice, delta band LFP power decreased on correct trials whether or not the mouse was running, consistent with their ability to perform the task well when running or stationary. However, the most reliable driver of changes in LFP power was locomotion. It decreased both delta and alpha band LFP in 80-20 mice, and decreased delta band LFP and increased gamma LFP in 50-50 mice. It is possible we did not have enough statistical power to detect smaller changes. Regardless, locomotion-induced changes in LFP appear to be larger and more reliable than task-related changes. Perhaps locomotion is simply a more reliable driver of synchronization; locomotion causes increased firing rates in all interneuron subtypes (Dipoppa et al., 2018; Pakan et al., 2016), which are thought to be major drivers of synchronization in cortex (Buzsáki and Wang, 2012). Furthermore, in 80-20 mice, locomotion decreases low-frequency LFP power yet increases spike count correlations, contrary to previous findings. This shows that low frequency oscillations and correlated variability are not necessarily linked and

can change independently. Correlated variability may be more reflective of brain state while changes in oscillations may be more reflective of synchronized inhibitory neuron activity.

Movement-related activity

Our results are also consistent with recent studies showing that animal movement accounts for a large amount of cortical activity (Musall et al., 2018; Stringer et al., 2018), and demonstrate the importance of recording multiple movement variables in any experiment with an awake animal. This raises the possibility that some effects on recorded electrophysiological activity could be due to movement or at least some combination of movement and task related neural activity. During training sessions, we only recorded locomotion, pupil diameter, and licking, but occasionally the mice performed several other distinct behaviors such as grooming. Our task design did not incorporate a delay period, making it difficult to fully separate detection from response, but we did reliably see increases in activity prior to the typical reaction times of approximately 450ms (Figure 2.8, 2.11). We largely confined our analyses of post-change activity to time windows before the mice responded, so we are confident that the act of licking was not primarily responsible for the increases in response to the contrast change on correct trials. Future studies should record more movement variables in order to disentangle movement-related from task-related activity.

Conclusion

To a coffee or tea drinker, it should be subjectively obvious that local and global interactions are complex and depend on task specifics. One cup of coffee may provide just the right amount of alertness for the task of writing a scientific paper, while two cups may be too much for writing, but optimal for spike sorting. In this way, each task or category of tasks has its own inverted-U, and thus its own optimal state to produce optimal behavior. Our results shed light on why this extra dimension affects behavior. Local selection mechanisms, generally associated with more difficult behaviors, are more specific and likely more vulnerable to perturbation. Too much global arousal may disrupt the local optimal state by injecting noise into the system, such as an overall increase in firing rate with locomotion in our experiments. In other circumstances, these same global perturbations can improve behavior, but it depends a great deal on the task specifics.

Many questions remain. What are the neural circuits and cell types that facilitate and control these local and global modulations of visual information? Which brain areas participate in this modulation and how, including extrastriate visual areas, thalamus, and superior colliculus? Do the local and global effects use the same or different modulatory mechanisms? Moving forward, our mouse spatial selection task will enable us to use available genetic tools to investigate these questions and elucidate the neural circuit mechanisms of local and global sensory modulation.

Materials and Methods:

Animals and surgery

All animal procedures followed institutional and national guidelines and were approved by the Salk Institute IACUC. 13 C57/B16 (Jackson Laboratory stock # 000664) and 5 PV-Cre (Jackson Laboratory stock # 008069) were used. Due to length of training, mice aged 4-12 months were used.

Before behavioral training, all mice were implanted with a metal head post for head fixation during training. Briefly, animals were anesthetized with 2% isoflurane in oxygen and were placed on a heating pad in order to maintain their body temperature. A small patch of skull was exposed and the head post was attached with dental cement (C&B-Metabond, Parkell Inc.) posterior to the known location of V1, with the remaining exposed skull covered by additional dental cement. The locations of bregma and lambda were marked with small pieces of plastic embedded in the cement for future reference. Carprofen (5mg/kg) and ibuprofen (0.11mg/mL in ad-lib water) were given for postoperative analgesia for all procedures, and for craniotomies dexamethasone (2mg/kg) was also delivered.

For virus injections, after mice recovered from headframe surgery, we again anesthetized the mice and made small craniotomies over the center of V1 using coordinates from bregma (3mm posterior, 2.5mm lateral), and pressure-injected 100nl of AAV1.EF1a.DIO.hChR2(H134R).EYFP.wPRE.HGH (AAV1-DIO-ChR2; Addgene 20298; from UPenn vector core) at depths of both 300um and 600um. Following injections, the craniotomy was first sealed with a clear silicone elastomer (Kwik-Sil,

World Precision Instruments) or gel (3-4680, Dow Corning), then the site was covered with clear dental cement (C&B-Metabond, Parkell Inc.) and a 3mm coverslip was placed over the injection site to create a window through which light for optogenetics could be directed. Finally, we built small wells with dental cement around these windows and painted the cement with black nail polish to minimize the spread of optogenetic light (though we could not completely rule out the possibility that light from one side could reach the other, particularly with higher light levels).

For electrophysiology recordings, we anesthetized the mice and made 1-2mm diameter craniotomies over the center of V1 to provide the space for up to 5 consecutive recordings. Dura was left intact. Before the craniotomy and each subsequent day of recording, mice were given carprofen as an analgesic and dexamethasone to limit brain swelling. After each recording session, the craniotomies were covered first with non-bioreactive silicone elastomer (Kwik-cast, World Precision Instruments), then a thin layer of dental cement to ensure the silicone stayed in place and the mouse could not inadvertently remove it.

Behavior rigs

Mice were trained on custom behavior rigs, which used custom MATLAB software to present visual stimuli with Psychtoolbox based on visual stimulus software described previously (Juavinett et al., 2017; Marshel et al., 2011), with extensive modifications to record behavioral variables and deliver rewards using Arduinos. The rigs consisted of a running wheel attached to a base plate, with clamps to hold the headframe

above the wheel. A rotation encoder was attached to the wheel to record locomotion, and an infrared sensor was used to record licking, while a metal tube was positioned just behind the sensor to deliver rewards. Two monitors controlled by a dedicated visual stimulus computer were positioned in the center of the mice's hemifields, and were calibrated to ensure linear gamma response. A second, master computer controlled the stimulus computer and the Arduinos by sending relevant parameters and saving behavioral data each trial. All components were synchronized by a digital pulse generated by the stimulus computer once the graphics card built and started to play the stimulus for that trial (the rate-limiting step).

Behavioral task and training

In order to motivate mice to perform the task, we restricted their water intake. Water restrictions began after mice fully healed from head-post implant surgery (~1 week). Each mouse received ~1 mL water per day until 15% ad libitum weight is lost (1-2 weeks). During training days, mice received all water during training (0.5-2 mL), but excess water was given after training if the animal did not drink enough to sustain health (at least 0.5mL). On break days, we gave enough water to maintain health and thirst, which depended on weight (minimum 0.5 mL).

Behavioral Training

We acclimated mice to being handled by hand-delivering water during initial days of water restriction, and habituated mice to the behavior rig by placing their cages between the two monitors and playing stimuli for 0.5-1 hour. Once water-restricted mice had lost at least 15% of their body weight, and after 1-2 days of habituation, mice were trained in four main phases. In the first phase, rewards were associated with a large contrast change (increase of 40-50%). During this phase, rewards were automatically delivered at the same time as the contrast change, with no punishment for early licks. Once mice began to anticipate the reward by licking, we moved to the next phase. In the second phase, mice had to lick within the correct window to receive the reward, but were still not penalized for early licks. At this point, some mice began to restrict their licks to the response window, others licked throughout the trial, and a few never learned to lick on their own (these last ones usually did not move on to the next phase). Once mice reliably licked to receive rewards on their own, we moved them to the third phase. In the third phase, an early lick would prevent a reward on that trial, even if the mice subsequently licked in the correct window. In addition, on those early lick trials the mice would be punished with a timeout, which would elongate the inter-trial-interval by 5-15 seconds. This was often the hardest part for mice to learn. Some mice performed above chance within 30 sessions but only gradually reduced early licks over the next 30-60 sessions. Once mice were able to withhold licking to the initial stimulus onset and then lick in response to the contrast change, they were moved to the final phase. In the final phase of training, the magnitude of the contrast change and the length of the response

window were gradually decreased until the mouse performed well with the target contrast change of 20% and response window of 750ms.

We used a few additional parameters in most cases to aid in training. We observed that most mice would lick at the initial stimulus onset, so we implemented a one second forgiveness period after the stimulus onset so that these licks would not trigger an early response and a timeout. In addition, we delayed the response window by at least 100ms to ensure that the mouse could not lick and receive a reward before the visual information could have possibly been perceived. We also observed a great deal of variability between mice in terms of tendency to lick and rate of licking, so we varied the definition of a “response” depending on the mouse’s licking tendency. A single lick in the response window was counted as a correct response, but only if no licks occurred before the contrast change. If the mouse did lick prior to the contrast change, it only counted as an early response if the mouse licked twice within a certain time window, usually 300ms. However, if the mouse did lick just once prior to the change on a trial, the mouse could still earn a reward with a double lick in the response window. In this way, what counted as a “response” could dynamically adjust to individual tendencies of the mice, even variation between days.

Behavior analysis

This behavior was difficult for mice to learn, taking between 30-90 days (Figure 2.8). 5/22 mice did not learn the task, likely due to a failure to lick frequently enough to receive reinforcement. Even once mice reached proficiency, there was still a great deal of

variability in performance between individuals, thus we developed a detection index to normalize animals' performance to chance in order to better assess their performance. Since this task is neither a Go-Nogo nor a two-alternative forced choice task, the assumptions underlying typical calculation of d-prime were inaccurate (namely, that chance = 50%). Thus we bootstrapped percent chance by shuffling lick responses relative to stimulus time within each training session for each mouse, and averaging over 1000 shuffles (chance = ~15%). We also separately shuffled running and stationary trials in order to compare performance under those conditions to what would be expected by chance. Our detection index roughly corresponds to the number of standard deviations away from chance performance.

detection index = $z(\text{correct}) - z(\text{early})$

$z(\text{correct}) = (\text{correct} - \text{correct}_{\text{shuff}}) / \text{std}(\text{correct}_{\text{shuff}})$

Pupil recording and analysis

Pupil videos were recorded using an infrared USB camera (DMK 21BU04.H, The Imaging Source) with infrared illumination and the MATLAB image acquisition toolbox. Acquisition occurred at 7.5Hz or 15Hz and was triggered using the synchronization signal sent by the stimulus computer. Before analysis, images were rotated so that the horizontal axis of the eye was horizontal in the image. Pupil diameter was determined by using custom MATLAB software (generously shared by Dr. Céline Matéo in Dr. David Kleinfeld's lab and modified to fit our requirements). Briefly, videos were cropped to

include only the eye, then manually thresholded to segregate the pupil from the rest of the eye. Then the MATLAB image processing toolbox was used to connect areas of the pupil that were occasionally separated by an out-of-focus eyelash. Finally, the horizontal and vertical diameters were extracted by summing in either the vertical or horizontal directions, then plotting these sums across time, and cropping out any confounding dark areas, such as shadows in the corner of the eye. Diameters were manually verified by viewing every other frame of the video at 10x speed with the diameters superimposed on the eye. Horizontal diameter was most reliable, because sometimes the eyelid would occlude part of the vertical extent of the pupil. In cases of eyelid closure or other obstruction of the pupil, those frames were excluded from analysis. Due to individual differences in eye size and slight differences in camera angle and zoom, we normalized pupil diameter to the average pupil diameter observed during >1 second bouts of locomotion within the same session because locomotion pupil diameter was reliably large. If there were no bouts of locomotion long enough, we excluded those sessions from analysis.

Optogenetic stimulation

For optogenetics experiments, we used two Thorlabs LED drivers (LEDD1B) with 470nm LED modules (M470F3), positioned with micromanipulators (17011702, Märzhäuser Wetzlar GmbH & Co). LEDs were controlled through the same Arduino used to record behavioral variables and deliver reward, using digital-to-analog converters to enable precise light stimulation at different intensities. In behavioral only experiments,

optic fibers were positioned above each implanted chronic window. In combined electrophysiology and optogenetics experiments, both electrodes and optic fibers were positioned near the craniotomies (see below for electrophysiology methods). Optic fibers were positioned such that the light cone covered as much of the craniotomy as possible, and always covered the recording site. This was sufficient since with the skull removed, much less light power was required to activate ChRs.

Electrophysiology

For electrophysiological recordings, we used the Intan system and software with 64-channel laminar silicon probes from Sotiris Masmanidis at UCLA (64D configuration) (Du et al., 2011). Before craniotomies were performed, wells were built using dental cement and silver epoxy (8331-14G, MG Chemicals) was applied to the headframe and to surrounding surfaces near the future recording sites to provide a ground. Once craniotomies were performed (as described above), the mouse was placed on the wheel and clamped into the headframe holder, then electrodes were positioned with micromanipulators (1760-61, David Kopf Instruments) above sites both clear of blood vessels and stereotactically determined to be within V1. Electrodes were advanced to the brain surface, then agarose (A6138, Sigma-Aldrich) in ACSF was applied to the craniotomy wells to provide both stability and electrical grounding. Once the agarose solidified, a thin layer of transparent silicone gel (3-4680, Dow Corning) was added to the surface of the agarose to prevent drying. (In some cases, drying agarose moved electrodes). Once the silicone was set, we slowly advanced each electrode approximately

1mm while watching and listening for spikes. Once both electrodes were at 1mm, we determined the receptive field of neurons to make sure it was in the relative center of the screens. We then performed a current course density (CSD) analysis (see below) to determine if the electrodes were advanced far enough and also to confirm that this location looked like V1. If we could not distinguish layer 4 in the CSD, we tried removing and re-placing the electrode, but if the recording on the other hemisphere was good, we limited ourselves to only 1-2 additional tries because each retry risked a bump that could ruin the quality of the other recording. 15/66 hemisphere recordings were ultimately excluded because we could not distinguish layer 4.

Electrophysiology data analysis

Analyses were performed on both the low-frequency (LFPs, CSDs) and high-frequency (spikes) components of the signal recorded from electrodes. For 80-20 mice we examined only likely change trials unless otherwise noted, because the small number of correct trials on unlikely change trials prevented useful analyses. Thus we largely compared activity in the likely and unlikely hemispheres on likely trials in 80-20 mice. For 50-50 mice, we combined data from the two hemispheres in one of two ways. We either combined the neurons from both hemispheres in response to the contralateral change to examine changes in the stimulus response (spike rate analyses, local field potential analyses, linear classifier analyses), or kept hemispheres separate and combined responses on both contralateral and ipsilateral change trials to examine whether and how responses in the two hemispheres differed (spike count correlations, fano factor).

As mentioned above, for each recording in each hemisphere, we performed a current source density (CSD) analysis to determine the laminar position of the electrode. CSD was performed using CSDPlotter (Pettersen et al., 2006), and involves taking the second spatial derivative of the low-pass-filtered (<1000Hz) local field potential across all channels during transitions from black to white and white to black on the screen (Mitzdorf, 1985). This allowed identification of supragranular, granular, and infragranular layers, information we used to identify effects in these different layers. If we could not discern layer 4 in the CSD, we excluded that recording from analysis (15/66 were excluded).

To analyze the local field potentials we first downsampled raw voltage traces to 1000 Hz and low-pass filtered at 1000Hz. We then used a multitaper method included in an open-source package for MATLAB (Chronux, <http://chronux.org>, (Bokil et al., 2010)) to compute LFP power spectra between 2 and 80Hz. To examine changes in spectral power in different trial conditions, we separately computed spectra with subsets of LFP trials corresponding to when the mice correctly responded, missed the change, or were running or stationary. We restricted analyses to the one second time window prior to the contrast change on each trial, and excluded spectral peaks corresponding to 60Hz line noise from further analyses. To avoid inclusion of trials with either movement or electrical artifacts, we removed trials where the LFP amplitude deviated more than one standard deviation of the average LFP voltage deviation for all trials. Group analyses were performed on the average spectra from each recording in each condition.

Analysis of spikes

To extract spike times from raw voltage traces, we used the open source automated spike sorting package Kilosort (Pachitariu et al., 2016) and manual curation with phy (Rossant et al., 2016). Subsequent analyses were performed with custom MATLAB software. We only included units that had clear refractory periods and neuronal waveforms. For most analyses, spike times were binned, into either 50ms bins for peri-stimulus time histograms (PSTHs), or larger bins for spike count correlations, fano factor, or linear classifier analyses. Spikes were aligned to three events: initial stimulus onset, contrast change, and time of the first lick. For all analyses, we only included units that significantly responded to either the initial stimulus onset or the contrast change relative to the baseline firing rate (Wilcoxon sign-rank test, $p < 0.01$), 1709 of 2218 total units or 77.05%. We also occasionally observed drift in our recordings, and on a few occasions a neuron would either drop out or suddenly appear. For these units we only analyzed the subset of trials when the unit was present.

To compute the pairwise correlated variability, we z-scored spike counts across orientations in order to remove the effect of different orientations on spike count variability. We then found the Pearson's correlation between the z-scored firing rates of every pair of simultaneously recorded single units across different conditions (subsets of trials) and using different spike count time windows. For population measures, we averaged these correlation values across all pairs from all recording sessions. To examine how the correlated variability changed across sessions, we averaged the Pearson's correlation between pairs of simultaneously recorded neurons across all trials during each

session, and correlated those values with the behavior of the recorded mice the corresponding sessions.

We compared how different conditions affected firing rates by first z-scoring each unit's firing rate relative to its baseline firing rate, then subtracting averages between correct and miss and running and stationary trials to compare the relative impact of each condition. To visualize these changes across layers, we averaged z-scored firing rates of units that were recorded at the same depth relative to the base of layer 4, and concatenated the layer-delineated activity aligned to the initial stimulus onset and the contrast change. Heatmap values were smoothed with a Gaussian kernel. We also examined average firing rate differences in upper layer versus lower layer units by averaging according to whether the units were in layers 2-4 or 5-6. Statistics were calculated using these values, see Figure 2.11.

To examine how responses to preferred stimuli changed relative to responses to non-preferred stimuli, we first determined which units had a significant orientation preference by performing Hotelling's T-squared test for equality of means. We included units with $p < 0.05$ for further orientation-tuning related analyses. We then compared changes in responses to the preferred orientation, which triggered the maximum average firing rate, to changes in responses to the adjacent orthogonal orientations, across correct versus miss and running versus stationary conditions. If responses to the preferred orientation changed more than responses to the orthogonal orientation, the neuron experienced a more multiplicative gain, whereas if the changes were equal, the neuron experienced an additive gain. Thus we calculated $|\Delta_{\text{preferred}}| - |\Delta_{\text{orthogonal}}|$ for correct-miss and running-stationary changes in the different groups and hemispheres.

We also examined within-unit variability with fano factor, the ratio of variance of spike counts across trials to the mean spike count. To calculate the fano factor, we binned spike rates into 100ms bins and divided the variability and mean spike counts in those bins for each unit in response to its preferred orientation. Only units that were significantly tuned, as described above, were included in fano factor analysis. We then computed the average fano factor in different conditions, and directly compared either correct versus miss trials or running versus stationary trials.

For the linear classifier, we binned pre- and post-change spike counts within differently sized windows for each recording. We trained a linear classifier to decode pre- versus post-change counts from the population activity with custom MATLAB code using a regularized support vector machine with leave-one-out cross validation. We then averaged classifier performance across recordings, either including all trials or a subset such as correct trials to determine if classifier performance changed in different conditions. We also trained the linear classifier on modified neural population activity, both with summed neural activity across all simultaneous neurons to examine the impact of firing rate alone, and with trial-shuffled activity to determine the contribution of correlated neural variability to classifier performance.

Acknowledgements:

Chapter 2 is currently being prepared for submission for publication of the material. McBride EG, Lee SJ, Callaway EM. “Local and global influences of spatial selection and locomotion in mouse primary visual cortex.” The dissertation author was the primary investigator and author of this material.

Figure 2.1: Spatial selection task and behavioral performance.

(A) Schematic of behavioral rig. Mice were head-fixed on a wheel and allowed to walk or run at will. Computer monitors for displaying visual stimuli were angled to the left and right sides of the mouse, centered in each hemifield and avoiding the binocular zone.

(B) Spatial selection task. Mice were water restricted, and to receive a water reward they had to lick in response to a contrast change in an oriented drifting grating stimulus that could occur on either the right or left side (correct trial). If mice licked prior to (early) or after the change (miss) or failed to respond (miss) they did not receive water on that trial. We trained two groups of mice with different change probabilities: asymmetric (80%-20%) or symmetric (50%-50%). This simple difference in change probabilities produced differences in behavior between the two groups.

(C) Differences in behavior between groups. 80-20 trained mice performed selectively well when the more likely change occurred, and near chance levels when the unlikely change occurred. (Detection index represents the number of standard deviations away from chance performance. For further explanation of detection index, see main text or methods.) In addition, 80-20 mice performed much worse while running. 50-50 mice performed well when either change occurred, and were unaffected by running. Some 50-50 mice performed slightly better on one side; when aligned to this bias, there was a significant difference in performance between different side change trials. 80-20: N=11 mice; 50-50: N=7 mice. Error bars SEM.

(D) Changes in pupil diameter. Running reliably increased pupil diameter in both groups, so we normalized to the average diameter during running (magenta line). We divided stationary trial pupil diameter (black line) into correct (green line) and miss (blue line) trials and aligned to trial timepoints and averaged across trial types. Pupil diameter in 80-20 mice was not different between correct and miss trials, while pupil diameter in 50-50 mice was larger on correct than miss trials across all time points. Comparisons between correct and miss trial pupil diameters using rank-sum test. 80-20: N= 3249 trials, 4 mice; 50-50: N=2752 trials, 4 mice. Error bars SEM.

(E) Optogenetic inactivation of V1 impairs performance. To determine the necessity of V1 to the task, we expressed ChR2 in PV+ inhibitory neurons in both hemispheres of V1 allowing optogenetic V1 silencing (see Methods and Main text). Optogenetic silencing in the hemisphere contralateral to the change significantly impaired behavior in both groups of mice. Ipsilateral silencing also impaired behavior, though this could be due to light spread across hemispheres. 80-20: N=45 sessions, 2 mice; 50-50: N=34 sessions, 2 mice. Error bars SEM.

(All plots: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, sign rank test, unless otherwise noted)

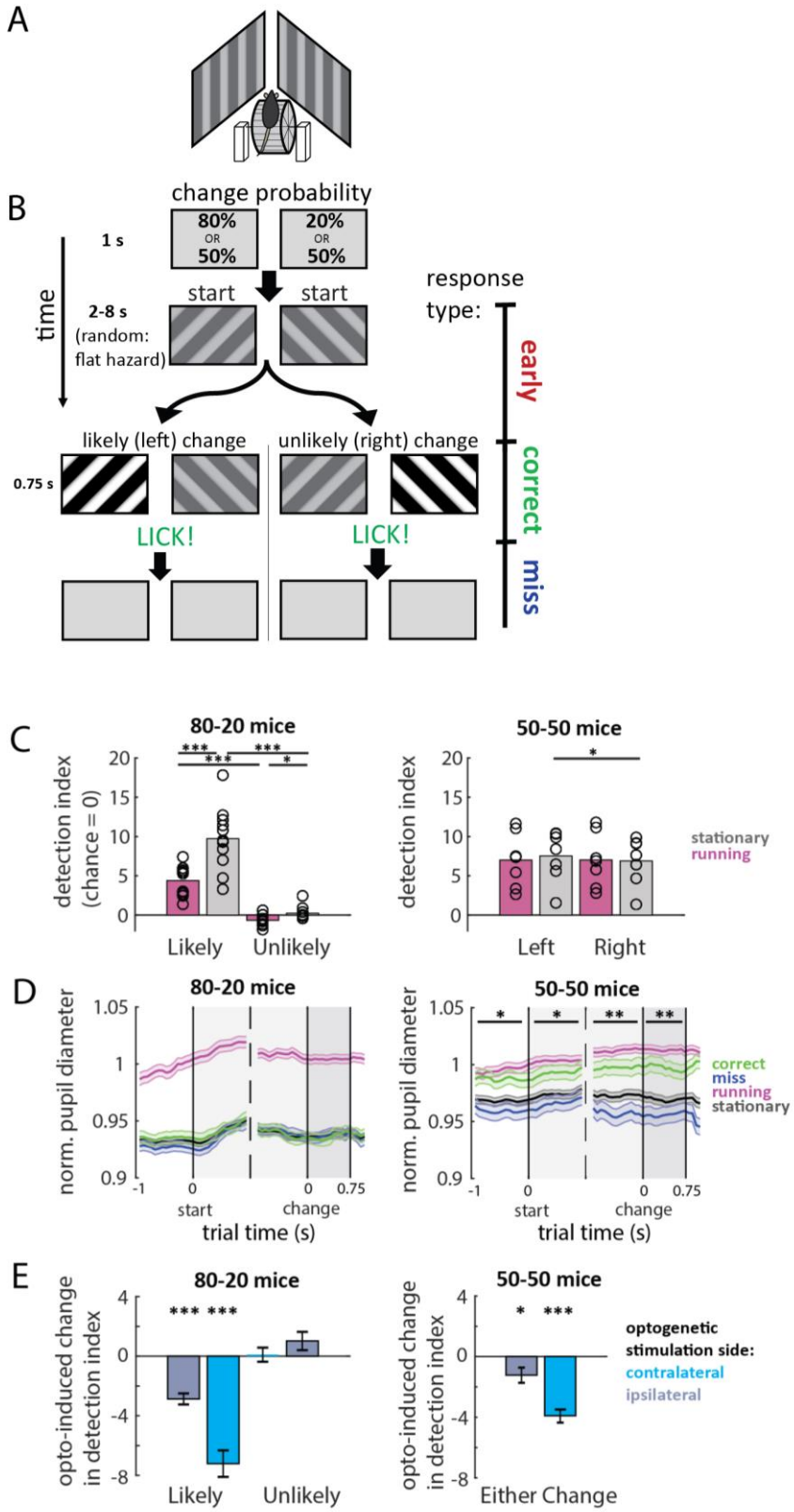


Figure 2.2: Local and global modulation of correlated variability.

(A) Schematic of hemisphere comparisons and terminology. In 80-20 mice, the likely hemisphere represents the more likely contrast change, and the unlikely hemisphere represents the less likely change. In 50-50 mice, we examined activity in both hemispheres, aligning the sides to their behavioral bias if they had one.

(B) Illustration of examined timepoints: pre-stimulus onset, just after stimulus onset, just prior to the contrast change, and just after the contrast change.

(C) Local reduction of spike count correlations (r_{sc}) in 80-20 mice. Prior to the contrast change, r_{sc} in the likely hemisphere decreases selectively on correct trials (solid red line) relative to miss trials (dotted red line), while pre-change r_{sc} in the unlikely hemisphere slightly increases (blue lines). Black lines show r_{sc} calculated with shuffled trials. Likely hemisphere, N=4785 pairs; unlikely, N=3187 pairs.

(D) Global reduction of r_{sc} in 50-50 mice. Across all time points and in both hemispheres, r_{sc} decreases on correct (solid lines) relative to miss trials (dotted lines). When aligned to the slight behavioral biases of these 50-50 mice, the hemisphere corresponding to higher performance had lower r_{sc} ($p < 0.05$, rank-sum test). Hemisphere contra to bias, N=2890 pairs; ipsi, N=7365 pairs.

(E) Locomotion globally increases r_{sc} in 80-20 mice. Across both hemispheres, locomotion (solid lines) increased r_{sc} in 80-20 mice relative to stationary trials (dotted lines).

(F) Locomotion globally decreases r_{sc} in 50-50 mice. Across both hemispheres, locomotion (solid lines) decreases r_{sc} relative to stationary trials (dotted lines).

(G) Variations in overall r_{sc} (not separated by trial) across sessions correlated with variations in detection index across sessions. Data combined between both 80-20 and 50-50 groups of mice. Red, r_{sc} versus contralateral behavioral performance, N=36 sessions. Blue, r_{sc} versus ipsilateral behavioral performance, N=33 sessions. 80-20 unlikely trials excluded because of low performance.

(plots C-F: * $p < 0.001$, sign-rank test. Error bars SEM. Different colors correspond to comparisons within that hemisphere, i.e. red * reflect comparisons in the likely hemisphere in 80-20 mice)

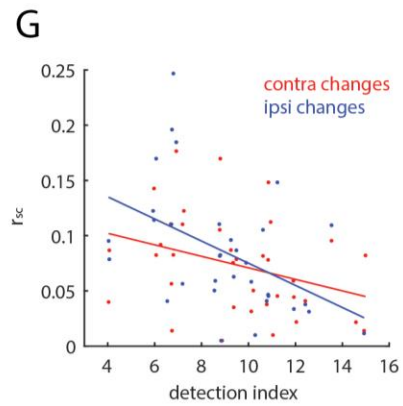
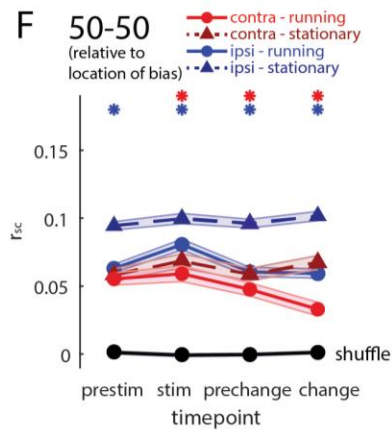
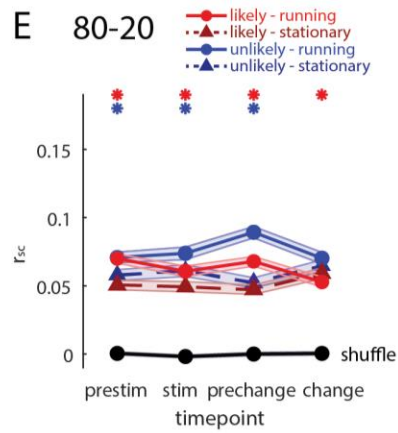
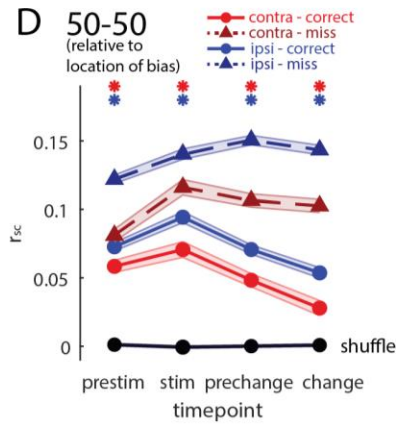
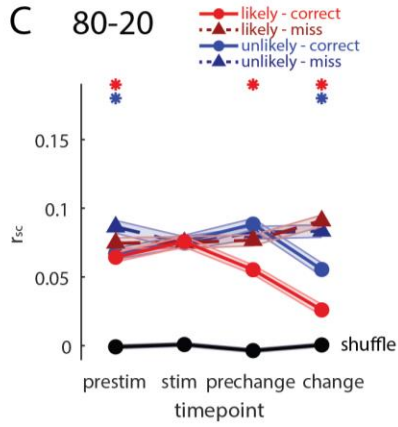
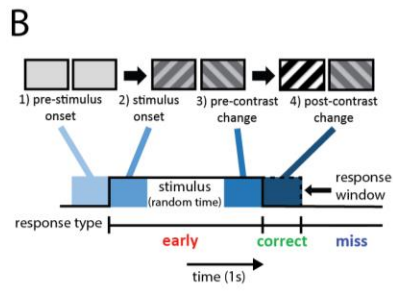
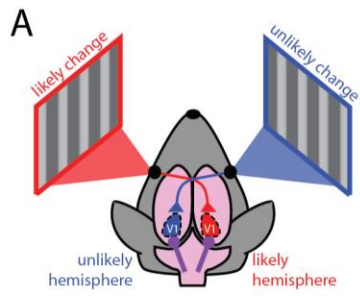


Figure 2.3: Changes in firing rate across conditions.

(A) Example z-scored firing rates averaged from deep-layer (infragranular, below layer 4) neurons in the likely hemisphere of 80-20 mice. Different trial conditions are shown and aligned to stimulus start and contrast change: correct (green line), miss (blue line), running (magenta line), and stationary (black line) trials. To compare conditions we subtracted correct minus miss (*correct-miss*) and running minus stationary (*running-stationary*) z-scored firing rates, example corresponds to average of deep layer units (panels B and E). Significant differences shown in Figure 2.11.

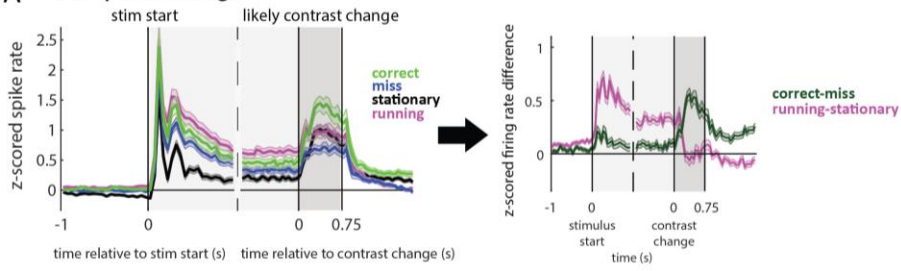
(B-D) Effect of locomotion on stimulus-aligned z-scored firing rates versus recording depth. Color indicates magnitude of firing rate difference. Locomotion increases stimulus-evoked firing rates relative to stationary trials across layers in both 80-20 and 50-50 mice, which is sustained until the contrast change, but the increase is not sustained after the contrast change.

(E-F) Selection affects firing rates differently to locomotion. On correct versus miss trials in 80-20 mice, stimulus-evoked firing rates increase slightly in deep layers and decrease in superficial layers. The response to the contrast change is selectively enhanced on correct trials versus miss trials.

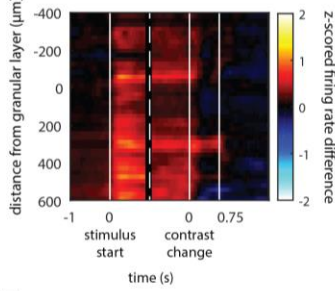
(G) In 50-50 mice on correct trials, both stimulus-evoked and change-evoked activity are increased across layers in 50-50.

80-20 likely hemisphere N=643 neurons; unlikely N=403 neurons; 50-50 N=658 neurons.

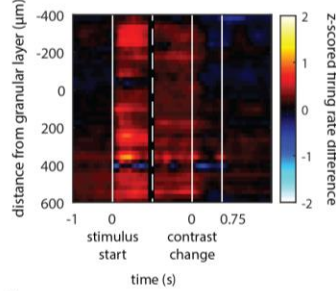
A example recordings:



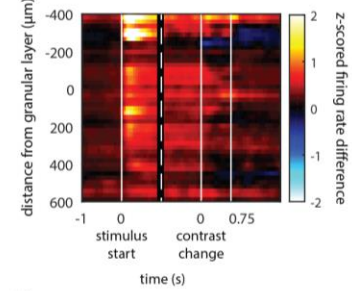
B likely hemisphere run vs stationary



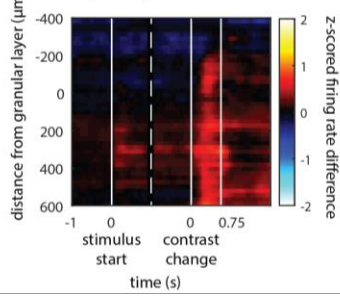
C unlikely hemisphere run vs stationary



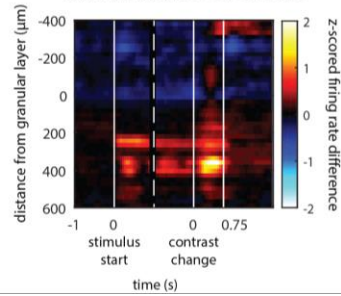
D 50-50 run vs stationary



E likely hemisphere correct vs miss



F unlikely hemisphere correct vs miss



G 50-50 correct vs miss

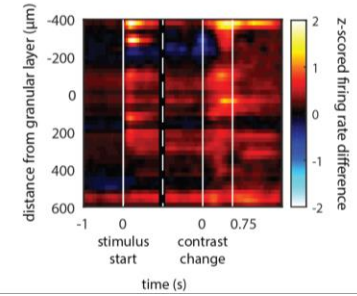


Figure 2.4: Local and global decreases in individual variability

(A) Comparison of mean fano factor (variability/mean) across timepoints on correct (solid lines) versus miss (dotted lines) trials in likely (red) and unlikely (blue) hemispheres of 80-20 mice. Fano factor in the likely hemisphere on correct trials is selectively decreased relative to other conditions. Likely hemisphere, N=303 neurons; unlikely, N=217 neurons.

(B) Correct versus miss fano factor in 50-50 mice. Fano factor decreases in both hemispheres on correct versus miss trials. Hemisphere contra to bias, N=91 neurons; ipsi, N=121 neurons.

(C-D) Locomotion has inconsistent effects on fano factor.

(All plots, * $p < 0.05$, sign-rank test. Error bars SEM. Different colors correspond to comparisons within that hemisphere, i.e. red * reflect comparisons in the likely hemisphere in 80-20 mice)

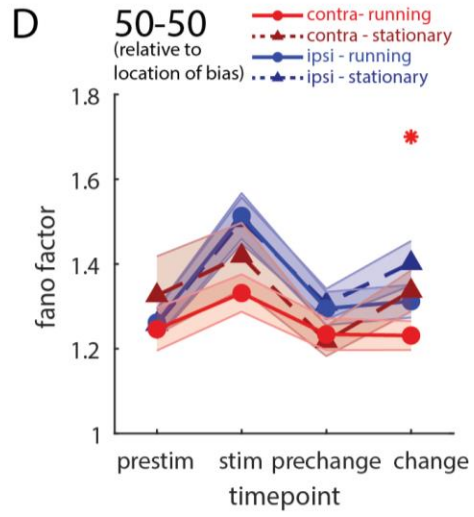
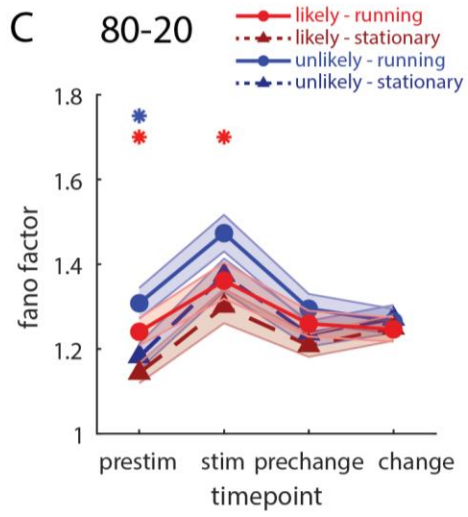
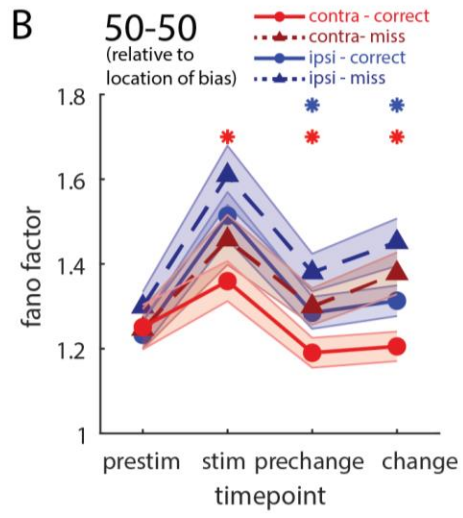
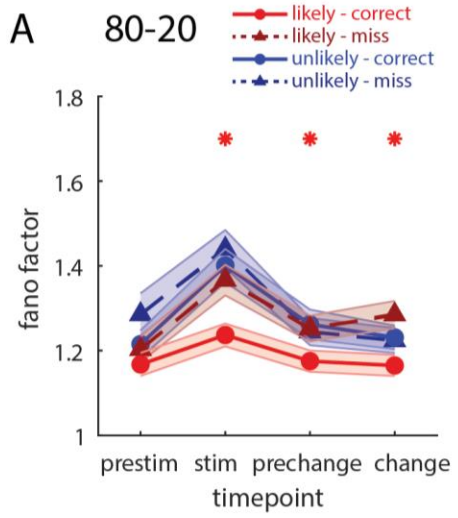


Figure 2.5: Local field potential changes consistently with locomotion

(A) Comparison of local field potential (LFP) spectra across conditions in 80-20 mice. Correct versus miss LFPs were plotted separately for running and stationary trials, and running versus stationary LFPs were plotted separately for correct and miss trials. N=15 included recordings. Error bars SEM.

(B) LFP power differences in different frequency bands between correct and miss and between running and stationary trials in 80-20 mice. Differences between correct and miss LFP power were separately calculated on running and stationary trials, and running versus stationary differences were similarly separately calculated on correct and miss trials. N=19 included recordings (both hemispheres' responses to contralateral change trials combined). Error bars SEM. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, sign-rank test.

(C) Same as (A) but for 50-50 mice.

(D) Same as (B) but for 50-50 mice.

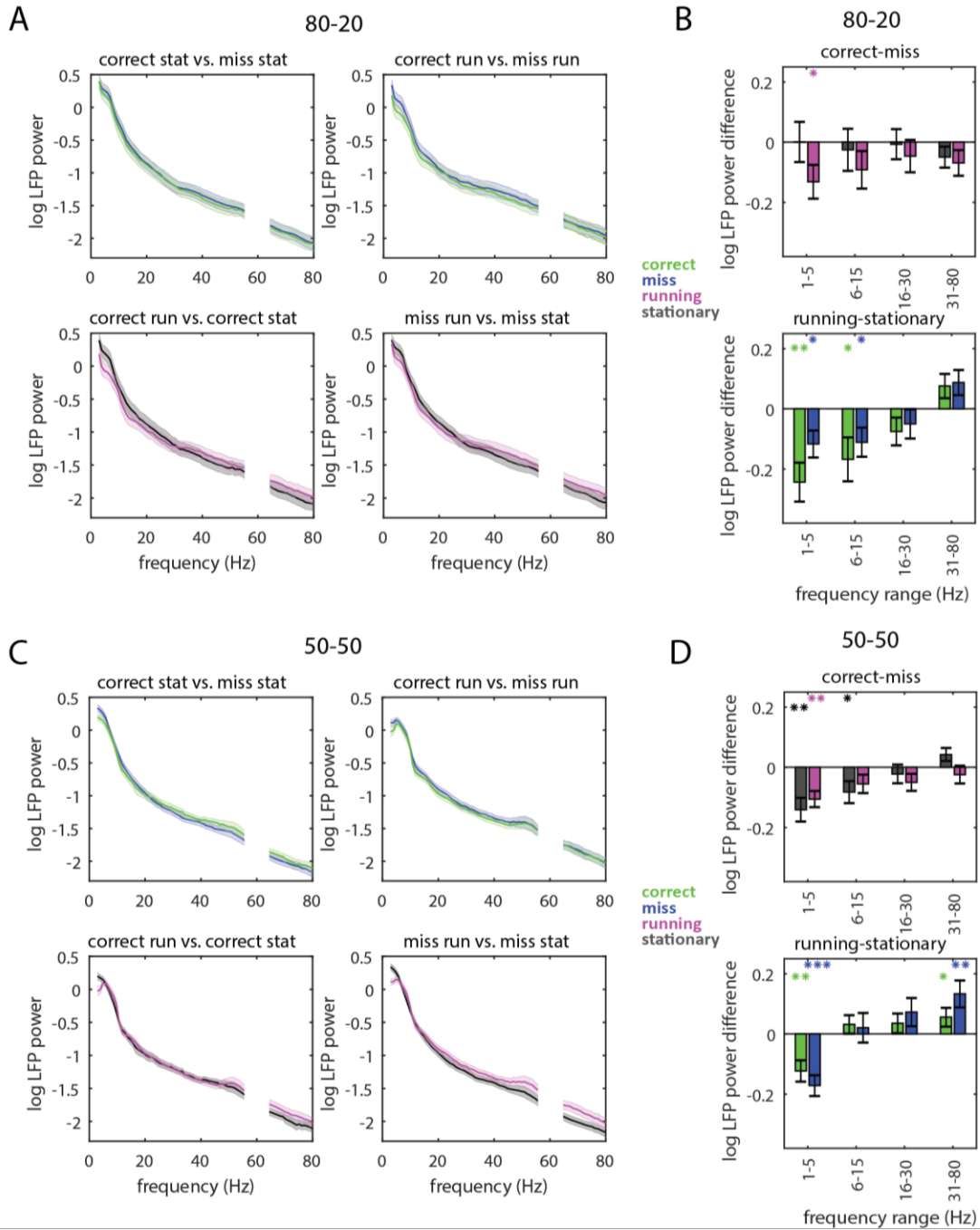
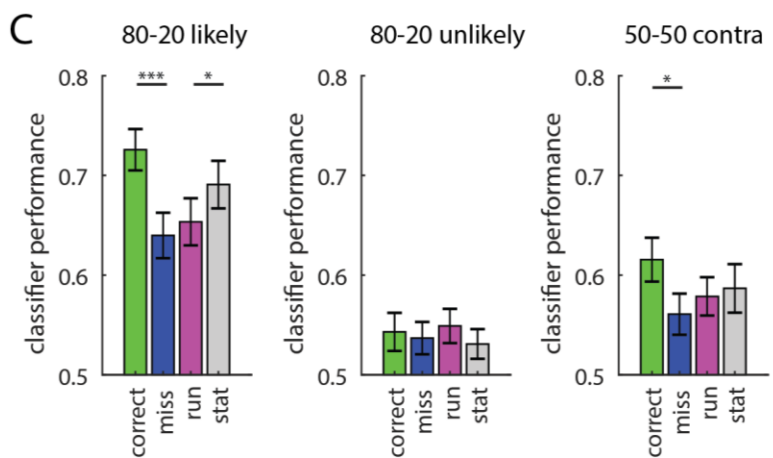
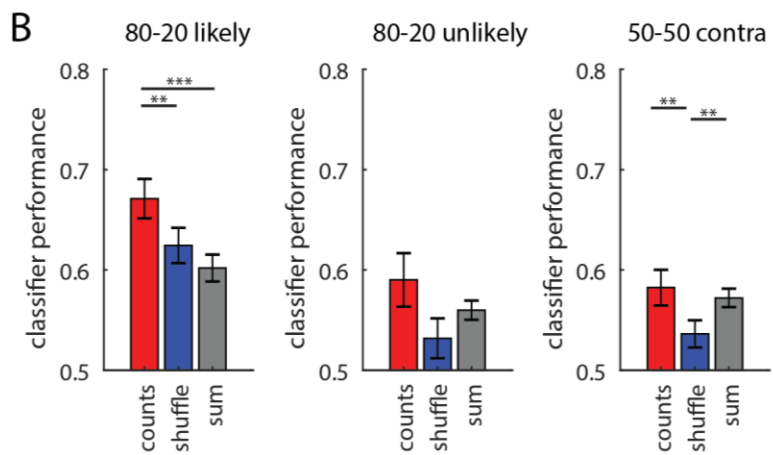
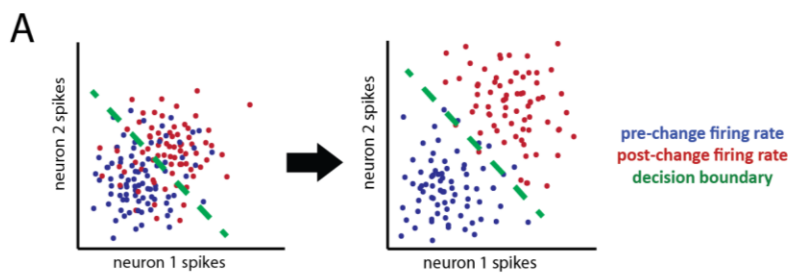


Figure 2.6: Local and global effects on linear classifier performance

(A) Schematic of hypothetical firing rates for two simultaneously recorded neurons across multiple trials (dots), prior to (blue) and following (red) the contrast change. The green line indicates an approximate linear boundary that optimally separates pre- and post-change firing rates. In different conditions, pre and post can be less (left) or more (right) easily separable. We measure this in real neural data from up to 70 simultaneously recorded neurons by training a linear classifier on pre versus post firing rates, and testing its accuracy. Higher accuracy means the pre and post firing rates were more separable, and thus there was more information in the population activity about the contrast change.

(B) Linear classifier performance decoding pre- versus post-change population activity when using raw spike counts (red bars), trial-shuffled spike counts (blue bars), and spike counts summed across simultaneously recorded neurons (grey bars) in different groups of mice and different hemispheres. The classifier performed best overall using raw spike counts from the 80-20 likely hemisphere (left panel). Trial shuffling decreased performance in both the 80-20 likely hemisphere and in 50-50 mice (right panel). Summing spike counts across units decreased performance only in the 80-20 likely hemisphere.

(C) Linear classifier performance using spike counts on different subsets of trials: correct (green), miss (blue), running (magenta), and stationary (gray). Performance differed across different trial conditions, particularly in the likely hemisphere of 80-20 mice. Error bars SEM. 80-20 likely N=18 recordings; 80-20 unlikely N=18 recordings; 50-50 N=18 recordings (both hemispheres' responses to contralateral change trials combined). * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, sign-rank test.



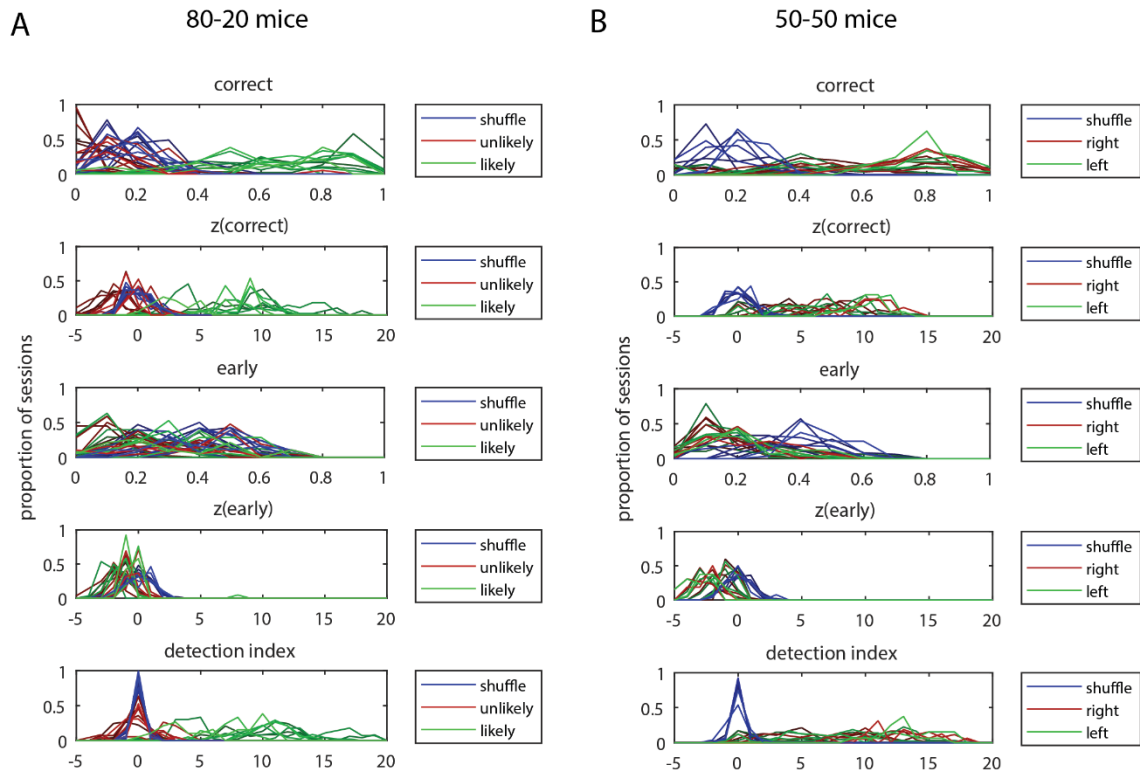


Figure 2.7: Calculation of detection index

Related to Figure 2.1. Examples showing process of calculating detection index from raw correct trial rate and raw early trial rate.

(A) 80-20 mice. First panel, raw correct trial rate. Green lines show distribution of correct trial rates on likely trials across sessions. Red lines show distribution on unlikely trials, and blue lines show the distribution when lick times were shuffled with respect to stimulus times. Different shades of each color correspond to distributions from different mice. Second panel, correct trial rates were z-scored to with respect to the shuffle performance, now showing number of standard deviations from chance performance. Third and fourth panels, same as first and second but for early lick trials. Fifth panel, detection index which was computed by subtracting $z(\text{correct}) - z(\text{early})$.

(B) Same as (A) but for 50-50 mice.

Figure 2.8: Behavior details

Related to Figure 2.1.

(A) Learning curves. Red line shows 80-20 learning curve (n=11 mice), blue line shows 50-50 learning curve (n=7 mice). Learning progress of the different groups was similar. Error bars SEM.

(B) Response tendency of mice. Response tendency was calculated as $(z(\text{correct})+z(\text{early}))/2$. Higher response tendency indicates a higher chance of responding. 80-20 mice were more likely to respond to likely versus unlikely changes overall (likely, stationary: 3.40; unlikely, stationary: -1.38; $p<0.001$, sign-rank test), though less likely to respond on running trials (likely, running: 2.35; $p<0.01$, sign-rank test) N=11 mice. 50-50 mice were equally likely to respond to either change, but also less likely to respond on running trials (stationary: 1.62, running: 2.28; $p<0.05$, sign-rank test) N=7 mice.

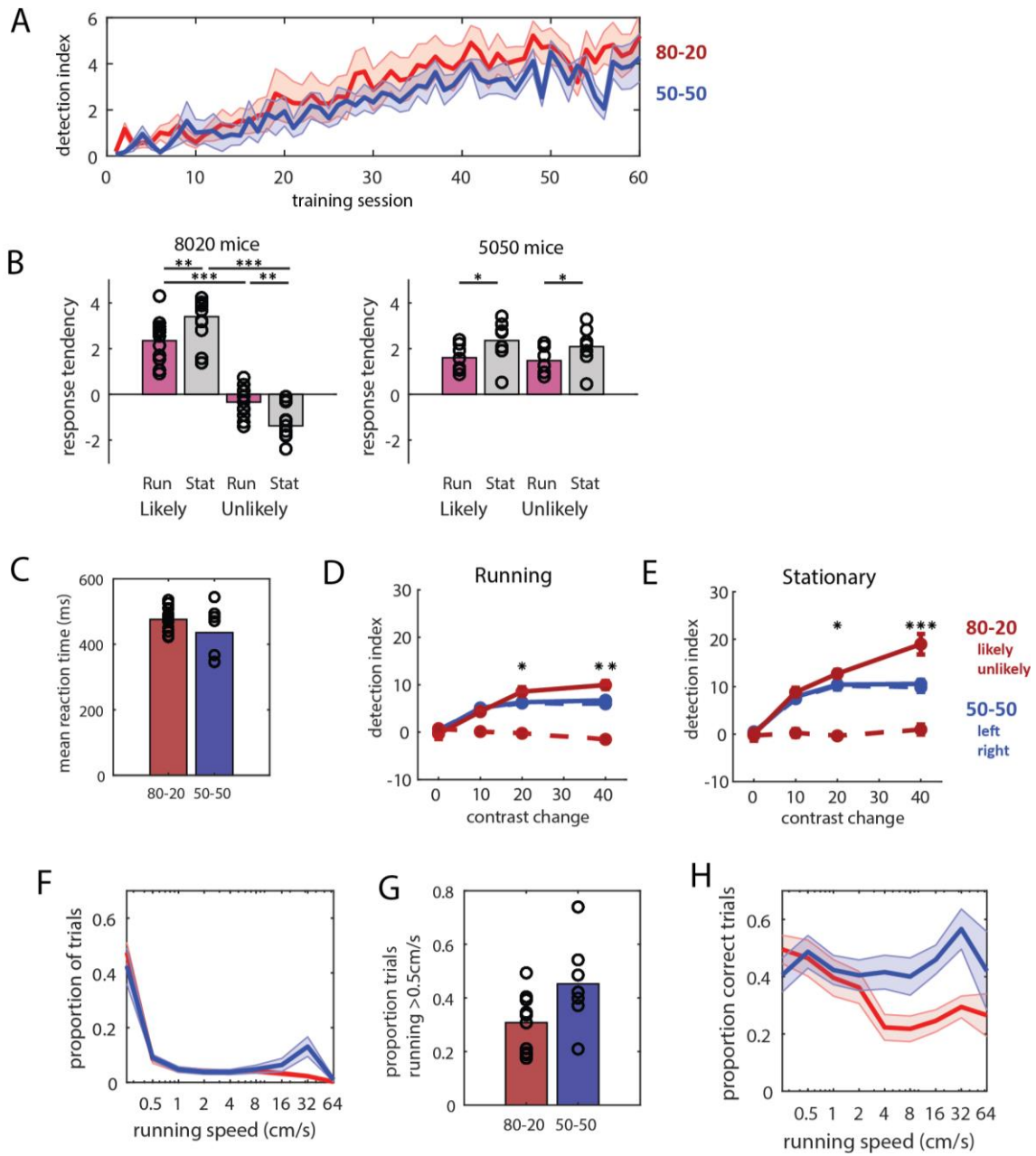
(C) Reaction times of each group were not significantly different. 80-20: $475\pm 39\text{ms}$; 50-50: $435\pm 81\text{ms}$; $p=0.479$, rank-sum test.

(D, E) Dependence of behavior on magnitude of contrast change under different conditions. Both groups of mice performed better with larger contrast changes, and 80-20 mice outperformed 50-50 mice with 20% or greater contrast changes, even when running. 80-20 N=51 sessions, 3 mice; 50-50 N=100 sessions, 5 mice. Error bars SEM. * $p<0.05$, ** $p<0.01$, *** $p<0.001$, rank-sum test.

(F) Proportion of trials versus running speed. Both groups of mice spent most of their time stationary, but 50-50 mice (blue line) spend more trials running ≥ 16 cm/sec than 80-20 mice (red line). Error bars SEM.

(G) Proportion of trials spent running >0.5 cm/sec. 80-20 mice ran >0.5 cm/sec on fewer trials than 50-50 mice. 80-20: 30.8% of trials, 50-50: 45.3% of trials; $p=0.0346$, rank-sum test.

(H) Proportion of correct trials versus running speed. 80-20 mice performed progressively worse with higher running speeds, while 50-50 mice performed as well or better than they did when stationary.



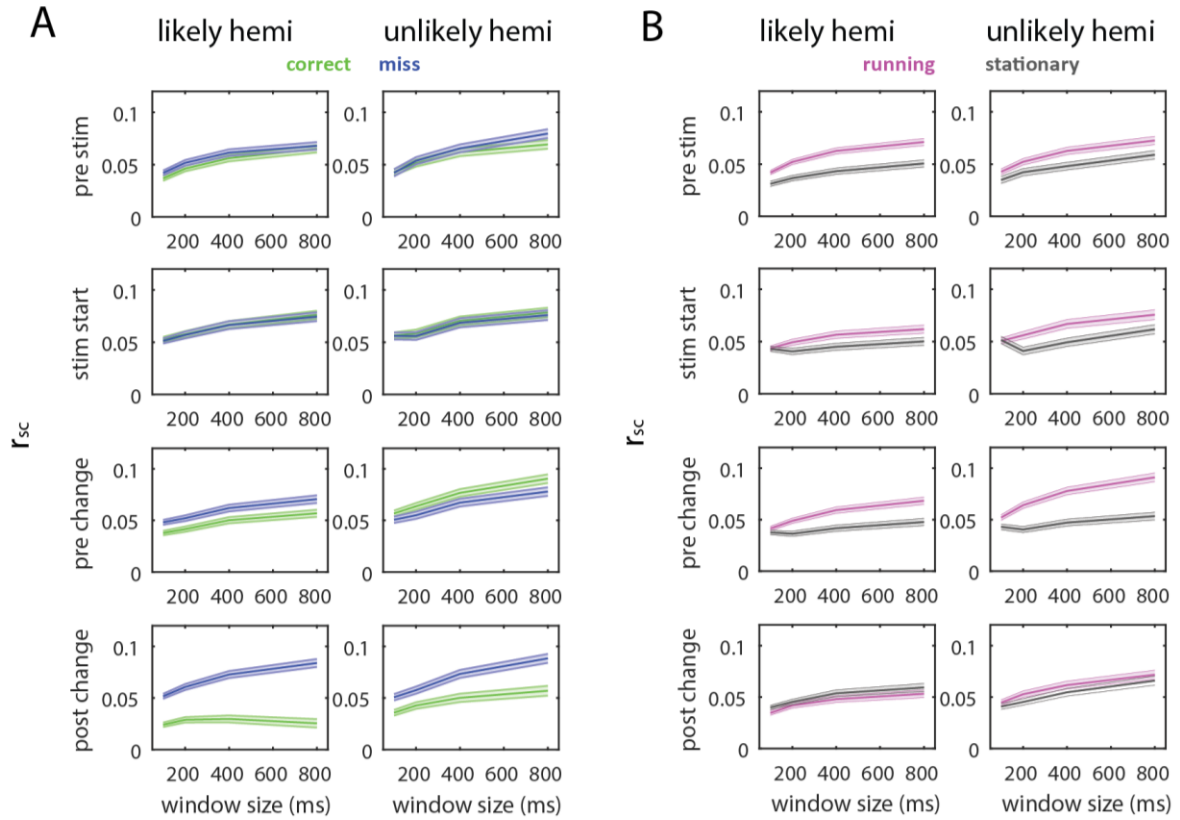


Figure 2.9: Dependence of r_{sc} on size of time window

Related to Figure 2.2.

(A) Example comparison of r_{sc} on correct (green) and miss (blue) trials using different spike count time windows, and across different trial time points. Example data from 80-20 mice. In general, r_{sc} increased with larger time windows, but our observed decreases on correct trials were present in time windows as small as 100-200ms.

(B) same as (A) but comparing running (magenta) versus stationary (black) trials, observed increases of r_{sc} on running trials was present down to 200 ms. Error bars SEM.

Figure 2.10: Effects on responses to preferred versus non-preferred stimuli

Related to Figure 2.3.

(A) Average tuning curves of neurons in 80-20 likely hemisphere at different time points across different conditions: correct (green), miss (blue), running (magenta), and stationary trials (black). Preferred orientation aligned to 90 degrees. Error bars excluded for clarity.

(B) Tuning curve differences between correct and miss (green) and running and stationary (magenta) across time points. Error bars SEM.

(C) Scatter plot comparison between absolute change in firing rate at preferred and orthogonal orientations at different time points. Each point corresponds to a single neuron. Green points are each neurons' correct versus miss absolute change in firing rate at their preferred versus orthogonal orientations. Magenta points are for running versus stationary change in firing rate. Lines are linear least-squares regression.

(D) Summary data. Average difference between absolute change in firing rate in response to preferred versus orthogonal orientation. In 80-20 mice at pre-change and post-change time points and in both hemispheres, the response to the preferred versus orthogonal stimulus is more specifically affected on correct (green) compared to running (magenta) trials (likely N=303; unlikely N=217 significantly tuned neurons). In 50-50 mice, effects of selection and locomotion were not significantly different (N=177 significantly tuned neurons). * $p < 0.05$, ** $p < 0.01$, sign-rank test.

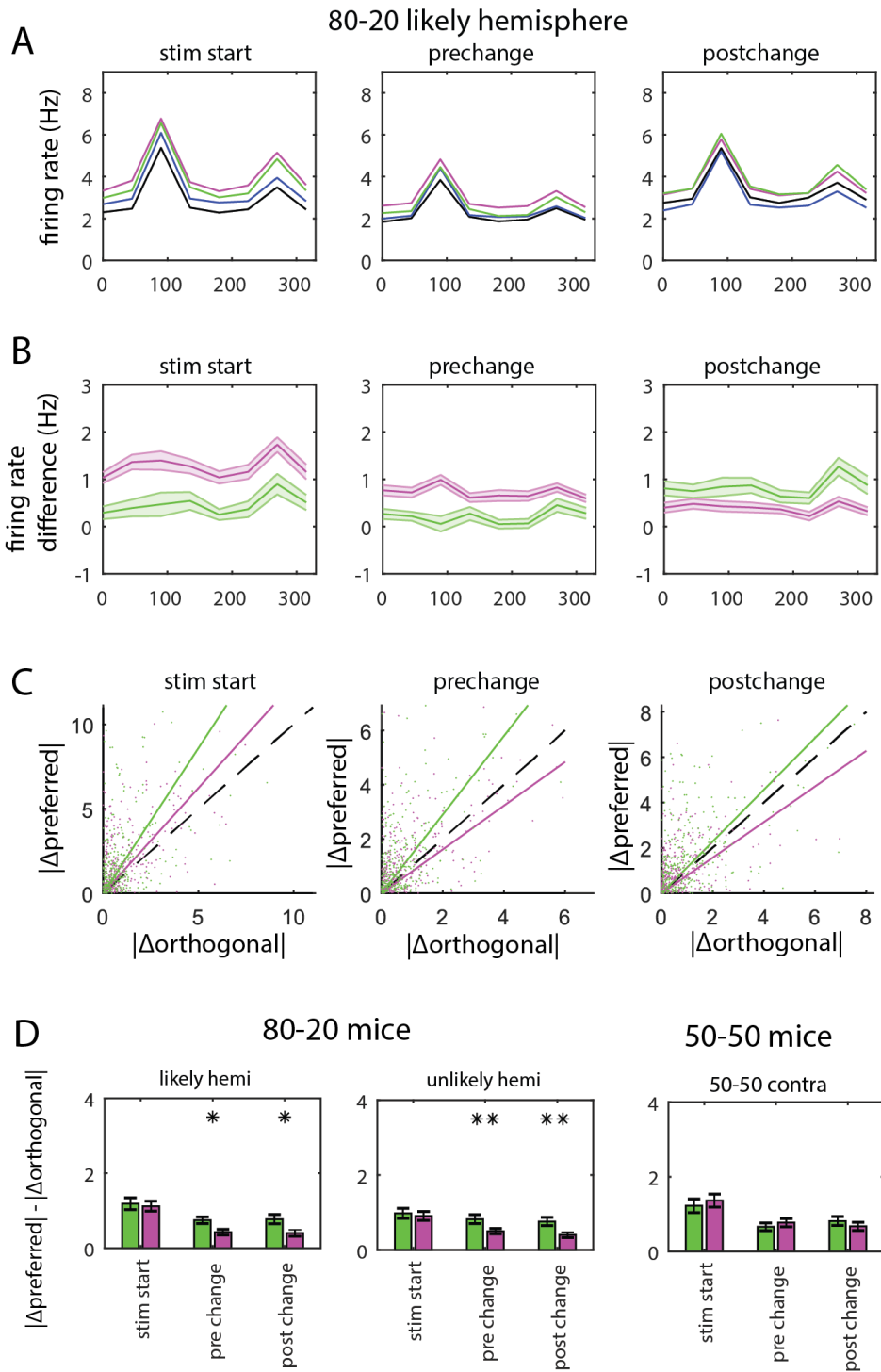


Figure 2.11: Effects on spike rates

Related to Figure 2.3. Z-scored firing rate differences between conditions averaged across superficial (2-4) or deep layers (5-6).

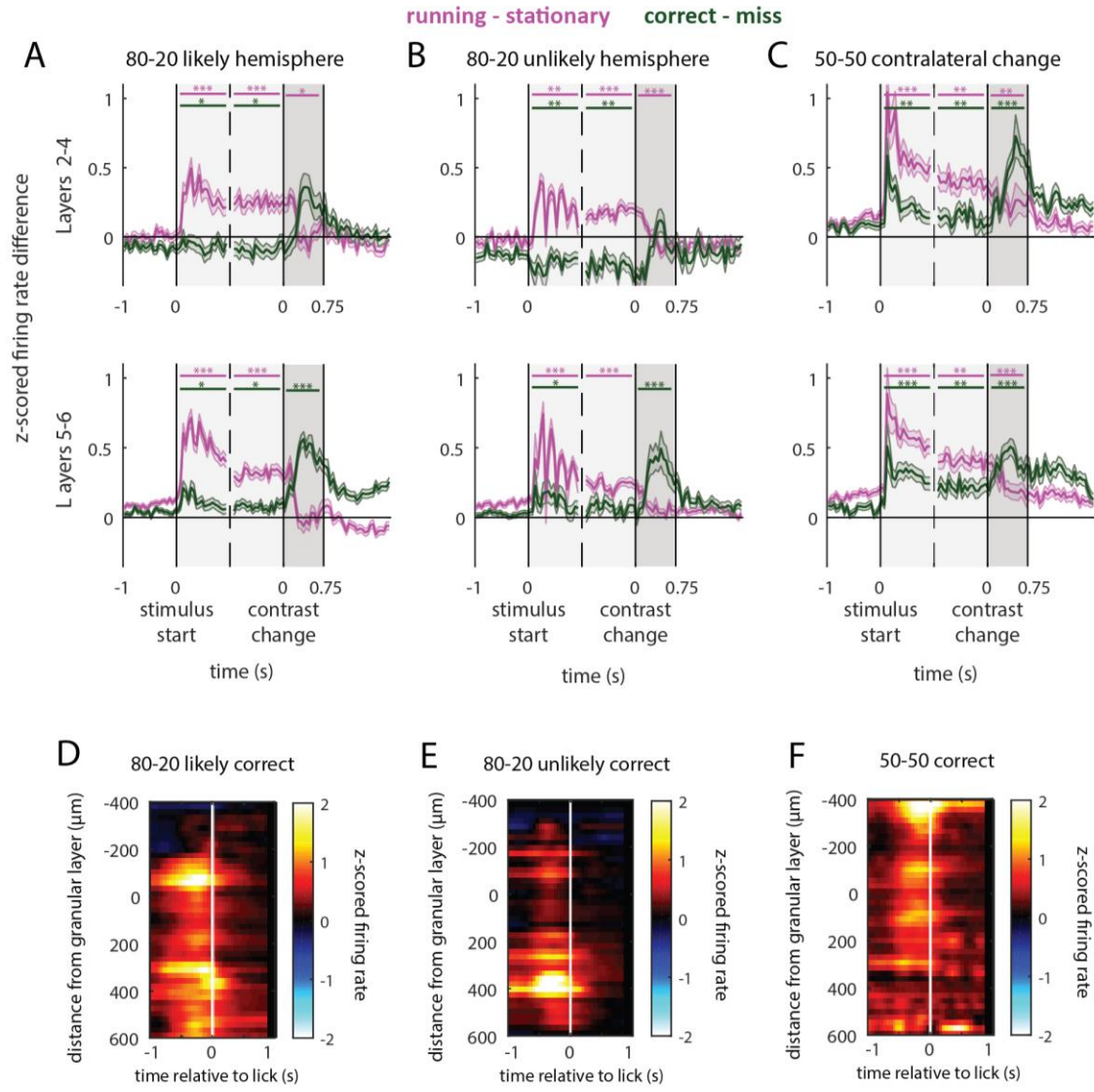
(A) Differences in 80-20 likely hemisphere. Running enhances stimulus onset response (magenta line) in all layers, selection (green line) enhances contrast change response in all layers, and stimulus onset response slightly in deep layers. Upper layer N=139 neurons; lower layer N=504.

(B) 80-20 unlikely hemisphere. Running has similar effects as in likely hemisphere (magenta), but selection suppresses firing rates in upper layers (green). Upper layer N=107 neurons; lower layer N=296.

(C) 50-50 mice, contralateral change. Running and selection have similar effects, except running enhances stimulus onset response more, while selection enhances contrast change response more. Upper layer N=299; lower layer N=359.

(D-F) Z-scored firing rates across layers aligned to lick onset on correct trials. Peak of activity precedes lick in all mice and hemispheres.

Statistical comparisons relative to zero; * $p < 1e-4$, ** $p < 1e-6$, *** $p < 1e-8$, sign-rank test.



* $p < 1e-2$ ** $p < 1e-4$ *** $p < 1e-8$ Wilcoxon signed rank test

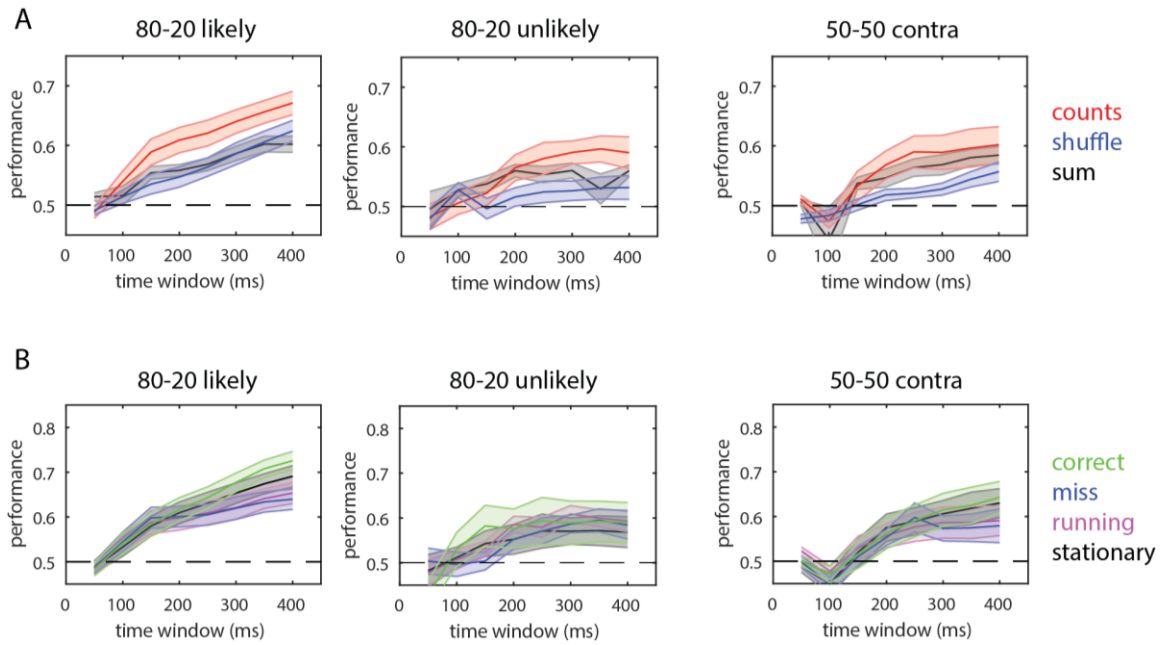


Figure 2.12: Linear classifier performance at different time windows

Related to Figure 2.6. Performance of linear classifier trained with spike counts from different sized time windows prior to and following the contrast change.

(A) Performance of linear classifier trained on either the raw spike counts from all neurons (counts, red), trial-shuffled spike counts to remove correlated variability (shuffle, blue), or summed firing rates across all simultaneously recorded neurons (sum, black).

(B) Performance of linear classifier trained on raw spike counts on subsets of trials: correct (green), miss (blue), running (magenta), and stationary (black). Error bars SEM.

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