Cortical Dynamics for Active Vision

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This dissertation by Seth Akers-Campbell is accepted in its present form by the Department of Neuroscience as satisfying the dissertation requirements for the degree of Doctor of Philosophy.

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2021 Analyzing an Allelic Series of Rare Missense Variants of CANCA1I in a Swedish Schizophrenia Cohort. Baez-Nieto D, Allen A, **Akers-Campbell S**, Yang L, Pupo A, Shin YC, Genovese G, Liao M, Perez-Palma E, Lal D, Lipscombe D, Pan JQ. *Brain* (2021) https://doi.org/10.1093/brain/awab443

2019 Transsaccadic Information and Corollary Discharge in Local Field Potentials of Macaque V1. Paradiso MA, **Akers-Campbell S**, Ruiz O, Niemeyer JE, Geman S, Loper J. *Frontiers in Integrative Neuroscience* (2019) https://doi.org/10.3389/fnint.2018.00063

Manuscripts in Peer Review

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Preface and Acknowledgements

In addition to the dissertation author, James Niemeyer, Michael Paradiso, and Aaron Gregoire contributed to this work. James Niemeyer and Michael Paradiso designed the experiment described in Chapter 2 and analyzed in Chapters 2, 3, and 4. James Niemeyer and Aaron Gregoire performed the animal training and carried out this experiment. Data were analyzed by James Niemeyer and Seth Akers-Campbell. Seth Akers-Campbell and Michael Paradiso designed the analyses in Chapters 3 and 4. Michael Paradiso provided funding and oversight for all aspects of this work.

Portions of Chapters 1 and 4 have been submitted for publication as "Saccadic enhancement of natural scene processing in active vision" (authors: Seth Akers-Campbell, James Niemeyer, and Michael Paradiso), a work which is undergoing peer review in the journal *Frontiers in Cellular Neuroscience*. Chapter 2 has been previously published (June 2022) in *Current Biology* as "Perceptual enhancement and suppression correlate with V1 neural activity during active vision" (authors: James Niemeyer, Seth Akers-Campbell, Aaron Gregoire, and Michael Paradiso).[1]

A related study, referred to throughout this work, is "Transsaccadic information and corollary discharge in local field potentials of macaque V1," published in *Frontiers in Integrative Neuroscience* in January 2019 (authors: Michael Paradiso, Seth Akers-Campbell, Octavio Ruiz, James Niemeyer, Stuart Geman, and Jackson Loper)[2]. Another related publication which touches on several themes of this dissertation is "Vision: Optimizing each glimpse," a commentary on Chapter 2 written by Paola Binda and Maria Concetta Morrone in *Current Biology*.[3] Many previous studies from the Paradiso lab are relevant to the present work, including "V1 neural activity, contrast sensitivity, and natural vision," by James Niemeyer and Michael Paradiso, published in *Journal of Neurophysiology*[4].

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CHAPTER 1: INTRODUCTION

Vision is an important and dominant sensory modality in humans and other primates. To a significant degree, vision is the substance of our daily experience, our dreams, and our memories. Research in the past 60 years has revealed that the primate visual system is an elaborate network that makes up a large percentage of the brain. Yet, despite the thousands of research studies published in this period, there is great uncertainty about the neural basis of our perceptual experience. The research described here investigates what has come to be called "active vision". The term refers to the observation that visual experience consists of a sensory-motor loop. That is, guided by behavioral goals and salient stimuli, our gaze is directed to an object of interest and we then scrutinize the object with our fovea. Subsequent visual processing then leads to a new eye movement. This circular sensory-motor process is repeated endlessly in our daily visual exploration. For most of the history of vision research, perception and its neural basis have been studied independently from visual behavior (i.e. eye movements). However, it has become increasingly apparent that understanding natural visual experience and neural processing will require studies of active vision that involve the simultaneous examination of perception, neurophysiology, and eye movements.

I. The Primate Visual System

Perception has been studied for millennia, but there was an explosion of work in the 20th century. Early on, understanding brain mechanisms of vision was largely based on deficits associated with lesions, an endeavor that expanded considerably during World War I as large numbers of soldiers survived head injuries[5]. Following the Second World War, the ability to record from the brain advanced rapidly, and there are now many methods for measuring neural activity. Microelectrode recordings, extracellular optical imaging, and intracellular calcium or voltage imaging have revolutionized brain science by providing detailed information on neuronal processing. Advanced extracranial methods such as functional magnetic resonance imaging

(fMRI), elecroencephalography (EEG), and magnetoencephalography (MEG) provide complementary, large-scale data in human subjects, often as they perform complex cognitive tasks. We now have considerable knowledge about which parts of the brain respond to visual stimuli. However, there remains great uncertainty about how the numerous visual areas of the brain cooperate and give rise to perception – the awareness and interpretation of visual input.

Arguably, vision is the most well-understood of the human senses, both at the neuronal and psychophysical levels. Photons from the environment are transduced by retinal photoreceptors into chemical signals which are then converted into electrical impulses that are processed by the brain[6]. In primates, most of the signals from the eyes are routed to the lateral geniculate nucleus of the thalamus (LGN), although a portion is sent to the superior colliculus (SC), a visuo-motor region critical for generating eye movements. After passing through the LGN, most of the visual signal is first routed to the primary visual cortex (V1), and then to a complex network of dozens of brain areas[6,7]. Both feedforward retinal input to V1 as well as cortical feedback from other areas appear to be critical, and possibly necessary, for conscious visual perception[8–21]. V1 makes up a disproportionately large portion of the primate brain[7,22]; its neurons are generally tuned to simple features, such as the orientation of object contours where there is lightness or color contrast[23,24]. V1 is generally believed to be one of, if not the, most well-understood areas of the brain, although only a small fraction of its function appears to be understood[25].

The processing of more complicated objects is thought to occur primarily in the ventral stream, a system of visual areas that stretches from V1 towards the memory centers of the brain in the temporal lobe. As the signal is processed by the intermediate levels of this stream, such as area V4, the neurons seem to represent more complicated things, such as shapes and textures[26–28]. At the final stages of processing, in the inferotemporal cortex (IT), the neurons appear to encode specialized objects such as faces[29–31]. This view of encoding by the visual system (depicted in **Figure 1a**) has not only been extremely successful in explaining human and animal

perception, but it has also led to the development of deep neural networks and other forms of artificial intelligence that mimic its organization[32,33].

The visual system of primates, including humans, differs from other species in significant ways. Primates have a specialized region of the retina, the fovea, which encodes signals with high spatial resolution[6]. Thus, primates need to make eye movements to shift the sensitive portion of the eye to new locations. In rodents and other non-mammalian species, a majority of the retina input is routed to the superior colliculus (SC), with a minority sent to the LGN[6]. The structure of V1 in primates (and some other mammals) appears to be specialized for edge detection[34] which is important for object recognition[35]. The ability to rapidly recognize and differentiate between complex objects is a hallmark of primate perception and behavior[36–39]. Because the primate visual system is so specialized, animal studies in non-human primates, such as the macaque monkey, are critical to understanding the human visual system.

II. Methods for the Study of Visual Processing

Due to recent advances in recording technology, neurophysiological experiments have expanded beyond studying single neurons to studying networks of neurons, either within or between brain regions. This work has demonstrated that perception and cognition are often more closely correlated with properties of the neural network (i.e. interactions between neurons) than with the activity of single cells[40–43]. It is now feasible to record separate electrical signals from up to thousands of neurons simultaneously[44]. Recent work has even imaged the activity of tens or hundreds of thousands of cells, although with poor temporal resolution[45,46]. Relevant to the present study, recording with high temporal resolution can be achieved using arrays of extracellular electrodes, which sample tens of thousands of times per second and capture both continuous-time local field potential (LFP) signals and discrete spiking events (**Figure 1b**). These two types of signals convey complementary information: the LFP reflects the combined synaptic and cellular activity of large numbers of neurons[47], while the spikes (action potentials) reflect the information encoded by single neurons.

The use of high temporal resolution recording is especially important for the present work, as saccades are very brief (typically less than 50 ms in duration), and visual processing is extremely fast, with the entire process of object recognition capable of occurring in less than 100 ms[36–39,48] Non-invasive, long-timescale methods such as fMRI cannot resolve the time course, or dynamics, of these fast computations. Invasive methods such as calcium imaging provide 1-2 orders of magnitude better temporal resolution than fMRI, but still several orders of magnitude less than electrical recordings. Calcium imaging allows for the visualization of very large neural populations, but this method is often inappropriate for studying neuronal computation on fast timescales as sampling rates are low, and important spiking events may be missed[49,50], including the critical first few visually-evoked spikes in visual cortex which are sufficient for forming a percept[48,51,52]. Thus, to understand the effects of saccades on population coding and perception, it is critical to study neural activity at the appropriate timescale using electrophysiological recordings.

In addition to the neuronal recording method used, other methodological factors are critically important for the work reported here. Typically, non-human primate subjects are trained to hold fixation for unnaturally long periods of time, and they view unnatural abstract and isolated stimuli flashed onto computer displays (**Figure 1a**). This laboratory paradigm, which allows for well-controlled experiments, differs from natural vision in several key ways. For example, primates typically make two or more saccadic eye movements each second to scan the environment (or read from a screen). Each fixation lasts only approximately 200-300 milliseconds, after which a new saccade begins[53–57]. This cycle occurs endlessly, like the beating of the heart – except saccades are more frequent! Saccades are the primary way in which new visual information is acquired by the brain. However, physiological studies have studied primarily how the brain uses sensory information to generate saccades. Much less is known about the reverse: how saccades influence the processing of sensory information.

Regarding visual input, the bars of light and Gabor patches commonly used in visual neuroscience experiments have been critical to learn much of what we know about visual processing in the brain. That said, they are obviously unnatural and there is considerable evidence that, in certain regards, there are significant differences between responses to abstract and natural stimuli[58,59]. Thus, depending on the goals of an experiment, the unnatural behavioral paradigm and/or stimuli may be important factors. Both of these methodological issues are relevant to the experiments described here. Moreover, as discussed throughout this thesis, simultaneous quantification of neural activity and perception is critical for understanding the neural basis of perceptual effects[60–62].

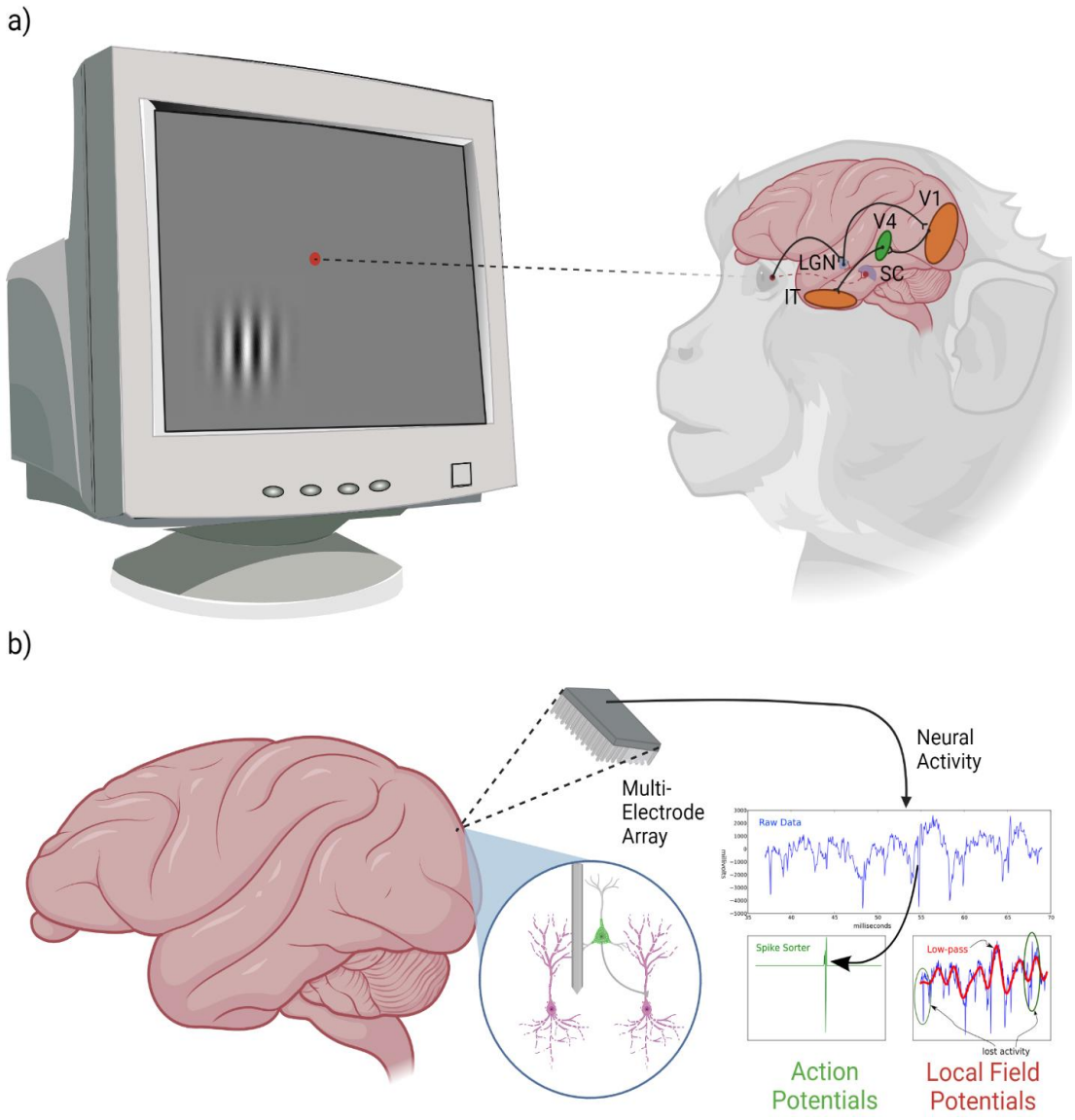

Figure 1: Experimental methods for studying the neural basis of visual perception.

a) A macaque monkey (right) fixates on a small dot on a computer monitor. An abstract image, here an isolated Gabor stimulus, is flashed onto the screen. The animal is typically asked to report a feature (such as the orientation) or the location of the stimulus. The signal travels from the retina in the eye mostly to the lateral geniculate nucleus (LGN), but partially to the superior colliculus (SC). From the LGN, the signal travels to primary visual cortex (V1), and to the ventral stream regions which are critical for the recognition of more complex objects. Highlighted here are area V4, a mid-level ventral stream area, and the inferotemporal cortex (IT), which contains representations of complex objects. Note that most visual areas, including V2 and V3, are not depicted, and the projections between regions are shown for illustrative purposes and do not depict the actual trajectories. **b)** Electrical activity is recorded by implanting electrodes in the brain. These electrodes record raw neural activity which can be separated into action potentials, which represent the activity of single neurons located near the tips of the electrodes, or local field potentials, which represent the collective activity of a large population. Illustrated here is a 96-channel "Utah" multi-electrode array, manufactured by Blackrock Microsystems.

III. Eye Movements

The use of fixation paradigms would not be an important issue if there weren't indications that eye movements alter perception. There is now strong evidence that eye movements do alter perception and neural coding[63–65]. Thus, to understand vision, eye movements must be considered. Eye movements, like perception, have been studied for thousands of years (extensively reviewed by Wade[66]). They are generally grouped into five categories: smooth pursuit, saccades, vergence movements, vestibulo-ocular movements, and "fixational" eye movements[67].

Smooth pursuit eye movements occur in response to, or with the prediction of, visual motion and allow for the tracking of objects while maintaining a steady gaze on the retina[68,69]. In contrast, saccades are large jumps that suddenly and dramatically change the direction of gaze. With each saccade, the two eyes move together. Vergence movements are used to shift focus to objects further or closer away, and the two eyes move separately. Vestibulo-ocular movements are reflexive eye movements which occur to compensate for changes in head position. The category of fixational eye movements has traditionally included ocular drifts, in which the eye appears to wander randomly, and microsaccades, which are small jumps that occur during extended fixations. Recent research suggests that ocular drifts are not as random as previously believed, and are controlled to some extent by the brain[70–72]. Microsaccades have garnered considerable interest recently due to advances in eye tracking technology, and the large number of experiments which utilize prolonged fixations. These miniature, slow saccades were previously believed primarily to refresh the retinal image and counter neural adaptation, but more recent work argues that this function is incidental and that, in natural situations, their purpose is to enhance fine spatial detail[73]. Recently microsaccades have been shown to be generated by similar mechanisms, and sometimes have similar neural and perceptual consequences, as large saccades[74,75]. Evidence also suggests that to some degree, smooth pursuit and saccadic eye movements are controlled by shared neural resources[76]. In close coordination, all these eye

movements orchestrate visual processing. Eye movements are essential – in fact without them we are blind.[77,78]

In this work, we focus on saccades, which aid vision in numerous ways. An obvious example is foveation. The primate visual system, extending from the retina to cortex, is designed for the highest resolution only in the central retina. As guided by salience and ongoing behavioral goals[79–83], saccades move the fovea to scrutinize objects of interest. In this way, the system makes best use of the small retinal area that has the highest acuity. Increasingly, it appears that saccades also benefit vision in less obvious ways by preparing the system to process the information generated by new fixations. This predictive modulation changes excitability and functional interactions between cortical neurons in ways that may ultimately aid in object recognition[55,84,85].

IV. Eye Movements Modulate Visual Perception and Brain Activity

For decades, it has been clear that saccades modulate ongoing brain activity, rather than purely being a product of brain activity. Importantly, saccades modulate neural signals even in the absence of visual input. Evans[86] described "lambda waves" in the EEG signal when human participants made eye movements in the dark. These low-frequency waves of activity were time-locked to saccades and, critically, appeared primarily in the signals recorded by posterior (occipital) electrodes, suggesting that they were not an artifact of the movement of the eyes.[†] Saccadic (or microsaccadic) modulation of neural activity in visual cortex has also been demonstrated using fMRI[91–93], MEG[94–96], LFPs and intracranial EEG[2,54,84,97–105], and the action potentials of single neurons[4,101,105–129]. The fact that saccades alter widespread brain activity, even in complete darkness, suggests that signals from motor areas are routed to other areas to

[†]The eyes are electrically charged, with a positive potential in the cornea and a negative potential in the retina. This makes them electrical dipoles. Thus, rotations of the eye (i.e. eye movements) change the electrical potential of the scalp, and this potential is recorded by extracranial electrodes[87]. Saccades, microsaccades, and blinks contaminate EEG and MEG signals with instantaneous high-frequency bursts of activity, primarily in anterior electrodes[88–90].

inform them of impending eye movements. These predictive signals, which allow the visual system to prepare to receive new visual input, are known as corollary discharges[130,131].

Corollary discharges (CD) were first theorized hundreds of years ago by leading philosophers and scientists such as Descartes and Helmholtz, before the disciplines of psychophysics or neuroscience were well-established[132–134]. Several early models of CD action on visual perception were proposed, including a "central anesthesia" which totally shut down visual processing during saccades[135] or an "efference copy" which canceled out the sensory consequences of eye movements[136]. Despite centuries of study, the functions and consequences of CD signals are still an active research topic. For example, recent work has suggested that deficits in corollary discharge signaling may underlie symptoms of brain disorders such as schizophrenia[137–143] or Parkinson's[144]. Whether or not CD disruption is a core component of neuropsychiatric disease, saccadic corollary discharge in primates is an important model system for studying coordination among large-scale brain networks[130,145].

Previous research suggests that corollary discharges originate in the superior colliculus (SC), a region of the brainstem which generates signals that move the eye muscles, and therefore the eyes[146,147]. When the SC encodes a saccade, rather than solely sending a signal to the oculomotor system, the SC encodes another, related (corollary) signal that informs the brain of the impending saccade. Saccadic CDs are then routed to different regions of the visual cortex via one of several pathways (**Figure 2**).

The first corollary discharge pathway runs from the SC through the LGN, a region of the thalamus, to V1 – the same pathway as the visual signal from the retina. Previous research suggests that at least some of the effects of saccades in V1 come via the LGN[106]. The other two pathways also run through the thalamus, although through different nuclei[146,148,149]. These routes are through the mediodorsal and pulvinar nuclei of the thalamus, which route signals to anterior and posterior cortical regions, respectively. Both of these pathways have been demonstrated to influence visual processing and the signals that they convey contribute to visual stability and

physiological saccadic suppression[149,150]. Early visual cortex may effectively receive multiple corollary discharge signals, as signals are routed and processed through various brain regions (**Figure 2**).

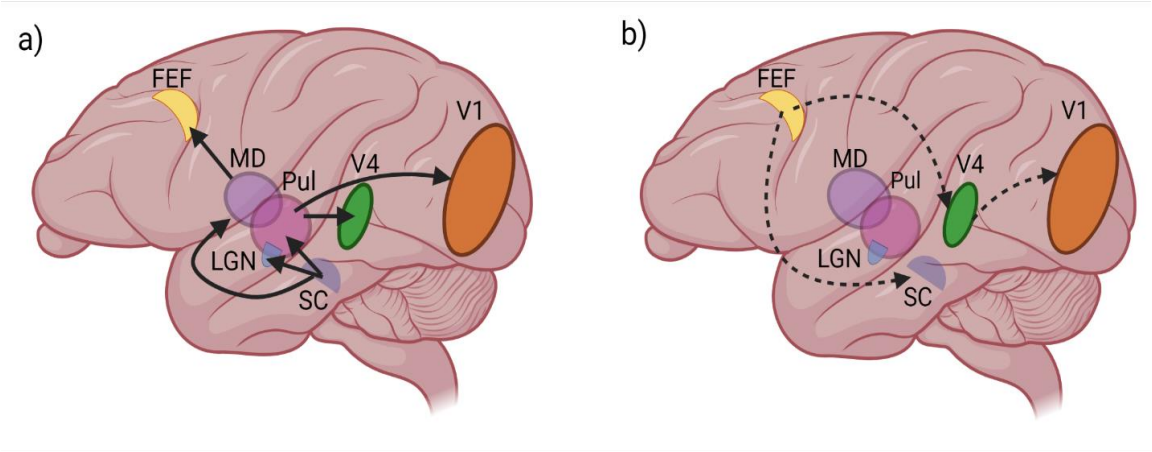

Figure 2: Circuits for routing corollary discharges to early visual cortex.

a) "Feedforward" corollary discharges originating in the superior colliculus (SC) project to the lateral geniculate nucleus (LGN), pulvinar (Pul), and mediodorsal nucleus (MD). These three thalamic regions then relay the signal to anterior regions such as the frontal eye fields (FEF) and posterior visual cortex, including primary visual cortex (V1) and the visual association area V4. **b)** "Feedback" corollary discharges originate in the FEF (in coordination with the SC) and are routed to posterior regions. Note that both the feedforward and feedback pathways overlap substantially with circuits for attentional modulation, highlighting the close relationship between eye movements and attention[116,151–155]. Adapted from Rao et al. (2016)[148].

The focus of most previous research on the influence of saccades, and their associated corollary discharges, on the early visual system is intrasaccadic visual processing, that is, responses to stimuli presented during saccades[64,101,109,112,156–161]. In this work, I focus on post-saccadic visual processing. Thus, rather than focusing on what *is not* seen during the saccade, I will focus on what *is* seen during the subsequent fixation. To appreciate the effects that the saccades involved in active vision have on visual processing, it is essential to start with the nature of the visual input and how the input is encoded in the early visual system.

V. Natural Scene Statistics and Efficient Coding

In addition to unnatural prolonged fixations, visual neuroscience has typically used unnatural abstract and isolated stimuli to probe the responses of the visual system. These stimuli are useful for isolating specific functions, such as sensitivity to contrast and orientation. But if the visual system operates efficiently, one would expect that the system is set up to encode the stimuli which are most common in vision outside the laboratory[162–165]. These "natural scenes" have very different statistical properties from the stimuli commonly used in experimental neuroscience. Both psychophysical and physiological evidence suggest that perception and neuronal processing are different under more natural conditions[58,59,123,166–169].

Our everyday visual experience is clearly not based on unconstrained visual stimulation[170–174]. Because of spatial and temporal correlations, the power spectrum of natural scenes has a characteristic distribution, falling off approximately as $1/f^a$ where f is spatial frequency and $a \approx 2$ [173–178]. However, low spatial frequencies (SFs) have less impact on vision than their predominance in the environment suggests. For example, after adapting to natural images, human and macaque perceptual sensitivity is reduced at low SFs, compared to standard experiments that measure sensitivity against a blank background[4,169,179]. Thus, adaptation to the prevalent low SFs in the environment reduces the response to them.

Theoretical and experimental evidence suggest that the early visual system may function to "whiten" the representation of natural images, such that the retinal output is more evenly weighted across the SF spectrum. This likely happens via multiple mechanisms. For example, there is evidence that the gain of retinal ganglion cells increases with SF, to some extent equalizing (whitening) responses across the spectrum[173,180,181]. Additionally, receptive fields and nonlinear processing in the retina and lateral geniculate nucleus decorrelate and whiten incoming visual signals such that the neural activity is less redundant than the input image[181–184]. Because of the spatial layout and receptive field structure of the retina, decorrelation leads to

whitening[181]. The net effect of retinal processing may not be perfect equalization across spatial frequency, but the retina certainly alters the spatial-frequency-sensitivity profile by decreasing responses to the predominant low SFs in natural images.

Linked to the concept of spectral whitening is the idea that the visual system extracts information as efficiently as possible given its constraints[162–165,170,185,186]. A key component of many efficient coding theories, first detailed by Barlow in 1961, is redundancy reduction, as redundancy is antagonistic to high information transmission[162]. Spectral whitening is a canonical example of efficient coding, as it removes redundant low-frequency signals while maintaining less-prominent higher frequencies. A related strategy that is a component of some efficient coding schemes is sparse coding in which a relatively small number of neurons or response patterns is used to represent visual input[165,171,186]. Sparse codes appear to have numerous benefits in addition to low redundancy, as they exhibit a large coding capacity and are easy to read-out (reviewed by Olshausen and Field[186]). Consistent with sparse and efficient coding, V1 responses to natural images, compared to artificial stimuli, are highly sparse and decorrelated[187–191].

VI. Behaviorally Appropriate Coding

One factor that efficient coding does not consider is behavioral goals. That is, even when the natural visual input is static, the information most useful for different behaviors may vary. Empirical evidence suggests that sensory systems prioritize information relevant for behavior, whether as a design principle or via an active mechanism such as attention[40,192–197]. In the case of vision, spectral whitening of an image dominated by low spatial frequencies may be suboptimal for situations in which low frequencies are important for behavior. Conversely, biasing sensitivity toward higher spatial frequencies or even "over-equalizing" may be beneficial when the behavioral goals are based on high frequency information.

The visual system must also deal with multiple sources of noise including photon noise[198], retinal noise[182,199], and noise introduced in the LGN and visual cortex[200,201]. Also, one can view any non-visual (or task-unrelated) signal as a type of noise, potentially including corollary discharges during active sensing[156,202]. "Robust" codes prioritize the reliability of information transmission, which is critical to generating sensory representations in the presence of noisy signals[182,184,203–206]. Synchronous neural activity, which adds redundancy to rate-coding networks, is a commonly proposed mechanism for robust coding in neural systems[43,98,207]. When multiple excitatory inputs arrive simultaneously at a neuron, it is more likely to spike, and therefore more likely to propagate information to other cells[208,209].In general, sparseness increases susceptibility to noise; information transmission that is both robust and efficient can be achieved by combining sparse coding with a somewhat "overcomplete" (i.e. redundant) representation[210,211]. Several lines of evidence support the hypothesis that neural systems balance efficient and redundant coding to maximize information transfer[41,212–215]. Sparse and synchronous coding of behaviorally relevant stimuli may be an effective strategy for overcoming the challenges associated with active sensing.

VII. Active Sensing, Spectral Sensitivity, and Visual Coding

The discussion above briefly summarizes the advantages of efficient and robust coding and the research demonstrating that the visual system whitens its input. In addition to this foundational research, there is mounting evidence that the coding and transformations the system implements are dynamically modulated by active sensing and natural vision. Even when saccades are made in the dark, there is a period of elevated neuronal excitability shortly after the start of fixation[100]. This modulatory effect appears to be due largely to phase resetting of local field potentials (LFPs), presumably by a saccade-related corollary discharge signal. Interestingly, the timing of these LFP inflections in area V1 is sufficiently precise that the time of fixation onset can be accurately estimated from them[2]. Phase alignment at the start of fixation appears to influence the timing of early spikes in response to visual stimulation and synchronize early spikes

across neurons at a fine time scale[55,98–100]. Thus, it appears that a corollary discharge signal associated with the eye movement puts visual cortex in an optimal state at the time that visual input arrives. The transient increase in synchrony may also ensure that visual signals are robustly encoded and transmitted to other areas of the cortex, especially the ventral stream[84,85].

In addition to an optimally-timed increase in excitability, active sensing has a significant impact on relative power across spatial frequencies, an effect that starts even before neural processing begins. Mostofi et al. quantified the spatio-temporal effects of saccades based on eye movements recorded from subjects who freely viewed natural images[216]. They found that as the eyes traverse a static image, the retinal input shifts toward higher spatial and temporal frequencies. The power of luminance modulation at higher SFs is largely unaffected by the saccades, but there is a significant reduction in power at lower SFs. A related shift in spectral sensitivity is found to occur with fixational eye movements[217–219]. Thus, active vision produces a pre-neural whitening of the input.

Subsequent visual processing and perception can be either suppressed or enhanced by saccades. For example, in standard demonstrations of saccadic suppression in humans, sensitivity is reduced to a visual stimulus that is presented during a saccade[63–65,202,220,221]. Importantly, suppression occurs even when stimuli appear up to about 50 ms into the subsequent fixation[202], indicating that saccades influence perception for stimuli seen during fixation rather than just trans-saccadically. A key observation was that saccadic suppression occurs largely at low spatial frequencies[157]. The loss of low-frequency sensitivity may benefit perception by decreasing perceived blur and by enhancing visual stability across fixations[63,157,161,222]. Reports of post-saccadic enhancement are less numerous, but several lines of evidence suggest that there can be increased perceptual sensitivity and decreased reaction times following a saccade.

VIII. Dissertation Outline

Previous research, as described above, has addressed the influences of corollary discharge on visual processing. However, major gaps in our understanding remain. This work will address three of those gaps by utilizing careful controls, by simultaneously quantifying perception and neural activity, and by isolating the effects of corollary discharge on population coding.

Few studies have rigorously controlled for the image motion on the retina that a saccade causes. Many studies have examined perisaccadic visual processing, but used no control conditions[55,98,99,101,103,106,112,223,224]. Thus, it is impossible to tell whether the intra- and post-saccadic effects were due to the saccade or the high-velocity transients induced by it. In other studies, responses to a stimulus introduced via saccade are compared to responses to a flashed stimulus[100,122,125,127,157]. Unfortunately, the flash paradigm removes both retinal motion and any CD signal from visual processing. Isolating the CD signal requires comparing the effects of saccades to simulated saccades, meaning the same image motion without an eye movement. Several psychophysical and physiological studies have attempted to implement controls using simulated motion on the computer monitor[104,109,110,113–115,117,120,121,123,128]. There are several limitations of this approach. For one, motion across the monitor is limited by refresh rate. Thus, these simulated saccades instantaneously jump from stationarity to high velocity, and then move in steps across the screen before instantly stopping. However, true saccades have smooth and skewed trajectories, with rapid acceleration to peak velocity followed by an extended period of deceleration.[225] Also, digitally simulating motion across the screen fails to control for the edges of the computer monitor, so the effects of previous physiological studies were possibly contaminated with, or caused by, the strong responses of neurons in V1 and other cortical areas to the edges of the screen. To get around these complications, we generate analog simulated saccades by rotating a mirror. The mirror reflects the entire image of the computer monitor, including its edges. Two previous studies have used this sophisticated technique, but only measured perception, and not neural activity[202,226].

The next major gap in our knowledge is that no previous research has simultaneously quantified perisaccadic neuronal activity and perception. A handful of studies have measured both neural activity and perception within the same animal, but they did so using different paradigms and on different days, making it difficult to compare the neural and perceptual data[112,128]. Other studies have compared physiology in animals to humans (again, using different paradigms), making the results difficult to interpret[109,113,121]. Studying perisaccadic perception and neural activity is critical for understanding the neural basis of perisaccadic perceptual effects[130,227], and the lack of quality data has led to much confusion.[‡] We will simultaneously quantify both perception and neural activity so that changes in neural activity at perceptual threshold can be quantified and direct comparison can be made.

Finally, very little is known about how CD modulates population coding in early visual cortex. A previous study on V1, examining responses during visual exploration of natural scenes, recorded simultaneously from a handful of neurons at a time in V1 and measured synchronous spiking, but used no control condition to isolate extraretinal effects[55]. Other work has utilized voltage-sensitive dye imaging, which reflects the combined effects of many neurons within each pixel, to examine the effects of microsaccades on population coding[232,233], but also utilized no control conditions. We will record from and analyze populations of up to 92 individual neurons at a time and isolate the effects of CD on population coding. Furthermore, no studies have attempted to isolate the CD signal while recording, simultaneously, from multiple cortical regions. In the final chapter, we present preliminary evidence that CDs modulate functional connectivity in the ventral stream.

[‡]One recent study quantified the neural responses to digitally simulated saccades in *ex-vivo* (i.e. non-living) retinas of mice and pigs using one paradigm, and compared the data to human perisaccadic perception measured using a different paradigm – thus, the results are impossible to interpret properly. However, based on a qualitative interpretation of these results, the authors concluded that corollary discharges do not contribute to saccadic suppression[113], contrary to overwhelming evidence[64,109,149,202,228,229], even from their own previous work[112]. After follow-up work in macaques and humans, they have since walked back their claims[230,231], demonstrating why it is crucial to study perception and neural activity simultaneously and quantitatively.

The results and analyses contained within this work make major contributions to visual neuroscience both by filling in the gaps left by previous studies and providing novel insight into the functions of corollary discharge in early visual cortex. First, this work demonstrates that corollary discharge signals modulate both macaque visual perception and V1 neural activity in a spatial frequency-dependent manner, and that the neuronal and perceptual modulations are tightly correlated. The saccadic suppression and enhancement occur at low and high spatial frequencies, respectively, and influence the critical first spikes of the new fixation. This effect may counteract the spatial frequency spectra of natural scenes and enhance object recognition. Furthermore, corollary discharge signals appear to dynamically modulate neural variability and population coding such that visual processing is optimized in the critical time window at the start of fixations. Finally, this work presents evidence that corollary discharge signals alter the functional connectivity both within and between visual brain regions critical for object recognition.

CHAPTER 2: PERCEPTUAL SUPPRESSION AND ENHANCEMENT CORRELATE WITH V1 NEURAL ACTIVITY DURING ACTIVE SENSING

I. Introduction

In active perception, behavior is guided by sensory input and sensory input depends on action in the form of exploratory behavior. A critical form of exploratory behavior is sensory sampling driven by motor action. The various forms this takes include sniffing in olfaction, "whisking" in somatosensation, and saccadic eye movements in vision. A question of fundamental importance in each of these modalities is whether the active form of sampling has some role in perception beyond simply providing a series of sensory snapshots to the brain. Here we explore saccades which, in humans and monkeys, occur several times per second in order to move the sensitive foveal portion of the retina to objects of interest. A range of studies have reported changes in perception associated with saccades[152,216,227,234–236] and extensive research has explored the connections between saccades and attention[151,237]. The hypothesis examined here is that saccades initiate a process by which brain activity is altered to facilitate and benefit visual perception at the start of each fixation. To test this hypothesis, we made simultaneous recordings of macaque contrast sensitivity and the activity of multiple single units in area V1.

Several lines of evidence suggest that saccades may benefit perception by decreasing or increasing sensitivity to visual input. A heavily-studied perceptual effect is saccadic suppression – the decrease in visual sensitivity that occurs during saccades[65,220], which may enhance visual stability[63]. Studies in humans show that suppression occurs primarily at low spatial frequencies[157,238]. Reports of improvements in visual sensitivity associated with saccades are less common than studies of saccadic suppression, but they are potentially equally as important. In certain situations, saccades appear to increase visual sensitivity[239–242], decrease reaction times[243], and increase contrast sensitivity on the subsequent fixation[202]. Conceivably, these enhancements in visual sensitivity and reaction time could benefit aspects of perception that rely on higher

spatial frequency information, such as facial recognition[244–247], letter identification[248–251], word recognition[252], and categorization[253–255].

Complementing the perceptual studies are a range of neuronal studies that have shown response modulation by saccades. EEG lambda waves associated with saccades were first reported over 60 years ago[86]. Since that time, numerous studies have shown saccade-related neural activity in BOLD signals, local field potentials (LFPs), and spiking activity in visual cortex[55,97,98,100,127,256]. Local field potentials in area V1 carry precise information about the direction of saccades and the timing of saccades and fixations[2], and multiple visual areas carry information about eye-position in the orbit[110,257]. The modulation of neural activity by saccades has also been reported in subcortical structures including the LGN[114,115,120,258–263] and the superior colliculus[112,224,264,265].

The demonstrations of perceptual and physiological effects of saccades raise the critical question, what is the connection between the two? An answer to this question requires data demonstrating if and when animals experience decreases and increases in perceptual sensitivity, there are changes in neural activity, and whether there is a consistent connection between perceptual and neural effects. The experiments presented here were designed to address these questions and fill two gaps in our knowledge: First, little is known about the perceptual effects of saccades in macaques (but see[112,224,266]), especially on contrast sensitivity. Second, prior research has not simultaneously measured saccade-based changes in neuronal responses and perception. A previous study[128] measured both neural and perceptual effects using somewhat different paradigms whereas the present study is based on simultaneously-collected data which is crucial for understanding the neural basis of peri-saccadic perception[227]. We made neural recordings in area V1 because multiple studies suggest that saccadic suppression occurs early in visual processing[92,106,157,229,267,268] and there is strong evidence that an extraretinal signal modulates V1 activity[2,63]. Neural activity was recorded using 96-electrode Utah arrays so that both single cell and population-level activity could be compared with perception. A critical experimental detail

was the use of a mirror system to simulate saccades without movement of the eye. This allowed us to distinguish changes in V1 activity linked to the movement of the eye versus movement of a stimulus across the retina.

II. Results

Saccade Effects on Macaque Perception

Previous studies of saccade effects on visual perception have been conducted almost exclusively in humans (but see[112,128,150,224,269]), and never, to our knowledge, simultaneously with neural recordings. Thus, our first experimental goal was to determine if macaque perception is altered by saccades in a manner similar to humans. We developed an experimental paradigm using a rotating mirror apparatus to present gaze-contingent stimuli to macaque subjects (**Fig 3a**). We compare results from two main trial types: the saccade condition, in which the animal moved its eyes across the visual image, and the simulated-saccade condition, in which the mirror rotated to replicate the motion associated with a saccade but without any actual eye movement (**Fig 3b-c**).

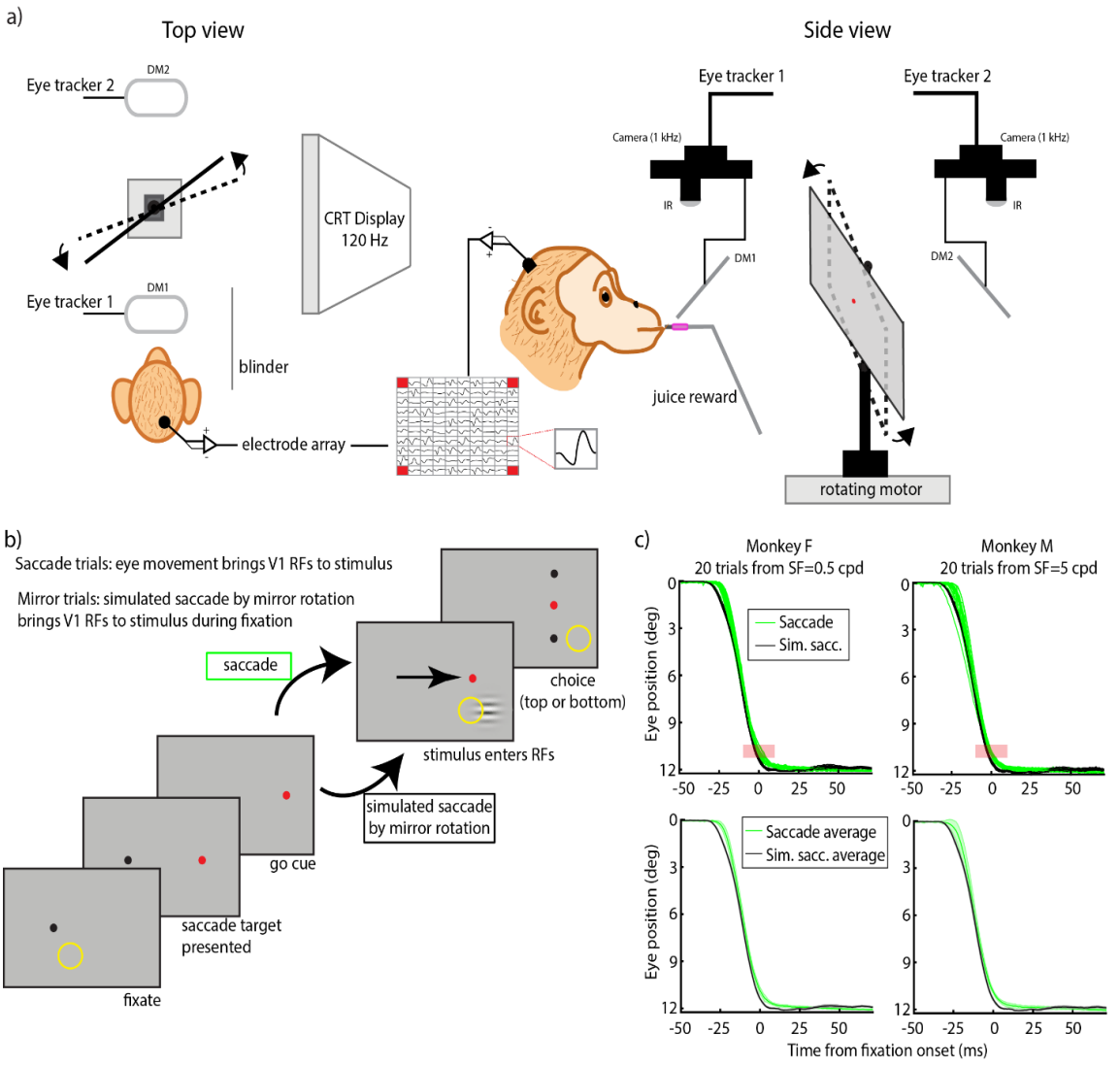

Figure 3: Experimental design.

a) Top view (left) and side view (right) of the experimental apparatus. Two eye trackers were used, one measured the animal's eye movements (Eye tracker 1) and a second recorded mirror rotations on simulated saccade trials (Eye tracker 2). DM = dichroic mirror, IR = infrared light source. **b)** 2AFC Task: The color of an initial fixation point indicated trial type. After the initial fixation period in the saccade condition, a saccade target spot appeared, followed by a go cue. In the saccade condition, the animal initiated a saccade to the target and the Gabor stimulus was presented at the site where the V1 receptive fields would land or at a corresponding location in the upper visual field. In the simulated-saccade condition, the animal maintained fixation on the initial fixation target and the mirror rotated; the Gabor stimulus was presented at one of the two same retinotopic locations as in the saccade condition. A 96-channel electrode array recorded V1 neural activity. **c)** Top: Eye tracker traces from 20 randomly-chosen trials in each animal (0.5 cycles per degree [cpd] in monkey F and 5 cpd in Monkey M). The pink shaded regions show the time of Gabor onset. Bottom: average traces from the trials above them; shaded area (hardly visible) shows +/- one standard deviation.

Contrast sensitivity was measured using large horizontally-oriented Gabor patches presented at the end of the eye movement in the saccade condition or the end of mirror rotation in the simulated saccade condition. In a two-alternative forced-choice, animals indicated whether the stimulus appeared at an upper or lower location. Percent correct was calculated for a range of contrasts at each spatial frequency. Contrast threshold (70% correct) was determined by fitting a logistic function to the data. **Figure 4** shows psychometric curves at two spatial frequencies and contrast sensitivity functions (inverse of threshold) for the two animals (**Figure 8** shows data for all spatial frequencies in both animals.) The dependence of contrast sensitivity on spatial frequency was found to be comparable to that seen in humans (e.g.). Also, the difference in CSFs between the two animals is in line with between-subject variation in humans[157,239]. At low spatial frequencies, sensitivity is lower for both animals in the saccade condition than in the simulated-saccade condition (permutation test, $p<0.05$). This is reminiscent of the lower contrast sensitivity at low spatial frequencies reported with saccades in humans compared to normal fixation[157,202,239]. The reduction in contrast sensitivity, seen primarily at low spatial frequencies, is the hallmark of saccadic suppression.

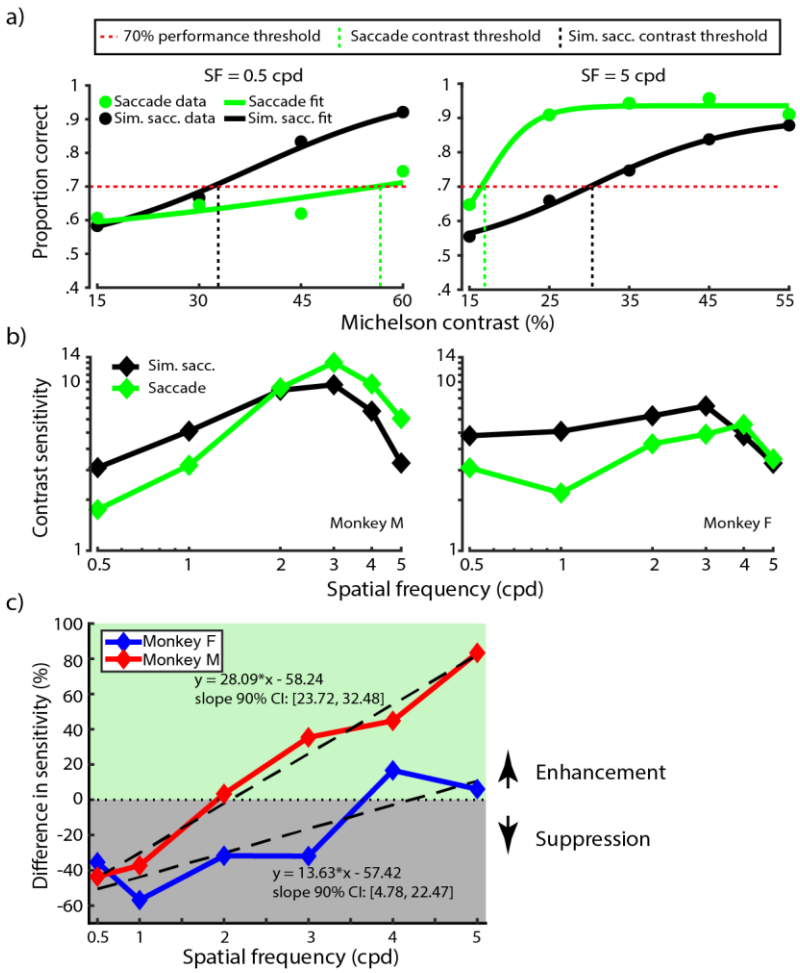

Figure 4: Perceptual contrast sensitivity.

a) At each spatial frequency, logistic functions were fit to percent correct data in saccade and simulated-saccade conditions. Here, data from animal M at 0.5 and 5 cpd are shown. Contrast threshold was defined as the contrast that gave 70% correct (red dotted lines). **b)** Contrast sensitivity functions for the saccade (green) and simulated-saccade (black) conditions in both animal subjects. **c)** Percent change in sensitivity, measured as the percent difference of simulated saccade minus saccade conditions, is shown across frequencies for both animals. Gray shaded region shows where simulated saccade conditions yield better perceptual performance. Green shaded region shows spatial frequencies at which contrast sensitivity was higher in the saccade condition.

Interestingly, as spatial frequency increases, the saccade and simulated-saccade sensitivity curves cross such that sensitivity becomes higher with real saccades. This effect was seen in both animals, though it was noticeably larger in animal M (**Figure 4b**). At 5.0 cpd, sensitivity in the saccade condition was higher at the $p<0.05$ level in animal M but not in animal

F (saccade performance in animal F showed the largest difference ($p<0.1$) at a threshold of 80% correct). **Figure 4c** highlights the effect of saccades by showing the difference in percent correct between saccade and simulated-saccade conditions. At the lowest spatial frequencies, we observed ~40-60% suppression; at the highest spatial frequencies, we observed ~8-80% enhancement. Despite the variations between animal subjects, both showed a clear positive trend (Monkey M Pearson's r=0.97, $p<0.001$; Monkey F r=0.85, $p<0.05$). A similar crossover with spatial frequency has also been reported in humans and that effect varies with the observer and stimulus luminance[157]. An increase in contrast sensitivity at higher spatial frequencies raises the possibility that saccades may benefit perception for processes that rely on those frequencies.

Saccade Effects on V1 Neural Activity

While the animals performed the contrast sensitivity task, the activity of neurons in area V1 was recorded with Utah arrays. **Figure 5** shows responses to Gabor stimuli of different spatial frequencies and contrasts that appeared at the start of fixation. In both single unit and population activity, responses peak 50-75 ms after the end of the saccade or simulated saccade. The peak response times in the saccade and simulated-saccade conditions were not different (α=0.05, Wilcoxon signed-rank test), but the response amplitudes were different. In **Figure 5a**, the flat dashed green and black lines along the abscissa show that there were no measurable responses when the Gabor stimulus was outside the RF under study. The solid green and black lines show that at 0.5 cpd the saccade response is lower than the simulated-saccade response and at 5.0 cpd the saccade response is higher. It is noteworthy that the neural activity for animal F at 5.0 cpd is significantly different in the saccade and simulated-saccade conditions even though this animal had a modest enhancement in contrast sensitivity at 5.0 cpd. Animal M had a more pronounced perceptual enhancement at 5.0 cpd in the saccade condition, and the neural population responses were more different than in animal F. The population response at 5.0 cpd is more complex than the single unit example: during and just after the saccade, neural activity is lower in the saccade condition than in the simulated-saccade condition; when the Gabor

response kicks in at a later time, the saccade response increases past the simulated-saccade response.

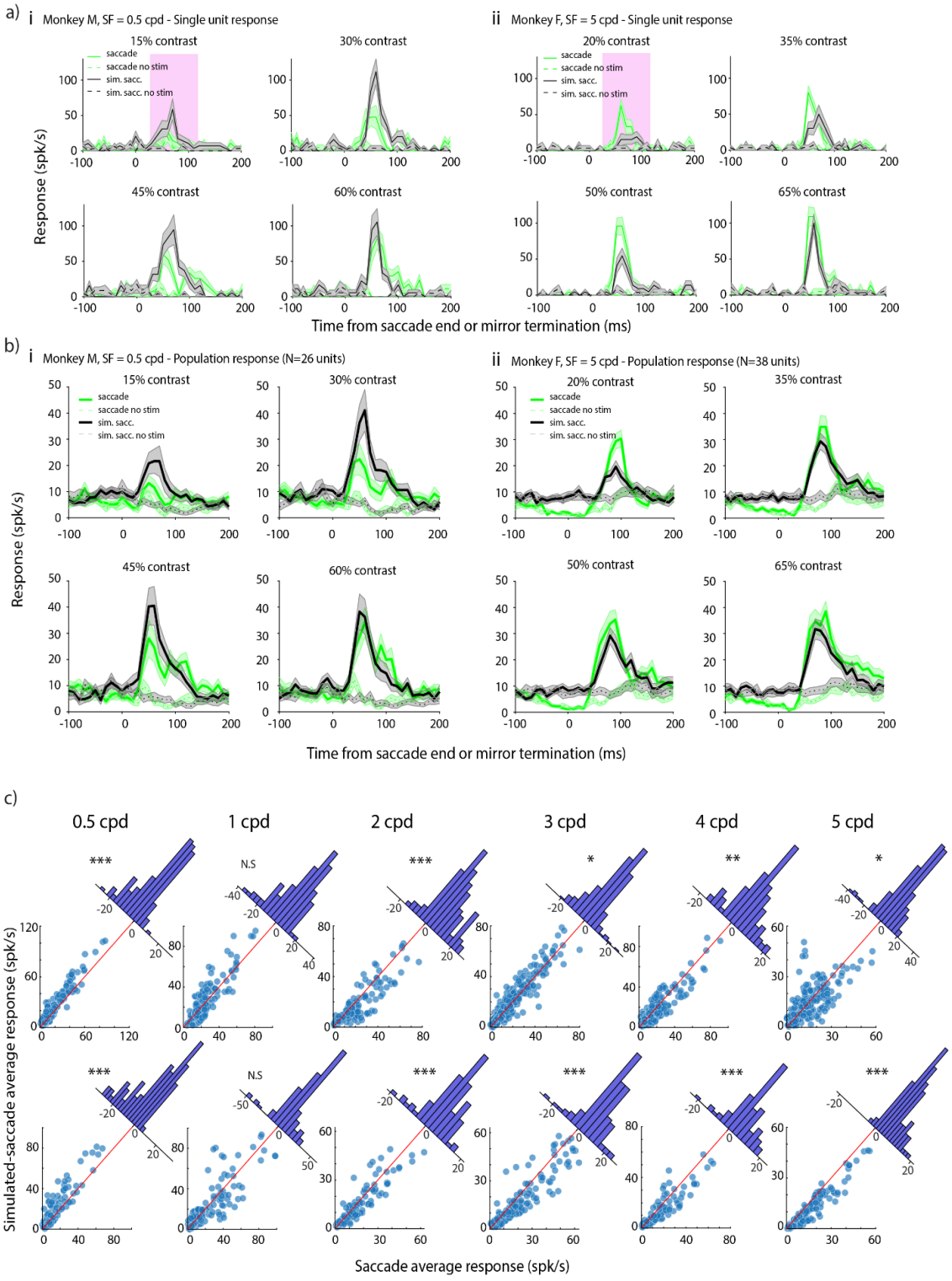

Figure 5: Neural responses. (Legend on next page)

Figure 5 (continued). **a)** Single unit examples in monkey M (i) and monkey F (ii) at 0.5 and 5.0 cpd, respectively. The cell shown for 0.5 cpd, has a greater response in the simulated saccade condition and the cell shown for 5.0 cpd has a greater response with a real saccade. **b)** Average population responses for both animals as in (A), N=26 units (i), N=38 units (ii). Shaded regions show +/- one standard error. **c)** Population data aggregated over all tested contrasts and spatial frequencies. Monkey F on top row, Monkey M bottom row. Scatter plots show simulated saccade condition responses (ordinate) and saccade condition responses (abscissa) for individual cells (Monkey F: N=35, N=32, N=30, N=52, N=40, N=38. Monkey M: N=26, N=28, N=21, N=25, N=21, N=24) across contrast levels. Histograms show deviations from equal responses in the saccade and simulated-saccade conditions (red unity line). Population data statistics: Wilcoxon signed-rank test: * $p<0.05$; ** $p<0.01$, *** $p<0.001$.

To summarize saccade-related response suppression and enhancement for the population across spatial frequency, we took the average spike rate in a window 30-110 ms from the end of the saccade or mirror rotation (magenta shaded regions in **Figure 5a**). **Figure 5c** plots the saccade and simulated-saccade Gabor responses as a function of spatial frequency. The scatter plots and summary histograms show that at the lowest spatial frequency more cells have a lower response in the saccade condition. Conversely, at the highest spatial frequency, more cells have a greater response in the saccade condition. Overall, there is a trend from lower to higher spatial frequencies in which the majority of neurons transition from response suppression to response enhancement. In each of the plots of **Figure 5**, the neural response differences between saccade and simulated-saccade conditions parallel the crossover in perceptual contrast sensitivity that occurs between 0.5 and 5.0 cpd.

We constructed neural contrast response functions (Naka-Rushton) across contrast for both saccade and simulated-saccade conditions. This allowed us to estimate neural activity at perceptual threshold. **Figure 6a** shows single cell functions from exemplary cells in the two animals (here data are shown for animal F at 0.5 cpd and animal M at 5.0 cpd, the opposite of Figure 5). The perceptual contrast thresholds from **Figure 4** are indicated by the vertical lines for both saccade and simulated-saccade conditions. **Figure 6** (lower panels) shows curve fits to the average neural population data.

The curves in **Figure 6** (lower panels) show that population average responses at 0.5 cpd are lower in the saccade condition than in the simulated-saccade condition at all contrasts. Conversely, at 5.0 cpd, the responses in the saccade condition are higher than responses in the simulated-saccade condition. The frequency-dependent differences in neural activity with saccades and simulated-saccades parallel the perceptual changes shown in **Figure 4**.

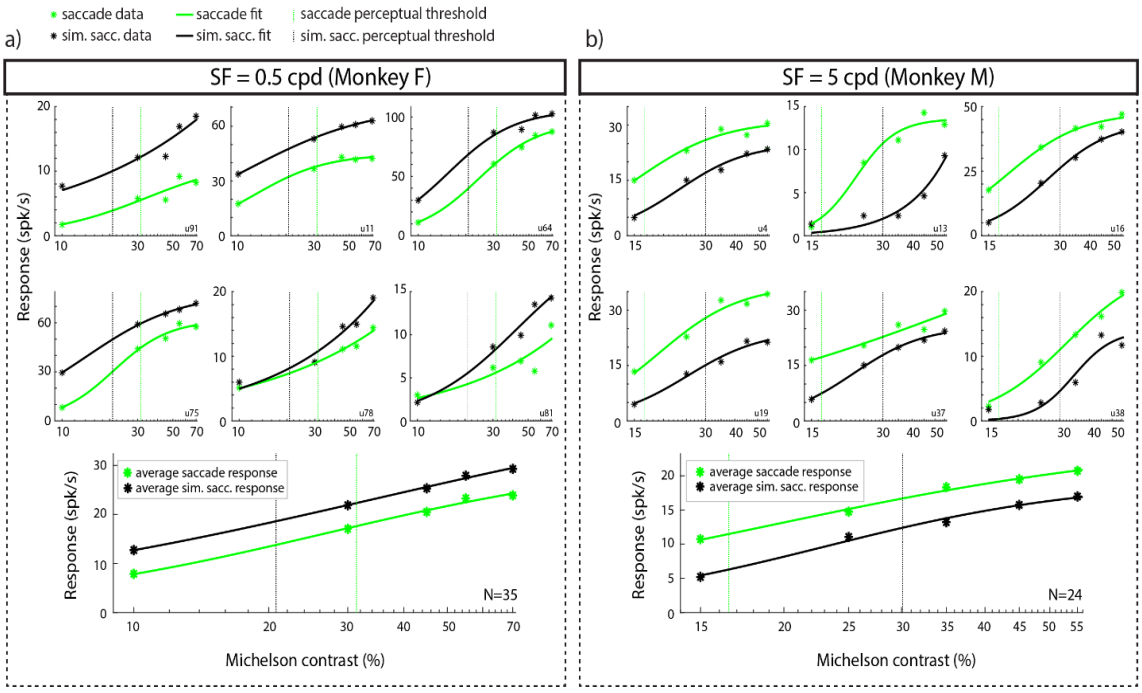

Figure 6: Contrast response functions of single units and population average.

Upper panels: Exemplary single unit responses in saccade (green) and simulated-saccade (black) conditions at 0.5 and 5.0 cpd (lines are Naka-Rushton equation fits). The dotted vertical lines show perceptual contrast thresholds in saccade (green) and simulated-saccade (black) conditions from Figure 4A; N=475 trials (left), N=834 trials (right). Bottom panels: Average population responses (N=35, N=24).

Figure 7 summarizes the dependence of neuronal saccade effects on stimulus spatial frequency. **Figure 7a** plots the difference in response rates between saccade and simulated saccade conditions at the perceptual contrast thresholds in **Figure 4**; the response rates are averaged over all cells. In plots for both animals, there is a positive trend from neural suppression to enhancement as spatial frequency increases (Monkey M, Pearson's r=.41, $p<0.001$; Monkey F r=0.17, $p<0.01$) consistent with the perceptual (**Figure 4**) and neural

(**Figures 5 and 6**) data shown above. An alternative analysis to the difference in firing rate between saccades and simulated saccades is the number of cells that responded more in one of the conditions. **Figure 7B** combines data from the two animals and plots the number of cells at each spatial frequency that responded at a higher rate in the simulated saccade condition than in the saccade condition. Again, there is a positive trend, with more cells responding at a higher rate in the saccade condition, as spatial frequency increases. While our data cannot address single cell response changes across days, and therefore spatial frequencies, the trend in **Figure 7b** suggests that, in the saccade condition, more cells exhibit response suppression at lower spatial frequencies and response enhancement at higher spatial frequencies.

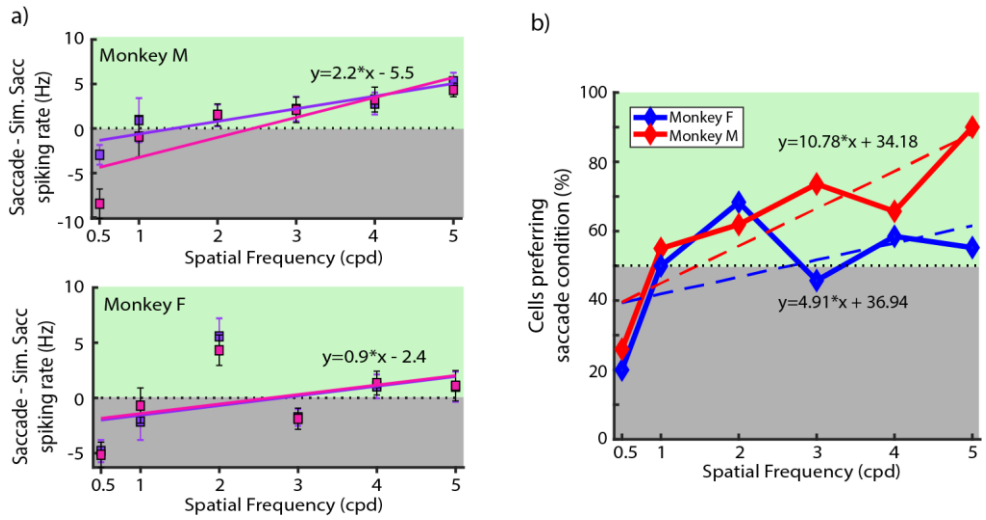

Figure 7: Dependence of saccade-based neural response suppression and enhancement on spatial frequency.

a) At each spatial frequency, the average difference between saccade and simulated saccade responses is plotted at the perceptual thresholds established in Figure 4. Purple: thresholds taken from saccade condition; pink, thresholds from simulated saccade condition. Line fit equations are shown for thresholds from simulated saccade condition. Values below zero indicate suppression (gray shading); positive values indicate enhancement in the saccade condition (green shading). **b)** Percentage of cells with stronger responses in the saccade condition (vs simulated saccade). The responses were taken at the perceptual threshold for contrast obtained in the simulated saccade condition. Line fits are shown with slope estimates for both animals.

V1 Activity and Perception

To further assess the relationship between changes in perception and neural activity on a trial-to-trial basis, we examined the effects of saccades on the sensitivity of population decoders and the choice probabilities of individual neurons.

To assess the contrast sensitivity that might be possible using the neural population activity, we conducted a decoding analysis at each spatial frequency using logistic regression classifiers. To reduce overfitting, classifiers were trained on the highest contrast at each spatial frequency and then tested on the remaining contrasts. **Figure 8** shows the performance of the decoders based on the population of neurons simultaneously recorded. Comparisons with the animals' psychometric functions (dotted lines) show that decoder performance generally exceeded the performance of the animals.

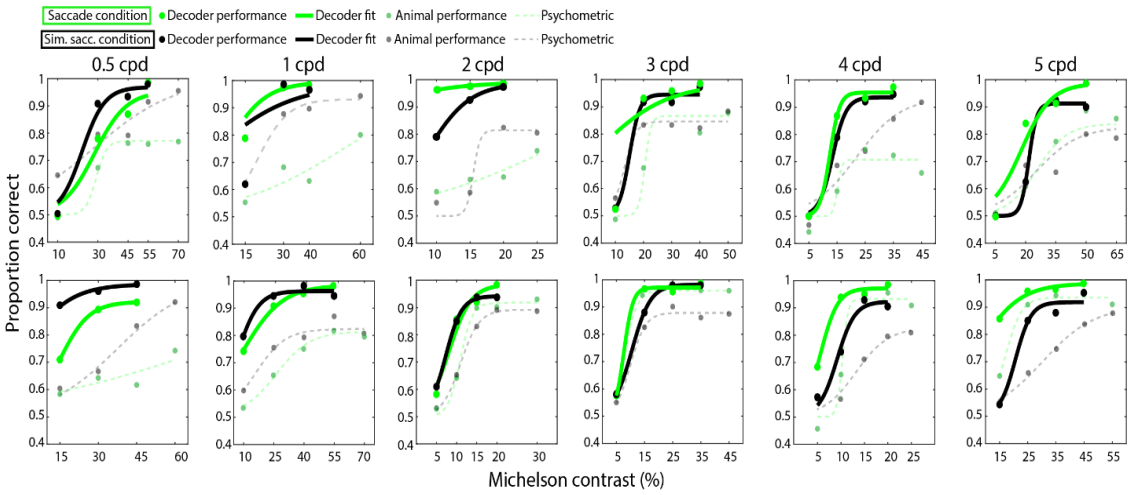

Figure 8: Decoder contrast sensitivity.

Animal (dotted lines) and decoder (solid lines) performance at six spatial frequencies and across stimulus contrast. Decoders were trained on the highest contrast (not shown), which did not serve as a test contrast. Test contrasts vary as they were determined by preliminary behavioral tests to span perceptual threshold at each spatial frequency. With the exception of the lowest contrast, at which behavioral performance approached chance levels, decoder performance generally exceeded behavioral performance. The decoders exhibit the same trends as the animals – performance is worse in the saccade condition at lower spatial frequencies (left panels) and better in the saccade condition at higher spatial frequencies (right panels). Top: animal F, Bottom: animal M.

The superiority of optimal decoders based on V1 activity is a common finding when macaques perform a variety of tasks, suggesting that the animals' pooling of information is sub-optimal[46,270]. Even though pooling in the present experiments appears to be suboptimal, the multivariate analysis demonstrates that trends in the decoder performance across spatial frequency are consistent with trends in perceptual contrast sensitivity: in both animals, classifier performance was lower in the saccade condition at 0.5 cpd, relative to the simulated-saccade condition. Conversely, decoder performance was generally higher in the saccade condition at the highest spatial frequencies tested. To quantitatively compare decoder performance in the saccade and simulated-saccade conditions, we extracted the contrasts needed to reach the threshold used in the behavioral experiments (i.e. 70% correct). Permutation tests established the significance of differences in threshold contrasts between the conditions. At spatial frequencies of (0.5, 1, 2, 3, 4, 5) cpd, p-values for Monkey F were (0.037*, NA, NA, NA, 0.27, 0.003$^{\#}$) and for Monkey M they were (NA, NA, 0.438, 0.87, 0.002$^{\#}$, NA), where "NA" indicates p-values that could not be computed, * indicates worse performance in the saccade condition, and $^{\#}$ indicates better performance with a saccade. Note that, to compare threshold contrasts, decoder performance needed to cross 70% correct in both conditions. At some spatial frequencies, decoder performance was always greater than 70% correct at the contrasts used and, in these cases, p-values could not be calculated. Based on the permutation test p-values, the decoder trends in Monkey F were significant and in the same direction as the animal's performance at the highest and lowest spatial frequencies. The effects of saccades on decoder performance at the highest and lowest spatial frequencies in Monkey M were quite large (greater than in Monkey F) and in the same direction as the perceptual effects, but they could not be compared at 70%. Overall, information in the V1 population activity is consistent with the observed perceptual effects and thus, V1 activity may underlie the perceptual changes in contrast sensitivity across spatial frequency.

As perceptual and neural data were collected simultaneously, we were also able to investigate whether trial-to-trial variability in the neural responses, independent of the stimulus,

was predictive of the animal's perceptual decisions. We computed the choice probability (CP) for each neuron, which measures the likelihood that the neuron's firing rate is higher on trials with one decision vs an alternative decision[271] in our 2AFC task. CPs were computed after normalizing within contrast levels for trials in which the stimulus was in the neurons' receptive fields (see Methods). Because there was no significant correlation between spatial frequency and CP (Pearson's r= -0.03, p=0.31), cells recorded across different spatial frequencies were pooled together for comparison. **Figure 9** shows choice probabilities for cells, in both saccade and simulated-saccade conditions. There was considerable scatter in the data, with single-cell CPs ranging from about 0.3 to 0.7 in each condition. A handful of neurons had large CPs in both conditions, but more commonly a cell with an unusually large CP in one condition did not have an uncommonly large CP in the other condition. Based on a permutation test, 9% of units in the simulated condition and 5% of units in the saccade condition had choice probabilities that were significantly different from chance ($p<0.05$). After applying false discovery rate correction, 1.1% and 0.5% of units had significant CPs in the simulated saccade and saccade conditions, respectively. Interestingly, we found a small difference in mean choice probability between the simulated saccade (<CP> = 0.52) and saccade conditions (<CP> = 0.50) (**Figure 9b**). This difference was found to be statistically significant ($p<0.001$, Wilcoxon signed-rank test , N=371; Cohen's d=0.23). An average choice probability of 0.52 is also comparable to choice probabilities previously observed in V1 and other visual areas[270]. As others have argued, if a large population of neurons contributes to a decision, such small CP values are expected[272,273]. Thus, V1 activity could contribute to the behavioral decisions we recorded based on either a small population of neurons combined with non-linear weighting across neurons (cf.[274,275]) or, in the simulated-saccade condition, linear weighting of a larger population of neurons[272].

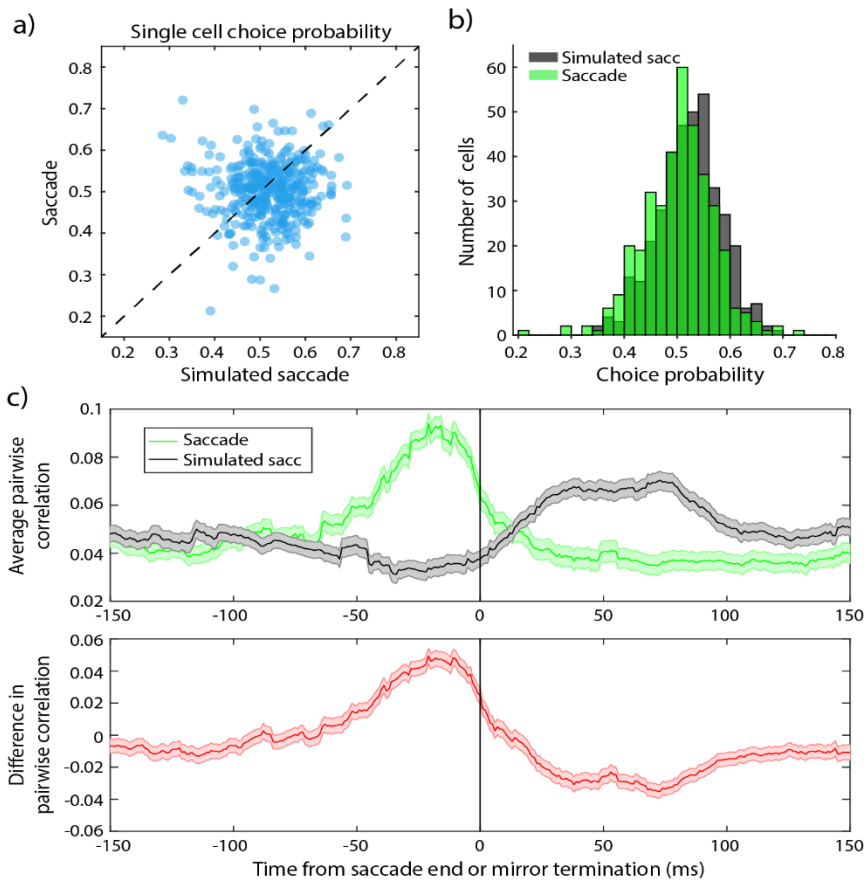

Figure 9: Choice probability and noise correlations in saccade and simulated-saccade conditions.

a) Single-cell choice probabilities for all cells in the saccade and simulated-saccade conditions. **b)** Choice probabilities are significantly higher in the simulated-saccade condition than the saccade condition. **c)** Pairwise noise correlations in the saccade and simulated saccade conditions and the difference between the two (bottom). The noise correlations are averaged over all neurons across spatial frequencies.

The interpretation of choice probabilities is complex as the value one neuron exhibits can be influenced by connected neurons. As a result of network covariance, choice probabilities do not necessarily reflect the read-out weights that contribute to an animal's perception[276–278]. To investigate the potential contribution of network covariance, we examined noise correlations[279,280]. We found that the correlation matrices in the saccade and simulated saccade conditions were significantly different in both animals at all spatial frequencies ($p<0.001$, Jennrich's test[281]). The average pairwise correlation was significantly lower in the saccade ($\langle r \rangle = 0.035$) compared to the simulated saccade condition ($\langle r \rangle = 0.070$; $p < 0.001$, t-test, N=6011;

Cohen's d=0.21), but there were no significant differences across spatial frequencies (Pearson's $r = 3x10^{-4}$, p=.97). Thus, if an effect of a corollary discharge signal is to alter noise correlations, this effect is not stimulus dependent. Because CP does not purely reflect the causal contribution of a neuron to perception, the reduction in average choice probability from the simulated-saccade to the saccade condition might be a consequence of the difference in the network covariance structure. This reinforces our speculation above, that the perceptual decisions could be based on either a small number of neurons with large contributions or a large population of neurons with small contributions.

In addition, we observed differences between real and simulated saccades in the time course of noise correlations. To examine temporal changes, noise correlations were quantified in 80 ms analysis windows, where the center of the window ranged from -150 to 150 ms relative to the end of the saccade or simulated saccade (**Figure 9c**). This analysis revealed different time courses of noise correlations for the two conditions. In the saccade condition, noise correlations were highest during the saccade and fell to a lower level when the eyes were stationary. In the simulated saccade condition, correlations were lowest during the simulated saccade and peaked in the first 100 ms after the simulated eye movement. The difference between the two conditions shows biphasic temporal modulation. These temporal changes in noise correlations are likely involved in the choice probabilities measured in our analysis window at the start of new fixations (30-110 ms). In this critical time window, average CPs are relatively high in the simulated saccade condition and noise correlations are also relatively high. As others have argued, the higher network covariance increases the likelihood that neurons with large read-out weights influence the activity of other neurons, thus increasing average CP. Conversely, lower choice probabilities are expected during fixation in the saccade condition when noise correlations are lowest.

III. Discussion

The hypothesis underlying this study is that saccades initiate a process that modulates neural activity such that visual perception at the start of fixations is enhanced. The experiment tested this active vision hypothesis by quantifying perception and neural activity when a stimulus appeared in V1 receptive fields at the start of a new fixation. To isolate the non-visual effects of saccades, measurements of neural activity and perception were compared with the same measures when visual stimulation was the same, but no saccade was made. We used a custom analog mirror system for simulated saccades, to avoid pitfalls of video simulations where a stimulus can only be presented at discrete screen locations for fixed frame durations. Our focus on the start of fixations is important as this is when stimuli come into receptive fields in natural vision. This stimulus timing contrasts with previous psychophysical studies such as most saccadic suppression experiments in which a stimulus is commonly introduced *well before* fixation begins and typical neurophysiological experiments which generally introduce a stimulus *well after* fixation starts. Experimental design factors that were critical to the goals of the study were the quantification of saccade effects on perception in macaques (something little is known about), the simultaneous collection of neural and psychophysical data to allow trial-to-trial comparisons, and simultaneous recording from a population of V1 neurons to assess response heterogeneity and population coding. Below we discuss our data in the context of past work on changes in perception and brain activity associated with saccades and we discuss what can be concluded about possible benefits of saccades for vision.

Perceptual Benefits of Saccades

To study perception and saccade-based changes in neural activity at the start of new fixations, we presented a Gabor test stimulus at the end of saccades. This is the time at which a saccade would bring a stimulus into receptive fields in natural vision and it is a critical time for the formation of a visual representation[38,282]. To our knowledge, ours is the first study of macaque contrast sensitivity in the peri-saccadic interval that allows direct comparison to human

studies (but see[128] who used a novel paradigm with fixational saccades). The contrast sensitivity functions we obtained are comparable to those previously reported for macaques using paradigms without saccades[283]. Comparing CSFs obtained with real and simulated saccades suggests that saccades have two effects on macaque perception: sensitivity at lower spatial frequencies is reduced after an eye movement and sensitivity at higher spatial frequencies is enhanced.

The effect at low spatial frequencies is reminiscent of data reported in multiple saccadic suppression experiments in humans[157,202,238,239]. Saccadic suppression is strongest for stimuli that appear during a saccade and the suppression extends and weakens for approximately 50 ms into the subsequent fixation. Peak suppression in humans, with stimuli as used here, is approximately a tenfold reduction in sensitivity[65,157,238]. As our data were collected with stimuli presented at the start of fixation, they can speak to saccadic suppression and its neural correlates, but the magnitude of the perceptual effect is reduced relative to its peak. We find that the spatial frequencies at which macaque contrast sensitivity is reduced are comparable to the human data and to previous findings in macaques[128]. In the human studies and our macaque data, there is a loss of sensitivity below about 2-3 cpd and the peak reduction is about 50%[157].

In contrast to saccadic suppression, we are not aware of previous animal research demonstrating an enhancement of contrast sensitivity at higher spatial frequencies. In humans, studies of peri-saccadic vision have focused on stimuli that appear in the middle of saccades; an enhancement of contrast sensitivity is not generally observed. That said, sensitivity to high frequency stimuli that appear mid-saccade is enhanced at low luminances[239], reaction times are faster after a saccade[243], and saccadic suppression of contrast sensitivity in humans has been reported to be followed by a smaller enhancement in sensitivity[202].

Perceptual suppression observed at low spatial frequencies may play a role in visual stability and blur reduction, but what about enhancement at higher spatial frequencies? It has been speculated[284,285] and there is data suggesting[98,100,104,286,287] that saccades initiate a reset

process that enhances perception at the start of fixations. Our working hypothesis is that at the beginning of new fixations, there are complementary processes in which low frequency suppression and higher frequency enhancement combine to bias perception toward visual attributes that favor rapid object recognition. Psychophysical and computational studies have shown that visual functions that rely on higher spatial frequencies include letter identification[248–251], word recognition[252], face recognition[245], recognition of facial expression[244,246,247], object recognition[288], and basic and subordinate perceptual categorization[253–255].

Changes in Neural Activity Associated with Saccades

The present study investigated correlations between peri-saccadic perception and neural activity in V1 because V1 is an early cortical area thought to play an important role in visual perception and multiple experiments have shown it to have neural activity modulated by saccades[2,55,98–100,104,117,121,124,124,127,128,223,232,232,289–291]. Moreover, some studies suggest that neural activity in the LGN and/or V1 plays a particularly important role in saccadic suppression[92,106,157,229,263,267,268].

Our data show that spike rates were different in saccade and simulated-saccade conditions in response to a Gabor stimulus presented at fixation onset. When the Gabor stimulus had a low spatial frequency (below about 2cpd), the firing rates were lower in the saccade condition than in the simulated saccade condition. Conversely, the response rates were higher in the saccade condition when the Gabor stimulus had a higher spatial frequency. As the real- and simulated-saccade conditions involved the same stimulus movement on the retina, the findings suggest that a non-visual signal associated with the saccade modulates V1 activity. This inference is consistent with studies showing V1 modulation when saccades are made in the Dark by animals[100,121,267,292] and humans[256].

It should be noted that some earlier experiments reported no difference in V1 activity when stimuli were brought into receptive fields with a saccade versus a flash[125,293]. However, the absence of a saccade effect may have resulted from the methodology[63]. More closely related to

the present study are experiments which reported that there are changes in V1 activity associated with microsaccades[117,128,223,290,294]. However, as these experiments did not include simulated saccades and they weren't focused on variations across spatial frequency, comparisons with our data are limited.

Relating Neural Activity to Perception

A key question we hoped to address with simultaneous measurements of perception and neural activity is the possible relationship between the two. We addressed this question with three analyses – average spike rates, the output of optimal decoders, and choice probability. We found that macaque perception exhibits saccadic suppression at low spatial frequencies as previously shown in humans[157,202] and saccadic enhancement at higher spatial frequencies (less studied in humans, but see[240,242]). There was a consistent correlation between average V1 firing rates and the perceptual effects.

Making use of the simultaneous recordings that the electrode arrays provided, we constructed logistic regression classifiers to decode the population neural activity. Performance of the decoders generally exceeded the performance of the animals but the frequency-dependent trends were similar. We found that the decoders were less sensitive to contrast at the lowest spatial frequency in the saccade condition (compared to the simulated-saccade condition). Conversely, the decoders were more sensitive to contrast at the highest two spatial frequencies with a saccade. Thus, performance of the decoders suggests that the population neural activity that was recorded in V1 can support the perceptual decisions that the animals made (evidently, with suboptimal pooling).

The simultaneous recordings of perceptual decisions and V1 activity allowed us to compute choice probability from trial-to-trial variations in perceptual decisions and neural activity. This was not possible in previous neurophysiological studies because they did not quantify perception at the same time and with the same stimuli. V1 choice probabilities reported in previous studies in other domains have generally been low or nonexistent[295–299]. Our study is

consistent in that 9% of units in the simulated condition and 5% of units in the saccade condition had choice probabilities that were significantly different from chance. This percentage was lower still ($\leq 1\%$) after false discovery correction. It is noteworthy that our measures of choice probability come from a narrow early response interval, presumably prior to feedback which is known to increase CP[277,297]. Interestingly, when choice probabilities were averaged across neurons and compared between saccade and simulated-saccade conditions, a significant difference was found. The observation that average choice probability was greater in the simulated saccade condition led us to investigate noise correlations across the network of recorded neurons. If a large network of correlated neurons contributes to a perceptual decision, the choice probability of any given neuron can be more dependent on network covariance than on that neuron's read-out weight[278]. We found that the noise correlation matrices in the saccade and simulated saccade conditions were significantly different at all spatial frequencies, and the average pairwise correlation was significantly lower in the saccade (<r>= .035) compared to the simulated saccade condition (<r>= .070). The average pairwise correlation we observed at the start of fixation in the simulated saccade condition (**Figure 9**) is similar to the initial pairwise correlation reported previously with flashed stimuli in experiments unrelated to saccades[295]. A further analysis of the time course of noise correlations reveals the effect of saccades: compared to a simulated saccade, a real saccade is associated with higher noise correlations during the saccade but significantly lower noise correlations on the subsequent fixation.

To account for the data described here, our working hypothesis is that an extraretinal signal associated with saccades modulates neural excitability and functional connectivity in V1[2,55,98–100]. Analysis of choice probability and noise correlations suggests that in the simulated-saccade condition, without the corollary discharge signal, the neurons are more coupled and the significant choice probability of a subset of cells is presumably shared with others in the network, thus raising the average CP. In the saccade condition, the corollary discharge signal presumably reduces the ability of the neurons with significant read-out weights to influence the choice probability of other cells in the network. Consistent with this general interpretive framework,

noise correlations did not vary with spatial frequency but they were lower in the saccade condition at all spatial frequencies. This is what one would expect of a corollary discharge that alters network covariance in a stimulus-independent manner. It is interesting to note that noise correlations in the simulated-saccade condition follow the general rule that correlations increase along with spike rate[300]. However, the consequence of a saccade is to reverse this effect – noise correlations decrease when spike rate increases, an effect that may enhance information transmission[40,41,279].

Broader Implications

It is of particular interest to contrast the present results with sensory systems that use actions analogous to visual saccades to sample sensory input; examples are whisker movements and sniffing by rodents[301,302]. In these systems, is there evidence that a motor action alters perception, neural activity, or noise correlations? Analogous to the present study, a whisker-related signal appears to produce correlated changes in somatosensory perception and network activity. Fanselow and Nicolelis[303] reported that responses in S1 and VPM thalamus, to identical electrical stimulation of the trigeminal nerve, had lower magnitude and latency when the rat was making whisking movements compared to stationary whiskers. Hentschke et al.[304] found that a motor signal appears to rapidly switch rat barrel cortex responses from one mode of sensory response with stationary whiskers to another when the whiskers are actively moving. Finally, Lee et al.[305] saw that when detection rates for small whisker deflections in mice were high, noise correlations in primary somatosensory cortex (S1) decreased and when detection rates were lower, noise correlations increased. There are also analogous findings in the rat olfactory system where active sampling involves higher frequency respiration (sniffing) compared to the resting respiration rate. During active sampling, there is sniff-frequency-specific filtering of olfactory neuron responses for novel odorants relative to the olfactory background[306]. Consistent with the findings in other systems described above, Miura et al.[307] found that pairwise noise correlations in piriform cortex were high prior to odor onset and both noise correlations and choice probability

decreased to low levels when the odorant was sampled. In summary, in the visual, somatosensory, and olfactory systems, motor actions actively sample the sensory landscape and the motor signals alter neural activity and network noise correlations as well as perception. As suggested by our findings and the studies in other systems, the benefit of the motor-sensory interaction appears to be improved information flow and sensory discrimination.

IV. Methods

Subjects

Two male rhesus monkeys were used in this study: monkey F weighed 10.4 kg and monkey M weighed 9.6 kg. The experiments were carried out in accordance with the recommendations of the United States National Institutes of Health; the protocol was approved by the Brown University Institutional Animal Care and Use Committee. Animals were housed at Brown University in enclosures that allowed for a mixture of separate- and pair-housing. In aseptic surgeries, animals were implanted with a custom titanium headpost and a 96-electrode "Utah" array (Blackrock Microsystems, UT, USA). Monkey F had participated in three previous studies[2,4,124]. The electrodes, 1 mm in length and spaced at 400 μm, were inserted in V1 of the left hemisphere to obtain receptive fields in the lower right visual quadrant.

Recording Procedures

An animal under study sat in a primate chair (Crist Instrument Co., Hagerstown, MD, USA) in a dimly lit recording room. The animal faced a mirror through which it viewed a CRT monitor (Iiyama Viewmaster HM204DT) placed to the front and side (**Figure 3**). The mirror was rotated to simulate saccades (see below). The monitor's resolution was set to 1280 x 1024 at a refresh rate of 120 Hz. The field of view of the mirror was 35H x 28V degrees of visual angle. A dark blinder to the animal's side prevented any viewing of the CRT except through the mirror. Neural recordings were made with the Utah array and a Blackrock Cerebus system while the animal performed the visual psychophysics task described below. In most sessions, all 96-

channels were recorded after setting an automatic RMS threshold (variable, but typically RMS ~5); spiking responses were recorded at 30 kHz and local field potentials (LFPs) were recorded continuously at 30 kHz. Receptive fields were initially hand mapped during fixation to locate the aggregate RF of all neurons recorded by the array. The approximate centroid of this aggregate RF in both animals was 6-7.5 degrees eccentricity. At subsequent experimental sessions, stimuli were positioned relative to this aggregate RF, but individual RFs were not remapped. The onset times and durations of visual stimuli were measured using a photodiode attached to the lower corner of the CRT, this signal was recorded at 10 kHz by the Blackrock system. Two Eyelink1000 infrared trackers (SR Research, ON, Canada) were used. One tracker recorded eye position by looking down through a hot mirror positioned between the animal and the mirror used to view the CRT. The second Eyelink1000 tracked a spot on the axle of the motor that rotated the mirror the animal used to view the CRT (**Figure 1**). Eye position and mirror rotation were recorded separately at 1 kHz on four analog inputs to the Blackrock system. Monkeylogic software[308], was used to present stimuli and to record trial information and the signals recorded by the eye trackers.

Simulated Saccades

An important feature of the experimental design was the comparison of psychophysical performance and neural activity between trials in which the animal either made a saccade or held fixation steady while the rotating-mirror system simulated a saccade. To implement simulated saccades, the animal viewed the CRT display through a lightweight plastic mirror as described above. The mirror was attached to a rotating NEMA 23 stepper motor with a 5:1 ratio gearhead (Applied Motion, CA, USA), run by a 7080i motor controller (Applied Motion). Si Programmer software was used to control the rotation of the motor so that image translation viewed through the mirror matched that of actual saccades with a static mirror. The full saccade velocity profile was matched as closely as possible, including acceleration and deceleration phases (**Figure 3c**). Smooth motion was achieved by programming movement in a microstepping mode that provided

346 steps per degree of rotation. A simulated saccade was initiated by a TTL pulse sent from the control system on mirror-rotation (simulated saccade) trials. On saccade trials, the mirror did not move.

Visual Stimuli and Task

A 2-alternative forced choice task (2AFC) task was employed. Experimental trials were initiated by the presentation of a fixation point at the center of the CRT (**Figure 3b**). A blue point indicated a saccade trial and a red point indicated a simulated-saccade trial (aka "mirror trial"). If the animal successfully held fixation on the central point for 500 ms, the experimental trial proceeded. In the saccade condition, a second fixation point (red) appeared 12 deg to the right of the central point and the animal moved its eyes to this second point. In mirror trials, the animal maintained central fixation and the mirror rotated the image of the visual display across the retina with the same dynamics as the actual saccades. In both types of trials, the visual stimulus was a 5-degree diameter Gabor patch sized to encompass the aggregate receptive field (RF) of all cells being recorded (the "array field"). The Gabor appeared either at a lower location that covered the array field or an upper location at the same eccentricity. The Gabor stimulus was horizontally oriented to minimize motion in the RF during the real and simulated horizontal saccades and for consistency with psychophysical studies in humans[157].

Presentation of the Gabor stimulus was initiated when the eye tracker detected that the eye moved 0.5 deg toward the second fixation point. The goal was to have the Gabor appear just before the array field arrived at that location on saccade trials. In this way, the paradigm would activate neurons in a manner as close as possible to natural vision in which saccades sweep receptive fields onto pre-existing stimuli. In practice, there was some variation in the timing of the Gabor presentation; due to processing time and CRT triggering, there was a variation of +/- 1 frame at 120 Hz (a range of +/-8 ms in Gabor onset time.) This meant that the Gabor could appear slightly before to slightly after arrival of the array field, but there was no clear difference in the data collected with Gabor presentations spanning this narrow temporal window. Data were

analyzed if the Gabor onset was between -10 ms and 10 ms relative to fixation onset (see pink region, **Figure 3c**) The stimulus was left on for 70 ms; thus, it extended from approximately the start of the fixation to 60-80 ms after fixation onset, a time interval in which saccade suppression is consistently observed[65,202,220]. Immediately after the Gabor stimulus disappeared, two targets were presented, one above and one below the second fixation point. The animal made an eye movement to indicate whether the Gabor had previously appeared at the upper or lower location. (**Figure 3b** represents a trial with the stimulus in the lower visual field). Animals were required to maintain fixation at the second fixation point for at least 200 ms prior to moving their eyes to one of two choice targets.

The goal of these experiments was to simultaneously record psychophysical and neural data sufficient to construct contrast sensitivity functions and V1 neural response functions in both saccade and simulated saccade conditions. The required number of stimulus contrasts, spatial frequencies, and trials per condition, in both saccade and mirror paradigms, made it impractical to interleave all conditions in a single recording session. To address this limitation, on each recording day, Gabor contrast was varied and both saccade and mirror trials were run, but Gabor spatial frequency was fixed. The order of spatial frequencies presented across days was randomly chosen and differed for the two animals. In the absence of any previous macaque contrast sensitivity data collected with saccades, spatial frequencies were chosen based on the results of human saccade studies[157,202] and macaque contrast sensitivity measured with static stimuli[283]. For each spatial frequency, we tested 4 or 5 contrast levels in both simulated saccade and saccade conditions in a 2AFC paradigm (2 trial-types X 2 stimulus locations X 4 or 5 contrast levels = 16 or 20 unique conditions) and obtained ~25-40 trials per unique condition. When four contrast levels instead of five were used we collected more trials per contrast to ensure that we obtained ~500-800 trials per spatial frequency tested. Saccade and mirror conditions were presented in blocks, typically of 100 trials.

Quantification and Statistical Analyses

Across all trials, Gabor Michelson contrast was randomly varied, where:

$$Contrast = \frac{L_{max} - L_{min}}{L_{max} + L_{min}}$$

where L_{max} and L_{min} were the maximum and minimum luminances, respectively, of the Gabor. The method of constant stimuli was used for contrast; contrast values were selected for each spatial frequency based on human contrast sensitivity data.

Contrast Sensitivity Functions

Psychophysical performance was analyzed using the Palamedes toolbox[309] and custom MATLAB scripts. Contrast sensitivity was found by making a maximum likelihood fit of the percent correct values for each animal within each spatial frequency to the logistic function:

$$F(x;\ \alpha, \beta, \gamma, \lambda) = \gamma + \frac{1 - \gamma - \lambda}{1 + e^{-\beta(x-\alpha)}}$$

where α is the detection threshold, β is the slope factor, γ is the guess rate 50%, and λ is the lapse rate. Contrast threshold was defined as the contrast at which the subject correctly reported the Gabor location on 70% of trials. Contrast sensitivity is the inverse of contrast threshold.

Permutation testing was used to determine the significance of perceptual suppression or enhancement. For each spatial frequency, the saccade and simulated-saccade labels were shuffled 1000 times and curves were fit to the resulting shuffled data sets. P-values were computed by counting the fraction of shuffles (including the one non-shuffled dataset) for which the difference in threshold was greater than or equal to the experimentally observed difference.

Neuron Response Functions

Neuronal spike rates were fit by the Naka-Rushton function[310]:

$$R(C) = R_{max}\left(\frac{C^n}{C^n + C_{50}^n}\right) + M$$

where R is the neuronal response in spikes/sec, C is the contrast level (varied randomly over trials), R_{max} is the maximum neural response, C_{50} is the contrast that gives a half-maximal response, M is the average baseline firing rate, and n is the fitted rate exponent.

Decoding Methods

At each spatial frequency, we constructed decoders to assess the contrast sensitivity of the population vector $\boldsymbol{x}$, where x_i is the firing rate of neuron i. We used a logistic regression classification model[311,312] to predict the probability of the stimulus location:

$$P(in\ RF|\boldsymbol{x}) = \frac{1}{1 + e^{-\boldsymbol{\beta x}+b}}$$

For each classifier, equal numbers of trials were randomly selected from each contrast, stimulus location, and trial condition (saccade or simulated saccade). Each decoder was then fit on both conditions at the highest contrast and tested on the lower contrast conditions. This method ensured that the classifiers were trained on high-signal trials and not overfit to noisy signals at lower contrasts[101]. The vector of decoding weights $\boldsymbol{\beta}$ and scalar bias term b were fit to the training data using *fitclinear.m* in MATLAB, with the default ridge regularization term of $1/n$ where n is the number of trials used in training. The accuracy of the model was assessed using the test contrasts in both the saccade and stimulus conditions. This process was repeated 100 times at each spatial frequency. Overall classification performance was computed by averaging across the 100 repetitions. Decoder accuracy was fit to logistic curves in the same manner as the animal's psychophysical performance to determine contrast thresholds and assess the significance of suppression or enhancement with permutation testing.

Noise Correlations and Choice Probabilities

To compute noise correlations and choice probabilities we examined trials in which the Gabor stimulus appeared in the receptive fields. Firing rates during the response period 30-110 ms were normalized within condition using balanced z-scoring[297,313–315]. To increase statistical

power, responses from contrast levels with at least three incorrect trials were pooled together for analysis. Choice probability (CP)[271], which quantifies the relationship between neural and perceptual trial-to-trial variability, was computed for each neuron using the normalized firing rates. Permutation testing with 1000 shuffles was used to assess whether CP values differed significantly from chance[271,316]. Unlike all previous CP studies of which we are aware, we chose to correct for multiple comparisons. To do this, we employed the Benjamani-Hochberg procedure[317]. The results are presented both with and without correction so that they can compared to previous studies of CP.

Noise correlations, which quantify the stimulus-independent co-variability between pairs of neurons, were computed as the Pearson correlation between z-scored firing rates for each pair of simultaneously-measured units[280]. The mean noise correlation was computed by pooling all simultaneously-recorded pairs from each recording session. Noise correlations were transformed using the Fisher z-transformation before statistical comparison with t-tests. To examine how the noise correlations changed over time, we slid the center of the 80-ms analysis window from -150 ms to 150 ms relative to the end of the saccade or simulated saccade.

CHAPTER 3: EXTRARETINAL SIGNALS CONTROL NEURAL DYNAMICS AT FIXATION ONSET TO OPTIMIZE VISUAL PROCESSING

I. Introduction

During natural behavior, perception is the result of a closed-loop process in which action leads to the acquisition of new sensory input that, in turn, informs new behaviors[318,319]. There is widespread evidence that motor systems send corollary discharge signals which modulate sensory systems during active sensing[130]. In rodents, sniffing and whisking initiate oscillatory activity which controls the dynamics of odor and somatosensory responses, respectively[301,302,320,321]. Primates, including humans and macaque monkeys, use frequent saccadic eye movements, occurring 2-5 times per second, to actively explore their environments and acquire novel visual information[53–57]. These saccades are performed in alternation with brief fixations, during which most of visual processing occurs.

It appears that at the start of a fixation there is an early temporal window that is critical for the formation of a new object representation. For example, RSVP tasks (rapid serial visual presentation) suggest that complex recognition and discrimination tasks can be performed based on 100 ms or less of visual processing[52,322]. As perception involves a hierarchy of visual areas, the speed of recognition implies, and neural evidence indicates, that the initial representation is formed by at most a few spikes per neuron in each visual area[36–39,48,51,52,323–326] . To ensure that an accurate visual representation is constructed in this period, it seems critical that the visual system "knows" precisely when a new fixation starts so that it can parse neural signals associated with successive fixations. It is unlikely that the onset of new fixations can simply be determined by the onset of the response to a new image[236,286]. The spike latencies of individual neurons are highly variable and depend upon stimulus properties, such as contrast and spatial frequency[327–337]. Additionally, the transient nature of visual responses indicates that a lack of visual drive cannot necessarily be taken as a reliable indicator of the end of a fixation[286,338].

The speed of visual processing and the apparent need to establish the start of fixation led us to hypothesize that a corollary discharge (CD) plays an important role in shaping visual

processing at the start of fixations. In other words, a signal associated with the motor command to move the extraocular muscles might reach visual cortex and be used to establish fixation onset while enhancing early processing. CD signals have previously been implicated in saccadic suppression and the establishment of a sense of visual stability across saccades[149,150,339,340]. To expedite visual processing, maintain stability, and overcome blur, the system not only suppresses perception during the saccade, it also quickly restarts processing at the onset of new fixations[100,106,109,113,114,157,161,202,223,240,242,286]. This repeated pattern of suppression and restart in visual processing likely contributes to the perception of visual stability via a combination of active suppression during the saccade and backwards masking of the intra-saccadic image[63,64,157,202,339]. It may also be important that saccadic suppression extends into the new fixation as this is the critical time for the formation of an object representation. Suppression may assure that the representation is not "contaminated" by spiking associated with any pre-saccadic or saccadic visual input[202,341,342].

In primary visual cortex, CDs have been demonstrated to reset the phase of ongoing local field potential (LFP) oscillations at the start of new fixations[54,100]. This reset aligns with changes in neuronal excitability, correlated variability, and sparseness[4,127,341]. Following fixation onset, spiking is more synchronized on millisecond timescales and this rapid increase in synchronization is time-locked to fluctuations in the LFP[55,98]. V1 LFPs carry precise information at the onset of new fixations which could be used by the system as a parsing mechanism[2]. The information about fixation onset that is seen in LFPs is likely to derive from a CD signal, as it occurs even in complete darkness[100] and carries information about the direction of the eye movement[2].

The goal of the present study was to examine in detail the spiking activity of V1 neurons in the critical early temporal interval during which the initial visual representation is made. The studies described above suggest that saccades and corollary discharge are involved in parsing the visual input and resetting visual processing, and that neural activity and perception are enhanced at the start of fixations. The current evidence for these functions derives from a handful of

LFP[2,54,100], single-neuron[106,223,294], and perceptual studies[286,342]. Little is known about how V1 neural populations encode oculomotor signals on short timescales (though see Morris and Krekelberg[110] for an analysis on long timescales). It is also unclear whether the perisaccadic modulations of V1 activity are shared gain fluctuations which modulate the excitability of the entire population[100,106], or exert different effects in different sub-populations of neurons[127,130]. It is likely that there are multiple, distinct effects of saccades on neural processing[109,241,343]. Here we investigate information about fixation onset and visual input in the activity of individual V1 neurons and the neural population after fixation onset. We looked for evidence that a CD signal is found in the spiking of V1 neurons, and we examined the extent to which CD signals influence the same or different neurons in the population.

A few methodological points are notable in the present study. We examined neural data from two macaque monkeys performing a contrast sensitivity task in which a stimulus was presented at the end of either a saccade (fixation onset) or a simulated saccade (**Figure 3**). Crucially, we used an analog system to generate simulated saccades with the same spatiotemporal dynamics as the eye movements of the animals[202,226]. This control condition is critical for isolating extraretinal effects of saccades on visual processing, as it accounts for the saccade-driven spatiotemporal transients both with and without stimulus presentation. This system improves on previous physiological studies which had no control condition or which compared postsaccadic visual responses either to flashed stimuli during fixation or the effects of saccades made in darkness. With our task design, we can isolate extraretinal modulation both with and without visual processing. Because we recorded neural activity with 96-channel Utah arrays, we were able to record simultaneously from larger populations than past work.

II. Results

Spike Timing at Fixation Onset

We first examined if an extraretinal signal present in V1 modulated the timing of the first spike following fixation onset[98]. **Figure 10** shows the distribution of first spike times collected

across all recorded neurons pooled across contrasts (**Figure 10a**), and across the simultaneously recorded population within one exemplary session (**Figure 10b**). In the simulated-saccade conditions in **Figure 10b**, there is an extended and very early time period with high spike probability. The distribution of spike latencies for the conditions with a simulated saccade and no stimulus presentation (out-RF trials) are nearly exponential, indicating near-Poisson spiking statistics.

Compared to the simulated-saccade condition (black), with a saccade (green) there is a sharp reduction in the probability of observing a neuron's first post-fixational spike within the first 20 ms and a rapid and reliable increase in probability around 40-50 ms after fixation onset. The early drop in probability is significant in all 12 recording sessions both when a stimulus is presented out of the receptive fields of the neurons (out-RF, $p<.001$ permutation test) or in the receptive fields (in-RF, $p<.001$ permutation test). The suppression of spiking precedes the common peak firing rate latencies for visual responses in V1, which are typically longer than 25-30 ms[55,330,333,334]. This result suggests precise extraretinal control over the timing of the neuronal activation after fixation onset. The latency of this effect and the fact that it occurs for saccades but not simulated saccades suggests that it occurs independently of visual drive. However, the presence of a stimulus in a neuron's receptive field appears to interact with this extraretinal effect, making the spike latencies even more consistent (**Figure 10a,b**). There was a positive correlation between average latency and spatial frequency for both the saccade ($r=.16$, $p<.001$) and simulated saccade ($r=.20$, $p<.001$) conditions, consistent with coarse-to-fine processing. However, no significant correlation was found in the average latency difference between saccade and simulated saccade conditions ($r= -.04$, $p=.22$), suggesting that the changes in latency are independent of spatial frequency.

We also compared differences in the first inter-spike interval between the saccade and simulated saccade conditions. There was no significant effect of the saccade on the probability of second spikes occurring within 20 ms of the first (i.e. >50 Hz rate) in the out-RF condition,

except in one session (session 1, Monkey F 0.5 cpd) where there was a significant reduction in the 1st inter-spike interval ($p<.001$ permutation test). However, a second spike within 20 ms of the first was significantly more likely in the saccade compared to the simulated saccade condition for all sessions with a stimulus in the receptive field (in-RF; permutation test $p<.001$). These results suggest that, while extraretinal signals modulate the precise timing of the first spike of new fixations regardless of visual input, the subsequent increase in the first inter-spike interval (i.e. initial firing rate) relies on interactions between visual drive and extraretinal modulation. This result was also supported by the observation that, relative to simulated saccade trials, average responsiveness (defined as percentage of trials in which there was a spike within 150 ms of saccade onset) decreased somewhat on saccade trials when a stimulus was not presented but increased with stimulus drive (out-RF: 45% compared to 48%, $p<.001$ Wilcoxon sign-rank test; in-RF: 69% compared to 65%.) Previous results were unable to clearly make this distinction between the effects of CD and CD-visual interactions because they did not employ simulated saccade controls.

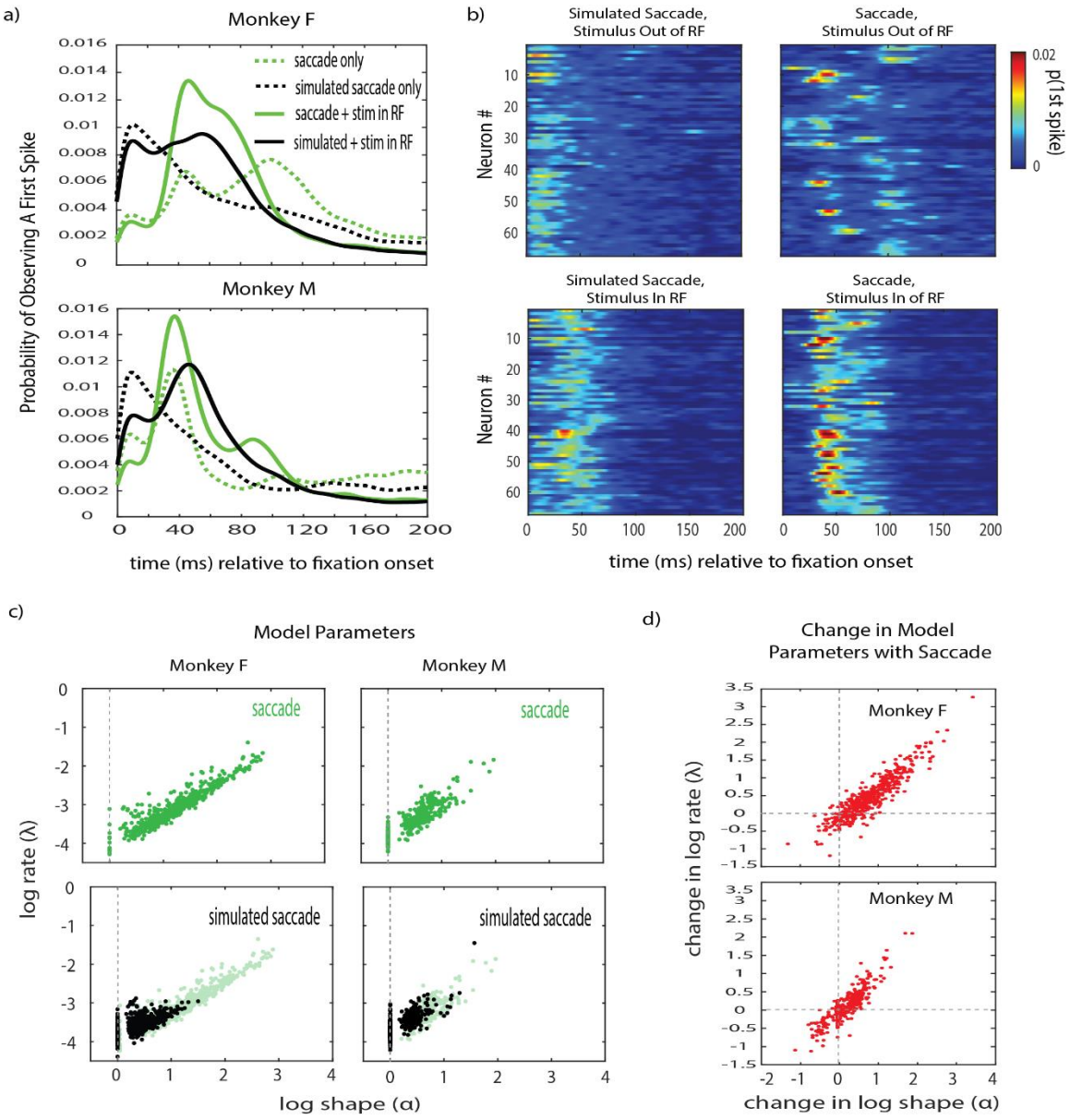

Figure 10: Spike latencies following a saccade or simulated saccade.

a) Kernel density estimate (width=5 ms) of first spike time (latency) distribution, collected across all neurons and all recording sessions, top: Monkey F, bottom: Monkey M. Saccades significantly reduce the probability of observing a first spike in the first 20 ms after the new fixation. **b)** Latency distributions across simultaneously recorded neurons for a single session (Monkey F, 2 cpd stimulus, session #3). **c)** Shape (abscissa) and rate (ordinate) parameters for spike latency distributions estimated for each neuron in the saccade (top) and simulated saccade (bottom) conditions. Left Monkey F, Right: Monkey M. **d)** Change in estimated parameters from simulated saccade to saccade. Saccades have the effect of increasing both the rate and shape of the latency distribution, speeding up spikes but imposing a strong refractory period.

To better understand the spiking at fixation onset, we modeled the latencies of each neuron as a renewal process (see Methods). Separately for the saccade and simulated saccade conditions, and utilizing only out-RF trials, each neuron was determined to either have gamma-distributed latencies (with rate λ and shape α) or an exponential distribution of latencies (with rate λ and shape parameter $\alpha = 1$), using the Akaike Information Criterion for model selection. The spiking of most cortical neurons has been shown to be approximately Poisson during steady-state time periods[344]. In both of our animals, the effect of saccades was to increase the rate and shape parameters and draw the distribution away from Poisson spiking (**Figure 10c**), indicating an underlying change not just in the rate of incoming spikes but also the shape of the distribution from which they are drawn. As shown in Figure 10d, the extraretinal signal increases the rate and shape parameters in most neurons. The effect of increasing both the shape and rate parameters is to impose a refractory period after fixation onset, followed by a period of increased spike probability. Post-fixation latency distributions for 20% of recorded neurons were fit as exponential in the simulated but not the saccade condition, and 5% in the saccade condition, but not the simulated condition. 4% of neurons had latency distributions which were fit as exponential in both conditions.

Encoding of New Fixations by Spike Latency

From the modeled distributions of spike latencies, we computed the coefficient of variation (CV) for each neuron in the saccade and simulated conditions (see Methods). As shown in **Figure 11a**, the average latency CV (which is a function of the shape parameter α) was significantly larger in the simulated compared to saccade condition ($p<.001$, permutation test) and 34% of neurons had a significantly smaller CV value in the saccade condition (permutation test, $p<.05$ corrected), indicating that saccades increase the reliability of spike latencies, even without a stimulus in the receptive field (as visualized in **Figure 10b**). We speculated that because the neuronal latencies were less variable, they could be used by the system to predict the onset of new fixations. We quantified the degree to which the spike latencies are informative

of new fixations using two approaches: mutual information (MI) for single neurons and decoding for neural populations.

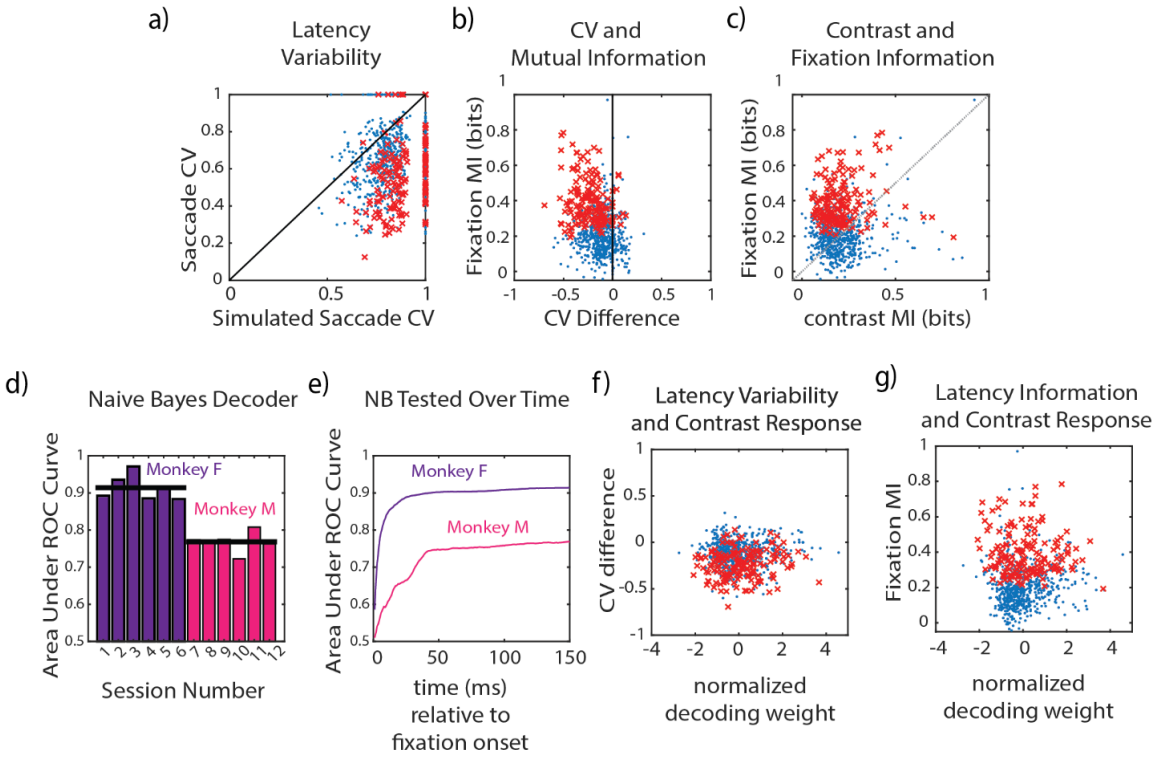

Figure 11: Information about fixation onset in V1 spike latencies.

a) Saccades reduce the variability of neuronal latencies (as measured by CV, see Methods) at fixation onset. Red marks are neurons with significant mutual information (MI) between latency and fixation onset. Note that a small number of neurons with significant MI are Poisson in both the saccade and simulated-saccade conditions – their information comes from a change in the rate of arrival of the first spike. **b)** Neurons with higher mutual information between spike latencies and fixation onset ("fixation MI") have larger saccade-based reduction in variability at fixation onset. **c)** The latencies of most neurons encode more bits about fixation than contrast ("contrast MI") and there is no correlation between the two measures, suggesting that temporal coding of fixations does not interfere with the encoding of visual stimuli. **d)** Naïve Bayes decoding of fixation onsets using spike latencies is extremely effective, demonstrating the code's robustness to trial-to-trial variability. **e)** Average cumulative decoding performance of NB decoders demonstrates that decoding performance saturates in the first 30-50 ms after fixation onset. **f,g)** There was no observed relationship between CV of neurons and their relative contribution to encoding of stimuli, as quantified by their relative decoding weight, as determined by a linear classifier trained to distinguish between in-RF and out-RF trials.

We computed MI between the spike latencies and the onset of fixation to quantify the degree to which the timing of the first spike was informative of new fixations (see Methods). For this latency code, 22% of all recorded neurons individually had significant mutual information with fixation onset (permutation test, $p<.05$ corrected; 31% in Monkey F, 9% in Monkey M). Only 6% of neurons had significant MI between fixations and the first inter-spike interval, supporting the conclusion that the latencies are more effective than the initial rates at encoding fixation onsets. **Figure 11b** demonstrates the relationship between MI and the change in CV across recorded neurons, revealing a significant dependency (Kendall's tau = -.16, $p<.001$). Neurons with larger decreases in latency variability due to the saccade tend to encode larger amounts of information about fixation onsets ($r= -.25$, $p<.001$), reinforcing the hypothesis that the concentration of first spikes around 30-50 ms after the saccade could be used by the system to indicate fixation onsets.

To assess the overlap between neuronal latency encoding of fixation onset and neuronal latency coding for contrast, we computed MI between the latencies and the stimulus contrast, for simulated saccade trials in which the Gabor was presented in the RFs under study. Less than 1% of neuronal latencies had significant MI with stimulus contrast (permutation test, $p<.05$ corrected), suggesting that this latency code was not particularly informative about stimulus attributes in this task (see Discussion). We observed no dependence between contrast- and fixation-related MI for the latency code (**Figure 11c**, Kendall's tau =0.005, $p=.82$). This suggests that the coding of fixations and of stimulus contrast are largely independent for this task, and that the visual reset does not interfere with stimulus coding on the subsequent fixation (although it likely interferes with the encoding of the previous fixation[286,342]).

We next asked whether the effects on spike timing were consistent on a trial-to-trial basis so that the distribution of spikes across the population was sufficient to distinguish between saccades and simulated saccades and thus predict the onset of new fixations[2,286]. We trained Naïve Bayes classifiers on the spike times across training trials and assessed their performance

on held-out testing trials (see Methods). Classifier performance is high and above chance in all 12 recording sessions (**Figure 11d**; $p < .001$, permutation test). The average classifier performance is 92% in Monkey F and 77% in Monkey M, demonstrating that in both animals the extraretinal modulation in spike latency is consistent on a trial-to-trial basis despite the inherent variability of neural responses. Thus, this signal could be used by the brain to accurately predict fixation onsets. To better understand the time course of this predictive power, we progressively increased the window of available spike information on test trials from 0 to 150 ms (the full time interval used for training). In both animals, classifier performance saturates within the first 50 ms of fixation onset (**Figure 11e**). These results indicate that the first spike times after a saccade reliably indicate fixation onset.

The results presented above demonstrate that spike latencies in V1 carry sufficient information to predict the onset of new fixations and appear to do so without interfering with the encoding of stimulus contrast (see Discussion). We next examined the relationship between latency coding of new fixations (detailed above) and spike count coding of the stimulus (discussed in Chapter 2). We trained classifiers to distinguish between trials in which a stimulus was presented in or outside of the receptive field using the spike counts across the recorded population (as in Chapter 2; see Methods). No dependency between the change in CV and the spike count decoding weights was observed (**Figure 11f**; Kendall's tau = -5x10^-4, $p = 0.98$); see Methods). For neurons with significant information about fixation onset (red), there was no significant dependency between decoding weight and mutual information (**Figure 11g**; Kendall's tau=-.05, p=0.31), however there was a modest relationship between the decoding weights and neurons without significant information (Kendall's tau = .06, $p = .01$).

We utilized the criterion from our previous analysis to label which neurons were visually responsive in the task. Note that, for the purposes of the psychophysical experiment, we did not optimize the Gabor to each individual neuron, and therefore slightly more than half of all recorded neurons did not elicit a visual response. We estimated that 36% of neurons were

visually responsive in this task, but did not encode fixation information (visual neurons). 10% of neurons encoded fixation information but were not visually responsive (fixation neurons), while 12% of neurons had both properties (visual-fixation neurons).

Spiking Variability and Neural Population Coding

Above we observed that saccades reduce response variability in the population of neurons informative about fixation onset. A follow-up question we investigated is whether this effect of saccades on single spikes is associated with reduced variability in spike counts on longer time scales. Previous work has suggested that single-neuron variability might decrease around fixation onset because the timing of the first spikes after fixation are coupled with the phase of the local field potential,[98,100] but during this time period noise correlations between pairs of neurons are also reduced (Chapter 2). We first examined the spike count variance-to-mean ratio, or Fano factor, in sliding 80 ms windows across the three groups of neurons defined in the previous section (**Figure 12a**). In all three groups, the Fano factor rises during the saccade, but the effect is strongest in visual-fixation neurons. Because of the decrease in spike latency CV observed primarily in the fixation and visual-fixation populations, we expected that post-saccadic Fano factors in these neurons would also be reduced. A reduction in average Fano factor after fixation onset was seen in the visual population, but not the visual-fixation or fixation populations. However, the effect in the visual neurons was not significant after correction for multiple comparisons. This result suggests the reduction latency variability (as measured by CV) in the neurons of the fixation and visual-fixation populations is not a product of a long-timescale reduction in spike count variability (as measured by the Fano factor).

We previously reported changes in spike count correlations, or noise correlations, between pairs of visually-responsive neurons in this task (Chapter 2). Given these previous results and the hypothesis that corollary discharge signals optimize coding at fixation onset, we examined if there were differences in the dynamics of perisaccadic noise correlations within and between the three neuronal categories (**Figure 12b**). Noise correlations are important for

neuronal population coding because they can reduce or enhance the information content of the network[41,45,49,279,345–348]. Within and between all classes, we found an increase in average pairwise noise correlations during the saccade, and the increase was strongest in visual-fixation neurons (**Figure 12b**). This result qualitatively parallels the results of the Fano factor analysis. The increase in intrasaccadic noise correlations was weakest for the visual population. Following fixation onset, we observed a reduction in the magnitude of noise correlations which was significant only in the visual population (**Figure 12b**, far right). Thus, the intrasaccadic increase in correlated variability appears to target different neurons than those primarily targeted in the post-saccadic decrease. This result suggests that there are at least two distinct components of CD modulation in V1, occurring in two phases before and after the reset in spiking described above. This modulation is reminiscent of the generally observed sequence of suppression and enhancement.

Changes in the relationship between signal and noise correlations are more likely to enhance or suppress perception and behavioral responses than changes in the magnitude of noise correlations alone[41,41,279,349–351]. To better understand how extraretinal modulations optimize population coding at fixation onset, we compared signal and noise correlations for each simultaneously recorded neuron pair. Signal correlations quantify similarities in stimulus responses (i.e. tuning or sensitivity), in contrast to noise correlations which quantify similarities in trial-to-trial variability independent of the stimulus. Typically, neuron pairs with high signal correlation have higher noise correlations[352–354]. In other words, the two measures of correlation are correlated with each other. Noise correlations which are strongly dependent on signal correlations are detrimental to information transmission[41,279,345]. Reductions in the strength of the relationship between signal and noise correlations within a subpopulation are thought to optimize coding and reflect a prioritization of that population's signal[40,41].

In contrast to noise correlations, we found that the average signal correlation increased within all three populations during visual processing following saccades, relative to simulated

saccades (.32 vs .23 for fixation neurons, .50 vs .46 for visual-fixation neurons, and .61 vs .56 for visual neurons; $p<.05$ Wilcoxon signed rank test). This increase in signal correlation may increase the robustness of the neural coding of contrast[213]. We looked at the relationship between the signal and noise correlations by plotting the running average of the pairwise noise correlations during the response period as a function of signal correlation. This method revealed that, in the visual population, saccades reduce the dependence of noise correlations on signal correlations (**Figure 12c**, center), which suggests enhanced information transmission by reducing information-limiting (or information-reducing) noise[41,345]. Within the visual population, this effect was strongest for neuron pairs with high signal correlation, as expected for a targeted prioritization of the task-relevant subpopulation. The combined redundancy and increased information flow may ensure robust encoding of new signals at fixation onset.

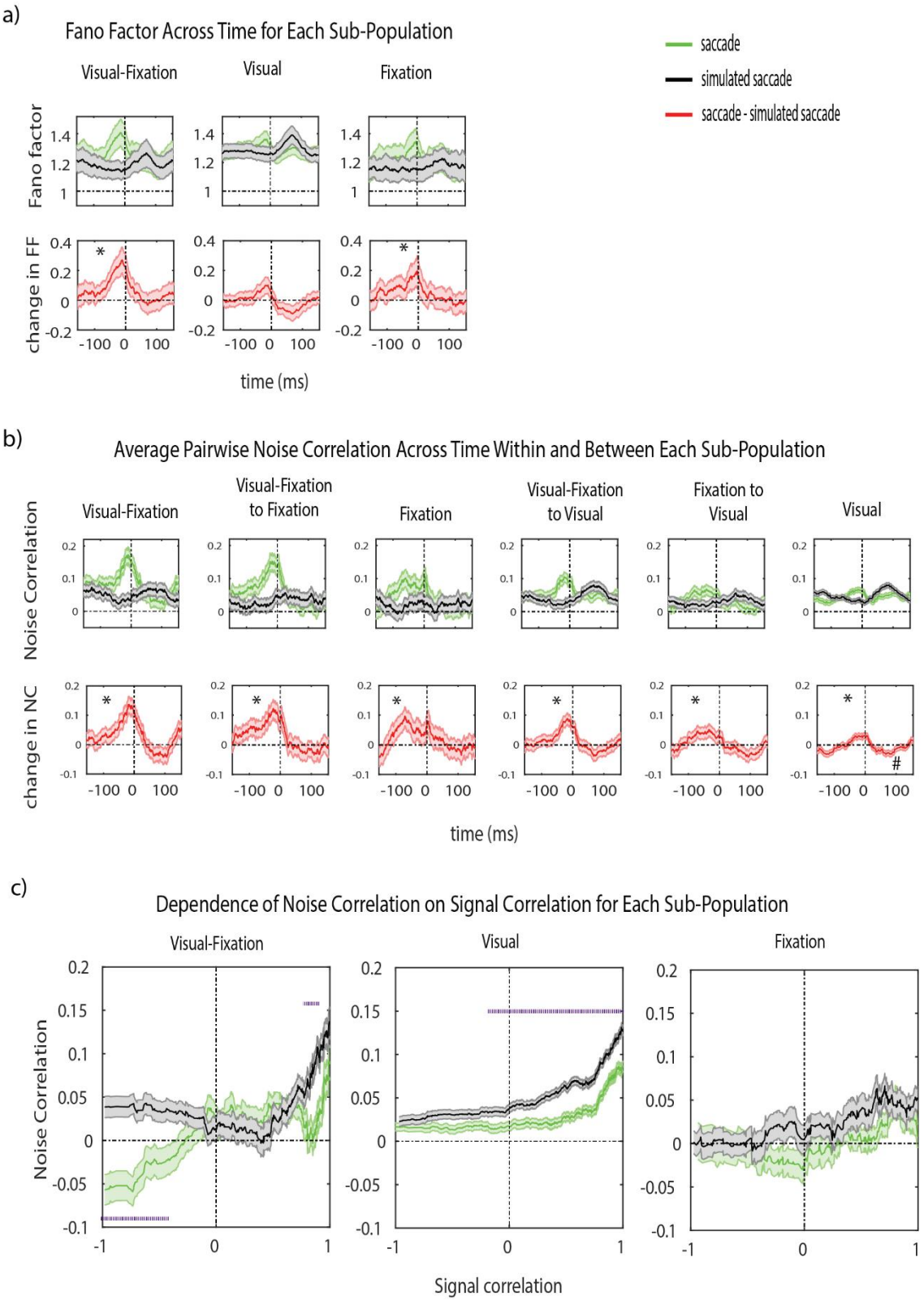

Figure 12: Single-neuron and interneuronal variability changes due to extraretinal effects. (Legend on next page)

Figure 12 (continued). **a)** Neurons with significant MI between latency and fixation onset (fixation and visual-fixation neurons) have sharply increased variability during the saccade but show less Fano factor modulation than those without significant MI; after correcting for multiple hypotheses there was no observed decrease in single-neuron variability in any subpopulation following the saccade, suggesting the decrease in CV (timing statistic) is not strongly related to the long-timescale Fano factor (count statistic). **b)** The dynamics of average pairwise noise correlations within and between subpopulations vary, with a large observed increase before the saccade (~ -50 ms) for the visual-fixation and fixation populations, as well as between them. There is a significant increase in noise correlations within and between all sub-populations during the saccade. A statistically significant decrease in noise correlations is found only within the visual population. **c)** During the response period, saccades reduce the dependency of noise correlations on signal correlations in visual and visual-fixation neurons, but there is no change in fixation neurons (as demonstrated by running average of noise correlations). In the saccade condition, visual-fixation neuron pairs with large, negative signal correlations tend to have negative noise correlations. The change in dependency between signal and noise correlations and the reduction in average noise correlation may combine to enhance information flow at fixation onset. Lines above the curves (purple) represent significant increase in noise correlation for level of signal correlation * represents a significant positive peak and # indicates a significant negative peak (both $p<.05$, two-sided permutation test, corrected). All error bars are estimated 95% confidence intervals.

A similar reduction in dependency between signal and noise correlations was found for pairs within the visual-fixation population (**Figure 12c**, left), but this effect occurred primarily either in pairs with very high signal correlations, close to 1, or very low correlations close to -1. The reduction in noise correlation for pairs with high signal correlation may have similar effects as in the visual population. However, for pairs with low signal correlation, the average noise correlation flipped signs and became negative – this may suggest that corollary discharge signals actually increase information-reducing correlations within this portion of the population, as signal and noise correlations of opposite signs are believed to be detrimental to neural coding[41]. No effect was found on average in the fixation population (the neurons which are not stimulus-responsive). Overall, there appears to be an enhancement in signal correlations across the population but a targeted reduction in pairwise noise correlations for the neurons with the strongest tuning similarity. This may work to increase both the robustness of the neural code as well as enhance its coding capacity at fixation onset.

Extraretinal Modulation of High-Dimensional Population Codes

Given the evidence presented above which suggests that there are two distinct neural codes (or modes of neural coding) before and after the spiking reset, we next assessed the relationship between the three subpopulations of neurons and the full recorded population. We trained two types of spike count decoders for each session (see Methods). The "motor" decoders distinguish between saccades and simulated saccades using the spike counts of simultaneously-recorded neurons in 30-ms windows. The decoders were trained on windows slid in 1-ms intervals relative to fixation or rotation offset so that there was a set of decoders trained within each session. The second type of decoder distinguishes between trials when the stimulus was presented in or outside of the receptive fields (i.e. a visual decoder which performs the same task as the animal). These decoders were trained on the spike counts during the visual response period, using trials at the highest contrast (as in Chapter 2).

The motor decoders were tested on all possible training windows (cross-temporal decoding), generating a matrix of train and test pairs. Cross-temporal decoding assesses the stability of codes over time by testing the ability of decoders trained on one time period to generalize to test trials from other time periods. **Figure 13a** shows the performance of neural decoders. In both animals, around the time of the saccade there are stable population spiking statistics which rapidly change after fixation onset, at approximately the same time as the reset of single-neuron spiking described above. After the reset, the code appears to switch – decoders trained pre-reset are ineffective post-reset, and vice-versa. The duration of the pre-reset stable code is much larger in Monkey F compared to Monkey M, but is visible in both animals. There are more substantial differences in the post-reset population spiking between the two animals.

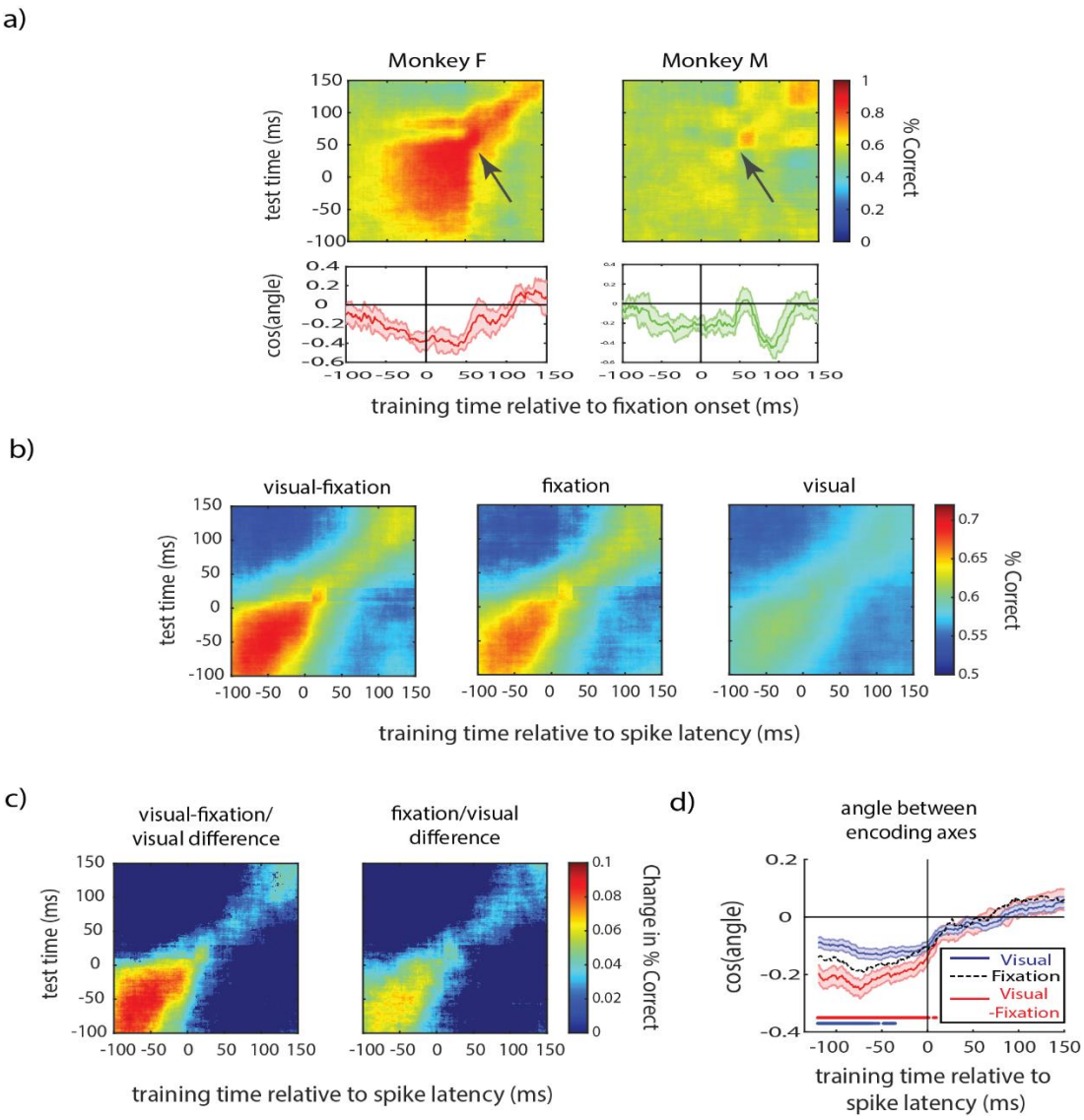

Figure 13: High-dimensional population coding is reset by first spikes.

a) The performance of fixation-triggered cross-temporal decoding of saccades versus simulated saccades, in both animals (top), and the angle between motor and visual encoding axes over time (bottom). Immediately after fixation onset, both animals show increased decoder performance and non-orthogonal angles between the two axes. Around 50 ms after fixation onset (when the decoder integrates from 21-50 ms), the code is reset (black arrow) and does not generalize to the earlier period. At the same time, the angle between visual and motor axes rotates towards orthogonality. **b)** Latency-triggered cross-temporal decoding performance for the three sub-populations of interest. **c)** Difference between the two fixation-predictive populations and the visual population (masked by $p<.05$ permutation test, corrected). Decoders trained on windows relative to the latencies of visual-fixation (left) and fixation (center) neurons significantly out-perform, on average, those aligned to visual neurons (right), both before and after the reset. **d)** The latency-aligned angle between motor and visual encoding axes for the three subpopulations. The angle is significantly further from orthogonal for the fixation and visual fixation populations. The confidence interval for fixation neurons (in black) is not shown for clarity, but the effect is significant (bars on bottom show $p<.05$ permutation test, corrected).

Each decoder is defined by a hyperplane which separates the two classes. A vector normal to the hyperplane lies in the direction in neural population space which encodes the quantity of interest. We refer to this vector as the encoding axis. Averaged across 12 sessions, the angle between the visual and motor axes diverged from orthogonality (with angle > pi/2 radians) shortly before the beginning of the saccade, before returning to orthogonality after about 50 ms, although this effect, too, was much stronger in Monkey F than Monkey M (shown separately in **Figure 13a**, bottom). This demonstrates interference between the CD signal and the visual encoding axis around the time of the saccade which is rapidly reduced around the time of the reset, as demonstrated by the apparent rapid rotation towards orthogonality. Note that the timing of the decoder performance at 50 ms represents the integration of signals from 20 ms to 50 ms after fixation onset, the same time period as the clustering of first spikes. Because of this timing, we hypothesized that the first spikes were coupled to this rotation towards orthogonality.

To more directly test the hypothesis that the first spikes are associated with a reset and rotation of the population code, we constructed decoders after aligning the population firing rates to the spike latencies of individual neurons (i.e. spike-triggered decoding) and assessed the relationship between the three classes of neurons and the total neural population. **Figure 13b** and **c** compare the latency-triggered cross-temporal decoding performance averaged across neurons in the three classes. Compared to visual-only neurons, pre- and post-latency decoding performance is much higher when aligned to the first spike of neurons with fixation-predictive latencies, compared to the visual population. This finding suggests that the first spikes of fixation-predictive neurons are more strongly associated with the orthogonalization of the population code. As with the increase in noise correlations, the strength of this effect is strongest for visual-fixation neurons. The lack of generalization between pre- and post- latency decoders demonstrates a clear difference in the population code before and after the first spikes. We also observed a larger pre-latency angle between the visual and motor encoding axes for both fixation and visual fixation neurons, compared to the visual population, with a significantly larger angle approximately 50-100 ms before the first spikes (**Figure 13d**, $p < .05$ permutation

test, corrected). Together these results support the hypothesis that the spiking reset following fixation onset is associated with a rapid shift in the neural code.

III. Discussion

In this study, we tested the hypothesis that saccades initiate a process in V1 that optimizes visual processing at the start of new fixations. We specifically tested whether an extraretinal corollary discharge signal facilitates stimulus processing by robustly encoding new fixations in spike latencies while also facilitating information flow. Our study differed from, and expanded upon, previous studies of the dynamics of active sensing in V1 by simultaneously recording from neuronal populations while having the animals actively engaged in a task, instead of scanning natural images or making eye movements in the dark. Unlike previous studies, we were able to isolate the effect of CD signals on V1 processing, which was accomplished by using simulated saccades that preserved movement on the retina but without eye movement on the accompanying CD.

Knowledge of fixation onset is likely critical for the ability of the visual system to rapidly recognize objects after a saccade[286]. By comparing true saccades to simulated saccades, we demonstrated that the first spike following a saccade is precisely timed and contains information about the onset of a new fixation (**Figure 10**, **Figure 11**). Across the population of recorded neurons, the latency to the first spike was more predictive of new fixations than the first inter-spike interval. Neural decoders readily distinguished between saccades and simulated saccades; the most informative time period was the first 20 ms following fixation onset when spiking was significantly less probably in the saccade than in the simulated-saccade condition (**Figure 11d)**.

We found that the latency coding of fixation onsets and contrasts were largely independent (**Figure 11c**), suggesting that there is little interference between the encoding of new fixations and visual information. Many previous studies have demonstrated that contrast modulates the latencies of V1 neural responses[329–331,335,336,355]. However, we did not find any

significant information between the spike latencies and contrast. This null result may have occurred for several reasons. Previous work has suggested that the effect of contrast on V1 latencies occurs mostly for suprathreshold stimuli when firing rates are saturated[355], while this study focused on contrasts near perceptual threshold. Other work has demonstrated that V1 latencies have significant mutual information with small increases or decreases in stimulus contrast, but firing rates are more effective at encoding contrasts across a broad range[336]. Additionally, previous work found that mutual information between latency and contrast was much larger for sharp edges, rather than grating stimuli (as used in the present experiment)[335]. Latency coding of contrast is likely to be a critical factor of the neural code, especially at high contrast, but we found no evidence here that it interferes with the latency coding of fixations, which may be critical for optimizing active vision.

Our analysis of neuronal variability suggests that an early corollary discharge signal primarily targets the sub-population of neurons which carry information about fixation onsets in their spike latencies, and the effect appears to be strongest in neurons which also encode visual contrast by spike rate (**Figure 12a,b**). Single-neuron variability, as well as noise correlations within this fixation-predictive population, rise sharply during the saccade, just before fixation onset. Sharp increases in correlated variability are associated with sudden decreases in driving input[356], suggesting that the intrasaccadic increase in neural variability may be a result of strong suppression inherited from the LGN, as suggested by previous single-neuron studies[106].

The strong suppression immediately at fixation onset, followed by a concentration of spiking, suggests that a post-inhibitory rebound may be driving these first spikes[97,100]. This is supported by the fact that the saccade-associated concentration of latencies occurs with or without visual input. We also found that spike latencies coincide with a period of time when the corollary discharge code is shifting from being angled away from (or primarily inhibiting) the visual signal, and towards orthogonality (**Figure 13a,d**). While a post-inhibitory rebound at fixation onset might be considered disadvantageous for visual processing because it likely does

not reflect visual information, we find that this is not necessarily the case, as the shift in spike latencies occurs without stimulus presentation and appears to be independent of spatial frequency. Interestingly, a previous study of saccade effects on V1 neurons demonstrated that following a long period of suppression there is a brief period of enhanced spiking, which is uninformative about the visual stimulus[106]. If V1 inherits perisaccadic suppression from the LGN, which is subsequently released leading to rebound spiking, it would account for the reset aspect of our data as well as the firing rate modulations described by McFarland et al[106].

We found a clear difference in the population code before and after the resumption of spiking following fixation onset. Decoders trained to distinguish between saccades and simulated saccades failed to generalize between the pre- and post-reset time intervals. This result is consistent with previous research that suggests perisaccadic suppression followed by facilitation in V1[100,106,223,267,294]. However, our results expand on this previous research by demonstrating that the pre- and post-reset codes are not simply suppression followed by facilitation. If that were the case, one would expect that decoders trained on the early period and tested on the later would be anti-parallel, and the testing performance of these decoders would be substantially worse than chance. Instead, we find that the performance of decoders trained before the reset have near-chance performance after the reset (**Figure 13**), suggesting the CD modulation is more high-dimensional and not uniform throughout the population. Our analysis of correlated variability supports this conclusion, as different sub-populations have different modulations, both in terms of the time course of noise correlations and the relationship between signal and noise correlations.

Variability in neurons with reliable post-saccadic latency modulations sharply increases during the saccade, but on average these neurons do not exhibit a significant post-saccadic reduction in either Fano factor or noise correlations. In contrast, variability is reduced following the saccade, during the critical early period of visual processing, for neurons which are visually responsive but do not reliably encode latency. The relationship between signal and noise

correlation, which can be a critical determinant of neural coding and behavior[41,345,349], is altered only in the visual population following the saccade.

There appear to be three distinct phases of the perisaccadic sensorimotor interaction in V1: early suppression of the visual signal (**Figure 10**, **Figure 12**), the reset signal which does not interfere with visual processing (**Figure 11**), and a later period with a mix of facilitation and suppression (Chapter 2). During the first phase, both single-neuron variability (Fano factor) and correlated variability (noise correlations) rise sharply around fixation onset (**Figure 12**), when many studies have demonstrated there is a strong suppression of spiking activity[106,223,267,294] and visual perception[157,161,202,221]. The reset and switch between coding schemes begins after the strong suppression, with a cluster of spike latencies around 30-50 ms post-fixation (even on trials in which no stimulus is presented in the receptive field). After the reset, variability decreases and sensitivity to contrast is modulated in a spatial frequency-dependent manner (Chapter 2). Furthermore, during the visual response, the relationship between signal and noise correlations changes (**Figure 12**), as the reductions in shared variability are targeted towards the neuron pairs with high signal correlations. This effect of reducing the dependency of noise correlations on signal correlations likely reduces the impact of information-limiting correlations in the population code[41,349].

The post-saccadic modification and enhancement of population coding is in line with multiple experiments which have demonstrated post-saccadic perceptual enhancement[129,202,227,240–242], or increased reaction times[243]. Psychophysical experiments also suggest that saccades reset ongoing visual processing[286,342], and restart it in a way that emphasizes fundamentally different features of the visual scene[241,357] (Chapter 2). Thus, there is converging evidence from single-neuron, neural population, and local field potential studies as well as psychophysical experiments that corollary discharge signals alter visual processing at fixation onset to optimize the construction of new representations.

IV. Methods

Contrast Sensitivity Task

We analyzed recordings in which two macaque monkeys performed a two-alternative forced choice discrimination task (**Figure 3**). Details of this task have been described previously (Chapter 2). During each session, the animals detected the presence of a Gabor stimulus either in the receptive field of the recorded neurons or in an alternate location (Figure 3a). The Gabor was presented either at the end of a saccade, or at the end of a simulated saccade which reproduced the dynamics of the true saccade. Simulated saccades were generated using a rotating mirror mounted on top of a stepper motor (Figure 3b). This experimental design ensured that stimulus timing was consistent (+/- 10 ms from fixation onset or rotation offset) in both the saccade and simulated saccade conditions while controlling for the effects of motion in the surround, including the edges of the stimulus monitor. While the animals performed the task, we simultaneously recorded from populations of single neurons using a Utah multielectrode array. During each recording session, the Gabor was presented at varying contrasts but a constant spatial frequency, and thus the animals' contrast sensitivity functions could be determined. Each animal performed 6 sessions, in a random order, with a Gabor spatial frequency of 0.5, 1, 2, 3, 4, and 5 cycles per degree of visual angle (cpd). Saccades suppressed contrast sensitivity and neural firing rates at low spatial frequencies and enhanced sensitivity and firing rates at higher spatial frequencies (Chapter 2).

Modeling Spike Latencies

We modeled the latency arrivals of each neuron as a renewal process. Specifically, we assumed that the probability density $f(t)$ of the first spikes after fixation onset were distributed according to the gamma distribution:

$$f(t;\lambda,\alpha) = \frac{\lambda^{\alpha}}{\Gamma(\alpha)} t^{\alpha-1} e^{-\lambda t}$$

Where λ is the rate parameter, α is the shape parameter, t is the waiting time until the spike occurs and $\Gamma(\cdot)$ is the gamma function. When the shape parameter $\alpha = 1$, the distribution reduces to the exponential distribution:

$$f(t) = \lambda e^{-\lambda t}$$

To determine the better model, we fit each neuron's spike latencies using *gamfit.m* and *expfit.m* in MATLAB. We compared the likelihoods of each fit for each neuron using the Akaike Information Criterion:

$$AIC = 2k - 2\ln L$$

Where k is the number of parameters (2 for the gamma fit, 1 for exponential fit) and L is the likelihood. The model with the lower AIC was selected as the appropriate model for each neuron. To isolate the non-visual effects of saccades without the potential confound of changing stimulus contrasts, we only used trials in which the Gabor was presented outside of the receptive field to fit the models.

From the parameters α and λ the coefficient of variation, or standard deviation to mean ratio, was computed:

$$CV = \sqrt{\frac{\alpha}{\lambda^2}}\frac{\lambda}{\alpha} = \frac{\sqrt{\alpha}}{\alpha}$$

Note that for a homogeneous Poisson process with exponential waiting times, $\alpha = CV = 1$. In this work, we use CV to refer to the variability in spike latencies, and the Fano Factor to refer to the variability in spike counts.

Mutual Information

Mutual information[358] measures the dependence between two random variables. The more dependent the two variables are, knowledge of one gives more information regarding the

other, and thus the variables have higher mutual information. Mutual information (MI) between two random variables X and Y can be defined as

$$MI(X;Y) = D_{KL}(P_{(X,Y)}||P_xP_x)$$

Where D_{KL} is the Kullback-Liebler divergence, which measures the separation between two probability disributions. Thus, MI can be interpreted as the distance between the joint distribution $P_{(X,Y)}$ and the product of the marginal distributions P_x and P_y.

To estimate the mutual information between discrete and continuous random variables (i.e. the occurrence of a saccade and the first spike latency), we utilized a k nearest-neighbors approach[359,360], utilizing publicly available code (https://github.com/otoolej/mutual_info_kNN). We used $k = 3$ as recommended by the authors. Note that this estimation method occasionally led to values of mutual information slightly less than 0, but none of these values were found to be significantly different from 0.

To determine the significance of mutual information estimates, we shuffled the variable labels (either saccade and simulated saccade or the levels of contrast) 1000 times and repeated the calculation of MI for each of the shuffled data sets. MI values were considered significant at the level $p<.05$ following correction for multiple comparisons using the Benjamani-Hochberg procedure[317].

Fano Factor, Signal Correlations, and Noise Correlations

To estimate neural variability near perceptual threshold, and compare various measures of neural variability, we restricted analyses to conditions in which there were at least three correct trials. We utilized 80-ms windows to be consistent with the results previously outlined in Chapter 2, and because this is the same approximate length of stimulus presentation. The Fano factor of neuron i is the ratio of the variance in spike count (x) to the mean spike count within a given window:

$$FF_i = \frac{E[x_i{}^2] - E[x_i]^2}{E[x_i]}$$

Where the expectation was taken over all trials where a stimulus is presented in the receptive field, within the saccade and simulated saccade conditions.

The signal correlation ρ between neurons i and j measures the similarity in tuning or sensitivity between them, and is defined as the correlation between the increase in average change in firing rates (from trials with stimulus outside the RF to trials with stimulus inside the RF) across contrast conditions (the "signal"):

$$\rho_{i,j} = \frac{E[(\Delta\mu_i - E[\Delta\mu_i])(\Delta\mu_j - E[\Delta\mu_j])]}{\sigma_{\Delta\mu_i}\sigma_{\Delta\mu_j}}$$

Where $\Delta\mu_i = E\left[x_{i,inside\ RF}\right] - E\left[x_{i,\ \ out\ of\ RF}\right]$ is the signal of neuron i at a given contrast and $\sigma_{\Delta\mu_i} = \sqrt{E\left[\Delta\mu_i{}^2\right] - E[\Delta\mu_i]^2}$ is the standard deviation of the signal. Signal correlations were only computed during the period for which there was a signal, the response period of 30-110 ms.

The "noise" correlation r between neurons i and j quantifies the co-variability in trial-to-trial responses to identical stimuli. These correlations may arise due to a large number of factors. To estimate the noise correlation near perceptual threshold, we included only z-scored spike counts within each contrast level using balanced z-scoring (as in the previous chapter)[297,313,314] .

$$r_{i,j} = E[z_i z_j]$$

Where z_i is the z-scored spike count of neuron i such that $E[z_i] = 0$ and $\sigma_{z_i} = 1$. The expectation is taken over all trials in which a stimulus was presented in the receptive field.

Decoding

We first utilized Naïve Bayes classifiers to distinguish between saccade and simulated saccade trials. For this analysis, the training data consisted of vectors of spike latencies (up to 150 ms) for each trial. If a particular neuron did not spike on a given trial, the value was set to

NaN (not a number). Setting this to a missing value, as opposed to 0 or a randomly selected number, is more biologically plausible because if a spike is missing, a neuron reading out the information does not have access to it. Additionally, setting this value to a number would imply the time of a spike -i.e. a spike occurred at time 0 (an impossible spike time), which is close to 1 ms and would be interpreted by the classifier as being similar to a very early spike. Naïve Bayes classifiers, unlike linear classifiers, can still be trained with some missing data points. We randomly selected half the data for testing and held out the other half for testing, and trained the classifiers using *fitcnb.m* in MATLAB. As described in the Results, we first tested on the entire spike distribution (spikes occurring from 1 ms to 150 ms after fixation onset). We then gradually reduced the amount of available decoding time (or equivalently gradually increased it), to examine the periods of time that were most useful for decoding utilizing this method.

For all other decoding analyses in this work, we utilized logistic regression classifiers trained using *fitclinear.m* in MATLAB:

$$p(\theta|x) = \frac{1}{1 + e^{-\boldsymbol{\beta}\boldsymbol{x}+b}}$$

Where θ is the condition of interest (e.g. stimulus in the receptive field), $\boldsymbol{\beta}$ is the learned vector of decoding weights and b is the scalar bias. We utilized the default settings where the ridge regularization parameter is set to $\frac{1}{n}$ where n is the number of training trials. The visual decoders were trained to distinguish between trials in which the stimulus was presented in (in-RF) or out (out-RF) of the receptive fields under study, using the spike counts during the response period (30-110 ms following fixation onset). Only the highest contrast trials were used for training. This method is the same as in as our previous work (Chapter 2), except the full recorded population was used instead of only the visually responsive neurons. Only the highest contrast trials were used for training, and by utilizing the full population in an unbiased manner we were able to directly compare the visual decoder weights to the motor decoder weights.

The motor decoders were trained in 30-ms windows, slid in steps of 1 ms, to distinguish between trials with a saccade or with a simulated saccade. For these classifiers, 50% of data was randomly selected as training data and the other 50% was used as testing data. We utilized these decoders for three analyses: testing the temporal precision of neural coding near fixation onset, testing the generalizability of the neural codes over time, and for examining the angle between the visual encoding axis (defined by the visual classifier described in the previous paragraph) and the motor encoding axis (the vector normal to the hyperplane which defines the decoder).

For the cross-temporal analysis, decoders were tested on the held-out data from all possible training windows to yield a matrix of train-test window pairs. This technique (cross-temporal decoding) can be used to assess the temporal stability of high-dimensional codes. The angle θ between two classifiers with weight vectors $\boldsymbol{\beta}_1$ and $\boldsymbol{\beta}_2$ was computed as

$$\cos\theta = \frac{\boldsymbol{\beta}_1 \cdot \boldsymbol{\beta}_2}{\|\boldsymbol{\beta}_1\| \, \|\boldsymbol{\beta}_2\|}$$

Where $\|\boldsymbol{a}\|$ is the norm of a vector $\boldsymbol{a}$ and $\cdot$ represents the dot product.

Statistical Testing

To the extent possible, we employed nonparameteric statistical tests or permutation tests to determine the significance of the observed effects. Permutation tests were performed by randomly shuffling the labels (e.g. saccade and simulated saccade) 1000 times and recalculating the test statistic of interest. The p value was calculated by counting the number of times the shuffled data produced a test statistic greater (or smaller) than or equal to the empirical test statistic. This number was added to 1 (to account for the empirical data) and divided by 1001 to yield the p-value.

CHAPTER 4: EXTENDED RESULTS AND DISCUSSION

The evidence of the previous two chapters suggests that corollary discharge signals alter neuronal population codes around the time of the saccade in a dynamic fashion. As a result of these modulations, primary visual cortex appears primed to process new visual input at the start of new fixations, a critical time period for the formation of object representations. By comparing neural activity recorded around the time of true saccades to activity recorded during simulated saccades, we were able to isolate the non-visual effects of saccadic eye movements both with and without stimulus processing. The differences between saccades and simulated saccades generally fall into two categories: effects which are correlated with spatial frequency and effects which are independent of spatial frequency. Changes in perceptual contrast sensitivity and neuronal contrast responses were dependent on spatial frequency; changes in first spike latency and correlated variability were found to be independent of spatial frequency. The analyses of single neurons and neural populations support the conclusion that multiple corollary discharges influence V1 processing around the time of the saccade. These corollary discharges appear to work in unison to optimize processing at the start of fixation in ways that may serve behavioral goals such as object recognition.

Evidence for Corollary Discharge

The research presented in this thesis is derived from a working hypothesis that a corollary discharge signal associated with saccadic eye movements has beneficial effects on perception and visual processing. There are several solid lines of evidence that support the involvement of corollary discharge. It was noted long ago that the electrical activity of widespread visual areas of the brain is modulated by saccades made in the dark[86]. Similarly, local field potentials in area V1[100], as well as spiking activity, are modulated by saccades in the dark. Thus, it is clear that neural activity in visual cortex is modulated by eye movements in the absence of visual input. Consistent with the role of an extraretinal signal, changes in neural

activity associated with saccades have been shown to start before the eyes start to move[2,109]. These data cannot be explained by motion of a stimulus across the retina or proprioception. Instead, it appears that a corollary discharge signal associated with the motor plan for the impending saccade is able to modulate brain activity before the eyes move. This conclusion is consistent with evidence indicating that visual stability is likely attributable to a corollary discharge[63,147,150]. The methodology used in the present study provides further support for corollary discharge theory to the extent that it rules out effects due to retinal translation of stimuli. The basis for corollary discharge effects in V1 have not been worked out, but an analogous pathway to frontal cortex has been identified[63,146], as has a path to the visual motion area MT[149].

Parsing Successive Fixations

Chapter 3 discussed the apparent need for the visual system to parse perception and neural activity associated with successive fixations, a process that may rely on saccades and corollary discharge. Psychophysical evidence is consistent with such a process[286,342]. We found that saccades are associated with consistent changes to spiking activity: at the start of fixations there is a period of suppression followed by precisely-timed spiking rebound across the population. These changes in spiking are likely related to changes in LFPs at the start of fixation[2,54,98,100]. Both the timing of saccade-based changes in the LFPs and the latency of the first post-saccade spike are informative about the occurrence and timing of a saccade (i.e. potential reset signals)

Relevant to a possible role of first-spike latency, it is noteworthy that the change in spike latency associated with saccades occurred at all spatial frequencies and regardless of visual input, suggesting that the first spike following the saccade is informative about saccade occurrence but uninformative about the visual stimulus. This conclusion is similar to McFarland et al, who used a model-based approach to estimate gain changes in V1 neurons around the time of the saccade[106]. They found a multiplicative reduction in gain during the saccade followed by an

additive increase in firing rate afterwards. Additive changes in responses, as seen upon fixation are, by definition, unrelated to gain and therefore do not contain information about what is driving the spiking activity of a neuron. Because this increase was not found to be informative about the stimulus, they suggested it may be related to the perceptual reset. Our results build significantly on theirs because McFarland et al did not use simulated saccades. The brief additive increase they observed could plausibly have been a result of nonstationarities and nonlinearities not captured by their model (such as the frequency-dependent changes in sensitivity and time-varying variability detailed in the previous two chapters) or a result of a postsaccadic visual response to something other than their stimulus – e.g. a response to the edges of the monitor.

Our results largely support the conclusion that early spikes are uninformative about the stimulus. However, they still may play a role in visual processing and perception. Recent work suggests that additive increases may indeed increase detection rates to stimuli at perceptual threshold[361]. It may be that the reset of spiking plays a role in visual processing in addition to providing information about the timing of new fixations. Previous psychophysical work suggests that saccades reset and restart visual processing at the beginning of fixations, such that the influence of past inputs on perception is reduced[286,342]. The suppression followed by a clustering of spike latencies may effectively clear the representation of the previous fixation to enable the construction of a new one.

Neural Encoding: Sensitivity and Spatial Frequency

In addition to an apparent role in resetting visual processing, we have found that saccades have significant effects on visual perception and the associated single neuron responses and network interactions. In Chapter 2, postsaccadic modulations of contrast sensitivity were found to be correlated with spatial frequency. At low frequencies, perceptual sensitivity decreased. At higher frequencies, sensitivity increased. Multiple analyses of the simultaneously-recorded neural data support the conclusion that saccadic corollary discharges bias V1 spiking in a way that could support the perceptual changes. Both near and above the animal's perceptual

threshold, saccades led to a decrease in average firing rates at low spatial frequencies and an increase at higher frequencies. At low spatial frequencies, a majority of neurons were suppressed, while at higher frequencies, a majority of neurons were enhanced. The testing performance of linear decoders trained to do the same task as the animal using the simultaneously recorded neural activity paralleled the perceptual performance. Together these results support the conclusion that corollary discharge signals bias visual processing and perception towards higher spatial frequencies. We can only speculate, but functions based on higher spatial frequencies include facial recognition[244–247], letter identification[248–251], word recognition[252], and categorization[253–255].

These changes in spectral sensitivity would tend to counteract (whiten) the predominance of lower spatial frequencies in natural scenes. The timing of the modulation in spectral sensitivity is notable. Previous work suggests that the reduction in human sensitivity at low spatial frequencies supports visual stability by suppressing blur during the saccade[157,202]. However, the suppression of low frequencies may have broader significance. Psychophysical studies of suppression, which typically use only low spatial frequency stimuli in order to consistently observe suppression, find that suppression lasts after the end of a saccade and into the subsequent fixation[113,202]. If the function of changes to spectral sensitivity was solely to suppress motion blur, one might expect for it to occur only during the saccade. However, there is evidence that perception is biased towards higher frequencies before, during, and after the eye movement[152,157,242]. An additional role of low-frequency suppression may be to enhance the recognition of objects embedded within natural scenes. This enhancement, while perhaps energetically costly, may serve to ensure that objects can be seen immediately before and after the saccade.

The temporal dynamics of spatial frequency processing were not addressed in the previous two chapters but, that too, appears to be modulated by saccades. Typically, temporal changes are investigated by perturbation experiments in which a test probe is presented at

various times relative to the eye movement. This approach has revealed that both perceptual and physiological suppression are typically strongest right at the start of saccades[109,113,202,241]. Our paradigm only involves a test probe near fixation onset, so comparisons to the other approach are limited. However, we can speak to the neural dynamics after the test probe is presented. This time period is particularly important because the purpose of a saccade is to bring a new image onto the retina. As discussed in the previous chapters, the beginning of the new fixation is crucial for the initial representation of the new visual image[38,48,51,52]. Thus, it would be advantageous to optimize visual processing at this critical time.

Both psychophysical and physiological evidence suggest that the visual system processes low spatial frequencies before high spatial frequencies, a phenomenon known as "coarse-to-fine" processing[334,362–365]. This effect is believed to occur very early in visual processing because the parvocellular system (higher SFs) generally has longer latencies than the low-frequency preferring magnocellular system[366]. A previous psychophysical study examined the effects of saccades on coarse-to-fine processing[236], but compared processing immediately after a saccade to processing 800 ms later– a time period several times longer than the average fixation during natural vision. To examine the effect of corollary discharge on the time course of visual processing immediately after the saccade, we utilized the decoders trained to distinguish between trials in which a stimulus was presented in or out of the receptive field using the full 80-ms response period at the highest contrast (see chapter 3). We then tested those decoders on all trials at lower contrasts, using spike counts collected in 30-ms windows in 1-ms steps from -150 to 150 ms after fixation onset. This approach demonstrates that at a low spatial frequency, there is a small increase in the time until the decoder reaches a threshold of 70% AUC (**Figure 14**)**.** However, the situation is reversed at a high spatial frequency -- the effect of a saccade is to increase the early availability of information relative to the simulated saccade. In both monkeys, the reduction in latency is correlated with spatial frequency.

This change in decoder performance dynamics suggests a change in the usual coarse-to-fine processing that occurs immediately after fixation onset. Saccades appear to increase both the response amplitude and the processing speed of higher spatial frequencies. This state-dependent change in coarse-to-fine processing may aid in the rapid recognition of objects against naturalistic backgrounds. Relevant to this point is the observation that figure-ground segmentation relies in part on differences in spatial frequency between figures, which are typically higher frequency, and the low-frequency background[367,368]. Gilad et al. report that microsaccades speed up figure-ground segmentation in primary visual cortex[233], an effect that may result from changes in coarse-to-fine dynamics. Presumably, this shift in coarse-to-fine dynamics aides in the rapid recognition and categorization of objects[244–255], as opposed to the categorization of scenes, which relies on low-frequency information[369]. A previous study found that, within the cycles of saccades and fixations, reaction times for object recognition were fastest when the object was presented immediately after the saccade, the same time the stimulus was presented in our experiment[243]. This rapid change in priority from high to low frequencies is also consistent with work suggesting that saccades promote segregation of objects at the beginning of new fixations.[357].

Future work will need to address the relationship between these frequency-dependent changes in visual processing and the visual reset in the spikes. This could be achieved by aligning the decoders to the first spikes of neurons, instead of the onset of fixation (and stimulus). While it is plausible that the concentration of spikes around 30-50 ms after fixation onset contributes to enhanced sensitivity at higher spatial frequencies, it is unclear if this is the case in our data as the reset in spiking occurs whether or not a stimulus appears in the receptive fields under study.

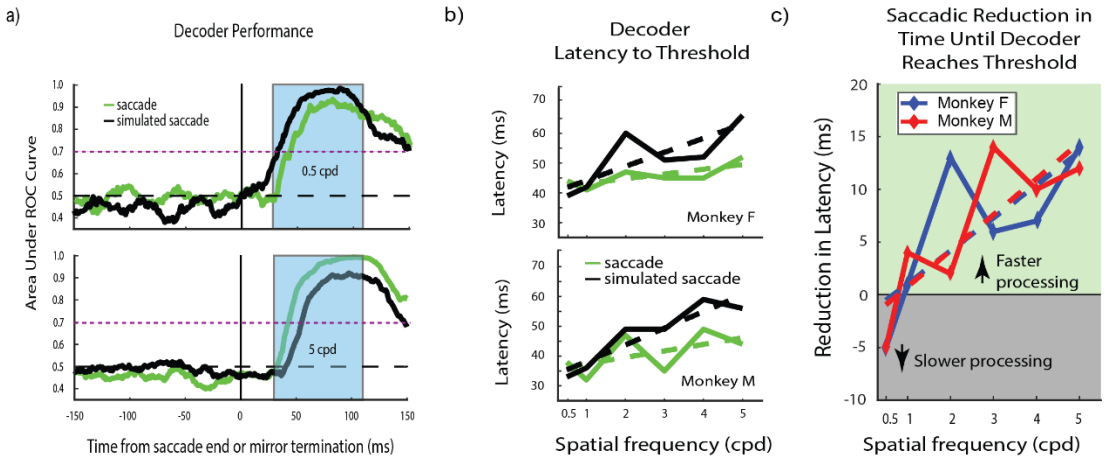

Figure 14: Saccades alter coarse-to-fine processing.

a) Saccades slow decoder performance at a low spatial frequency and speed performance at a high frequency. This effect is seen in the time to reach a threshold performance level **(b)** and is brought out by the difference in time-to-threshold on saccade and simulated-saccade trials **(c)**.

Neural Decoding: Choice Probability

Previous studies of either intra- or post-saccadic suppression did not simultaneously collect perceptual data. Therefore, the detection of a possible saccadic change in choice probability is novel and noteworthy. This result was unexpected, as there was little reason to believe that a uniform reduction in CP would occur independent of the stimulus. However, previous theoretical and experiment work have demonstrated that CP strongly depends on noise correlations, and that the chance of recording from a neuron with "true" large choice probability, meaning a large perceptual read-out weight, is very small [273,277,370,371]. Some authors have suggested that, despite this, choice probability measurements likely do inform about a neuron's relationship to perception[372]. In general, CP studies examine correlations between neural activity over very long time periods of enforced fixation, often seconds[295,298], as a noisy stimulus is presented. The durations of these trials are typically many times longer than a typical fixation, and higher choice probabilities are typically found later in the trial[295,297]. This suggests that much of the measured CP in early sensory areas reflects a decision processes in other cortical regions.

Feedback to V1 in particular begins almost as soon as the first spikes arrive[373], making it difficult to determine if CP values are truly causal or simply reflect feedback.

Despite the inherent difficulties in interpreting CP, theoretical work suggests that if the animal optimally reads out a stimulus for perception, the choice probability measurements and the neuronal sensitivity (measured as d', the difference in signal to noise ratio between in receptive field and out of receptive field trials) should be correlated[278]. We examined the relationship between choice probability and d' in both the saccade and simulated saccade conditions, and found that there was a significant correlation between d' (measured at the second highest contrast, to be near perceptual threshold) and choice probability in the simulated saccade condition, but not the saccade condition (**Figure 15**). There are several explanations for this. One explanation is simply that noise correlations are too low at fixation onset and the CP measurements, which are due to noise correlations, are simply noise. This argument is supported by the fact that the average CP fell to chance in the saccade condition. Another viewpoint is that the assumptions of the modeling framework which predicts a linear relationship between CP and d' are no longer valid in the saccade condition. The framework relies on the assumption of a linear readout of neuronal activity. If the read-out is sufficiently sparse and nonlinear in the saccade condition, one would expect the model prediction to fail. The results presented in this work as well as other recent research[127,189] suggest that neural activity is sparser and decorrelated following fixation onset. Future work which records from more neurons, and across multiple cortical areas, will be required to better understand the effects of saccades on the read-out of activity from V1. Our attempts to directly decode the animal's perceptual decisions were confounded by the use of different contrast levels, which were by far the most predictive variable of the animals' perception. The use of multiple contrast levels, with stimuli both inside and outside of the receptive fields, and with saccades and simulated saccades, led to 16-20 separate conditions per experimental session, leaving very few trials left for training decoders to predict perceptual decisions. Future work in this direction may be able to take into account varying levels of contrast and other covariates, such as the LFP signal, using generalized linear models[374,375].

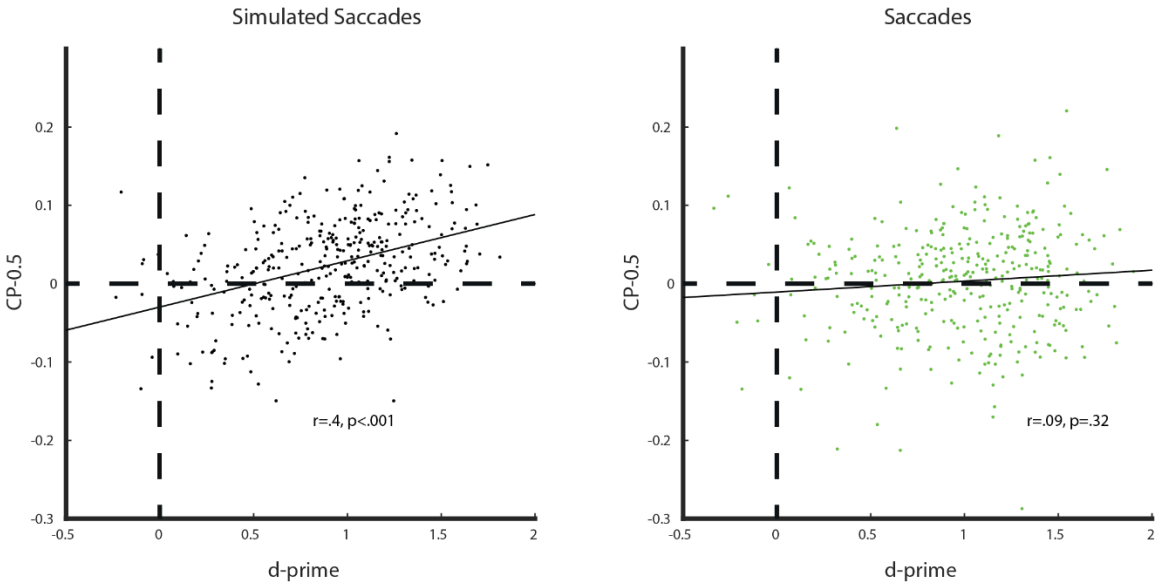

Figure 15: Test for optimal perceptual decision making.

CP and d' were significantly correlated for simulated saccade trials (r=.4, p<.001), as would be expected for a near-optimal linear readout. On saccade trials, this correlation is abolished (r=.09, p=.32), such that cells with high CP values are not as likely to have high d' values. This may indicate a change in the readout of information from V1 or alternatively is purely a consequence of reduced noise correlations in the saccade condition.

Noise Correlations and Population Coding

The observed changes in choice probability led us to examine changes in noise correlations between the saccade and simulated saccade conditions. During a saccade, average noise correlations are high and they fall to a minimum shortly after the start of fixation. This change is independent of spatial frequency. Similar results have been demonstrated with microsaccades using voltage-sensitive dye imaging[232]. In another study an increase in noise correlations was reported for trials in which the animal made a microsaccade during prolonged fixation, although this was explained as an effect of visual motion and treated as a nuisance to be removed before analysis, rather than a distinguishing feature of the neural code[376]. By controlling for visual motion, we were able to separate the early effect of increased noise correlations, which occurred primarily in neurons not responding to the visual stimulus from the later effect, which occurred primarily in responsive neurons.

The post-saccadic reduction in noise correlations suggests that saccades initiate a process which increases coding efficiency specifically in the critical time interval in which the initial formation of object representations occur[38,39,48,52]. Evidence also suggests that free viewing with saccades sparsens V1 responses[127,189], although the degree to which this is an extraretinal effect is somewhat unclear. Together these findings suggest that saccades act predictively to make visual processing temporarily less redundant at the start of new fixations, when novel visual input occurs.

Changes in noise correlations can also be interpreted as alterations in the ability of the cortical code to faithfully represent stimuli[41,345], or changes in the prioritization of information for behavior[40,377]. Depending on the structure of the system's noise, correlated variability between neurons can either increase or decrease the amount of information available for decoding, or even limit the maximum amount of information that can be encoded[45,49,276,279,346,347,378,379]. Pairwise correlations alone, even in the absence of higher-order correlations, can have substantial effects in large neuronal populations even if they are small[276,345]. In particular, noise correlations for neuron pairs with high signal correlation can be strongly detrimental to information transmission[41,345]. A transient decrease in noise correlations at fixation onset might enhance the coding fidelity of the novel input, or may reflect the prioritization of certain signals (e.g. higher spatial frequencies). As expected if the decrease in correlations improves information transmission, we demonstrated that the decrease in correlations was strongest in visually-responsive pairs with high signal correlations. The long timescale (~80 ms) decorrelation demonstrated in this work co-occurs with a transient increase in spike synchronization on short timescales (~5 ms)[55]. This may reflect a change in coding strategy for the start of fixations in which the neural code is more robust in some aspects and more efficient in others.

A particular category of correlations, known as "information-liming" or "differential" correlations, are patterns of correlated variability which occur tangential to the encoding axis, and thus cause large amounts of coding redundancy[315,347]. Unlike all other correlations, only

these can reduce the upper bound of information that the system can encode (as opposed to "information reducing" correlations which degrade the signal[347]). Interestingly, recent theoretical and experimental work has established a tight link between information-limiting correlations and choice probability (CP)[315,380]. This connection is seemingly paradoxical, as the interneuronal correlations which decrease the ability of the system to encode information are the same correlations which increase the likelihood of experimenters observing correlations between neural activity and behavioral choices. But this relationship implies that the decrease in CP found with saccades, compared to simulated saccades, is likely caused by a decrease in information-limiting correlations. In Chapter 3 we tested this indirectly by examining the relationship between the signal and noise correlations of neuron pairs. That analysis suggested that information-limiting correlations, as represented by the positive correlation between signal and noise correlation pairs[41], were reduced, particularly for visual neurons with high stimulus correlations (**Figure 12c**).

Alternative Perspectives: Attention And Bayesian Inference

As discussed in Chapters 1 and 2, there is a tight link between saccades and attentional allocation[151,381,382]. While evidence suggests that it is possible to allocate covert attention without preparing or executing an eye movement, there is also evidence for the "pre-motor" theory of attention[237]. The pre-motor theory posits that attention, at the most basic level, is the result of movement preparation towards the target of attention. Indeed, many previous studies of the effects of saccades on neural activity in V1, V2, and V4 have suggested that they are due to attention effects[54,100,104,105,116,154]. However, the number of phenomena which are labeled under the umbrella of attention is large and growing. There is a large literature on these different types: spatial attention, feature-based attention, and temporal attention have all been studied extensively. These effects are all closely related to eye movements and not totally separable from each other[383]. Furthermore, working memory is now called "internal attention" by some authors[40,384], and saccades have been linked to refreshing working memory[385].

Some researchers may prefer to explain the effects reported in this thesis as consequences of attentional allocation. The shift in latency would be explained as an effect of temporal attention allocated along with the saccade[54,100]. The shift in sensitivity might be viewed as a shift in feature-based attention. The frequency-independent effects, such as changes in noise correlations (which are often associated with attention[40,377]), could be interpreted as allocation of spatial attention towards the saccade target. However, there are reasons to doubt these classifications. For one, the animal is well-trained on the task and, even in the simulated saccade condition, knows when to expect at stimulus onset. So, one would expect similar temporal attention in both experimental conditions. Feature-based attention, on the other hand, is typically targeted towards the feature of interest, not specific spatial frequencies[196]. The animal was presented a Gabor of a given frequency on each day, and attention can be allocated to either low or high spatial frequencies, depending on task demands[196]. If the effects of saccades on sensitivity were due to enhanced feature-based attention, one might expect them to be specific for the frequency tested each day and performance would be enhanced across all spatial frequencies. Spatial attention is tightly linked with saccadic eye movements, however, in both conditions of our task, the animal should be allocating attention to both potential target locations on each trial. This is one of several reasons why we argue that the effects we observe are more likely due to corollary discharge. And, of course, these CD signals may interact with attention in various ways.

Another alternative explanation for our results lies within the framework of Bayesian inference. If the brain is Bayes-optimal, one would expect reduced sensitivity during the saccade (as demonstrated in standard experiments on saccadic suppression), as there is an increase in blur and/or internal system noise. A recent theory posited that saccadic suppression occurs because visual and motor areas share resources and the "noise" induced by motor commands is present in visual cortex[156]. Indeed, we find a large increase in noise during the saccade.

At fixation onset, a novel image is always expected. Thus, enhancement of processing at the start of fixations may be a result of the prior knowledge that fixation onsets bring about new stimuli to process. Additionally, recent work suggests that when a particular stimulus is expected, neuronal responses are suppressed[386]. Given the structure of natural scene stimuli, the brain would always expect the image following a new fixation to be biased towards low frequencies. Overall, there is little reason to think that the observations of this work contradict with the Bayesian perspective.

Micro- and Macro-circuit Mechanisms

As it appears that a corollary discharge signal plays a significant role in the effects of saccades on neurons in V1 at fixation onset, an important question is how a motor-related signal could lead to the broad reductions in pairwise correlations in synchrony across the network, as well as moving firing rates in opposite directions for low and high spatial frequencies. A hint at a possible explanation comes from the observation that increased interneuron activity is in general associated with a reduction in long-timescale noise correlations along with an increase in short-timescale synchronous spiking[387]. Interneuron activity is also critical for implementing sparse codes[388]. This suggests that many of the effects of active sensing in early visual cortex might be explained by distant brain regions exerting control over local interneurons in response to corollary discharges from the superior colliculus. Indeed, the observed increase in V1-V4 functional connectivity in the beta band supports a role for the "feedback CD" discussed in the introduction.

Sharp increases in noise correlations are associated with a sudden loss of driving input[356]. Thus, the intrasaccadic increase in correlated variability we observed could be due to strong suppression of the LGN by the superior colliculus during saccades. This conclusion would be parsimonious with other work that suggests that intrasaccadic suppression is targeted towards the magnocellular pathway in the LGN. However, LGN recordings (which did not use simulated saccades) around the time of saccades suggest that the suppression there is relatively weak[114,115]. Our observed effects thus may be a combination of CD inherited from the LGN[157,376],

"feedforward CD" which V1 receives modulatory input from the pulvinar[2,54,100,389] as well as the "feedback CD" discussed above.

We can only speculate, but recent rodent research suggests a specific local mechanism. Several labs have shown in mice that active sensing via locomotion reduces noise correlations in visual cortex and increases stimulus discriminability at higher spatial resolutions[390–392]. Locomotion also activates vasoactive intestinal peptide-expressing (VIP) inhibitory interneurons in V1 independent of visual input[393]. When VIP neurons are activated optogenetically, contrast sensitivity is enhanced[394]. Activating VIP neurons significantly alters the spatial frequency tuning of neurons in superficial layers of V1 – pyramidal cell tuning curves shift towards higher spatial frequencies[395]. This simple pathway that has been worked out based on the effects of locomotion in mouse V1 appears to have the properties required to account for many of the effects of active vision in macaque V1 – a behavior associated with active sensing shifts sensitivity towards higher spatial frequencies and it reduces noise correlations between V1 neurons. More recently, VIP neurons were proposed to control the time course of coarse-to-fine processing in mouse V1[362]. Even if the process documented in rodents does not occur in the primate brain, it is a clear demonstration of how a neuronal mechanism could account for the numerous effects of saccades in V1, an area critical for visual perception. Time will tell whether active vision via saccades causes a cascade of events in primates that is similar to locomotion in mice.

Concluding Remarks

The results presented in this work confirm that corollary discharge signals influence processing in primary visual cortex. They also expand on previous work by demonstrating that these signals influence the encoding of contrast in V1, in a way that parallels the animals' perceptual effects. These signals also provide useful information about the start of new fixations, and influence the neural population code in ways that likely enhance the ability of the system to encode visual information. It appears that these influences result from a shift in cortical dynamics such that different coding schemes are implemented before, during, and after each eye

movement**.** Ultimately, the changes driven by saccades optimize visual processing at the start of fixations in a way that likely enhances the recognition and categorization of objects in natural scenes.

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Illustrations were made, in part, using tools available at www.Biorender.com. A free stock image from www.rawpixel.com was slightly modified for use in Figure 1.