Mechanisms of attention in visual cortex and the amygdala

Jalal Kenji Baruni

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ABSTRACT

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Spatial attention enhances perception at specific locations in the visual field, measured behaviorally as improved task performance and faster reaction times. In visual cortex, neurons with receptive fields at attended locations display enhanced responses. This neural modulation is presumed to underlie the associated behavioral benefit, although the mechanisms linking sensory cortical modulation to perceptual enhancement remain unclear. In studies of spatial attention, experimentalists persuade animals to attend to particular locations by associating them with a higher probability or magnitude of reward. Notably, these manipulations alter in tandem both the absolute expectation of reward at a particular location, as well as the expectation of reward relative to other locations in the visual field. We reasoned that independently changing absolute and relative reward expectations could provide insight into the mechanisms of attention.

We trained monkeys to discriminate the orientation of two stimuli presented simultaneously in different hemifields while independently varying the reward magnitude associated with correct discrimination at each location. Behavioral measures of attention were controlled by the relative value of each location. By contrast, neurons in visual area V4 were consistently modulated by absolute reward value, exhibiting increased firing rates, increased gamma-band power, and decreased trial-to-trial variability whenever receptive field locations were associated with large rewards. Thus, neural modulation in V4 can be robustly dissociated from the perceptual benefits of spatial attention; performance could be enhanced without neural modulation, and neural activity could be modulated without substantial perceptual improvement.

These data challenge the notion that the perceptual benefits of spatial attention rely on increased signal-to-noise in V4. Instead, these benefits likely derive from downstream selection mechanisms.

In identifying brain areas involved with attention, a distinction is generally made between sensory areas like V4— where the representation of the visual field is modulated by attentional state— and attentional “source" areas, primarily in the oculomotor system, that determine and control the locus of attention. The amygdala, long recognized for its role in mediating emotional responses, may also play a role in the control of attention. The amygdala sends prominent feedback projections to visual cortex, and recent physiological studies demonstrate that amygdala neurons carry spatial signals sufficient to guide attention. To characterize the role of the amygdala in the control of attention, we recorded neural activity in the amygdala and V4 simultaneously during performance of the orientation discrimination task. In preliminary data analysis, we note two sets of findings. First, consistent with prior work, we found that amygdala neurons combine information about space and value. Rewards both contralateral and ipsilateral to amygdala neurons modulated responses, but contralateral rewards had a larger effect. Therefore, notably distinct from known attentional control sources in the oculomotor system, spatial-reward responses in the amygdala do not reflect the relative value of locations. Second, we found signatures of functional connectivity between the amygdala and V4 during task performance. Reward cue presentation was associated with elevated alpha and beta coherence, and attention to locations contralateral to the amygdala and inside the receptive field of V4 neurons was associated with elevated inter-area gamma coherence. These results suggest that the amygdala may serve a unique role in the control of spatial attention.

Together, these experiments contribute towards an understanding of the brain-to-behavior mechanisms linking neural activity in V4 and the amygdala to the dramatic perceptual and behavioral improvement associated with attention.

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Chapter 1. Introduction

From the torrent of visual information impinging on the retina, we are capable of perceiving and responding to only a limited subset. Visual attention refers to the filtering process, by which relevant aspects of the visual scene are readily perceived and irrelevant visual information discarded. The effects of directing attention to particular locations or features in the visual field are dramatic. Attended items are seen with higher contrast and spatial resolution (Carrasco et al., 2004; Yeshurun and Carrasco, 1998; but see Schneider and Komlos, 2008). Unattended visual stimuli, even when physically salient, can go entirely unnoticed (Simons and Chabris, 1999). In psychophysical tasks, at attended locations, performance is considerably higher, reactions markedly faster (Posner, 1980). These changes in behavior associated with attention are seen across sensory modalities, task design, and model organism, suggesting that attention is a general process by which certain stimuli gain preferential access to further processing and ultimately the control over behavior.

How do certain stimuli gain so much more leverage over perception than others? In the primate visual system, the neural correlates of spatial attention have been extensively investigated. When attention is directed into the receptive fields (RF) of neurons in visual cortex, visual responses are modulated in a stereotyped fashion. Firing rates are increased (Moran and Desimone, 1985; Motter, 1993), trial-to-trial variability (Mitchell et al., 2007) and inter-neuronal correlations are decreased (Cohen and Maunsell, 2009; Mitchell et al., 2009), and gamma-band power and synchronization are increased (Fries et al., 2001; Gregoriou et al., 2009a; Taylor et al., 2005; Womelsdorf et al., 2006). Each of these neural correlates may contribute to the

perceptual enhancement associated with attention, but the mechanisms linking neural modulation in sensory cortex to the associated behavioral benefit remain unclear.

This thesis is largely directed towards elucidating these brain-to-behavior mechanisms. We begin, in this Introduction, by describing the general mechanisms that have been proposed to link sensory cortical modulation with enhanced perception and then review the evidence in support of each. We next consider two phenomena closely related to attention— reward and arousal— which are associated with strikingly similar modulation of sensory cortex (Harris and Thiele, 2011; Maunsell, 2004). Because of the underlying similarity in cortical state modulation in differing behavioral contexts, a comparison of these processes is potentially informative about mechanistic links between sensory cortical modulation and behavior. Finally, I describe the causal evidence linking visual area V4 to attention. Among brain areas in sensory cortex, V4 is perhaps the most studied in the context of attention, and is also the focus of the present study.

1.1 Mechanisms of attention

Three general mechanisms link neuronal modulation to the associated perceptual benefit of attention: (i) signal enhancement, (ii) noise reduction, and (iii) ‘efficient selection' (Itthipuripat et al., 2014; Pestilli et al., 2011; Serences, 2011; Serences and Kastner, 2014). Signal enhancement and noise reduction refer to increases in the quality and fidelity of representation in sensory cortex. Efficient selection refers to the preferential selection of relevant sensory information by downstream decision processes. In other words, it refers to selectivity in the ‘readout’ of sensory cortex, rather than the representation in sensory cortex. These mechanisms are not mutually exclusive. Each may contribute to the perceptual benefit of attention, with weights that may be task-dependent.

While considerable progress has been made in describing the neural correlates of attention, elucidating the mechanisms by which these correlates confer perceptual enhancement has proven substantially more difficult. One key issue is that it is exceedingly hard to experimentally access the process by which sensory cortex is readout in support of a perceptual decision. Thus, efficient selection as a mechanism of attention is difficult to directly observe, and evidence for selection tends to rely on the insufficiency of signal-to-noise mechanisms. Moreover, because the details of readout are unknown, linking neural correlates of attention to their behavioral consequence generally depends upon an assumed readout model (like signal detection theory) that links neuronal activity to performance of some idealized observer. These are substantial impediments to disambiguating among candidate mechanisms of attention.

Signal enhancement

The disproportionate leverage of attended locations on behavior is often described as resulting from a competition for representation across sensory cortex. The central notion is that attentional 'source' areas in frontal and parietal cortices bias competition for representation in sensory areas towards attended locations. In this manner, cognitive factors such as task goals can serve to boost the sensory representation of behaviorally relevant locations at the expense of behaviorally irrelevant locations. This idea is strongly related to "limited resource" and "early selection" accounts of attention, which posit that limited representational bandwidth in sensory cortex require selective processes like attention, to bias representation towards relevant stimuli (Broadbent, 1958; Desimone and Duncan, 1995).

These ideas have received extensive support in the experimental literature. Specifically, in the primate model of visual attention, researchers consistently report enhancement of neural responses at attended locations (Moran and Desimone, 1985; Motter, 1993; Reynolds and Chelazzi, 2004). This robust neural correlate of attention, on its face, supports the competitive model. In sensory cortex, visual information at attended locations is encoded with more spikes (which is presumed tantamount to more signal), and the magnitude of this effect grows as visual information ascends the cortical hierarchy (Maunsell and Cook, 2002).

Noise reduction

Several studies have linked the behavioral benefits of attention with decreased noise in sensory representations. When attention is directed into the RF of V4 neurons, both trial-to-trial variability of individual neurons (Mitchell et al., 2007) and variability shared across neurons (i.e.

noise correlations) are reduced (Cohen and Maunsell, 2009; Mitchell et al., 2009; but see Ruff and Cohen, 2014).

One compelling experiment suggests that decreased noise correlations— more than increases in firing rate— contribute to the perceptual benefits of attention (Cohen and Maunsell, 2009). In order to arrive at this conclusion, the authors began by considering neural activity on each trial as a point in a high-dimensional space, where each dimension gives the response of a simultaneously recorded neuron. Because monkeys were tasked with detecting a change in orientation of serially presented Gabor stimuli, the authors propose that task performance might depend upon the extent to which the neural population discriminates between the penultimate stimulus and the final, 'changed' stimulus. To quantify this effect, the authors define a 'discrimination axis' that connects the mean responses to penultimate stimuli and changed stimuli, and then project responses from individual trials onto this axis. Consistent with their hypothesis, they find that behavioral performance and neural discriminability are strongly correlated across sessions. Having thus validated their model, Cohen and Maunsell probe the role of firing rate, trial-to-trial variability, and noise correlations in conferring perceptual benefits by separately simulating population responses with each feature of attentional modulation and calculating discriminabilities along the discrimination axis. Using this method, they find that noise correlations have dramatically larger impacts on discriminability than changes in either firing rate or trial-to-trial variability.

As noted above, a key challenge in determining which features of neuronal modulation are important for behavior is that this inference tends to be model-dependent. In this case, Cohen and Maunsell assume that discriminability along the discrimination axis determines perceptual sensitivity. This readout model is certainly reasonable and, moreover, it is strongly predictive of

session-to-session variability in behavior. Nevertheless, it is interesting to consider how the assumed model might affect their conclusions. Pairwise noise correlations decrease discriminability when neurons have similar tuning (positive signal correlation), but increase discriminability when neurons have dissimilar tuning (negative signal correlation) (Abbott and Dayan, 1999; Averbeck et al., 2006). Thus, the relative impact of noise correlations on discriminability should depend on the extent to which neurons share tuning for penultimate versus changed stimuli. As noted by Cohen and Maunsell, 92% of units fire more spikes in response to the 'changed' stimulus, presumably because of adaptation to the serially presented Gabor. In other contexts, where selectivity across stimuli is more balanced, it is unclear whether decreased noise correlations would provide a similarly large increase in discriminability.

Efficient selection

Evidence from contrast discrimination in humans

Seminal studies investigating the role of 'efficient selection' as a mechanism of attention have employed contrast discrimination tasks. In a contrast discrimination task, subjects are tasked with detecting small changes in the contrast of a visual stimulus. In visual cortex, firing rates increase with luminance contrast (Sclar et al., 1990), a relationship called the contrast response function (CRF). Signal detection theory provides a plausible linkage between CRFs and behavioral sensitivity to contrast increments (Boynton et al., 1999). For an ideal observer, the ability to discriminate contrast increments depends upon two factors: the difference in mean rate across contrasts and the rate variability associated with each contrast. Therefore, increasing the slope of the CRF or decreasing the trial-to-trial variability of contrast responses should lead to enhanced behavioral sensitivity, as measured by decreased discrimination thresholds.

With attention, contrast discrimination thresholds are decreased (Cameron et al., 2002; Lee et al., 1999). However, when examined with functional magnetic resonance imaging (fMRI), attention induces additive shifts, rather than multiplicative gain, of CRFs (Buracas and Boynton, 2007; Pestilli et al., 2011). Thus, response enhancement (being additive) does not account for the perceptual benefit of attention in contrast discrimination tasks (Pestilli et al., 2011). Because increased signal-to-noise in sensory representation cannot account for behavior, these data effectively argue that 'efficient selection' may be the critical mechanism linking neuronal modulation to the perceptual benefit of attention.

To explore whether additive shifts of CRFs could account for enhanced behavioral sensitivity via an 'efficient selection' mechanism, Pestilli et al defined a readout model in which the weights of individual sensory inputs are exponentially related to their magnitude. With large exponents, this model is effectively winner-take-all, and the largest sensory responses dominate downstream decision processes. Therefore, in this model, additive effects of attention serve to boost the leverage of relevant sensory signals on downstream decisions. This idea implies a startlingly different interpretation for the response enhancement frequently observed in sensory cortex. Rather than signal enhancement, this account suggests that elevated firing rates at attended locations might function as a continuous relevance tag, used to bias selection of relevant neural populations by downstream processes.

A key complication in the interpretation of contrast discrimination tasks is that CRF modulation is not consistent across studies. Whereas fMRI studies tend to show additive shifts of CRFs with attention, when neural activity is measured using evoked potentials, CRF modulation is multiplicative (Itthipuripat et al., 2014; Di Russo et al., 2001). Because the interpretation of these studies depends critically on the nature of CRF modulation, evoked potential data point to

signal enhancement (rather than selection) as the dominant mechanism of attention (Itthipuripat et al., 2014). The effect of attention on CRFs has also been examined in single units in primate visual cortex— here, as well, results are mixed. Attentional modulation of single unit CRFs has been characterized as multiplicative gain (Lee and Maunsell, 2010), contrast gain (referring to leftward shifts of CRFs, as in Martinez-Trujillo and Treue, 2002; Reynolds et al., 2000), or less frequently as additive shifts (Pooresmaeili et al., 2010; Thiele et al., 2009; Williford and Maunsell, 2006). Certainly, baseline effects (which effectively correspond to modulation at 0% contrast) are frequently observed (Luck et al., 1997; Luo and Maunsell, 2015), which is inconsistent with purely multiplicative accounts. Notably, when goodness of fit values for various models of CRF modulation are compared, differences are small (Williford and Maunsell, 2006).

Several key insights into inconsistent CRF modulation come from the normalization model of attention (Lee and Maunsell, 2009; Reynolds and Heeger, 2009). One key prediction of normalization is that the nature of CRF modulation should depend on the relative sizes of visual stimuli and the attention field (Reynolds and Heeger, 2009), which has since been experimentally verified (Herrmann et al., 2010). Interestingly, the normalization model also predicts that neurons well-tuned to the stimulus will display contrast gain, neurons poorly-tuned to the stimulus will show response gain, and the average of both effects (as may occur in fMRI) looks additive (Hara et al., 2014). Nevertheless, it is not clear that these insights fully explain the discrepant findings, and thus the evidence bearing on attentional mechanisms from contrast discrimination tasks is largely equivocal.

Evidence from primate single-unit physiology

Perhaps the first physiological data arguing for the insufficiency of signal-to-noise based mechanisms of attention came from a comparison of focal and distributed attention in V1 (Chen and Seidemann, 2012). Chen and Seidemann trained monkeys to detect an oriented stimulus at one of four locations. On some trials, monkeys were cued to the location where the target would appear. On other trials, the target could appear at any of the four locations. This yielded three attentional states with respect to a particular RF: focal attention into the RF, focal attention out of the RF, and a condition in which attention was distributed across all four locations. In this task, performance is higher in focal attention trials than in distributed attention trials. However, neuronal responses measured using voltage-sensitive dye imaging (VSDI) are indistinguishable in focal attention and distributed attention trials. To the extent that VSDI reflects firing rate, this finding is inconsistent with signal-to-noise based mechanisms of attention that depend upon the quality of sensory representation in V1.

Similarly inconsistent with signal-to-noise based accounts of attention are the superior colliculus inactivation experiments of Zenon and Krauzlis (Zénon and Krauzlis, 2012). Following inactivation of superior colliculus, monkeys trained to perform a motion change detection task exhibit decreased behavioral sensitivity (decreased hit rates, increased false alarms) at locations corresponding the response fields of inactivated neurons. Strikingly, despite this behavioral decrement, neural correlates of attention were unchanged in visual areas MT and MST, suggesting that modulation of extrastriate cortex does not, by necessity, confer perceptual benefits. These two results thus suggest a critical role for downstream readout in the mechanisms of attention.

One interesting recent experiment (Luo and Maunsell, 2015) has been interpreted as demonstrating signal-to-noise based mechanisms of attention in V4 (Buschman, 2015), but, in fact, does not bear on the signal-to-noise and selection mechanisms considered here. In this experiment, Luo and Maunsell address an interesting and under-appreciated confound in the standard detection tasks used to study attention. In such tasks, higher performance at attended locations could be driven by increased discriminability of detection targets (sensitivity) or a decreased threshold for responding to cued locations (bias or criterion). Luo and Maunsell artfully dissociate these two signal detection theory formalisms and demonstrate that changes in behavioral sensitivity but not criterion are associated with neural modulation in V4. This is an important result, especially because it invites a dissection of the set of behaviors and neural activity generally treated as a monolithic attention process. It is important to note, however, that the claim that increases in behavioral discriminability, but not criterion shifts, are associated with V4 neural modulation is not equivalent to the claim that V4 neural modulation functions by enhancing the discriminability of sensory representations.

To clarify the interpretation of this study in relation to signal-to-noise and selection-based mechanisms of attention, two key points are instructive. First, because detection targets and non-targets are associated with different actions and rewards, the authors examine neural activity in an epoch that precedes the appearance of target and non-target stimuli. Thus, neural sensitivity to targets is not measured. Rather, ‘sensitivity’ refers to the ability for the animal’s behavior to discriminate targets from distracters— not the neurons. Second, models of efficient selection (e.g. Pestilli et al., 2011) would produce a similar pattern of results. When V4 responses are enhanced (as in sensitivity sessions), efficient selection would predict that more modulated neurons would have greater leverage on readout, yielding higher behavioral sensitivity at

associated locations. By contrast, in criterion sessions, the absence of neural modulation across locations would yield no benefit to behavioral sensitivity. Therefore, despite the overlapping nomenclature, this experiment does not distinguish between signal-to-noise and selection-based mechanisms of attention.

Trial-to-trial correlations between visual cortical modulation and attentional behavior are also occasionally interpreted as evidence in favor of signal-to-noise based mechanisms of attention. Such correlations do exist in visual area V4 (Cohen and Maunsell, 2010; Womelsdorf et al., 2006). However, even if these correlations are taken as evidence that V4 modulation causally contributes to performance, they do not indicate the mechanism of causal contribution. Trial-to-trial correlations are similarly consistent with the behavioral benefit of attention being based upon either improved signal-to-noise, or being based upon a downstream selection mechanism. For example, consider a population of neurons representing the stimulus at a location A. On those trials when neural modulation is highest, performance is increased at location A (Cohen and Maunsell, 2010). Enhanced neural activity could contribute to performance by increasing signal to noise in the representation of location A. Alternatively, enhanced neural activity could contribute to performance by biasing selection of location A by downstream processes. Assuming trial-to-trial fluctuations are not correlated across locations (as demonstrated for locations in opposite hemifields, Cohen and Maunsell, 2010), both mechanistic models (signal-to-noise and selection) would lead to enhanced performance at location A when firing rates were increased at location A.

1.2 Reward and attention

In 2004, at the dawn of neuroeconomics, John Maunsell wrote an influential review comparing the then-distinct literatures of attention and reward expectation (Maunsell, 2004). His central argument was that although reward expectation and attention are potentially psychologically distinct phenomenon and generally studied as such, they are largely confounded in experimental neuroscience. In studies of spatial attention, experimentalists persuade animals to attend to ‘cued' locations by associating them with a higher probability or magnitude of reward. These reward manipulations are largely indistinguishable from those used to study reward processing (e.g. Lauwereyns et al., 2002; Platt and Glimcher, 1999). Thus, neural correlates of attention could equivalently be characterized as neural correlates of reward and vice versa.

Despite no lack of investigation over the last decade, reward and attention remain largely parallel nomenclatures for describing the influence of cognitive state on sensory processing and perceptual decision making. To some extent, this reflects the challenge of instantiating higher-level cognition in experimental animals. However, it also remains a strong possibility that matched components of the broad class of phenomena labeled as ‘attention' and 'reward expectation’ refer to the same underlying neural processes (Maunsell, 2004; Stănişor et al., 2013).

To clarify the relationship between reward and attention, it is useful to distinguish three categories of experimental configurations related to reward expectation and attention. In the first category, rewards are used to define task relevance. For example, in a standard attention task, rewards are used to instruct monkeys which among several locations or features are task-relevant. These manipulations are the paradigmatic example of the confound between selective

attention and reward expectation. In the second category, rewards are varied across trials, such that overall reward expectations change without specification of behaviorally relevant locations or features within a trial. This category likely bears strong resemblance to what the attention literature refers to as vigilance (Boudreau et al., 2006) or 'cognitive effort' (Spitzer et al., 1988), and is also perhaps related to temporal attention (Ghose and Maunsell, 2002; Nobre and Rohenkohl, 2014). In the third group, rewards are associated with task-irrelevant stimuli (distracters). These three categories are not exhaustive or mutually exclusive, but are useful for facilitating comparisons between the neural correlates of reward expectation and attention. We consider aspects of each category below, focusing on the links between reward expectation and attention, and highlighting instances where experiments framed in terms of reward expectation enrich our understanding of cognitive state modulation.

Rewards that define task relevance

In most attention tasks, one location is associated with a higher magnitude or probability of reward (labeled as the 'target' or 'attend-in' location) while another location is associated with a lower magnitude or probability of reward (labeled as the 'distracter' or 'attend-out' location). Interestingly, this standard attention task configuration manipulates in tandem two distinct forms of reward expectation. At attended locations, both the absolute expectation of reward is increased, as well as the expectation of reward relative to other locations in the visual field. Although the distinction between absolute and relative reward expectations may appear pedantic, it is potentially important for understanding the mechanisms by which top-down modulation of sensory cortex influences perception. First, note that absolute value and relative value are not inescapably correlated. They can be dissociated by a systematic manipulation of reward

expectation across spatial locations. Second, note that neural modulation reflecting the absolute value of a given location does not require competition for representation between visual stimuli. Relative value modulations, of course, do require some sort of comparative mechanism. Therefore, determining whether brain areas show modulation by relative value or absolute value may help unravel the seat of competitive interactions thought to underlie the behavioral benefits of attention.

Brain areas involved with action selection, value-based decision-making, and attentional control reflect relative, rather than absolute values. This has been most intently studied in the context of action values (reward associated with particular actions) in the lateral intraparietal area (LIP), a sensorimotor region involved with the control of eye movements (Barash et al., 1991), spatial attention (Bisley and Goldberg, 2003; Bushnell et al., 1981), and perceptual decision making (Gold and Shadlen, 2007; Roitman and Shadlen, 2002). In LIP, increasing the reward associated with non-RF choice targets decreases firing rates, a hallmark of relative value (Dorris and Glimcher, 2004; Louie et al., 2011; Platt and Glimcher, 1999; Rorie et al., 2010; Sugrue et al., 2004, but see Bendiksby and Platt, 2006; Mirpour and Bisley, 2012). Although systematic manipulations of relative and absolute reward have mostly been restricted to LIP studies, these effects are likely present throughout the oculomotor system. For example, results suggestive of relative value modulation have also been reported in the frontal eye fields (Leon and Shadlen, 1999) and the superior colliculus (Basso and Wurtz, 1997). Beyond the oculomotor system, relative value modulation is also observed in premotor cortex when monkeys choose among reach targets (Pastor-Bernier and Cisek, 2011). Relative value modulation in all of these brain areas has been interpreted as reflecting competition between action plans and attentional

priorities, as implemented via normalization or lateral inhibition (Bisley and Goldberg, 2010; Cisek, 2006; Louie et al., 2011).

In sensory cortex, only one prior physiology study has investigated whether absolute or relative value better accounts for neural modulation (Stănişor et al., 2013). In this experiment, two saccade targets were associated with varying reward while animals performed a mental curve tracing task through the receptive fields of V1 neurons under study. Relative (and not absolute) reward accounted for firing rate modulation in V1. This interesting and seminal study therefore argues that selective attention and relative value modulation constitute a unitary process reaching back to V1. However, the nature of reward modulation remains unclear for visual area V4, one of the most frequently studied cortical areas in visual attention, as well as other areas of visual cortex.

Rewards that define overall reward expectancy

In addition to varying across the visual field, reward can also vary across trials. For example, doubling the potential rewards associated with all task-relevant locations increases both the absolute reward at each location as well as the overall, average value of a trial. Increasing the average trial value leads to a suite of behavioral changes, including increased anticipatory licking (Cromwell and Schultz, 2003; Paton et al., 2006), higher trial completion rates (Leon and Shadlen, 1999; Roesch and Olson, 2004), and faster reaction times (Roesch and Olson, 2004), suggesting that non-spatial reward expectation modulates animals' motivational state. The neural correlates of this modulation have been examined extensively outside of sensory cortex. In visual cortex, however, this type of modulation has only been examined in V1 with one report of

reward timing signals in the rodent (Shuler and Bear, 2006) and another demonstrating no effect of average trial value in the primate (Stănişor et al., 2013).

Modulation of average trial value (or overall reward expectancy) may share neural mechanisms with the modulation of 'cognitive effort' or 'concentration,' as invoked via manipulations of task difficulty (Boudreau et al., 2006; Ruff and Cohen, 2014b; Spitzer et al., 1988). This relationship between nonspatial reward expectation and cognitive effort manipulations is notably different from the relationship between spatial attention and relative/absolute value manipulations. In this case, the experimental manipulations differ, potentially allowing comparison of the effects of reward-related and attention-related cognitive states. Given the limited and heterogeneous data available, however, this comparison is perhaps not yet instructive.

One key challenge in studying the effect of task difficulty is that these manipulations can inspire divergent behavioral strategies (Boudreau et al., 2006). In a representative task difficulty experiment, animals are trained to detect an orientation change that can occur at one of two locations, with 80% probability at the cued (attended) location, and 20% probability at the uncued location. Task difficulty is varied in blocks, with more difficult blocks characterized by smaller orientation changes. There are two places where uncontrolled differences in behavioral strategy can emerge. First, the orientation of detection targets differs in a predictable fashion between easy and difficult blocks. Thus, some monkeys may employ a feature attention strategy that differs across blocks, confounding neural and behavioral effects of task difficulty with those related to feature attention. Second, when task difficulty is increased, some monkeys respond by further biasing spatial attention to the cued location, while others do not (Boudreau et al., 2006). These challenges may explain the inconsistent results obtained with task difficulty

manipulations. In the first investigation of task difficulty, Spitzer et al. noted increased V4 firing rates in more difficult blocks, and also that orientation tuning bandwidths decreased (Spitzer et al., 1988). These changes to tuning bandwidth have largely not been repeated in attentional contexts outside of feature attention. In a subsequent experiment, Boudreau and Maunsell observed increased firing rates at the cued location and between-monkey differences in the direction of modulation at the uncued location in more difficult blocks (Boudreau et al., 2006). Recently, Ruff and Cohen observed no changes in firing rate, but rather decreased noise correlations in more difficult blocks (Ruff and Cohen, 2014b).

Two types of experiments may prove useful in clarifying the neural and behavioral consequence of motivational state. First, modulation of overall reward expectation might be used to influence motivational state without giving purchase to differential feature attention strategies. When the same task is performed, but the stakes are elevated, no change in feature attention strategy is adaptive. Second, combining overall reward expectation or task difficulty manipulations with 'divided' attention tasks in which all locations are equally task-relevant may limit uncontrolled shifts in spatial attention.

Rewards that are task-irrelevant

Classically, the control of attention is categorized as being either top-down or bottom-up, or equivalently endogenous or exogenous. Top-down, or endogenous, attention refers to the voluntary allocation of attention according to internal goals. Bottom-up, or exogenous, attention refers to the reflexive allocation of attention to physically salient stimuli. Most commonly, reward manipulations are used to define task relevance, and are thought of as invoking top-down attention. However, rewards can also be associated with task-irrelevant distracters. For example,

locations and stimuli formerly associated with reward continue to draw attention, even when task-irrelevant (Bourgeois et al., 2015; Chelazzi et al., 2014; Hickey et al., 2010). This form of attentional control, often called value-driven attentional capture (Anderson et al., 2011a), challenges the dichotomy of top-down and bottom-up attention (Awh et al., 2012). Value-driven attentional capture does not reflect task goals, but also does not depend on the physical properties of visual stimuli. It is internally-driven and yet reflexive. Thus, these reward manipulations argue for an additional category of attentional control (Awh et al., 2012), one whose importance for attentive vision and underlying neural mechanisms remain relatively unexplored.

One seminal physiological study has explored the neural correlates of this type of reward modulation (Peck et al., 2009). Peck et al. trained monkeys to perform a saccade task, in which a reward cue indicated whether a trial would be rewarded, but did not specify the saccade required to obtain reward. Thus, reward cues defined the overall reward expectancy of a trial, but the spatial location of reward cues was task-irrelevant. Nevertheless, cues indicating reward attracted spatial attention, and cues indicating no reward repulsed attention, as indexed via saccade metrics. These spatial attention shifts were reflected in LIP, with higher firing rates observed when RF cues signaled reward rather than no reward. These data argue that reward contingencies that define task relevance and non-task relevant attentional capture drive similar modulation in LIP. In other brain areas, including sensory cortex, the neural mechanisms of this form of attentional control have not been explored.

Negative reinforcers that define task relevance.

Task relevance is most often defined by reward contingencies, but can also be defined by punishment contingencies. Thus, punishment expectation might be used to distinguish reward

expectation from spatial attention. Neurons similarly modulated by positive and negative reinforcement expectations are described as coding salience, rather than reward or punishment. In parietal cortex— although perhaps not in LIP (Newsome et al., 2013)— visual cues indicating more intense reinforcement of either valence are associated with higher firing rates (Leathers and Olson, 2012), suggesting that LIP is modulated by salience, rather than reward expectation. In visual cortex, this issue has not been examined. Experiments from ferret primary auditory cortex, however, suggest that sensory cortex may be differentially modulated by task relevant stimuli defined by reward and punishment (David et al., 2012).

1.3 Pupil-linked arousal

The pupil is primarily responsive to luminance and depth of focus. However, investigators have long observed that pupil size also indexes internal states, likely reflecting the control of the pupil by the autonomic nervous system. Sympathetic activation increases pupil size, and parasympathetic activation decreases pupil size. Consequently, 'high-arousal' states are associated with more dilated pupils. For example, in humans, emotionally arousing images whether pleasant or unpleasant (Bradley et al., 2013), challenging mental arithmetic (Hess and Polt, 1964), and working memory load (Kahneman and Beatty, 1966) are all associated with larger pupil diameters.

The neural correlates of pupil-linked arousal in sensory cortex have recently been the subject of a flurry of investigation in the mouse. Head-fixed mice cycle through various behavioral states, characterized by a presently-expanding taxonomy. It has long been appreciated that mice sleep and awake. Within wakefulness, however, investigators have recently come to appreciate various substates of (or alternatively continuous fluctuations in) arousal, with higher arousal states indexed by increased pupil diameters (Mcginley et al., 2015; Reimer et al., 2014; Vinck et al., 2015) and active exploratory behavior like whisking and locomotion (Bennett et al., 2013; Niell and Stryker, 2010; Polack et al., 2013; Poulet and Petersen, 2008). Strikingly, all of the transitions to higher arousal states have broadly similar effects on sensory cortex. Higher arousal, whether indexed by wakefulness, pupil size, or active exploration tends to drive a similar suite of changes across sensory cortex, which include: increases in evoked firing rates, decreases in trial-to-trial variability, decreases in noise correlations, decreases in low frequency power in the LFP, and increases gamma-band power in the LFP (McGinley et al., 2015).

It has not escaped notice, especially among rodent physiologists, that the neural correlates of arousal in the rodent bear striking resemblance to correlates of spatial attention in the monkey (Harris and Thiele, 2011; McGinley et al., 2015). The set of changes associated with the two processes are virtually identical— all above-enumerated correlates of arousal are also seen with selective attention. This similarity suggests that top-down modulation of cortical columns may be a stereotyped process, employed both by selective/attentive processes and global arousal processes.

One key difference between attention and arousal is the distribution of modulation across the cortical surface. Arousal is global, leading to a suite of neuronal effects across cortex. By contrast, spatial attention is selective, leading to neuronal modulation restricted to specific populations of neurons involved with representing relevant portions of the visual scene. Given this difference, it would be hugely informative to understand how spatial attention and arousal differentially (or similarly) affect perception and behavior. The perceptual benefits associated with spatial attention are dramatic (Carrasco, 2014). If one accepts the equivalence of arousal and attention effects on modulated regions of cortex, a comparison of the associated behavior in psychophysical tasks would indicate whether and how the perceptual benefit of 'activated columns' depends on their distribution across the cortical surface. This would potentially provide a strong constraint on the mechanisms by which top-down processes influence perception.

The relationship between arousal and performance is complex. Generally, one of two patterns is observed. Either performance increases monotonically with arousal, or performance is an inverted U-shaped function of arousal. This latter relationship (dubbed the Yerkes Dodson Law) was first induced from a foundational experiment in which mice were trained to choose the brighter of two achromatic chambers (Yerkes and Dodson, 1908). Errors were penalized with

shock. Two interesting observations were made. First, for any given level of task difficulty, learning rate was an inverted U-shaped function of shock intensity. Second, the optimal shock intensity decreased for more difficult tasks. This pattern of results has been replicated extensively (Broadhurst, 1959; Ebitz et al., 2014; Mcginley et al., 2015), although it is far from universal (Bennett et al., 2013; Kristjansson et al., 2009). Presumably, in addition to task difficulty, the nature of the observed relationship between arousal and performance depends upon the range and density of arousal sampling, as well as perhaps the means (including valence of reinforcement) by which arousal is manipulated.

In the mouse, two recent studies have probed the relationship between arousal and performance, while simultaneously monitoring neural activity in sensory cortex. In a visual discrimination task, mice were trained to detect the appearance of full-field sinusoidal gratings (Bennett et al., 2013). During locomotion (a high arousal state), visual responses in V1 were larger and more reliable, as reported elsewhere (Niell and Stryker, 2010; Polack et al., 2013), and this neural modulation was associated with elevated detection performance. By contrast, in an auditory detection task where mice were trained to detect pure tones in embedded in complex noise stimuli (Mcginley et al., 2015), mice exhibit the Yerkes-Dodson relationship, showing enhanced behavior (as quantified by hit rate, lick latency, d') at intermediate levels of arousal (as indexed by pupil diameter). Interestingly, in this task, neural modulation in auditory cortex was also maximal at intermediate levels of arousal, leaving open the possibility that the relationship between sensory cortical modulation and performance is, in fact, always monotonic.

Ideally, to compare the effects of arousal and attention on neural activity and behavior, both processes would be instantiated in the same animals and tasks. Thus far, this has proved difficult, in part because of the still-limited behavioral repertoire of mice. While many labs are

currently developing selective attention paradigms in mice, most such paradigms instruct attentional allocation to entire sensory modalities (e.g. Wimmer et al., 2015), rather than particular regions or features of the visual scene as in primate visual attention. In the monkey, attentional paradigms are readily trained, but it is unclear whether state changes in arousal in primates are equivalent to those in the mouse. Laboratory macaques housed with 12-hour light/dark cycles nap infrequently, concentrating their sleep in darkness (Rachalski et al., 2014). By contrast, mice and rats cycle between sleep and wake over 100 times per day, with the mean sleep epoch lasting under 10 minutes (Campbell and Tobler, 1984; Van Twyver, 1969). These frequent transitions between sleep, waking, and arousal substates of waking make state changes especially accessible in the rodent, but also perhaps less readily comparable to the primate.

In primate sensory cortex, the neuronal correlates of arousal have received only sparse investigation. Several early studies in cats and monkeys demonstrated higher evoked responses in cat and monkey sensory cortex during waking epochs as compared to sleep (Evarts, 1963; Gross et al., 1972; Gücer, 1979; Livingstone and Hubel, 1981). Within waking, pupil-linked arousal has been induced via reward expectation (Kennerley and Wallis, 2009; Varazzani et al., 2015) or salient visual or auditory stimuli (Wang et al., 2014), but the associated modulation in sensory cortex has not been examined. However, many processes investigated in sensory cortex, especially "task difficulty" of perceptual decision-making tasks, may recruit similar mechanisms (Hess and Polt, 1964; Kahneman and Beatty, 1966). Generally, more difficult blocks of trials are associated with higher firing rates (Spitzer et al., 1988), but these effects may depend on behavioral strategy (Boudreau et al., 2006), and are not always observed (Ruff and Cohen, 2014b). Interestingly, pupil modulation during task difficulty manipulations in the primate has

not been reported — it would be interesting to find out whether the pupil accounted for some of the variance in firing rate effects.

The pupil is a phenomenally accessible measure that appears to correlate with arousal, but a great deal remains unknown about what precisely pupil diameter reflects. In monkeys, pupil diameters are strongly correlated with activity in the locus coeruleus (LC) (Rajkowski et al., 1993). This has led many to use pupil diameters as a proxy for LC activity and noradrenergic tone in cortex, despite the fact that no known anatomical pathway directly links the locus coeruleus to pupillary control (Aston-Jones and Cohen, 2005) and many brain areas are presumably correlated with pupil-linked arousal. For example, recent evidence suggests that stimulation of the superior colliculus— a brain area more often associated with orienting attention, rather than global arousal— drives pupil dilatation (Wang et al., 2012). These qualifiers challenge a facile association of the pupil with any particular underlying neural process.

1.4 V4 and attention

One of the primary aims of this work is to determine the mechanisms by which sensory cortical modulation (specifically in V4) confers perceptual benefits. V4 is robustly modulated by attentional state, showing increased firing rates and gamma-band synchronization (Fries et al., 2001; Moran and Desimone, 1985; Motter, 1993), and diminished trial-to-trial variability (Mitchell et al., 2007) and inter-neuronal correlations (Cohen and Maunsell, 2009; Mitchell et al., 2009) when attention is directed into neuronal receptive fields. Indeed, owing in part to the robustness of attentional modulation, V4 is perhaps the most studied sensory area in the context of attention. Nevertheless, we ought to consider the possibility that attentional modulation in V4 is epiphenomenal, and does not in fact contribute to the perceptual benefit of attention (Krauzlis et al., 2014). While certainly not conclusive, several lines of evidence argue for the causal role of V4 in visual attention. We briefly review these below.

Lesions in V4 lead to mild deficits in simple visual discrimination and more pronounced deficits in more complex visual discrimination. For example, orientation discrimination (Girard et al., 2002; Merigan, 1996; Schiller, 1993; Walsh et al., 1992; De Weerd et al., 1996) and hue discrimination (Walsh et al., 1993) are generally only mildly affected by V4 lesions. Much more severely disrupted are the discrimination of complex 3-dimensional shapes (Merigan and Pham, 1998), shapes defined by texture (Merigan, 1996, 2000; De Weerd et al., 1996), shapes defined by illusory contours (De Weerd et al., 1996), and partially occluded shapes (Schiller, 1995), as well as color constancy under varying illumination (Walsh et al., 1993). Very similar results are seen in human V4 lesions (Gallant et al., 2000). These deficits are consistent with V4's role as a mid-level form-processing region, involved in the transformation of visual information from low-level features in V1 to higher level features in inferotemporal cortex.

While V4 lesions produce only mild deficits in low-level discrimination of individually-presented stimuli, the same discriminations are more severely impacted in the presence of distracters. For example, in monkeys trained to detect a unique target amidst a field of identical distracters (an 'oddball' task), V4 lesions produce the strongest deficits when the detection target is less salient (e.g. smaller or lower contrast) than distracters (Schiller and Lee, 1991). Additionally, high contrast flanking distracters disrupt orientation discrimination in V4-lesioned monkeys, but not normal monkeys (De Weerd et al., 2003). Similar effects of flanking distracters are present in a human patient with parietal cortex lesions (Friedman-Hill et al., 2003), suggesting that V4 may be a part of an attention network that selects task relevant stimuli for further downstream processing.

Trial-to-trial correlations between neural activity and behavior are often interpreted as suggesting that a particular neuron is causally involved in a specific behavior. Of course, this does not quite constitute causal evidence— it falls short both for the obvious reason, as well as the specific concern that observing such trial-to-trial correlation depends upon the magnitude and structure of noise correlations (Cohen and Newsome, 2008; Nienborg and Cumming, 2010; Shadlen et al., 1996), as well as the means by which sensory cortex is read-out in support of behavior (Shadlen et al., 1996). Nevertheless, attention affects both behavioral performance as well as neuronal firing rates. The observation that these two variables are correlated across trials (and not just across groups of trials) strengthens the observed association. Correlated fluctuations in attentional behavior and neural activity are only rarely observed in single sensory cortical neurons (Galashan et al., 2013; Womelsdorf et al., 2006), likely due to intrinsic neuronal variability and the relatively small size of attentional effects in sensory cortex (Cohen and

Maunsell, 2010). However, with modest numbers (tens) of simultaneously recorded neurons, modulation of V4 activity robustly predicts behavior (Cohen and Maunsell, 2010).

Another important line of evidence linking neuronal modulation in V4 to the perceptual benefit of attention comes from the series of FEF microstimulation experiments performed by Tirin Moore and colleagues. Stimulation of FEF leads to enhanced behavioral sensitivity at topographically aligned locations of the visual field (Moore and Fallah, 2001, 2004), as well as neural modulation characteristic of attention in V4 (Armstrong and Moore, 2007; Armstrong et al., 2006; Ekstrom et al., 2009; Moore and Armstrong, 2003; Noudoost and Moore, 2011). These experiments have been influential in promoting the idea that attentional source areas like FEF direct spatial attention to particular regions of the visual field via modulation of sensory information in visual areas like V4. It is worth noting, however, that despite the use of a causal technique (microstimulation), these experiments do not constitute causal evidence that V4 is involved with attention, as behavioral effects could be mediated by other projections from the FEF, fibers of passage in the FEF, or antidromically activated neurons that project to FEF.

Chapter 2

Reward differentially modulates attentional behavior and activity in visual area V4

Abstract

Neural activity in visual area V4 is enhanced when attention is directed into neuronal receptive fields. However, the source of this enhancement is unclear since most physiological studies have manipulated attention by changing the absolute reward associated with a particular location as well as its value relative to other locations. We trained monkeys to discriminate the orientation of two stimuli presented simultaneously in different hemifields while independently varying the reward magnitude associated with correct discrimination at each location. Behavioral measures of attention were controlled by the relative value of each location. By contrast, neurons in V4 were consistently modulated by absolute reward value, exhibiting increased activity, increased gamma-band power, and decreased trial-to-trial variability whenever receptive field locations were associated with large rewards. These data challenge the notion that the perceptual benefits of spatial attention rely on increased signal-to-noise in V4. Instead, these benefits likely derive from downstream selection mechanisms.

2.1 Introduction

Spatial attention is associated with enhanced perception at specific locations in the visual field. These perceptual benefits are typically measured as improved task performance and faster reaction times (Carrasco, 2011), which we refer to as attentional behavior. Top-down factors such as goals, motor planning and reinforcement history as well as the intrinsic salience of visual stimuli can influence spatial attention (Awh et al., 2012; Bisley and Goldberg, 2010; Corbetta and Shulman, 2002; Desimone and Duncan, 1995; Fecteau and Munoz, 2006). Neurons with receptive fields (RF) at attended locations display modulated responses throughout striate and extrastriate visual cortex (Maunsell and Cook, 2002). Visual area V4 has often been the focus of physiological studies investigating the neural correlates of spatial attention, and directing attention into the RF of V4 neurons enhances firing rate (Moran and Desimone, 1985; Motter, 1993) as well as gamma-band power and synchronization (Fries et al., 2001; Gregoriou et al., 2009a; Womelsdorf et al., 2006), while diminishing trial-to-trial variability and inter-neuronal noise correlations (Cohen and Maunsell, 2009; Fries et al., 2001; Mitchell et al., 2007, 2009).

Most physiological studies control the locus of top-down spatial attention by manipulating subjects' expectations about which locations are more likely associated with reward (Maunsell, 2004). Correct task performance at one location is associated with higher reward magnitude or probability (labeled variously in previous studies as the 'target', 'attend-in' or 'relevant' location), while other locations are associated with lower or zero reward magnitude or probability ('distractor', 'attend-out' or 'irrelevant' locations). Therefore, changes in neural activity accompanying task manipulations can be equivalently described in terms of attentional allocation or reward configuration. Importantly, in terms of reward, these characteristic

manipulations alter in tandem both the *absolute* expectation of reward at one location as well as the expectation of reward *relative* to other locations in the visual field.

Relative value, in addition to its important role in choice and motor behavior (Lauwereyns et al., 2002b; Pastor-Bernier and Cisek, 2011; Platt and Glimcher, 1999; Rangel and Hare, 2010; Schultz, 2015), is also likely relevant for spatial attention. The relative values of locations are useful for directing preferential processing to one location at the expense of others (Bisley and Goldberg, 2006; Maunsell, 2004; Peck et al., 2013; Stănişor et al., 2013). The absolute expectation of reward at one location contributes to its relative value, but it also contributes to overall reward expectation. For example, doubling the rewards associated with all locations increases both the absolute reward at each location as well as the average value of a trial. This can change animals' vigilance, motivational state and arousal level in manners not linked to spatial location. Measures of these processes include increased anticipatory licking (Cromwell and Schultz, 2003; Paton et al., 2006), higher trial completion rates (Roesch and Olson, 2004; Varazzani et al., 2015), faster reaction times (Roesch and Olson, 2004; Varazzani et al., 2015), and increased pupil dilation (Kennerley and Wallis, 2009; Varazzani et al., 2015).

Prior studies of value-based decision-making have manipulated reward expectations to determine whether absolute or relative reward better accounts for neural activity. For example, in the lateral intraparietal cortex (LIP), neural activity predominantly tracks relative value when making value-based decisions between two locations (Dorris and Glimcher, 2004; Platt and Glimcher, 1999; Sugrue et al., 2004). This relative value encoding may underlie perceptual enhancements during spatial attention. However, in these studies of relative value in LIP, attentional behavior was not measured, and the focus was not on how neural modulations relate to perceptual performance. In visual cortex, one study has shown that V1 neurons are modulated

by relative value when stimuli appear at locations close together in space (Stănişor et al., 2013). However, it is not known whether relative value across hemifields modulates visual cortex, nor whether the relative or absolute values of RF stimuli better account for neural modulation in visual area V4.

The characterization of how absolute and relative reward values modulate neural activity in V4 may help elucidate mechanisms underlying the perceptual benefits of attention. Three mechanisms have been proposed to link neural modulations of visual representations with attentional behavior (Serences and Kastner, 2014): increased signal, decreased noise, and efficient selection of sensory responses. Signal-to-noise mechanisms yield perceptual benefits through higher-fidelity sensory representations whereas efficient selection yields perceptual benefits through selective pooling of sensory signals (Mirpour and Bisley, 2012; Pestilli et al., 2011; Serences and Kastner, 2014). Each of these mechanisms potentially contributes to the benefits of attention, but their relative contributions are unclear (Chen and Seidemann, 2012; Cohen and Maunsell, 2009; Hara and Gardner, 2014; Itthipuripat et al., 2014; Pestilli et al., 2011; Zénon and Krauzlis, 2012).

We reasoned that independently changing absolute and relative reward expectations could provide insight into the mechanisms of the perceptual benefits of attention. We trained monkeys to perform a perceptual task at two locations simultaneously while independently varying relative and absolute rewards associated with correct performance at the two locations. We found that increasing the absolute reward value associated with the RF location enhanced firing rate, increased gamma-band power in local field potentials (LFPs), and decreased trial-to-trial variability in V4 neural responses. Changes in behavioral measures of spatial attention, on the other hand, tracked relative value manipulations. Indeed, attentional behavior could vary

without large changes in V4 activity, and V4 activity could vary without large changes in attentional behavior. Modulation of V4 activity representing a particular spatial location therefore does not necessarily predict improved perceptual performance at that location. This finding places a strong and unexpected constraint on models of how V4 activity relates to perception and behavior.

2.2 Results

Reward-biased, dual two-alternative forced choice task

We trained monkeys to perform a dual two-alternative forced choice (dual 2-AFC) orientation discrimination task where we independently varied rewards associated with correct performance at two different locations (**Figure 2.1a**). On each trial, monkeys acquired central fixation after which two colored discs briefly appeared to cue the potential reward associated with correct performance at each location. Then, at each location, a rapid stream of oriented Gabor patches cycled randomly and independently through different orientations. At a random time, the final oriented stimuli were presented for a longer duration before being abruptly extinguished and masked. Next, we queried monkeys about the final orientation of one of the Gabor patches by presenting two choice targets around one of the two locations. Monkeys indicated with an eye movement whether the final orientation at the queried location was more horizontal or more vertical. Each location was queried on half of trials selected randomly, allowing us to measure performance at each location. By employing a dual discrimination task, as opposed to a detection task, we ensured that performance differences across conditions did not depend upon adaptive shifts in response bias (Luo and Maunsell, 2015).

We characterized how the distribution of reward contingencies across the visual field modulated neural activity and behavior by independently varying the reward associated with correct discrimination at each location. Correct performance at each location was associated with either a large or small reward, yielding four trial conditions that were pseudorandomly interleaved (**Figure 2.1b**). We refer to the final oriented stimulus at the queried location as the 'target' and the opposite stimulus as the 'distracter'. In the two unbalanced conditions, the target and distracter differ in potential reward (LS—large reward target, small reward distracter; and

SL—small reward target, large reward distracter), and the locus of spatial attention presumably shifts to the large reward location. These reward manipulations are similar to those yielding 'attend-in' and 'attend-out' conditions in other attention studies (Maunsell, 2004).

In the two balanced conditions, both target and distracter have the same potential reward (LL—large reward target, large reward distracter; and SS—small reward target, small reward distracter), and there is no advantage to shifting spatial attention. Thus in the balanced conditions (LL and SS), the absolute target value changes similarly to the unbalanced conditions (LS and SL), but the relative target value remains fixed and equal. By contrast, in the balanced conditions, the average trial value (mean of the potential rewards at both locations) is different, and monkeys' motivation or arousal may be modulated accordingly. For example, in the LL condition, because correct performance at either location is associated with a large reward, the overall expected value of the trial is high, and monkeys may therefore be more motivated or aroused.

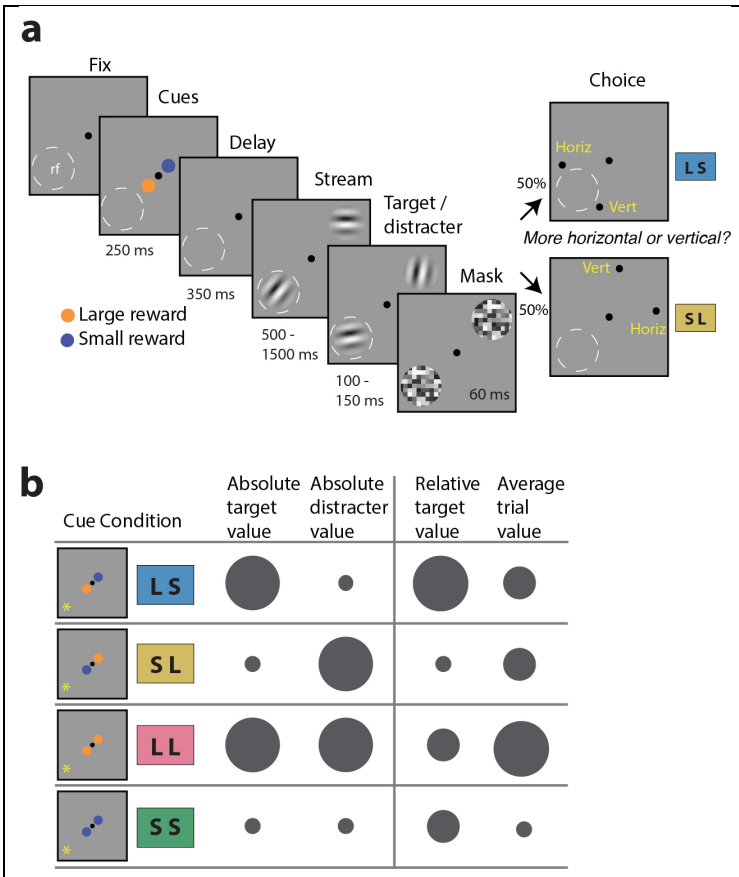

Figure 2.1. Task and behavior. (**a**) Schematic of the dual 2-AFC task. (**b**) Reward configuration defines four trial types. Correct performance at each location was associated with either a large or small reward, and each location was queried on a random 50% of trials. We refer to the queried stimulus as the target and the opposite stimulus as the distracter. In LS trials, the target was associated with a large (L) reward, and the distracter was associated with small (S) reward. In SL trials, the target was associated with small reward and the distracter was associated with a large reward. In balanced conditions (LL and SS), both target and distracter were associated with the same reward. Relative target value was highest in LS, intermediate in balanced conditions, and lowest in SL. Average trial value was highest in LL, intermediate in LS and SL, and lowest in SS. The schematics in the leftmost column show example configurations of reward cues and queried target location (asterisks).

Behavioral measures of spatial attention

The allocation of spatial attention—measured using percent correct and reaction time—was governed largely by relative target value. Percent correct was highest when relative target value was highest (**Figures 2.2a, 2.3**; 77.1% in LS condition; Cochran-Mantel-Haenszel test [CMH], $p<10^{-10}$ for all comparisons, uncorrected), intermediate in balanced conditions (72.7% and 70.7% in LL and SS conditions), and lowest when relative target value was lowest (57.2% in SL condition, $p<10^{-10}$ for all comparisons). Reaction times mirrored percent correct and were fastest in the LS condition, intermediate in the balanced conditions, and slowest in the SL condition (**Figure 2.2a**; Wilcoxon rank-sum test [WRS], $p<10^{-10}$ for all comparisons,

uncorrected). There was a small but significant benefit to performance (CMH, $p<10^{-3}$) and reaction time (WRS, $p<10^{-10}$) on LL compared to SS trials, suggesting that although relative value accounts for the bulk of the performance differences, average trial value also plays a minor role. Overall, we observed that the major behavioral benefits of attention occur when reward expectation differs across the visual field, with preferential selection of stimuli with high relative value.

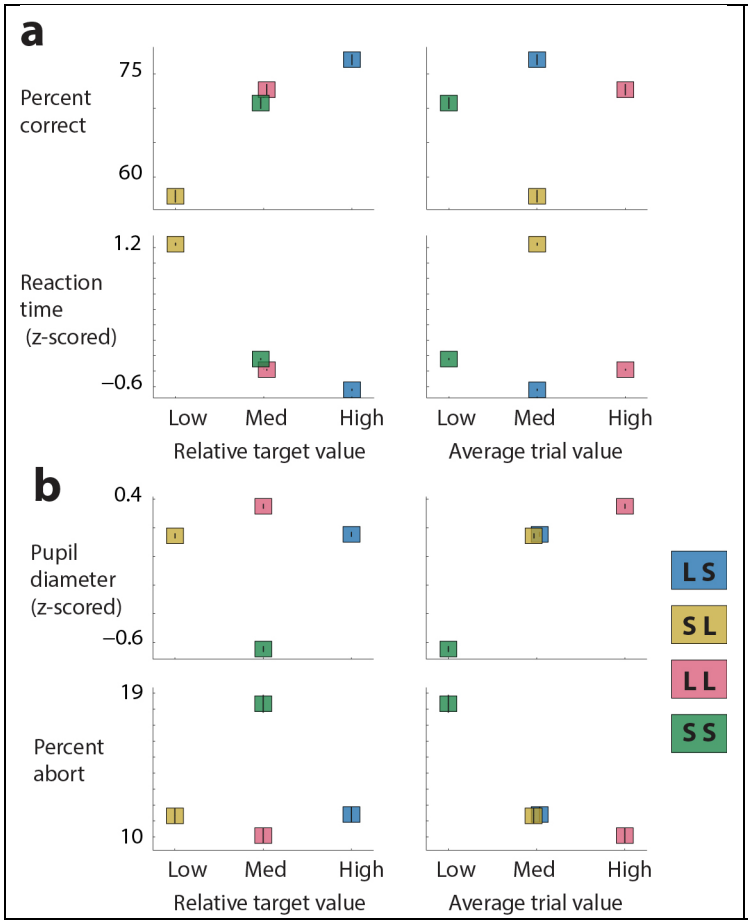

Figure 2.2. Behavior overview. (**a**) Performance and reaction time track relative target value. Behavioral data are presented as function of relative target value (left column), as well as average trial value (right column). Error bars indicate +/- 1 SEM. Overlapping points are slightly offset for visualization. (**b**) Pupil diameter and abort rate track average trial value. Plotting conventions as in (a).

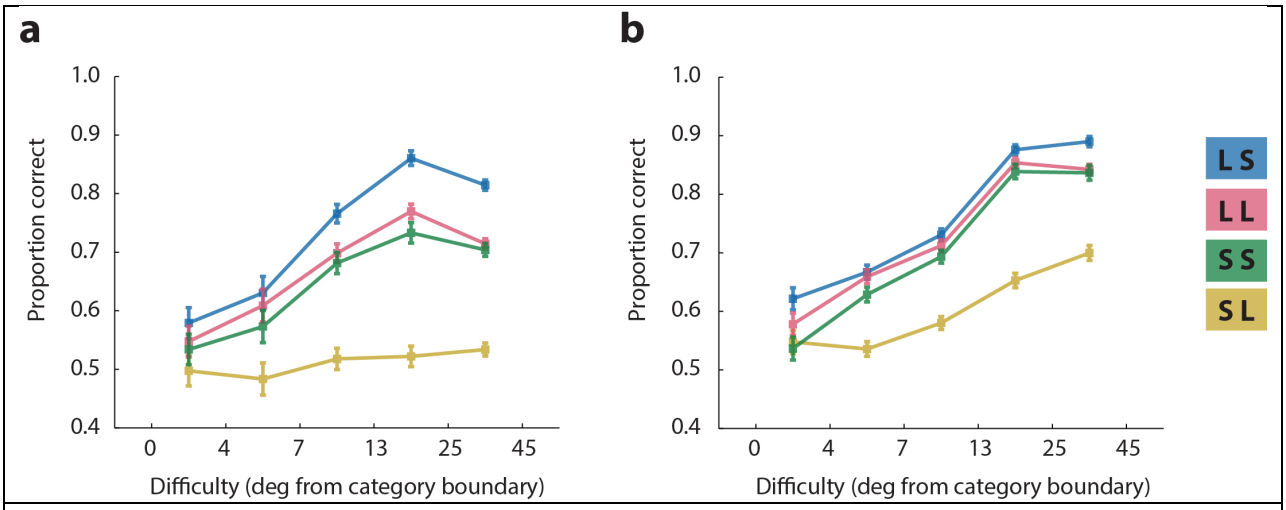

Figure 2.3. Psychometric functions. Proportion correct as a function of task difficulty, shown separately for Monkey 1 (**a**) and Monkey 2 (**b**). Labels on abscissa indicate orientation bin edges. Error bars indicate +/- 1 SEM.

Behavioral measures of arousal and motivational state

We found that arousal and motivational state—measured using pupil diameter (Kennerley and Wallis, 2009; Nassar et al., 2012; Reimer et al., 2014; Varazzani et al., 2015) and trial abort rates (Roesch and Olson, 2004; Varazzani et al., 2015), respectively—were correlated with the average trial value. Pupils were most dilated in the LL condition, intermediate in unbalanced conditions, and smallest in the SS condition (**Figure 2.2b**; WRS, $p<10^{-10}$ for all comparisons that differed in average trial value). Differences in pupil diameter were sustained for the duration of the Gabor stream (**Figure 2.4).** Average trial value also influenced trial abort rates (**Figure 2.2b**), with monkeys more frequently aborting trials of the lowest expected value (SS; CMH, $p<10^{-10}$ for all comparisons). One monkey also aborted LL trials significantly less frequently than LS and SL trials (**Figure 2.6**; CMH, $p<10^{-6}$ for both comparisons), whereas the other showed no significant difference in abort rate between LL and the unbalanced conditions (**Figure 2.6**; CMH, $p>0.1$ for both comparisons). All other behavioral measures were similar in both monkeys (**Figure 2.6**).

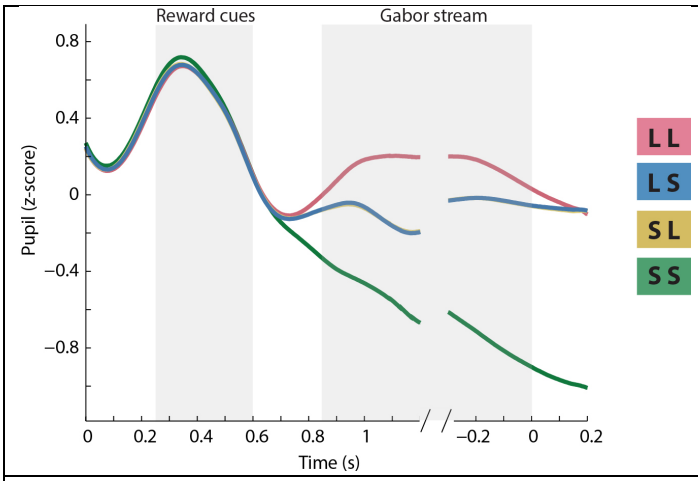

Figure 2.4. Pupil diameters diverge after reward cue presentation. Z-scored pupil diameters are aligned on two events in the trial. On the left, pupil values are aligned to acquisition of fixation. On the right, pupil values are aligned to onset of discriminanda. In all traces, line thickness exceeds +/- 1 SEM. After reward cue presentation (shaded box at left) and through streaming Gabor stimulus (shaded box at right), pupil diameters reflect average trial value. (n= 48,103)

Trial initiation behavior also indexed average trial value. Although trial types were pseudorandomly interleaved, advance information about trial types was available in a small subset of trials. This is because aborted trials were followed by trials of the same condition to ensure that monkeys could not increase their reward rate by aborting trials of low expected value. Thus, trials following aborts were conceivably of known condition. In this subset of trials, we found that the latency to acquire fixation was inversely related to average trial value (**Figure 2.5a)**. Latencies were highest in SS trials (mean 579 ms; WRS, $p<10^{-10}$ for all comparisons), intermediate in unbalanced conditions (mean 483 ms), and smallest in LL trials (mean 449 ms; WRS, $p<10^{-7}$ for all comparisons). Similarly, the monkeys' willingness to initiate trials was related to average trial value (**Figure 2.5b**), with fixation acquisition rates highest in LL trials (89.0%; CMH. $p< .005$ for all comparisons), intermediate in unbalanced conditions (87.5%), and lowest in SS trials (82.5%; CMH, $p<10^{-10}$ for all comparisons).

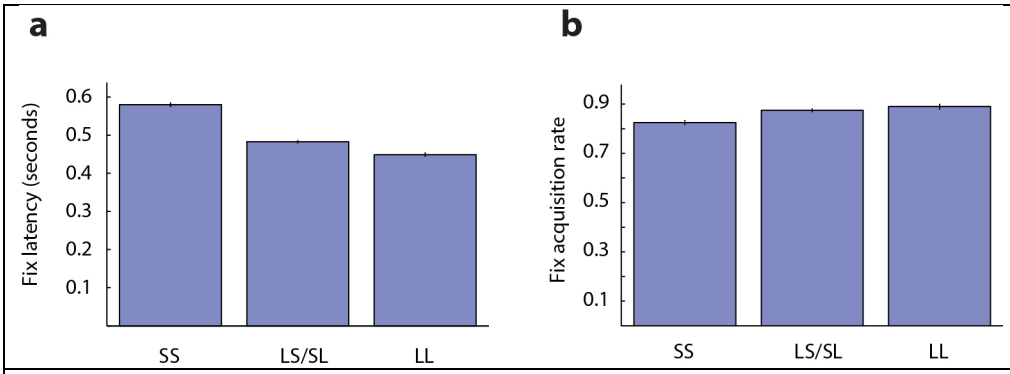

Figure 2.5. Trial initiation behavior reflects average trial value. (a) Fixation latency tracks average trial value. Trials from LS and SL trials are pooled and considered together. Error bars indicate +/- 1 SEM (b) Fixation acquisition rate tracks average trial value.

The pattern of results for pupil diameter, abort rate, and trial initiation differs markedly from that for percent correct and reaction time, indicating that the dual 2-AFC task effectively isolated changes in arousal and motivational state from changes in attentional allocation. These behavioral effects were observed in both monkeys (**Figure 2.6**) and at both locations (**Figure 2.7**).

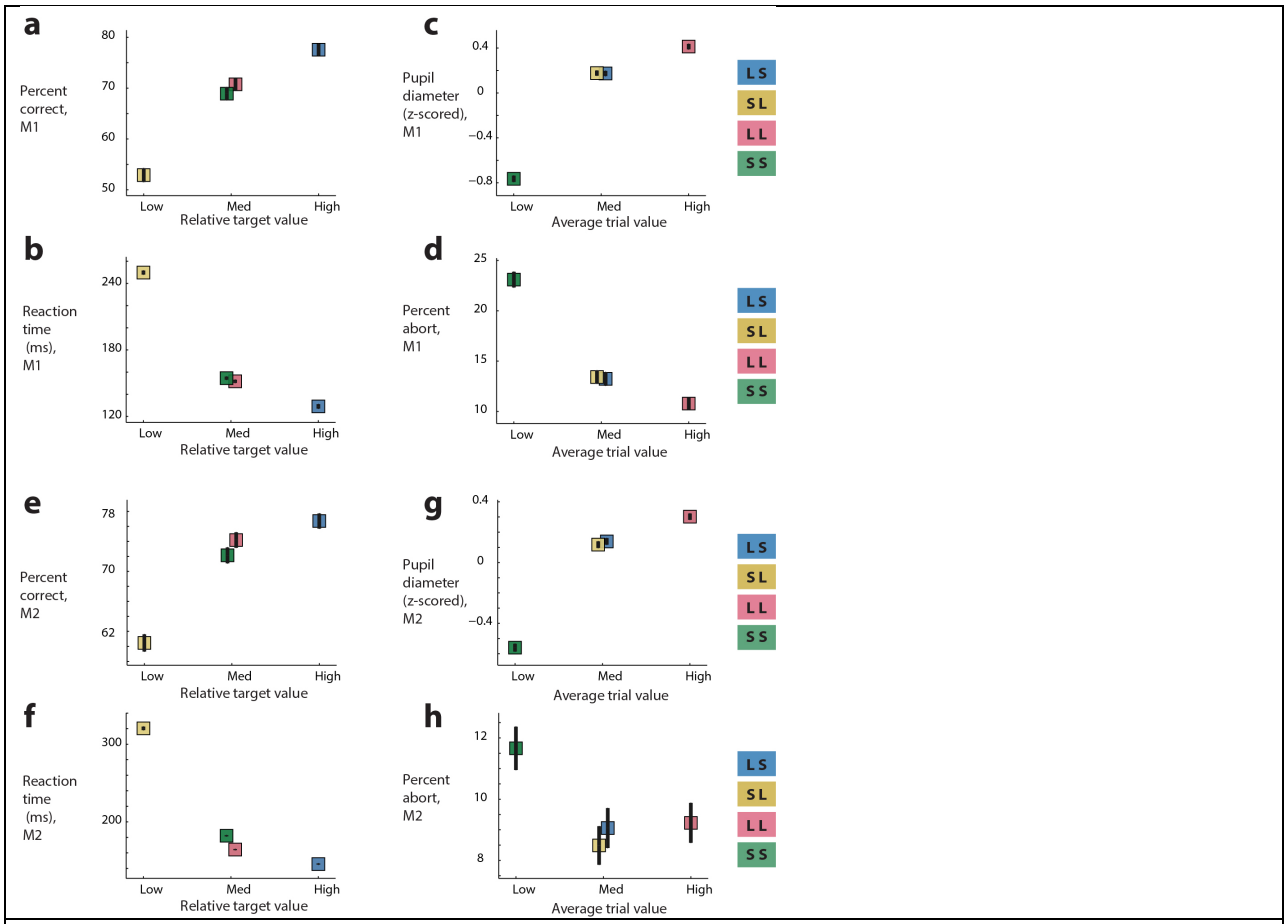

Figure 2.6. Behavioral effects were consistent across monkeys. Behavioral data are presented as function of relative target value or average trial value, from all trials completed during recording sessions in Monkey 1 (**a-d,** 5,174 LS; 5,230 LL; 5,312 SL; and 5,226 SS trials) and Monkey 2 (**e-h**, 6,881 LS; 6,965 LL; 7,018 SL; and 6,953 SS trials). Error bars indicate +/- 1 SEM. Overlapping points are slightly offset for visualization. **(a,b**) Performance and reaction time track relative target value in M1. Percent correct was highest in LS (CMH, $p<10^{-10}$ for all comparisons), and lowest in SL (CMH, $p<10^{-10}$ for all comparisons). Reaction times were fastest in LS (WRS, $p<10^{-10}$ for all comparisons), and slowest in SL (WRS, $p<10^{-10}$ for all comparisons). Performance was slightly higher (CMH, p=.0402) and reaction times slightly faster (WRS, $p<10^{-4}$**)** in LL compared to SS trials. **(c,d**) Pupil diameter and abort rate track average trial value in M1. Pupils were most dilated in LL (WRS, $p<10^{-10}$ for all comparisons) and least dilated in SS (WRS, $p<10^{-10}$ for all comparisons). Abort rate was highest in SS (CMH, $p<10^{-10}$ for all comparisons) and lowest in LL (CMH, $p<10^{-6}$ for all comparisons). **(e,f**) Performance and reaction time track relative target value in M2. Percent correct was highest in LS (CMH, $p<10^{-3}$ for all comparisons), and lowest in SL (CMH, $p<10^{-10}$ for all comparisons). Reaction times were fastest in LS (WRS, $p<10^{-10}$ for all comparisons), and slowest in SL (WRS, $p<10^{-10}$ for all comparisons). Performance was slightly higher (CMH, p=.0066) and reaction times faster (WRS, $p<10^{-10}$**)** in LL compared to SS trials. **(g,h**) Pupil diameter and abort rate track average trial value in M2. Pupils were most dilated in LL (WRS, $p<10^{-10}$ for all comparisons) and least dilated in SS (WRS, $p<10^{-10}$ for all comparisons). Abort rate was highest in SS (CMH, $p<10^{-5}$ for all comparisons), and did not significantly differ between the other three conditions (CMH, p>0.1 for all comparisons).

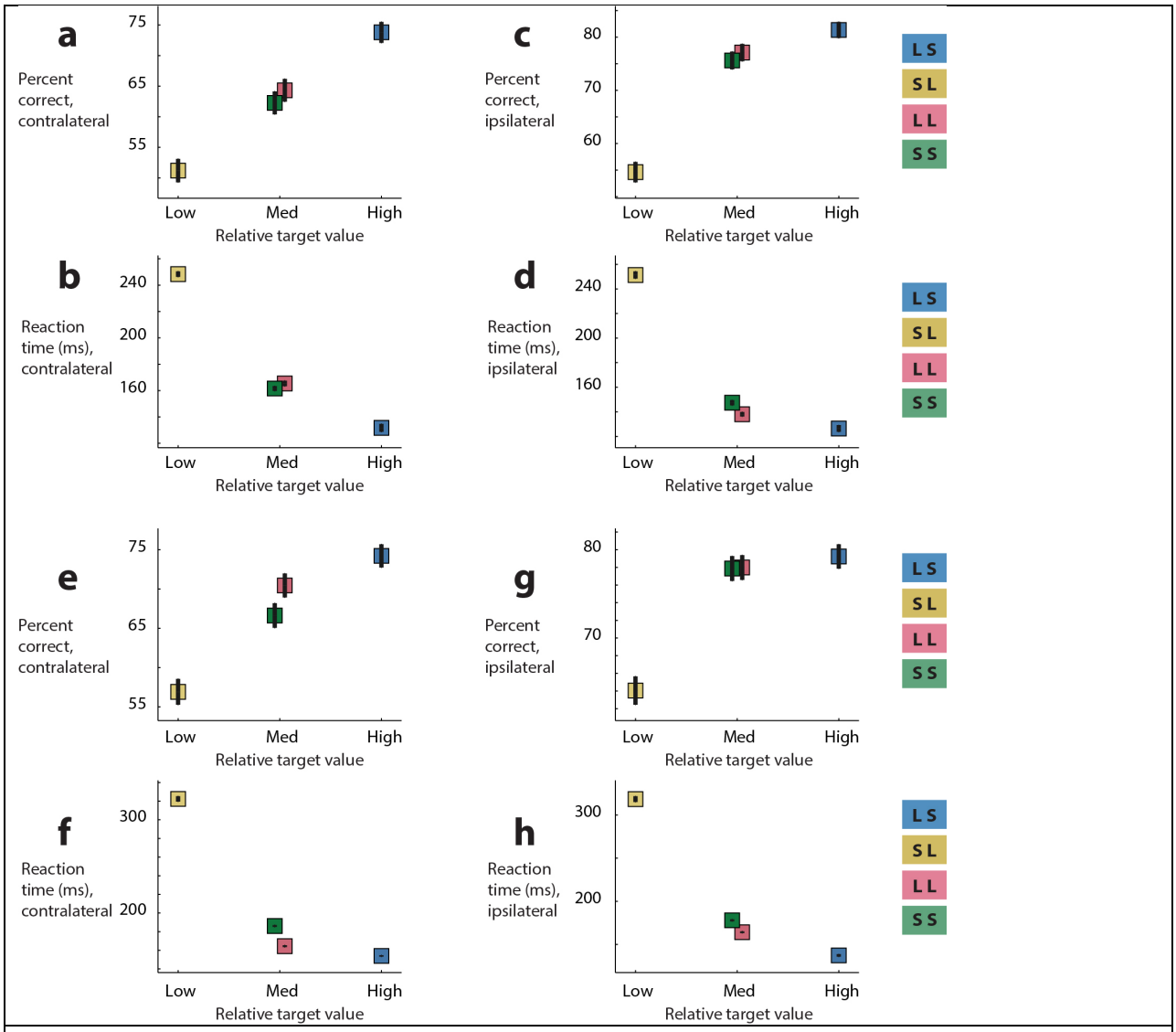

Figure 2.7. Behavioral effects were consistent across locations. Behavioral data are presented as function of relative target value, from all trials completed during recording sessions in Monkey 1 (**a-d**) and Monkey 2 (**e-h**). Behavioral data are shown separately for targets contralateral (**a,b,e,h**) and ipsilateral (**c,d,g,h**) to the recorded brain area. Error bars indicate +/- 1 SEM. Overlapping points are slightly offset for visualization. **(a,c)** Performance tracks relative target value at each location in M1. At each location, performance was highest in LS (CMH, $p<10^{-4}$) and lowest in SL (CMH, $p<10^{-10}$). **(b,d)** Reaction times track relative target value at each location in M1. At each location, reaction times were fastest in LS (WRS, $p<10^{-10}$), and slowest in SL (WRS, $p<10^{-10}$**)** **(e)** Performance tracks relative target value at the contralateral location in M2. Performance was highest in LS (CMH, $p<10^{-3}$) and lowest in SL (CMH, $p<10^{-10}$). (**g**) At the ipsilateral location, performance was highest in LS (79.24%), but not significantly higher than either LL (77.98%; CMH, $p>0.05$) or SS conditions (77.87%; CMH, $p>0.05$). Performance at the ipsilateral location was lowest in SL (64.05%, CMH, $p<10^{-10}$). **(f,h)** Reaction times track relative target value at each location in M2. At each location, reaction times were fastest in LS (WRS, $p<10^{-10}$) and slowest in SL (WRS, $p<10^{-10}$**)**.

Visual cortical activity reflects the absolute reward associated with receptive field stimuli

We predicted that V4 neural activity would track the relative value of RF stimuli if this activity conferred the performance and reaction time benefits associated with attention (e.g.(Luo and Maunsell, 2015; Spitzer et al., 1988; Stănişor et al., 2013)). In this case firing rates would be highest in the LS condition (large reward in RF, small reward opposite RF), intermediate in balanced conditions, and lowest in the SL condition (small reward in RF, large reward opposite RF). Figure 2.8 shows the responses of two neurons. Both neurons increased firing rate when relative RF value was high (**Figure 2.8a,c**; LS compared to SL trials; WRS, $p<0.01$ for both comparisons), reproducing prior findings of higher activity for 'attend-in' compared to 'attend-out' trials. Surprisingly, these neurons also showed similar firing rate enhancement in LL trials compared to SS trials (**Figure 2.8b,d**; WRS, $p<0.01$ for both comparisons), despite minimal differences in behavioral performance measures between these conditions. Finally, firing rates were not different for both neurons (WRS, $p>0.1$) when comparing conditions where the value of the stimulus in the RF was the same (SS vs. SL and LS vs. LL), despite the large differences in performance and reaction time observed between these conditions. This pattern of results was true across the population, with neurons showing higher firing rates in LS and LL trials than in SL and SS trials (**Figure 2.8e**).

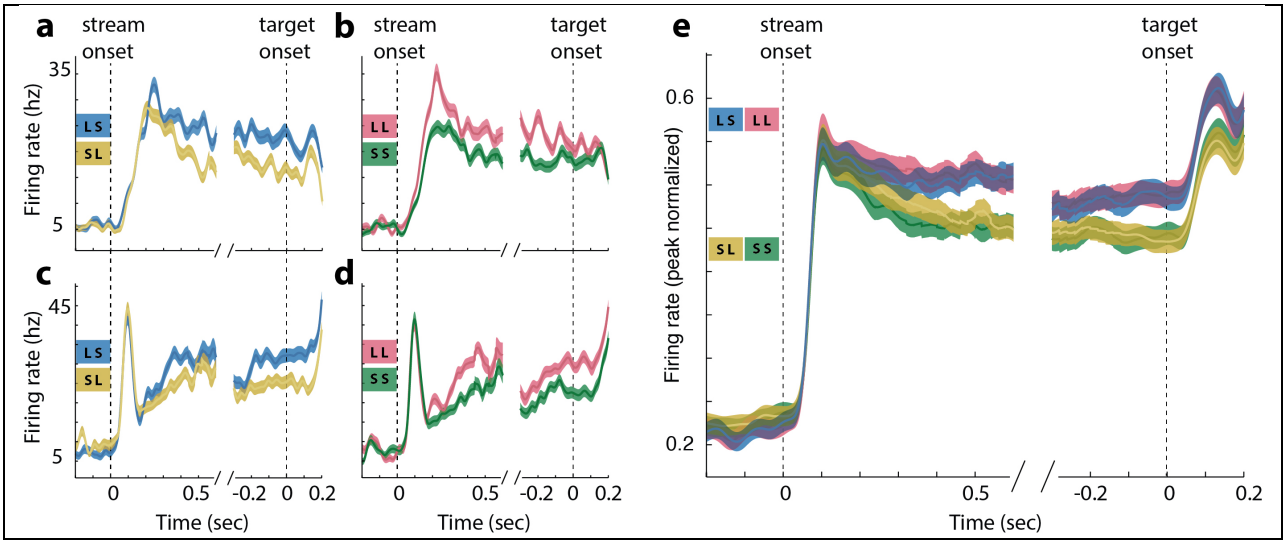

Figure 2.8. Firing rate modulation in V4 reflects absolute value of RF stimuli. (**a-d**) Spike density functions (σ = 15ms; shading, +/- 1 SEM) for two single units in V4. Responses are aligned to two events in a trial. On the left, responses are aligned to the onset of the streaming Gabor stimulus. On the right, responses are aligned to the target onset. Distractor appearance also occurs at this time. (**a,c**) Responses in LS (large reward in RF, small reward opposite RF) and SL (small reward in RF, large reward opposite RF) trials. (**b,d**) Responses in LL (large rewards both in and opposite RF) and SS (small rewards both in and opposite RF) trials. (**e**) Peak-normalized population average firing rate (n=190 units; 92 single, 98 multi; 106 from M1, 84 from M2).

We used multiple linear regression to quantify how the reward contingency at each location affected neuronal activity and behavior across the population (see Methods). For behavioral data, the regression coefficients separately characterize the influence of associating large rewards with target (β_1) and distracter (β_2) locations. For neural data, regression coefficients separately characterize the influence of associating large rewards with RF (β_1) and opposite-RF (β_2) locations. Consistent with average reaction times tracking relative value (**Figure 2.2a**), we found that associating a large reward with the target uniformly decreased reaction times, while associating large rewards with distracter locations uniformly increased reaction times (**Figure 2.9a**, Wilcoxon signed-rank test [WSR], $p<10^{-10}$). Similarly, consistent with average pupil diameters tracking average trial value (**Figure 2.2b**), large rewards at either target or distracter locations increased pupil diameters (**Figure 2.9b**, WSR, $p<10^{-10}$).

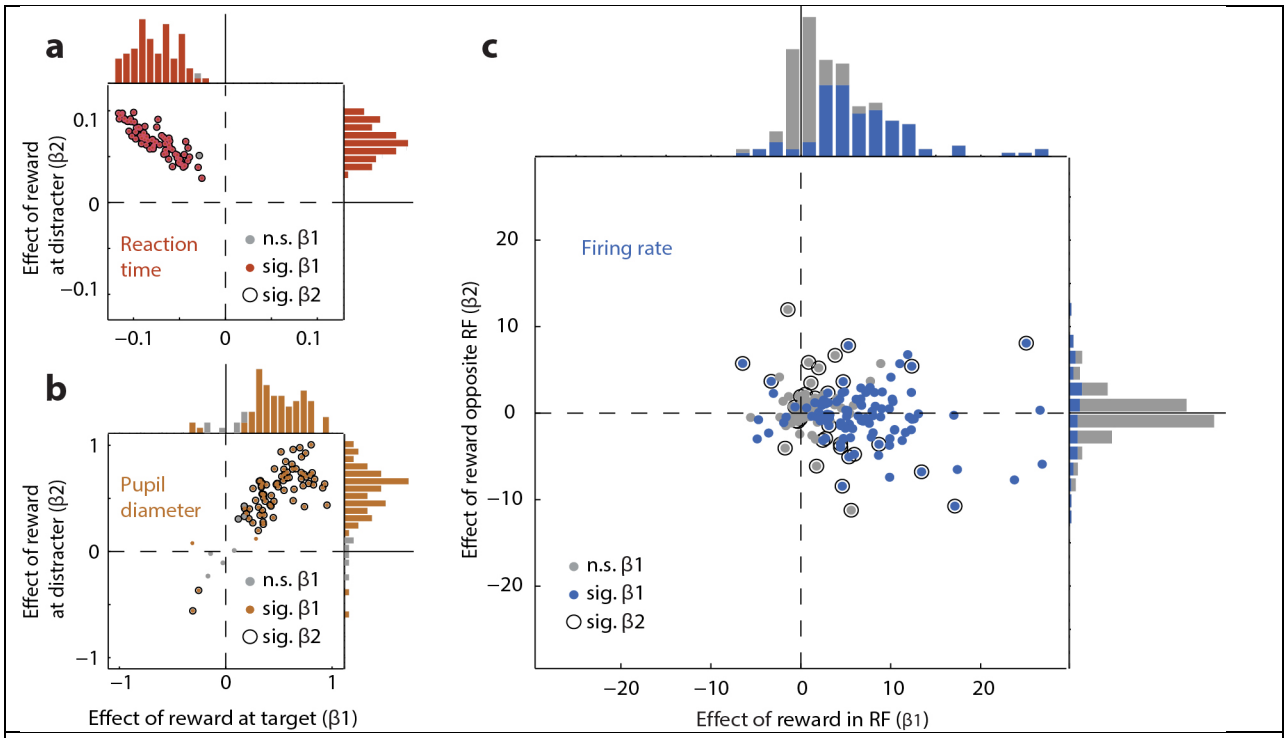

Figure 2.9. Regression summary of independently changing reward at two spatial locations. Joint and marginal distributions of regression coefficients across all behavioral sessions (n=79) and recorded units (n=190). (**a**) Reaction times reflect relative target value in all sessions. Associating the larger reward with the target location decreased reaction times (WSR, $p<10^{-10}$), whereas large rewards at distracter locations increased reaction times (WSR, $p<10^{-10}$). Symbol style denotes significance for individual data points ($p<0.05$). Colored shading in marginal histograms indicates significance for individual data points ($p<0.05$). (**b**) Pupil diameter reflects average trial value. Associating large rewards with either the target (WSR, $p<10^{-10}$) or distracter (WSR, $p<10^{-10}$) increased pupil diameters. (**c**) Neuronal modulation reflects RF value. Large rewards at the RF location were associated with increased firing rates (WSR, $p<10^{-10}$). On average, large rewards opposite the RF were not associated with a significant change in firing rate (WSR, p=0.964).

In contrast to behavior, neurons were modulated primarily by the value of the stimulus in the RF. Associating the larger reward with RF stimuli consistently and robustly enhanced neural activity, with a mean firing rate increase of 4.05 +/- 0.40 spikes/sec across all units (**Figure 2.9c**; WSR, $p<10^{-10}$). 97 units displayed a significantly positive (9 significantly negative) effect of large reward in the RF. By contrast, associating larger rewards with locations opposite the RF did not significantly affect firing rate (**Fig 2.9c**; mean=-0.046 +/- 0.21 spikes/sec; WSR, p=0.964). These effects were similar in each monkey (**Figure 2.10**). Thus, V4 neural modulation

primarily reflected the absolute rather than the relative value of rewards associated with correctly discriminating stimuli in the receptive field.

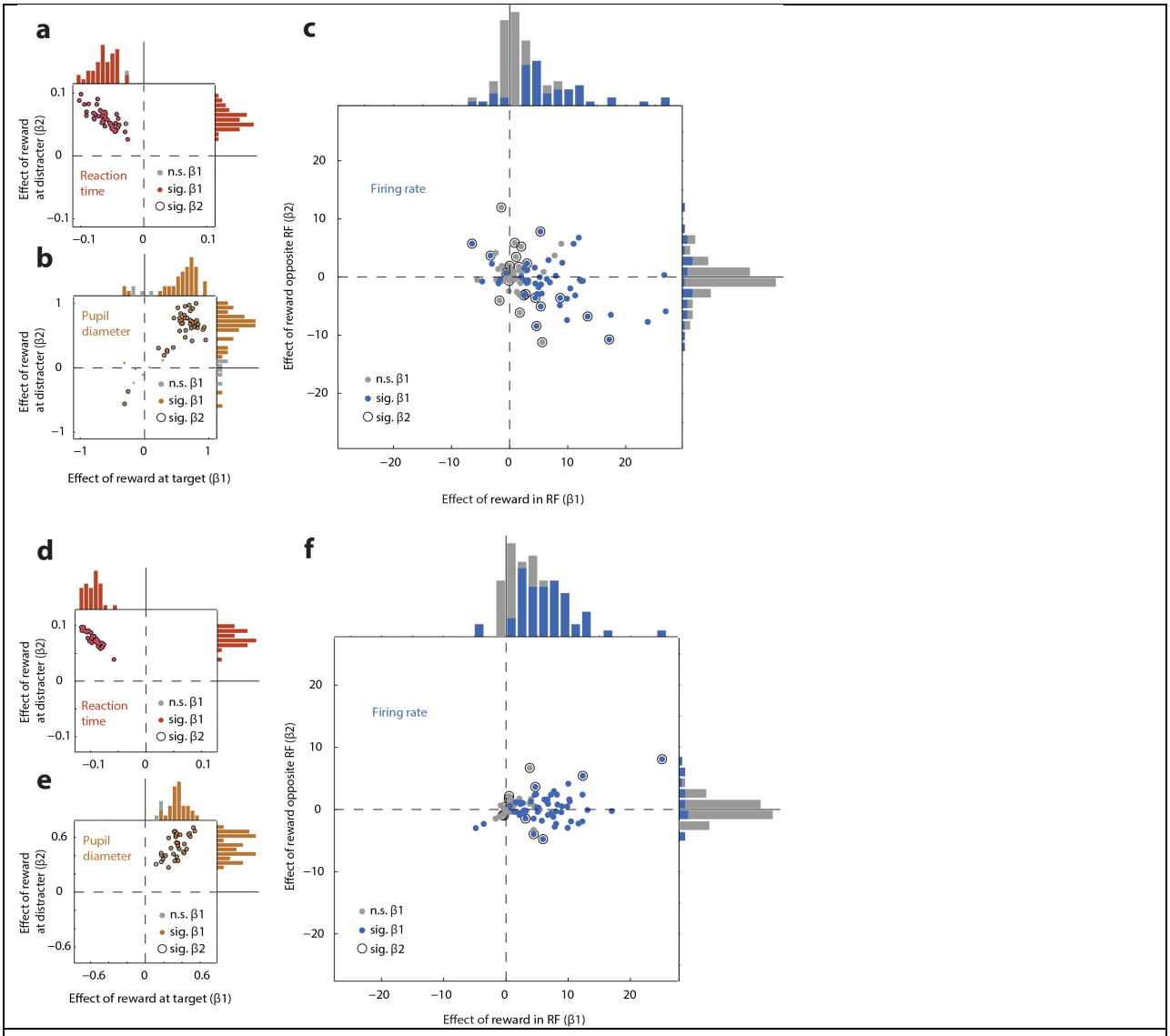

Figure 2.10. Neural and behavioral effects across the population were similar in each monkey. Joint and marginal distributions of regression coefficients for Monkey 1 (**a-c**, n=46 behavioral sessions, n=106 recorded units) and Monkey 2 (**d-f**, n=33 behavioral sessions, n=84 recorded units). Symbol style denotes significance for individual sessions/units. (**a**) Reaction times reflect relative target value in all M1 sessions. Associating the larger reward with the target location decreased reaction times (WSR, $p<10^{-8}$), whereas large rewards at distracter locations increased reaction times (WSR, $p<10^{-8}$). (**b**) Pupil diameter reflects average trial value in M1 sessions. Associating the large reward with either the target (WSR, $p<10^{-7}$) or distracter (WSR, $p<10^{-7}$) increased pupil diameters. (**c**) Neuronal modulation reflects RF value in M1. Large rewards at the RF location were associated with increased firing rates (mean= +3.55 spikes/s; WSR, $p<10^{-8}$). Large rewards opposite the RF were not associated with a significant change in firing rate (mean= -0.301 spikes/s; WSR, p=0.45). (**d**) Reaction times reflect relative target value

in all M2 sessions. Associating the larger reward with the target location decreased reaction times (WSR, $p<10^{-6}$), whereas large rewards at distracter locations increased reaction times (WSR, $p<10^{-6}$). (**e**) Pupil diameter reflects average trial value in all M1 sessions. Associating the large reward with either the target (WSR, $p<10^{-6}$) or distracter (WSR, $p<10^{-6}$) increased pupil diameters. (**f**) Neuronal modulation reflects RF value in M1. Large rewards at the RF location were associated with increased firing rates (mean= +4.69 spikes/s; WSR, $p<10^{-10}$). Large rewards opposite the RF were not associated with a significant change in firing rate (mean= +0.276 spikes/s; WSR, p=0.32).

The regression coefficients compactly describe reward modulation in our task by summarizing firing rate changes across the set of six possible condition comparisons. To further explore how reward modulation varied across the population of recorded units, we estimated effect sizes (*d'*) for four key condition comparisons (**Figure 2.11**). We first compared LS to SL trials, which is the comparison analogous to the 'attend-in' versus 'attend-out' difference explored in most attention studies. Across these conditions, the relative value of RF stimuli differs, but average trial value does not. Firing rates were increased in LS compared to SL trials (**Figure 2.11a**, mean *d'*=0.196; WSR, $p<10^{-10}$), corresponding to a mean increase of 10.2%, and mean neural modulation index (MI, see methods) of 0.038, effect sizes similar to prior reports for V4 (Cohen and Maunsell, 2009; Luo and Maunsell, 2015; Mitchell et al., 2007; Steinmetz and Moore, 2014).

When average trial value differed, but relative target value did not (LL and SS), we observed minimal effects on performance and reaction time (**Figure 2.2a**). Nevertheless, increasing average trial value enhanced firing rates (**Figure 2.11a**; mean *d'*=0.192; WSR, $p<10^{-10}$) to the same degree as increasing relative RF value (WSR, p=0.885). Therefore, despite dramatically different effects on attentional behavior and arousal, changing relative target value and average trial value similarly modulated V4 activity.

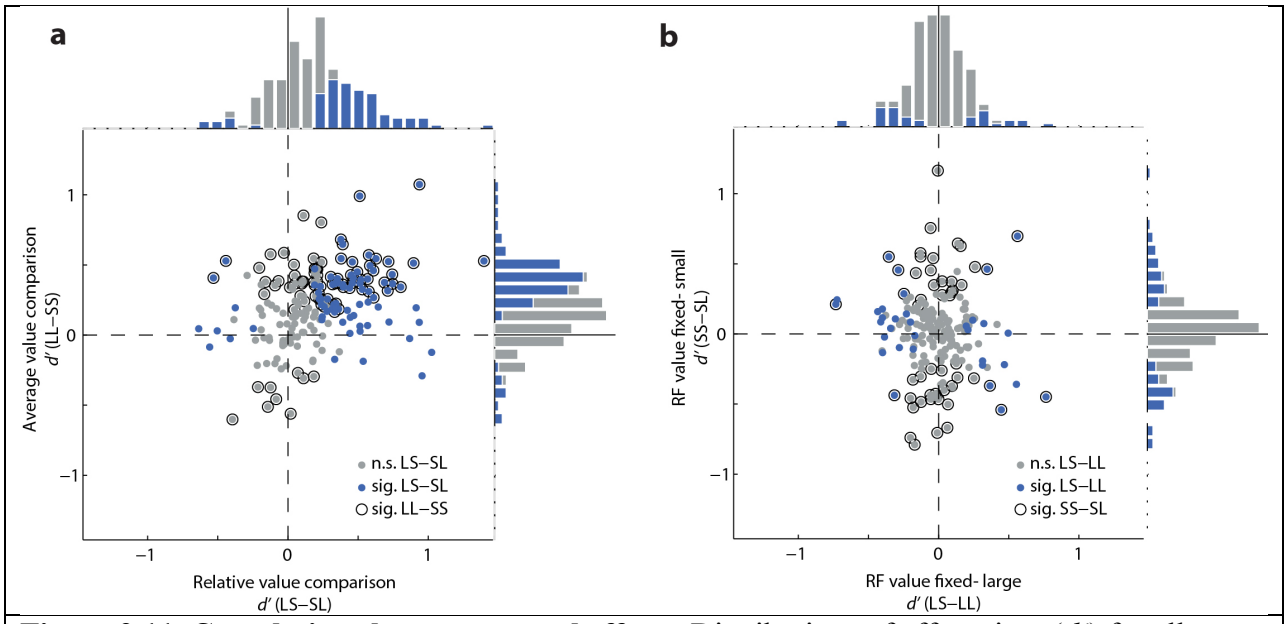

Figure 2.11. Correlations between neural effects. Distributions of effect sizes (*d'*) for all recorded units (n=190). (**a**) Relative RF value (LS-SL) and average trial value (LL-SS) similarly modulate neuronal activity. Both manipulations increase firing rate (WSR, $p<10^{-10}$), with effect sizes positively correlated across units r=0.31, $p<10^{-4}$). Symbol style indicates significance of selectivity for each unit (randomization test, p<0.05). (**b**) Absolute RF value is fixed in two condition comparisons (LS-LL and SS-SL). For both comparisons, effect size distributions do not significantly differ from zero (WSR, p>0.3), and effect sizes are not positively correlated across units (r=-0.092, p=0.207).

Relative value (LS-SL) and average trial value (LL-SS) manipulations similarly modulate neural activity (**Figure 2.11a**), but have separable effects on attentional behavior and arousal (**Figure 2.2a,b**). This dissociation between neural modulation and behavior could be reconciled if relative value and average trial value signals were encoded by distinct neuronal populations. We did not find support for this (**Figure 2.11a**, joint distribution). First, similar proportions of neurons exhibited activity modulated by relative and average value. 143 of 190 units (75.2%) were positively modulated by relative RF value (LS-SL), achieving significance in 73 units (38.4%). 149 of 190 (78.4%) units were positively modulated by average trial value (LL vs. SS), achieving significance in 80 units (42.1%). 49 units exhibited significantly positive effects for both relative RF value and average trial value (49/73, 67.1%). The proportions of units significantly positively modulated in these two comparisons were not significantly different (χ^2-

test, p=0.633). Moreover, the proportion of units exhibiting a significantly positive effect of both relative RF value and average trial value was greater than expected by chance (χ^2-test, $p<10^{-7}$). Finally, the degree of modulation observed in each comparison was correlated across units (**Figure 2.11a**, r=0.31, $p<10^{-4}$). We conclude that manipulating relative RF value and average trial value lead to similar modulations in the same neurons.

For two trial comparisons (**Figure 2.11b**, LS-LL and SS-SL), both relative RF value and average trial value differ, but the absolute value of the RF stimuli is constant. For example, the absolute reward associated with RF stimuli is the same on LS and LL trials, but the relative value is higher and average trial value lower on LS trials. Firing rates did not differ significantly between LS and LL trials (**Figure 2.11b**, mean *d'*= -0.008; WSR, p= 0.533) or between SS and SL trials (**Figure 2.11b**, mean *d'*=0.011; WSR, p=0.378). We next considered whether effect sizes across these two comparisons were related. If neurons were modulated by relative value, they should be positively modulated in both LS-LL and SS-SL condition comparisons (**Figure 2.11b**, upper-right quadrant of joint distribution). We found, however, that the proportion of units exhibiting positive (χ^2-test, p=0.329) or significantly positive (χ^2-test, p=0.946) modulation in both comparisons was not significantly different than chance. Moreover, the two effects were not significantly correlated (**Figure 2.11b**, r=-0.092, p=0.207). Therefore, modulation of neuronal responses in V4 was well described by absolute reward, and not relative reward.

Across conditions, attentional behavior is dissociated from firing rate modulation when examining neurons individually. We considered whether a population-based analysis of neuronal data would reveal differences between conditions accounting for the behavioral effects in our task. We addressed this by asking how changes in population activity associated with attentional behavior (LS and SL) are related to changes in population activity in other condition

comparisons. To do this we treated the activity of all neurons in the LS and SL trials as points in a space where the activity of each neuron defines a dimension (**Figure 2.12a-d**, details in Methods). In this space, we defined an "attention axis"(Cohen and Maunsell, 2010) as the vector linking the means of LS and SL trials. This allowed us to ask how population activity in different conditions varies along the axis most associated with the perceptual benefits of spatial attention.

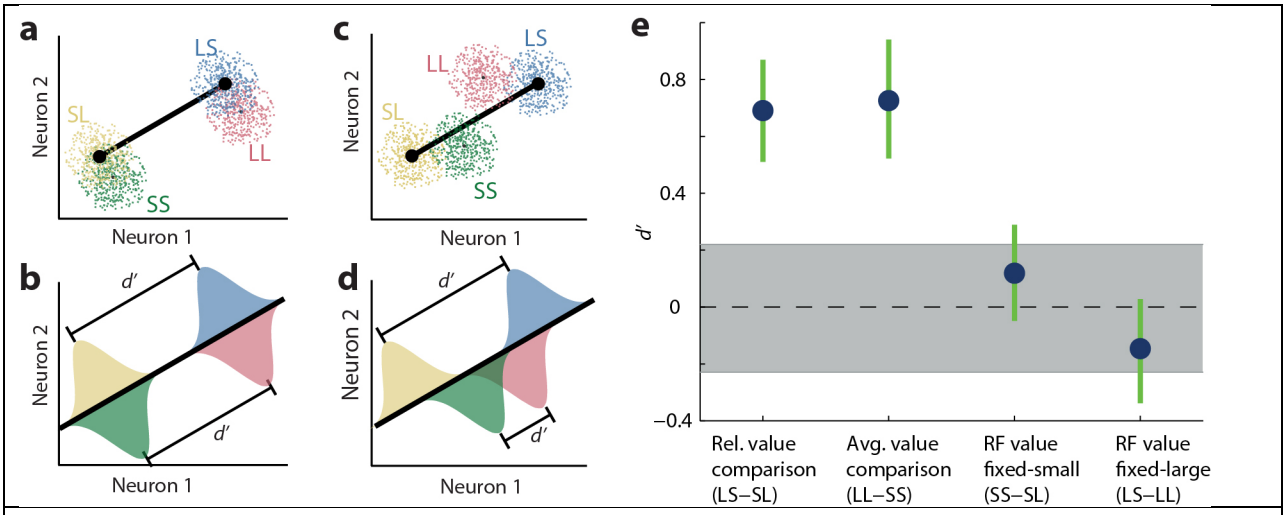

Figure 2.12. Differences in population activity when changing average trial value are similar to those when changing relative value. (a-d) Characterizing population activity along the attention axis(Cohen and Maunsell, 2010) (**a**) Population activity is represented by a point in the space defined by the activity of each neuron on each trial (2 neurons for illustration). The attention axis (bold black line) is the vector connecting the mean responses in LS and SL trials, which represents the axis along which changes in population activity are accompanied by changes in behavioral measures of spatial attention (Fig 1). (**b**) Projecting the population activity for each trial onto the attention axis to measure the discriminability (*d'*) between population activity in different conditions. In the scenario depicted in (**a,b**), changes in population activity during LL and SS trials resemble those during LS and SL trials, yielding similar *d'*. In the scenario depicted in (**c,d**), changes in population activity during LL and SS trials are different from those during LS and SL trials, yielding smaller *d'*. (**e**) Discriminability (*d'*) for different condition comparisons. Average trial value modulation (LL-SS) is similarly discriminable to relative value modulation (LS-SL) along the attention axis. Changes of population activity in conditions where the absolute RF value is constant but relative value changes (SS-SL and LS-LL) are not well discriminated along the attention axis (*d'* values not significantly different from 0). Circles denote mean *d'* values, green bars indicate 95% confidence intervals, and the shaded area indicates 95% confidence intervals associated with condition-shuffled data.

We characterized modulation across conditions by projecting onto the attention axis and quantifying discriminability (*d'*). Consistent with the individual neuron analysis (**Figure 2.11a**), we found that average trial value (LL-SS, mean *d'*=0.726) and relative RF value (LS-SL, mean *d'*=0.691) similarly modulate population representations (**Figure 2.12e**). Discriminability of the two pairwise comparisons did not differ significantly (randomization test, $p>0.05$), and both differed significantly from chance (randomization test, $p<0.05$). That is, the pattern of population activity varied similarly during average trial value (LL-SS) and relative value (LS-SL) manipulations. By contrast, in both pairwise comparisons where reward in the RF was fixed (SS-SL and LS-LL), discriminability along the attention axis was markedly decreased (**Figure 2.12e)**. For SS compared to SL trials, discriminability was slightly, but not significantly positive (mean *d'*=0.119, randomization test, $p>0.05$). For the LS-LL trial comparison, discriminability was slightly, but not significantly negative (mean *d'*=-0.147, randomization test, $p>0.05$). Therefore, changes in population activity did not account for modulations in behavioral measures of spatial attention.

In addition to firing rate changes, prior studies have also reported that attention lowers trial-to-trial variability in neural responses to attended stimuli(Mitchell et al., 2009), changes gamma-band LFP power (Gregoriou et al., 2009a; Taylor et al., 2005; Womelsdorf et al., 2006) and modifies stimulus tuning functions(McAdams and Maunsell, 1999; Reynolds et al., 2000; Williford and Maunsell, 2006). We found that relative RF value and average trial value manipulations had similar effects for all these measures. First, both have similar effects on local field potentials (**Figure 2.13a**), producing increased gamma band power (40-80Hz, WSR, $p<10^{-6}$). Power modulation by relative RF value and average trial value did not differ significantly in the gamma band (WSR, $p=0.776$). Second, both similarly decreased trial-to-trial variability

measured using the Fano factor (**Figure 2.13b**; LS-SL: MI:-0.022, WSR, p=0.014; LL-SS: MI=-0.029, WSR, p=0.001), and the extent of modulation by relative and average trial value did not differ significantly (WSR, p=0.920). Finally, we characterized orientation tuning functions using reverse correlation (Nienborg and Cumming, 2009; Ringach et al., 1997) and found that both relative RF value and average trial value manipulations predominantly affected tuning functions by additive shifts (WSR, $p<10^{-4}$) rather than multiplicative scaling (WSR, p>0.05). Although this contrasts with findings of multiplicative effects in visual cortex(McAdams and Maunsell, 1999), modulations inconsistent with pure multiplicative gain effects are also frequently observed (Luck et al., 1997; Thiele et al., 2009). Furthermore, recent studies find weak evidence for clearly distinguishing between additive and multiplicative models of response enhancement by attention (Sanayei et al., 2015; Williford and Maunsell, 2006). Critically, the extent of additive and multiplicative changes to orientation tuning functions did not differ between relative RF value and average trial value manipulations (**Figure 2.13c**, WSR, p>0.2). Therefore, modulation due to average trial value was largely indistinguishable from modulation due to relative RF value, suggesting that absolute reward is a key determinant of neuronal modulation in V4.

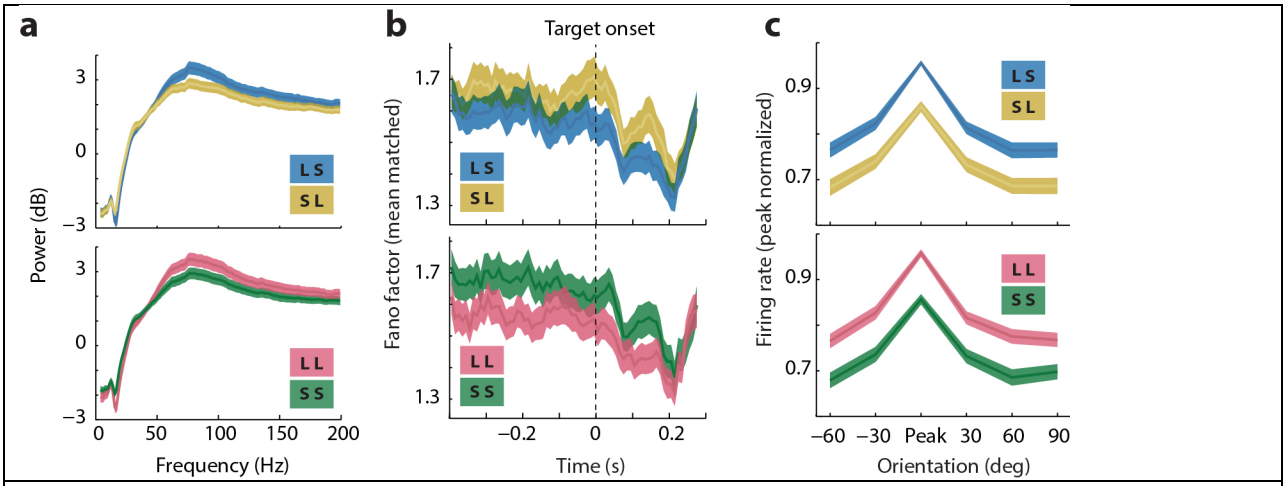

Figure 2.13. Relative RF value and average trial value similarly modulate power spectra, trial-to-trial reliability, and orientation tuning (**a**) Increases in relative RF value and average trial value both increased power in the gamma band (40-80hz, $p<10^{-6}$). Normalized power spectra are shown for each condition (n= 69 sites). Shading indicates +/- 1 SEM. (**b**) Increases in relative RF value and average trial value both increase trial-to-trial reliability. Mean-matched Fano factors aligned on target/distracter onset (bin width 50 ms, step size 10 ms). Shading indicates +/- 1 SEM. (**c**) Relative RF value and average trial value similarly modulate orientation tuning. Population orientation tuning functions (n=105) from subspace reverse correlation. Orientation tuning functions for each unit were peak normalized and aligned on the preferred orientation prior to averaging. Shading indicates +/- 1 SEM.

Eye movement plans do not account for dissociation between neural activity and attentional behavior.

Eye movement plans modulate V4 firing rates (Moore et al., 1998, 2003; Tolias et al., 2001), and one recent study argues that eye movement plans modulate firing rates independently of attention (Steinmetz and Moore, 2014, but see Luo and Maunsell, 2015). We therefore examined whether systematic differences in eye movement plans between conditions could account for our results. For example, if monkeys planned eye movements into the RF of recorded neurons during LL trials but not SS trials, this might account for elevated firing rates in LL that were unaccompanied by commensurate behavioral benefit.

To characterize eye movement planning across conditions, we examined the direction of frequency of saccades prior to presentation of choice targets. Unsurprisingly, given the strong link between attentional allocation and eye movement planning, we found that pre-emptive saccades were generally directed towards the high reward location in unbalanced conditions (**Figure 2.14**). In LS (large reward in RF, small reward opposite), 91% of all pre-emptive saccades were directed towards the RF stimulus, compared to 1% towards the opposite stimulus (χ^2-test, $p<10^{-10}$). In SL trials (small reward in RF, large reward opposite), 3% were directed towards the RF stimulus, compared to 78% towards the opposite stimulus (χ^2-test, $p<10^{-10}$).

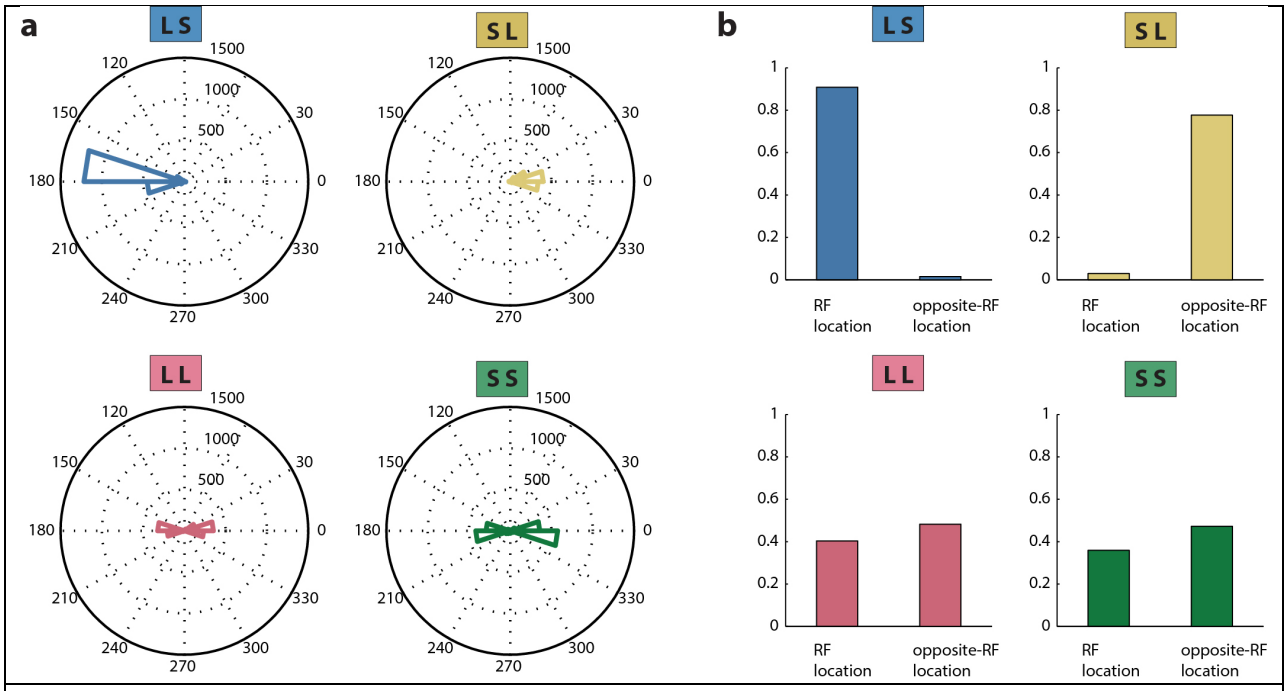

Figure 2.14. Eye movement plans do not account for dissociation of neural activity and attentional behavior. (**a**) Polar histograms indicating the direction of pre-emptive saccades, across all trials in each condition. Plots are aligned such that saccades to the RF stimulus are assigned an angular position of 180°, and saccades to the location opposite the RF are assigned an angular position of 0°. (**b**) Fraction of pre-emptive saccades directed to the RF stimulus and opposite-RF stimulus in each condition. In LS and SL, pre-emptive saccades were directed towards the high reward location. Between LL and SS, there was no significant difference in the fraction of saccades directed to RF and opposite-RF locations (χ^2-test, $p=0.26$).

In the balanced conditions (LL and SS), both monkeys showed a slightly increased tendency to make pre-emptive saccades to the opposite-RF compared to the RF stimulus (LL: 40% to RF, 48% to opposite-RF, χ^2-test, $p<10^{-5}$; SS: 47% to RF, 36% to opposite-RF, χ^2-test, $p<10^{-10}$). Importantly, of the saccades made to either stimulus location, the fraction directed to RF locations did not differ between LL and SS conditions (χ^2-test, $p=0.26$). Therefore, we conclude that differences in eye movement planning across conditions do not account for our results.

Eye position does not account for neural or behavioral effects.

Monkeys were required to fixate within a window of 1.0-1.5° throughout the duration of the trial. Nevertheless, small differences in eye position between conditions, if systematic, could have considerable effects on the measured behavior and neural activity. This is especially the case for pupil diameter measurements, which are known to be sensitive to eye position (Gagl et al., 2011). Eye position differences might also shift stimuli with respect to recorded neurons' receptive fields, producing uncontrolled changes in firing rate.

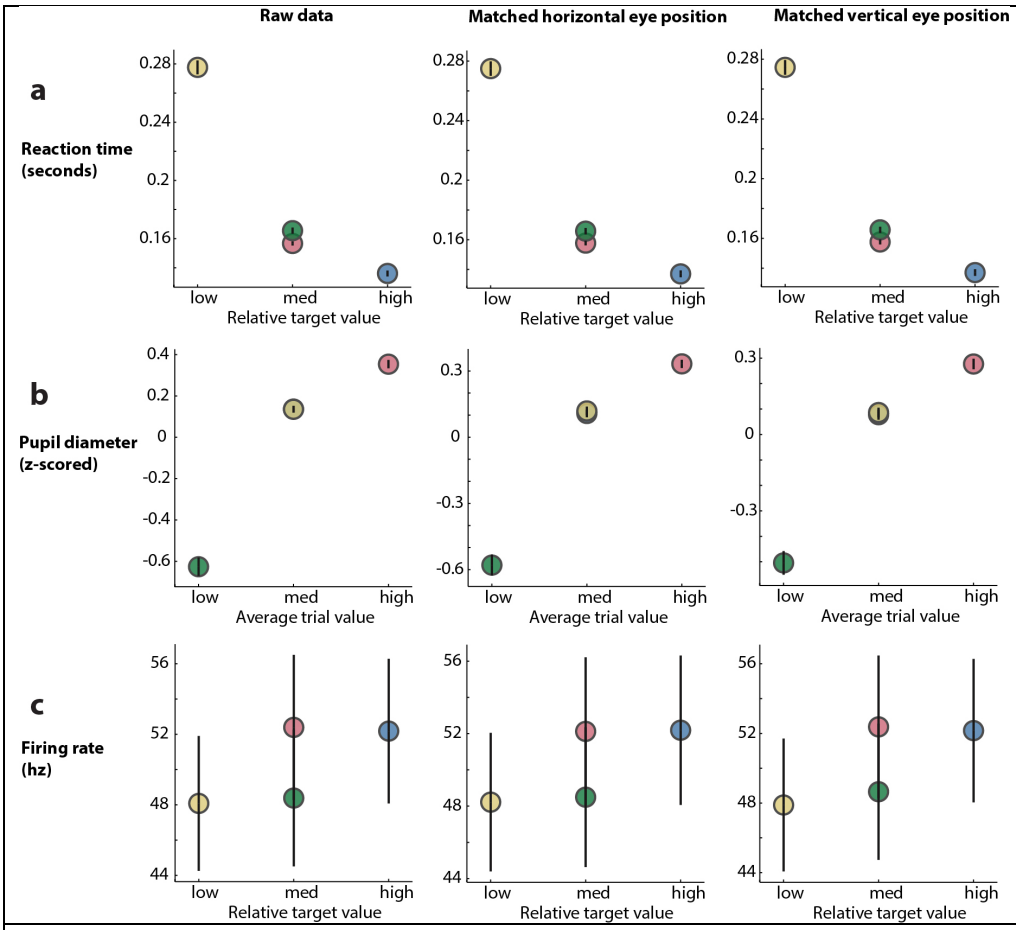

Figure 2.15. Eye position does not account for neural or behavioral effects. (a) Reaction times reflect relative value, even after matching eye position across condition. Raw reaction time data are shown in left panel, reaction time data in subdistributions of trials with matched horizontal eye position are shown in the middle panel, and matched vertical eye positions are shown in right panel. (**b**) Pupil diameters reflect average trial value, even after matching eye position across conditions. (**c**) Firing rates reflect RF value, even after matching eye position across conditions.

To determine whether differences in eye position across conditions could account for any of our reported findings, we performed a matching procedure (Churchland et al., 2010) to generate subdistributions of trials with matched eye position distributions across all 4 conditions. We performed the matching procedure separately for vertical and horizontal eye position, and then assessed whether the observed effects of reaction time, pupil diameter, and firing rate were preserved in eye-position matched data.

We found that— even after matching eye position across conditions— reaction times tracked relative value (**Figure 2.15a**), pupil diameters tracked average trial value (**Figure 2.15b**), and firing rate reflected the value of RF stimuli (**Figure 2.15c**). Therefore, we conclude that differences in eye position across condition do not account for our results.

Choice bias does not account for dissociation of neural activity and attentional behavior.

One interesting recent study (Luo and Maunsell, 2015) demonstrates that V4 firing rate modulation accompanies changes in behavioral sensitivity, but not changes in response criterion (or bias). This finding is important because higher performance (typically measured as a hit rate) in the detection tasks often employed to study attention can be achieved by either increases in sensitivity or decreases in criterion at attended locations. Because our task is a discrimination (rather than detection) task, and each location was queried on half of trials, no adaptive response bias strategy was available. Nevertheless, if animals had employed a peculiar, non-adaptive response bias strategy, it could possibly account for our results. Specifically, to explain higher firing rates without commensurate behavioral benefit in LL compared to SS trials, monkeys would have to be more biased in LL than SS. If this were the case, then sensitivity increases from SS to LL trials might be of similar magnitude to sensitivity increases from SL to LS trials, consistent with observed firing rate effects.

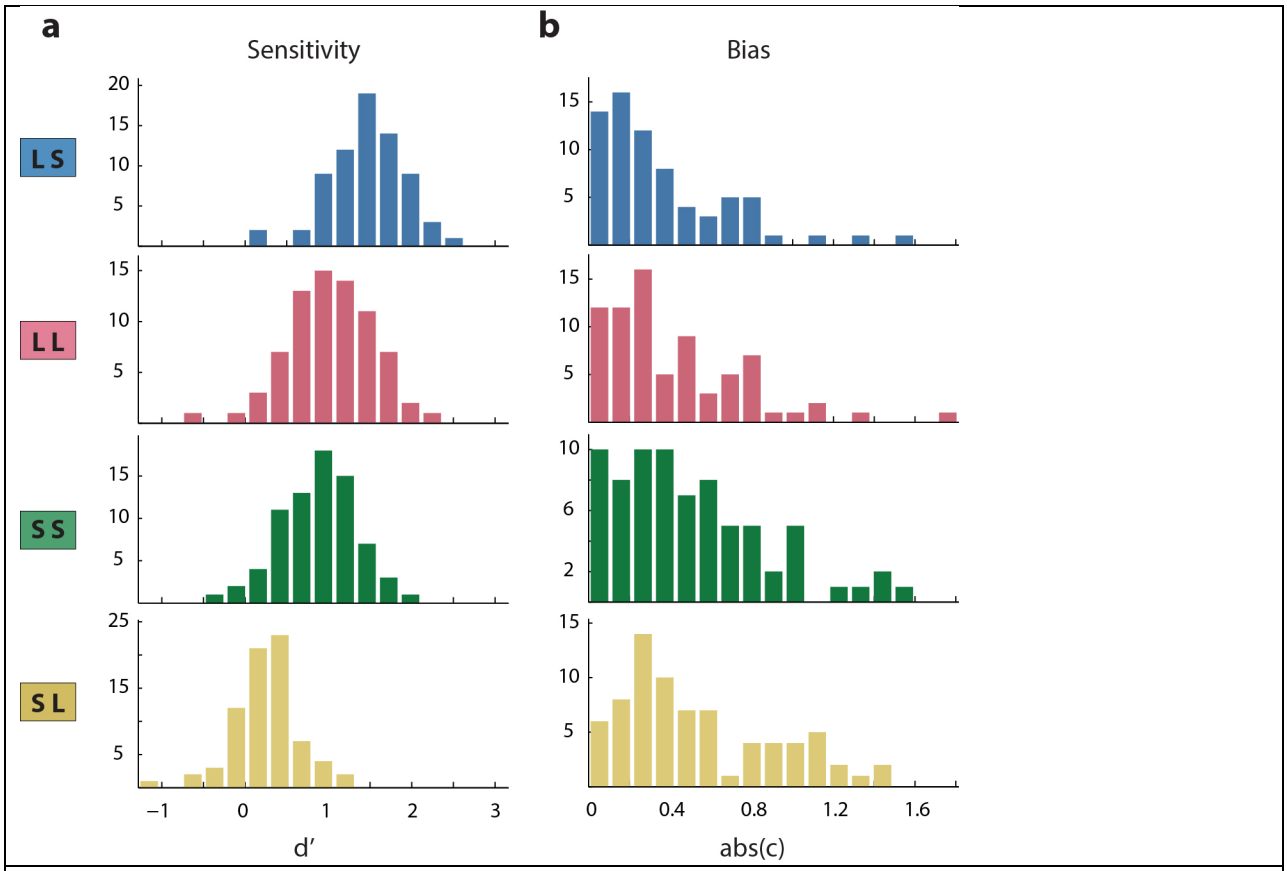

Figure 2.16. Behavioral sensitivity reflects relative value. Sensitivity (**a**) and bias (**b**) at the RF location for all behavioral sessions (n=79). Like performance, sensitivity increased with relative value (WSR, $p<10^{-7}$ for all comparisons differing in relative value) and there was a small but significant increase in sensitivity in LL compared to SS trials (WSR, $p<.005$). Bias did not differ significantly between conditions (WSR, $p>0.1$ for all comparisons), but trended towards an inverse relationship with relative value (highest bias in SL, lowest bias in LS).

We estimated behavioral sensitivity and bias, separately for each condition at the contralateral location. Because criterion shifts in either direction (favoring either horizontal or vertical choices) would have equivalent effects on performance, we computed 'bias' as the absolute value of criterion. We found that sensitivity, like performance, increased with relative target value (**Figure 2.16**). Bias was not significantly modulated by condition, but generally decreased with relative target value (**Figure 2.16**). Bias was higher in SS than LL trials (though not significantly). In summary, performance in our task largely indexed behavioral sensitivity,

and differences in bias and sensitivity across conditions can not account for the observed dissociation of neural modulation and performance enhancement.

2.3 Discussion

We discovered that neural modulation in V4 can be dissociated from the perceptual benefits of spatial attention; performance could be enhanced without neural modulation, and neural activity could be modulated without substantial perceptual improvement. These findings are inconsistent with signal-to-noise based mechanisms of attention that depend on the quality of V4's sensory representation at a given location. Our data instead suggest that modulation of neural activity in V4 reflects the absolute value of stimuli within the RF, and behavioral benefits accrue only when there is an imbalance in response modulation across V4. These observations imply that, at least in our task, efficient selection is the critical mechanism linking neural modulation in V4 to the behavioral benefits of attention. According to this hypothesis, the characteristic response enhancement observed in attentive states may primarily reflect a weighting of sensory signals by their associated absolute reward, which serves to bias competitive selection by downstream brain areas (Chen and Seidemann, 2012; Krauzlis *et al.*, 2014; Pestilli *et al.*, 2011 Zénon and Krauzlis, 2012). Together, these data argue that the link between neural modulation in V4 and its perceptual consequence may depend critically on downstream readout.

Although our results may appear at odds with prior studies of attention in V4, we actually find substantial agreement when considering comparable reward configurations. Consistent with prior reports, when we manipulated relative value (LS-SL), we observed large changes in attentional behavior that were associated with enhanced firing rate (Moran and Desimone, 1985; Motter, 1993) and gamma-band power (Gregoriou et al., 2009b; Taylor et al., 2005; Womelsdorf et al., 2006). In several prior studies, investigators have described robust trial-to-trial correlations between these neural correlates of attention in V4 and behavior (Cohen and Maunsell, 2010;

Womelsdorf et al., 2006), suggesting that neural modulation in V4 may be causally involved in conferring the associated behavioral changes. However, the observation of trial-to-trial correlations does not indicate the mechanism by which V4 neural modulation may affect behavior. Fluctuations in V4 activity at relevant locations could be correlated with perceptual performance either by modulating the signal-to-noise ratio in the relevant sensory representation or by biasing selection of relevant locations by downstream processes. These mechanisms can be distinguished by considering two reward conditions (LL and SS), which have rarely been studied in the context of visual attention. Varying average trial value while holding relative value fixed (LL-SS) had minimal effects on behavioral measures of attention, but effects on V4 activity were comparable to relative value manipulations (LS-SL). This striking dissociation of neural activity and perceptual performance suggests that, at least in our task, V4 neural modulation contributes to performance by promoting selection rather than by enhancing signal-to-noise.

Enhanced performance in the detection tasks used in many attention studies can result from both increasing sensitivity as well as shifting criterion to respond more readily to cued compared to un-cued locations. Recently, Luo and Maunsell (Luo and Maunsell, 2015) manipulated in tandem the relative and absolute reward of two locations to induce changes in sensitivity without modifying criterion; other reward manipulations changed criterion without affecting sensitivity. They found that modulation of neural activity in V4 is associated with sensitivity changes, but not criterion shifts. Our data are also compatible with these results. We used a dual discrimination task in which discriminanda are equally likely to fall on either side of an orientation category boundary; biasing choices towards horizontal or vertical categories was therefore maladaptive. Consequently, our task conditions are most analogous to conditions where Luo and Maunsell changed sensitivity, not response bias. When considering comparable

conditions to Luo and Maunsell, we observed that V4 activity is enhanced along with behavioral sensitivity (e.g. LS vs. SL). However, we independently manipulate relative and absolute reward; data from these conditions demonstrate that behavioral sensitivity can increase without V4 modulation (SS vs. SL) and that V4 modulation is not always accompanied by commensurate changes in behavioral sensitivity (LL vs. SS). These data reveal that the sensitivity changes quantified by signal detection theory are likely implemented by selection, rather than signal-to-noise, mechanisms.

The manipulation of average trial value in our task may recruit similar neural mechanisms to those involved with arousal (Harris and Thiele, 2011; Niell and Stryker, 2010; Reimer et al., 2014) and the heightened "cognitive effort" associated with more difficult tasks (Boudreau et al., 2006; Ruff and Cohen, 2014b; Spitzer et al., 1988). These non-spatial vigilance factors are associated with enhanced neural activity (Harris and Thiele, 2011; McGinley et al., 2015; Reimer et al., 2014), but the link between enhanced neural activity in these settings and perception remains unclear. The neural correlates of average trial value have rarely been reported in primate visual cortex. Beyond sensory cortex, neural activity in many brain areas is modulated by reward-related parameters that can be used to compute average trial value, including orbitofrontal cortex (Padoa-Schioppa and Assad, 2006; Roesch and Olson, 2004) , dorsolateral prefrontal cortex (Leon and Shadlen, 1999), cingulate cortex (McCoy et al., 2003), LIP (Dorris and Glimcher, 2004; Platt and Glimcher, 1999; Rorie et al., 2010; Sugrue et al., 2004), striatum (Kim and Hikosaka, 2013), basal forebrain (Peck and Salzman, 2014), and the amygdala (Paton et al., 2006; Peck et al., 2013). Some of these brain areas may provide direct or indirect inputs to V4 that underlie the modulation we observe.

Since manipulating relative reward value across the visual field shifts spatial attention, brain areas that reflect the selection underlying attentional behavior should exhibit signals modulated by relative, rather than absolute, reward value. However, the presence of modulation by relative reward may also reflect the spatial scale of the task used to characterize neural response properties. For example, modulation of neural activity in area V1 is correlated with relative value when two stimuli appear in the visual field (Stănişor et al., 2013). One critical difference between the task used to make this observation and ours is the spatial separation of visual stimuli. Whereas our data demonstrate that rewards associated with stimuli in the opposite hemi-field do not modulate activity in V4, the prior study employed competing saccade targets placed near each other in the same quadrant of the visual field. Interestingly, the pattern of results observed in both studies is predicted by the normalization model of attention (Reynolds and Heeger, 2009), where the response of a neuron to a stimulus in its RF is suppressed (or normalized) by a pool of neurons responsive to a broader range of features and spatial positions. We demonstrated this by using the normalization model of attention to simulate the response of a population of neurons to two visual stimuli that vary in location and associated reward (**Figure 2.17**). We found that top-down response enhancement by absolute reward leads to suppression of responses to stimuli presented at locations nearby but not far away, with the spread of suppression determined by the spatial extent of neurons within the normalization pool. If these considerations are correct, then V1 activity would not reflect relative value when tested with two stimuli located far enough from each other such that neurons in the normalization pool do not respond to both stimuli. In the model, the details of this change are dictated by the spatial scale of the top-down enhancement ("attention field") and the spatial scale of the normalization pool. The spatial scale of top-down enhancement is likely task dependent (Reynolds and Heeger,

2009); this emphasizes the critical importance of studying different brain areas with identical tasks in order to determine the contribution of relative and absolute reward on neural firing rates.

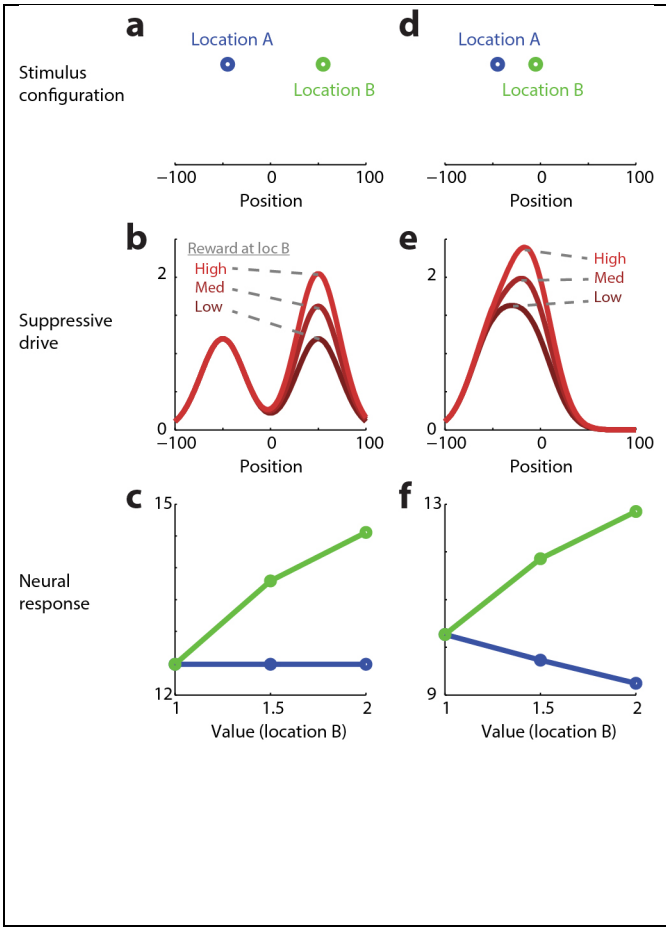

Figure 2.17.Normalization predicts interaction between reward and spatial scale. (**a-c**) When stimuli are far apart, top-down modulation by absolute reward at location B does not affect responses at location A. (**a**) Locations of the two Gabor stimuli, used as inputs to the normalization model (**b**) Each stimulus drives divisive suppression of neurons with nearby RFs. Suppressive drive is here plotted as a function of position, for three different reward levels at location B. (**c**) Neuronal response from a unit with RF at location A (blue), and another unit with RF at location B (green). When the reward associated with location B increases, firing rates at location B increase, but responses at location A are unchanged. (**d-f**) When stimuli are close together, top-down modulation by absolute reward at location B decreases responses at location A. (**e**) When stimuli are close together, suppressive fields overlap, and (**f**) increases in reward at location B are associated with decreased responses at location A.

One brain area that exhibits relative value modulation at a larger spatial scale is the lateral intraparietal area (LIP). Our data demonstrate that the classic attention-related modulations of V4 activity can be decoupled from behavioral measures of spatial attention. LIP receives inputs from V4, but displays relative value modulation characteristic of competitive selection both within (Falkner et al., 2010) and across hemi-fields (Louie et al., 2011; Platt and Glimcher, 1999; Rorie et al., 2010; Sugrue et al., 2004), suggesting that LIP may transform V4 activity into relative value through response normalization (Louie et al., 2011). LIP is unlikely to be solely responsible for selecting behaviorally relevant sensory signals. Similar transformations may occur at multiple points along sensorimotor pathways, which is supported by recent

evidence in visual search (Mirpour and Bisley, 2012). Characterization of these transformations is likely critical for understanding the sequential and interactive processing carried out in different brain areas to confer the perceptual benefits of attention. Our data indicate that the manipulation of absolute and relative reward values while measuring attentional behavior is a powerful tool for providing this characterization.

2.4 Methods

Animals and implantation. Two male rhesus monkeys (*Macaca mulatta*, 8–13 kg, 7-8 years old) were used in these experiments. All experimental procedures complied with US National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committees at the New York State Psychiatric Institute and Columbia University. Prior to training, we implanted a plastic head post secured to the skull using ceramic bone screws. Surgery was conducted using aseptic techniques under isoflurane anesthesia, and analgesics and antibiotics were administered postsurgically. After the monkeys were behaviorally trained, we acquired T1-weighted MRIs with fiducial markers attached to the head post. In a second surgery, we implanted a plastic recording chamber over dorsal visual area V4 guided by a neuronavigation system (Brainsight, Rogue Research, Quebec, Canada) registered to the MRI for each monkey. Recordings targeted the lunate gyrus posterior to the junction of the superior temporal sulcus and the sylvian fissure.

Data acquisition. Monkeys were seated and head-restrained in a darkened sound-attenuating booth. Eye position and pupil diameter were monitored using an infrared camera sampled at 1000 Hz (Eyelink, SR Research, Ontario, Canada). Visual stimuli were generated using EXPO (Center for Neural Science, New York University) and were displayed on a CRT monitor positioned 57 cm away from the monkey.

We recorded from the right dorsal V4 of each monkey using one or two electrodes individually lowered with a multiple-electrode microdrive (NaN Instruments, Nazareth, Israel**).** Extracellular activity was recorded using epoxylite-insulated tungsten electrodes (8-10 MΩ impedance; FHC Inc., Bowdoinham, Maine) or glass-coated tungsten electrodes (0.5-2.0 MΩ impedance; Alpha

Omega, Alpharetta, Georgia). Analog signals were amplified, band-pass filtered (250–7500 Hz) and sampled (30 kHz) for unit isolation (Blackrock Microsystems, Salt Lake City, Utah). Units were isolated using manual clustering on the basis of several waveform parameters including principal components, peak and trough amplitudes, as well as the presence of a refractory period (Plexon Offline Sorter, Plexon, Dallas, TX). LFPs were filtered between 0.3 and 500 Hz and sampled at 1 kHz.

Behavioral task and visual stimuli. Monkeys performed a dual 2-AFC orientation discrimination task for liquid reward. Trials were initiated when monkeys fixated a central spot. Monkeys were required to maintain fixation throughout the trial within a window of radius 1.0-1.5°. After 300 ms of fixation, two reward cues appeared for 250 ms. Reward cues were uniform chromatic discs of 0.5° diameter, 2.0-2.5° eccentricity, and an angular position matched to subsequently appearing Gabor patches. Reward cues indicated the amount of juice associated with correct discrimination of the associated Gabor patch. For each monkey, we employed two different, luminance-matched cue sets. Cue colors were defined in DKL color space (large reward azimuths: 220° and 340° [M1], 20° and 135° [M2]; small reward azimuths: 90° and 280° [M1], 220° and 280° [M2]). Cue sets did not substantially affect any of the reported behavioral results. Considering separately the subset of trials from each cue set in each monkey, performance was always highest in LS (CMH, $p<10^{-4}$) and lowest in SL (CMH, $p<10^{-10}$), reaction times were fastest in LS (WRS, $p<10^{-10}$) and slowest in SL (WRS, $p<10^{-10}$), pupils were most dilated in LL (CMH, $p<10^{-6}$) and least dilated in SS (CMH, $p<10^{-10}$), and aborted trials were most frequent in SS (CMH, $p<0.05$). Similarly, performing the regression analysis separately on the subset of trials from each cue set in each monkey yielded similar results. For each cue set in each monkey, associating a large reward with RF stimuli increased firing rates

(WSR, $p<10^{-6}$), and associating a large reward with the location opposite RF did not significantly alter firing rates (WSR, $p>0.1$).

The offset of the reward cues was followed by a 350 ms delay, after which two streams of stimuli appeared, one in the receptive field of the neuron under study, and the other diametrically opposed in the opposite hemi-field. The streams were composed of presentations of Gabor patches lasting 20 ms, interleaved with blank stimuli of the same duration matched to the background luminance of the monitor (probability of blank = 0.15). The orientation of each Gabor presentation was independently and randomly drawn from a set of 6 equally spaced orientations (0°, 30°, 60°, 90°, 120°, 150° from horizontal). The spatial frequency and size of Gabor patches were tailored to the neuron under study. On each trial, the streams of Gabor presentations were stopped at a random time, which was determined by adding a fixed minimal duration to a random draw from an exponential distribution (truncated at a maximum of 2 sec) to approach a flat hazard rate (Ghose and Maunsell, 2002). Across all experiments, the average stream duration was 685.7 ms.

Following the streams of Gabor presentations, a final pair of Gabors appeared at the two stimulus locations. We term these two final Gabor presentations the target and distracter (together, the discriminanda). Discriminanda were distinguished from prior stimuli in the stream primarily by a longer presentation duration. Mean discriminanda duration was 96.7 +/- 2.0 ms, which was adjusted to maintain consistent performance. The discriminanda were followed by noise masks lasting 60 ms. Choice targets then appeared at one of the two locations, which was the monkeys' first indication of the identity of the target and distracter. In other words, the location about which monkeys would be asked to render a perceptual decision was not revealed to the monkey until after extinction and masking of the discriminanda. Thus, the behavioral

relevance of discriminanda was exclusively determined by the associated reward signaled by prior appearing cues. Choice targets flanked the location of extinguished discriminanda, and monkeys reported whether the orientation of the target was more horizontal or more vertical by saccading to the choice target nearest the horizontal meridian or the choice target nearest the vertical meridian, respectively. Discriminanda orientations were randomly selected on each trial and varied between 3° (difficult) and 45° (easy) away from the category boundary (corresponding to 0°- 90° from horizontal).

Correct trials were rewarded as indicated by the cue associated with the target. Large rewards were 4-5 times larger than small rewards. For M1, the small reward was 0.10 mL, and the large reward was 0.50 mL. For M2, the small reward was 0.07 mL, and the large reward was 0.31 mL. Fixation breaks prior to the appearance of choice targets resulted in trials in which the payoff structure, queried location, and discriminanda orientation (but not the duration of Gabor streams) were repeated. This ensured that monkeys could not increase their reward rate by aborting trials of low expected value. Following completed trials, both correct and incorrect, the subsequent trial type was determined pseudorandomly by sampling without replacement from a 16-element matrix (4 conditions X 2 cue sets X 2 repetitions).

Data analysis

All statistical tests were two-sided. When parametric tests were employed, data distributions were assumed to be normal but this was not formally tested. We did not perform analyses blind to the identity of trial types. We did not run any statistical test to determine sample sizes a priori, but our sample sizes are similar to those generally employed in the field.

Conditions. For performance and reaction time data, conditions are defined with respect to the queried location (**Figure 2.1b**). For example, for performance and reaction time data, LS refers

to the unbalanced condition where the monkey is asked to report the orientation of the stimulus associated with large reward. By contrast, firing rate and pupil data were taken from an epoch prior to the appearance of saccade targets, before the queried location is determined. Therefore, for these metrics, the unbalanced conditions are defined with respect to the location of the receptive field. When referring to neural data, LS refers to the unbalanced condition where the large reward stimulus is in the receptive field.

In order to characterize the influence of reward expectation on neural activity and behavior, we distinguish between three types of value. 'Absolute value' refers to the reward associated with queried or RF locations, independent of the value of other stimuli in the visual field. 'Relative value' refers to the fractional payoff associated with the queried or RF location. ‘Average trial value’ describes the overall reward expectancy of the trial as the average reward for a trial prior to identification of target and distracter locations.

Behavior. For proportion data (percent correct and abort rate), we assessed statistical significance using the Cochran-Mantel-Haenszel test. Aborted trials were trials where monkeys broke fixation after onset of reward cues. For comparisons of reaction time and pupil diameter across conditions, we assessed statistical significance using two-tailed Wilcoxon rank-sum tests. Reaction times were defined as the beginning of a choice target-directed saccade. Pupil diameter values were taken from the same epoch as spike counts (300 ms prior to onset of discriminanda) and z-scored by session.

To characterize eye movement planning, we examined the direction and frequency of pre-emptive saccades. Pre-emptive saccades were defined as any saccade meeting speed and acceleration criteria that terminated outside of the fixation window. To quantify the fraction of

saccades directed to RF and opposite-RF locations, we considered any saccade with an angular direction within 45° of either stimulus to be stimulus-directed.

Sensitivity and bias were computed according to signal detection theory (Green and Swets, 1966). Sensitivity was computed as:

$$d' = \varphi^{-1}(\textit{hit rate}) - \varphi^{-1}(\textit{false alarm rate}),$$

where φ^{-1} is the inverse cumulative normal function, the *hit rate* is the fraction of vertical discriminanda reported as vertical (via the appropriate saccade), and the *false alarm rate* is the fraction of horizontal discriminanda reported as vertical. Bias was computed as the absolute value of criterion:

$$c = (-\tfrac{1}{2})*(\varphi^{-1}(\textit{hit rate}) - \varphi^{-1}(\textit{false alarm rate})),$$

where terms are defined as above.

Regression. We used multiple, linear regression to quantify how the reward contingency at each location affected neuronal activity and behavior across the population. The regression was performed on spike rates in the 300 ms epoch prior to onset of discriminanda. We chose this time epoch because it is close to measured behavior, yet prior to the appearance of discriminanda. Therefore, firing rates in this epoch are not affected by ultimate discriminanda orientation, attendant differential reward expectation (for easy vs. difficult discriminanda), and/or presaccadic activity related to choice. For each neuron, we regressed the firing rate in this epoch onto two predictors and a constant term:

$$FR = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2 ,$$

where x_1 is a categorical predictor indicating whether the receptive field location is associated with large reward (x_1=1 for LS and LL trials, x_1=0 for SL and SS trials), and x_2 is a categorical predictor indicating whether the opposite location is associated with large reward (x_2=1 for SL

and LL trials, x_2=0 for SS and LS trials). Therefore, β_1 indicates the effect on firing rate of high value in the receptive field and β_2 indicates the effect of high value opposite the receptive field. If neuronal modulation reflected the relative value of the discriminanda in the receptive field, this would be captured in the regression coefficients by oppositely signed β_1 and β_2. To assess statistical significance of regression coefficients, we performed two-tailed Wilcoxon signed-rank tests. We also examined an expanded model, which included reaction time and pupil diameter as additional predictors, which yielded similar results (**Figure 2.18**).

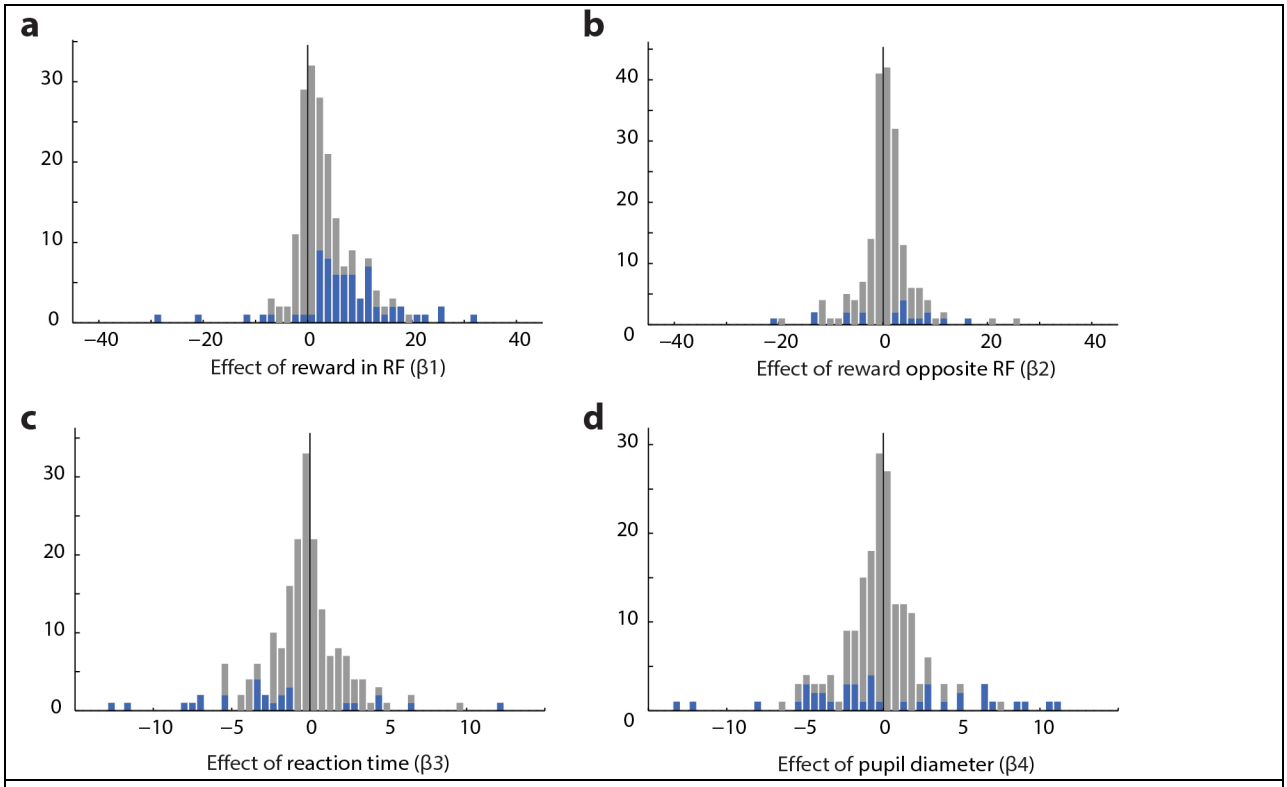

Figure 2.18. Regression coefficients for expanded model. Symbol style denotes significance for individual sessions/units, (n=190). (**a**) Large rewards at the RF location were associated with increased firing rates (mean β_1= +3.678 spikes/sec). (**b**) Large rewards opposite the RF were associated with small increases in firing rate (mean β_2= +0.397 spikes/sec), inconsistent with relative value modulation (**c**) Increased reaction times were associated with small decreases in firing rate (mean β_3= -0.350 spikes/sec). (**d**) Increased pupil diameters were associated with small decreases in firing rate (mean β_4= -0.350 spikes/sec).

To characterize reward modulation of behavior, we performed the same regression on our single-trial resolved measures of behavior. For each session, we regressed reaction times and pupil diameters from the 300 ms epoch prior to discriminanda onset onto two predictors and a constant term, e.g.:

$$RT = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2 ,$$

where x_1 is a categorical predictor indicating whether the target is associated with a large reward, and x_2 is a categorical predictor indicating whether the distracter associated with a large reward. As above, β_1 indicates the effect on behavior of high value at the queried location and β_2 indicates the effect of high value opposite the queried location.

Effect size (*d'*) analysis. We assessed differences in firing rate across conditions using *d'*, defined as:

$$d' = (\mu_1 - \mu_2) / \sqrt{((SS_1 + SS_2)/(df_1 + df_2))}$$

where μ_X is the mean, SS_X is the sum of squares and df_X is degrees of freedom (number of trials–1) for each condition. We assessed the statistical significance of *d'* values across all neurons using two-tailed Wilcoxon signed-rank tests. We assessed the statistical significance of individual neuron *d'* values by a randomization test. To perform randomization tests, reference distributions were constructed by computing *d'* value for 10,000 random assignments of conditions to trials. Comparisons were deemed significant if >97.5% of the reference distribution fell on one side of the observed value (equivalent to a two-tailed test at $\alpha = 0.05$). *d'* values were computed from firing rates in the 300 ms epoch prior to onset of discriminanda.

We also quantified effect sizes using modulation indices (MI), defined as: MI = (a-b) / (a+b), where a is the mean in the modulated condition (e.g. LS, LL), and b is the mean in the reference

condition (e.g. SL, SS). Quantifying effect sizes using modulation indices did not alter any of the reported results.

We used χ^2 tests to assess the statistical significance of differences in the proportion of units modulated by each pairwise condition comparison (e.g. relative value [LS-SL] vs. average value [LL-SS]), as well as the independence of this modulation across units.

Attention axis analysis. Population activity was analyzed using peak-normalized spike counts from the 300 ms epoch preceding discriminanda onset. We sought to characterize how activity across a population of V4 neurons changes in the different reward conditions. Since we did not record activity from many neurons simultaneously, we constructed a population response for each trial using the following procedure. First, to equalize trial numbers for each neuron-condition, we randomly resampled trials with replacement. Trial order within each neuron-condition was then shuffled to generate trial activity for a population of the same size as the number of neurons we recorded (n=190). Note that while this procedure allows us to examine population activity in a multivariate manner, it is limited in that we cannot determine the role of inter-neuronal correlations or across-trial fluctuations since neurons were not recorded simultaneously.

A random half of trials were selected to define the attention axis(Cohen and Maunsell, 2010). The remaining half of trials were projected onto the attention axis, and used to calculate the discriminability (*d'*) of pairwise condition comparisons. We repeated this process 1000 times. In **Figure 2.12**, we plot the mean *d'* across runs, as well as the intervals containing the middle 95% of values across runs. These confidence intervals were used to determine whether *d'* values differed significantly from each other. We determined whether *d'* values differed significantly from chance by using a randomization test. We randomly assigned conditions to trials and then

computed discriminability (*d'*) values along the attention axis as described above. The 95% confidence intervals for this reference distribution are plotted as the shaded area in Figure 2.12. Mean *d'* values for a given comparison were deemed significant if >97.5% of the reference distribution fell on one side of the observed value (equivalent to a two-tailed test at $\alpha = 0.05$).

Spectral analysis. We estimated power spectra using a multi-taper algorithm (Mitra and Bokil, 2007) implemented in the Chronux toolbox (www.chronux.org), using 7 tapers and a time-bandwidth product of 5. As with analyses of spike rate, we used the 300 ms epoch directly preceding onset of the discriminanda to compute power spectra. Raw power spectra during this period were converted to decibels with respect to reference power spectra collected during the 300 ms epoch preceding reward cue onset. To assess statistical significance in defined frequency bands, we used two-tailed Wilcoxon signed-rank tests.

Fano factor analysis. Fano factors were computed from spike counts in the 300 ms epoch directly preceding discriminanda onset. We characterized Fano Factor modulation using a modulation index, calculated as described above. Statistical significance of Fano factor modulation was assessed using a two-tailed Wilcoxon signed-rank test on the distribution of MIs. To determine whether Fano factor differences could be attributed to differences in firing rate across conditions, we performed a mean-matching procedure (adapted from (Churchland et al., 2010)). We computed Fano factors in sliding time bins (50 ms width, 10 ms steps) using subdistributions of units with matched spike count distributions across all 4 conditions. Because our interest was in differences across conditions (but not across time), we allowed the mean count distributions to fluctuate across time bins.

Orientation tuning analysis. We characterized orientation-tuning functions using reverse correlation (Ringach et al., 1997). To construct orientation-tuning functions, we first determined

a unit-specific time window in which to analyze responses to individual 20 ms Gabor presentations. Unit-specific time windows were employed because units displayed diverse temporal responses to orientation (**Figure 2.19**). For example, units varied substantially in the timescale over which orientation influenced firing rates and often displayed time-varying (e.g. biphasic) orientation tuning kernels. In defining spike-counting windows, we aimed to capture the epoch where orientation tuning was maximally expressed and temporally consistent. To define the counting window for each unit (**Figure 2.20**), we first determined the time with respect to Gabor presentation onset with the largest effect of orientation on firing rate. Effect size was computed in 5 ms-wide bins, stepped every 1 ms, using a standard eta squared measure, $\eta^2 = (SS_{ori} / SS_{total})$, where SS_{ori} is the sum squared error in firing rates explained by orientation, and SS_{total} is the total sum squared error. Spike counting windows were centered on the time of peak orientation effect and extended in both directions as far as two criteria were met. First, we mandated that η^2 values remain above 10 standard deviations beyond that measured during a baseline epoch (150 ms prior – 40 ms after presentation onset). Second, we computed a sliding Spearman's rank correlation with the time of peak orientation effect size, and mandated that correlation coefficients in the window be greater than 0.3. Rank correlation coefficients were performed on the set of 6 spike density functions (1 ms step, σ= 5 ms) split by orientation. This second correlation criterion was necessary to restrict the counting window to an epoch where orientation tuning was temporally consistent. Using this method, the mean window size across all units was 39.6 +/- 2.1 ms. For the minority of orientation-tuned units that did not meet the above criteria (53 of 171 units with a significant effect of orientation by ANOVA), we employed a conservative window of 20 ms (equal to flicker duration) centered on the time of peak effect size.

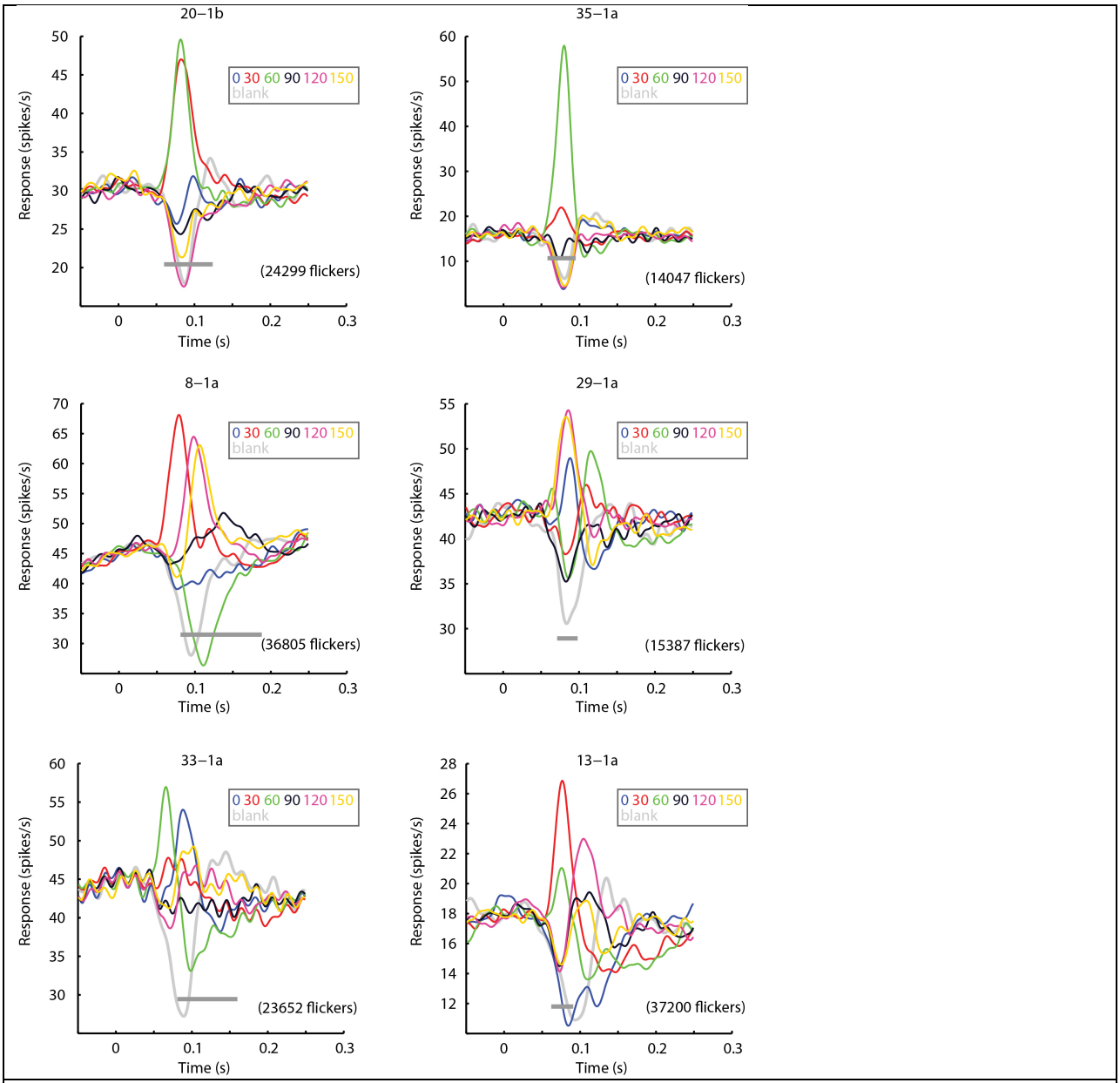

Figure 2.19. Diversity of orientation tuning responses. Spike density functions for 6 example units. Responses to individual 20 ms Gabor presentations within the stimulus stream were sorted by orientation, aligned on presentation onset, and averaged to generate spike density functions. Note that many neurons display multiphasic responses to orientation and time-varying orientation tuning. In each plot, the horizontal shaded line denotes the unit-specific counting window used to characterize orientation tuning.

Orientation tuning functions were calculated as the average spike rate elicited by stimuli of each orientation-condition. Because most units displayed pronounced transient responses to the onset of the stream of flickering stimuli, we excluded responses to the first three

presentations in the stream. Included in the population plot (**Figure 2.13c**) are all neurons (n=105) that showed (i) positive effects of relative value (LS-SL), (ii) positive effects of average trial value (LL-SS), and (iii) a significant effect of orientation by ANOVA (df=5, $p < 0.05$). Altering selection criteria had no effect on the qualitative outcome of orientation tuning analysis. For included units, the mean number of Gabor presentations used to construct tuning functions was 22,968 +/- 1,261.

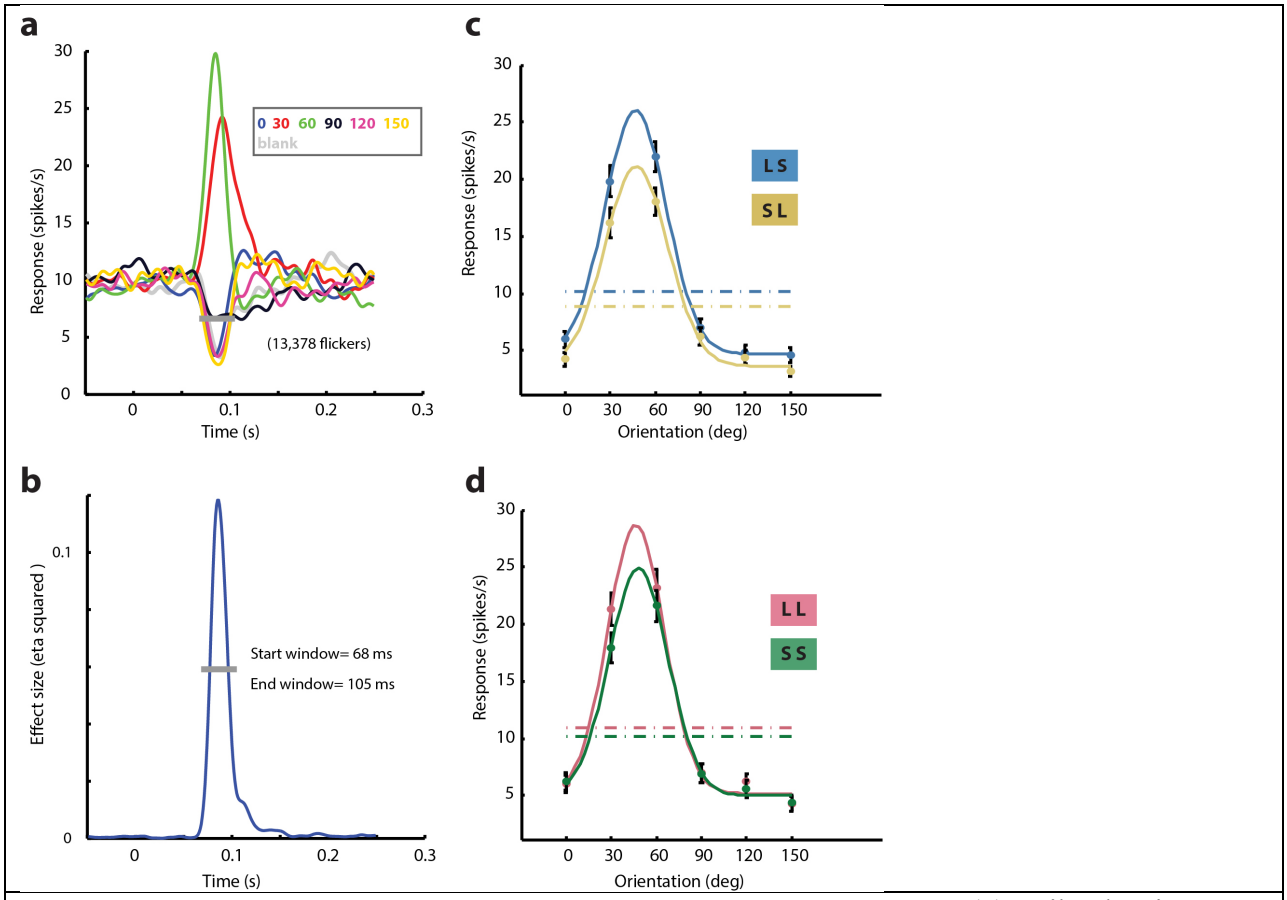

Figure 2.20. Procedure for constructing orientation-tuning functions. (**a**) Spike density functions (SDF) for an example unit. Responses to individual 20ms Gabor presentations within the stimulus stream were sorted by orientation, aligned on presentation onset, and averaged to generate spike density functions. (**b**) To determine a unit-specific spike count window, we computed the effect size (η^2) of Gabor orientation on firing rate in a sliding window (5 ms wide, 1 ms steps). Effect sizes, as well as correlation of SDFs across time, were used to define the window, denoted by the shaded line. (**c,d**) Spike counts were compiled into orientation tuning functions and fit with Gaussian functions. Error bars indicate +/- 1 SEM. Dashed lines indicate mean responses for each condition, averaged across orientation.

We characterized tuning function modulation by fitting a separate Gaussian to orientation-tuning functions for each of the 4 conditions. Each Gaussian had 4 free parameters: μ, σ, amplitude, and asymptote. Differences in μ and σ were interpreted as shifts in orientation tuning and bandwidth respectively. To summarize multiplicative scaling and additive shift of orientation tuning functions, we computed the ratio of fitted amplitudes and asymptotes respectively. We assessed statistical significance of differences in amplitude and asymptote ratios using Wilcoxon signed-rank tests on log-transformed ratios. For all statistical comparisons of Gaussian fit parameters, we included only the subset of units in Figure 2.13c with significant Gaussian fits to all 4 conditions, assessed using an F-test ($\alpha = 0.05$) that compared the Gaussian fits to fits to the mean response across all orientations (n=61 units with significant fits). Both average trial value and relative RF value had weakly positive but non-significant effects on the amplitude ratio of the fitted Gaussians (LS-SL, median ratio: 1.03, WSR, $p>0.05$, LL-SS median ratio: 1.006, WSR, $p>0.05$). By contrast, both average trial value and relative RF value modulations had significantly positive effects on the asymptote ratio of Gaussian fits (LS-SL: median ratio 1.10, WSR, $p<10^{-4}$; LL-SS: median ratio 1.14, WSR, $p<10^{-6}$). There were no significant changes to tuning bandwidth (σ).

Normalization model. We simulated reward modulation of population activity using the normalization model (Reynolds and Heeger, 2009) (http://www.cns.nyu.edu/heegerlab). The normalization model describes population activity as being shaped by an excitatory stimulus drive, a divisive suppressive drive, and a multiplicative attention field. In the spatial domain, the key parameters that determine whether the representations of two stimuli are mutually suppressive are the location and sizes of the stimuli themselves and the spatial spread of the suppressive field (*IxWidth*).

Figure 2.17 depicts two sets of simulations. For the simulation shown in **Figure 2.17a-c**, we used a stimulus consisting of 2 Gabors, each 10 units wide, with centers separated by 100 units. For the simulation shown in **Figure 2.17d-f**, we used a stimulus consisting of 2 Gabors, each 10 units wide, with centers separated by 20 units. In both cases, we simulated three levels of top-down modulation at location B by varying the *Apeak* parameter (*Apeak*= 1, 1.5, and 2). For all other parameters, we used the default values. To characterize the spatial profile of suppressive fields (**Figure 2.17b,e**), we plot the suppressive drive to only the segment of the population with orientation preference matched to the stimuli. To characterize response modulation of individual units (**Figure 2.17c,f**), we plot the response of two units, each having a receptive field center and orientation preference matched to the stimuli.

2.5 Author contributions

Brian Lau developed the task. Jalal Baruni and Brian Lau collected the data. Jalal Baruni performed the analysis, with assistance from Brian Lau. C. Daniel Salzman supervised all aspects of the project. Jalal Baruni, Brian Lau, and C. Daniel Salzman wrote the manuscript, reproduced in this chapter.

Chapter 3

The amygdala as attentional source

Abstract

The amygdala, long recognized for its role in mediating emotional responses, may also play a role in the control of attention. The amygdala sends prominent feedback projections to visual cortex, and recent physiological studies demonstrate that amygdala neurons carry spatial signals sufficient to guide attention. To characterize the role of the amygdala in the control of attention, we trained monkeys to discriminate the orientation of two stimuli presented simultaneously in different hemifields while independently varying the reward magnitude associated with correct discrimination at each location. During task performance, we recorded neural activity in the amygdala and V4 simultaneously. In preliminary data analysis, we noted two sets of findings. First, consistent with prior work, we found that amygdala neurons combine information about space and value. Rewards both contralateral and ipsilateral to amygdala neurons modulated responses, but contralateral rewards had a larger effect. Therefore, notably distinct from known attentional control sources in the oculomotor system, spatial-reward responses in the amygdala do not reflect the relative value of locations. Second, we found signatures of functional connectivity between the amygdala and V4 during task performance. Reward cue presentation was associated with elevated alpha and beta coherence, and attention to locations contralateral to the amygdala and inside the receptive field of V4 neurons was associated with elevated inter-area gamma coherence. These results suggest that the amygdala may serve a unique role in the control of spatial attention.

3.1 Introduction

In identifying brain areas involved with visual attention, a distinction is generally made between sensory areas that are modulated according to attentional priorities and "attentional source" areas that determine and control the objects of attention. Several such source areas have been identified, mostly oculomotor brain areas, including the frontal eye fields (Squire et al., 2013), lateral intraparietal area (Bisley and Goldberg, 2010; Cutrell and Marrocco, 2002; Wardak et al., 2004), and the superior colliculus (Cavanaugh and Wurtz, 2004; Goldberg and Wurtz, 1972; Lovejoy and Krauzlis, 2010; Müller et al., 2005).

In the frontal eye fields (FEF), for example, a particularly rich literature supports a role in the control of attention. Visually driven responses are enhanced when attention is directed into the receptive fields of FEF neurons (Gregoriou et al., 2012; Thompson, 2005). Lesions and reversible inactivation of FEF lead to attentional deficits in behavior (Monosov and Thompson, 2009; Wardak et al., 2006; Welch and Stuteville, 1958), as well as reduced attentional modulation in visual cortex (Gregoriou et al., 2014). Stimulation of FEF leads to enhanced behavioral sensitivity at topographically aligned locations of the visual field (Moore and Fallah, 2001, 2004), as well as neural modulation characteristic of attention in visual cortex (Armstrong and Moore, 2007; Armstrong et al., 2006; Ekstrom et al., 2009; Moore and Armstrong, 2003; Noudoost and Moore, 2011). Finally, when attention is directed into the RF of FEF and V4 neurons, gamma-band coherence (a putative measure of functional connectivity) is enhanced (Gregoriou et al., 2009b). Thus, converging evidence suggests that the FEF, in concert with other oculomotor structures, may control the locus of attention via its projections to visual cortex.

Brain areas beyond the oculomotor system may also contribute to the control of attention. One such area is the amygdala, which potentially influences visual cortex via two anatomical

pathways. First, the basal, accessory basal, and central nuclei of the amygdala project to the basal forebrain (Mesulam and Mufson, 1984; Price and Amaral, 1981; Russchen et al., 1985), from which cholinergic projections radiate broadly across cortex (Mesulam et al., 1983). In addition, the basal nucleus of the amygdala sends direct projections to large swaths of ventral visual cortex (Amaral and Price, 1984; Freese and Amaral, 2005; Iwai and Yukie, 1987). These projections reach back to V1 (Freese and Amaral, 2005; Iwai and Yukie, 1987) and, characteristic of feedback projections, target the upper layers of cortical columns (Amaral and Price, 1984; Freese and Amaral, 2005). Interestingly, unlike cortico-cortical connections (Felleman and Van Essen, 1991), the projections linking the amygdala to visual cortex are mostly unidirectional. Visual input to the amygdala arrives almost exclusively from anterior inferotemporal cortex (Iwai and Yukie, 1987), at the terminus of the ventral, visual form-processing stream. Thus, the anatomy linking the amygdala to visual cortex is highly suggestive. Along with convergent input from orbtofrontal and medial prefrontal cortices (Ghashghaei and Barbas, 2002; Ghashghaei et al., 2007), the amygdala receives high-level visual information about object identity, and directs modulatory feedback to the entire visual form-processing stream.

Feedback projections from the amygdala to visual cortex are generally regarded as functioning in aspects of vision related to emotion. Affectively significant stimuli— such as fearful faces, emotionally charged words (e.g. rape), or arbitrary visual stimuli associated with unconditioned stimuli (e.g. electric shock)— have privileged access to perception and behavior (Anderson and Phelps, 2001; Öhman et al., 2001). These visual stimuli are associated with elevated fMRI responses in visual cortex (Padmala and Pessoa, 2008; Pessoa et al., 2002; Vuilleumier et al., 2001) and the amygdala (Vuilleumier et al., 2001), and trial-to-trial fluctuations in amygdalar responses to affective stimuli, visual cortical responses to affective

stimuli, and detection performance in a capacity-limited task are significantly correlated (Lim et al., 2009). Similarly, bilateral amygdala lesions diminish the perceptual (Anderson and Phelps, 2001) and sensory cortical (Vuilleumier et al., 2004) enhancement associated with affectively significant stimuli, although these human lesion results are not consistently replicated (Bach et al., 2011).

The relationship between preferential processing of affectively significant stimuli and the more commonly studied preferential processing associated with spatial attention is unclear. Several lines of evidence, however, suggest a role for the amygdala in linking affectively-significant sensory stimuli to appropriate (often spatial) responses. For example, in a classic series of studies of a patient (SM) with bilateral amygdala damage, Adolphs et al. noted an inability to detect fear from facial expressions (Adolphs et al., 1994). Intriguingly, the deficit resulted from SM's avoidance of instructive regions of the face like the mouth and eyes—when verbally instructed to foveate the eyes, the impairment remarkably vanished (Adolphs et al., 2005), suggesting that amygdala lesions produce a deficit in linking visual stimuli to the appropriate overt attention response.

Stimulation of the basomedial amygdala in cats leads to an “orienting” response, characterized by the arrest of ongoing activity, an aroused body habitus, and contraversive head movements (Ursin and Kaada, 1960). Interestingly, at higher stimulation intensities, the orienting response is accompanied by behavior indicative of emotional states of both positive (licking, salivating, chewing) and negative (growling, hissing, micturition, and outright flight) valence. Electrical stimulation of the amygdala is also associated with EEG desynchronization (Kapp et al., 1994; Ursin and Kaada, 1960), as is seen in both spatial attention and arousal (Harris and Thiele, 2011). Moreover, blood flow (measured using intrinsic signal optical imaging) in visual

area V1 of anesthetized cats is increased by glutamate injections (and decreased by GABA injections) into the ipsilateral basal nucleus of the amygdala (Chen et al., 2013). These data suggest that the amygdala may function similarly to attentional source areas in the oculomotor system.

A key insight into the mechanisms by which the amygdala might link affective value to spatial attention comes from the recent discovery of amygdala neurons selective for the spatial configuration of reward (Peck et al., 2013). In the primate amygdala, many neurons encode the motivational significance, or value, of visual stimuli (Paton et al., 2006). Some neurons respond more to visual stimuli associated with higher rewards, and others show the opposite response profile. Surprisingly, value selectivity is systematically related to spatial selectivity, such that neurons that respond more to high value stimuli also respond more when high value is contralateral, rather than ipsilateral. This coordinated encoding of space and value in the amygdala is correlated across trials with reaction times, suggesting that it may be involved in linking visual information about the spatial distribution of reward to spatial attention.

Here, we further explore the amygdala as a candidate attentional source. First, we extend the prior findings of coordinated encoding of space and value by systematically varying the reward associated with contralateral and ipsilateral locations in an attentionally demanding task. Second, to directly probe the relationship between the amygdala and visual cortex, we performed simultaneous recording in the amygdala and visual area V4 and characterized the functional connectivity between these two areas.

3.2 Results

We trained monkeys to perform a dual two-alternative forced choice (dual 2-AFC) orientation discrimination task where we independently varied rewards associated with correct performance at two different locations. The task and associated behavior are detailed in Chapter 2.

Effect of contralateral and ipsilateral reward on amygdala neurons

We recorded 179 single units and 89 multiunit clusters from the amygdala of one monkey. Results were consistent for single and multiunits, and thus single and multiunits were combined for analysis. Consistent with prior studies (Peck et al., 2013), we found that amygdala neurons were modulated by both overall reward expectation and the spatial configuration of reward, and that reward and spatial selectivity were systematically related. Neurons that responded more strongly in high reward trials (REW+ neurons) were also more responsive to contralateral than ipsilateral rewards (**Figure 3.1a**). Neurons with higher firing rates in low reward trials (REW- neurons) were more active when rewards were ipsilateral, rather than contralateral (**Figure 3.1b**).

Prior studies have demonstrated this relationship between reward selectivity and spatial configuration using a reduced set of conditions (Peck et al., 2013). Here, we independently varied the reward associated with one location contralateral and one location ipsilateral to recorded amygdala neurons. This allowed us to characterize how the reward contingency at each location affected neural activity. To quantify the effect of contralateral and ipsilateral reward expectation across the population of recorded neurons, we performed multiple, linear regression on neural firing rates. The regression coefficients separately characterize the influence of associating large rewards with contralateral ($\beta 1$) and ipsilateral ($\beta 2$) locations (details in

Methods, Chapter 2). Therefore, if neurons were modulated by the relative value of locations, this would be captured in the regression coefficients by oppositely signed β1 and β2. Average trial value modulation would be captured by regression coefficients of the same sign, and insensitivity to reward expectations either contralaterally or ipsilaterally would be described a coefficient of value zero. We performed this analysis in two epochs, one during the presentation of reward cues (0 - 600 ms after cue onset), and another during the perceptual discrimination (0-500 ms after Gabor onset).

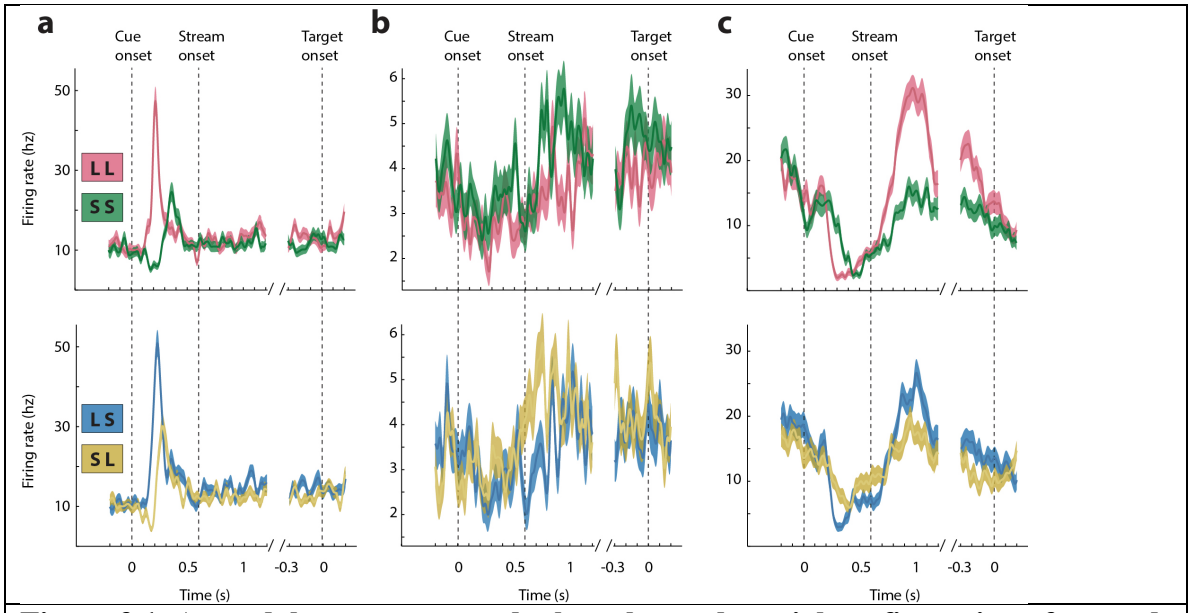

Figure 3.1. Amygdala neurons encode the value and spatial configuration of reward. (**a-c**) Spike density functions (σ = 15ms; shading, +/- 1 SEM) for three single units in the amygdala. Responses are aligned to two events in a trial. On the left, responses are aligned to the onset of reward cues. On the right, responses are aligned to the target onset. (**a**) REW+ neuron that had increased activity in trials with higher average trial value (LL vs. SS, top panel), as well as in trials when the large reward location was contralateral rather than ipsilateral (LS vs. SL, bottom panel). (**b**) REW- neuron that had increased activity in trials of low average value (LL vs. SS, top panel), as well as in trials when the large reward location was ipsilateral rather than contralateral (LS vs. SL, bottom panel). (**c**) Example neuron with biphasic responses and time-varying spatial reward selectivity. In the cue epoch, responses were similar to REW- neurons. In the streaming Gabor epoch, responses were similar to REW+ neurons. Within each epoch, overall reward expectation and spatial configuration of reward were consistently encoded.

We found that contralateral and ipsilateral reward expectations were generally associated with the same sign of modulation in individual amygdala neurons (**Figure 3.2**). In the cue epoch

(**Figure 3.2a**), 65 neurons were significantly positively modulated by contralateral reward, 18 by ipsilateral reward, and 12 by both contralateral and ipsilateral reward, an overlap greater than expected by chance (χ2-test, $p<10^{-4}$). Similarly, 22 neurons were significantly negatively modulated by contralateral reward, 23 by ipsilateral reward, and 6 by both contralateral and ipsilateral reward, an overlap greater than expected by chance (χ2-test, $p<0.005$). In the Gabor epoch (**Figure 3.2b**), 31 neurons were significantly positively modulated by contralateral reward, 20 by ipsilateral reward, and 13 by both contralateral and ipsilateral reward, an overlap greater than expected by chance (χ2-test, $p<10^{-10}$). Similarly, 50 neurons were significantly negatively modulated by contralateral reward, 28 by ipsilateral reward, and 16 by both contralateral and ipsilateral reward, an overlap greater than expected by chance (χ2-test, $p<10^{-7}$).

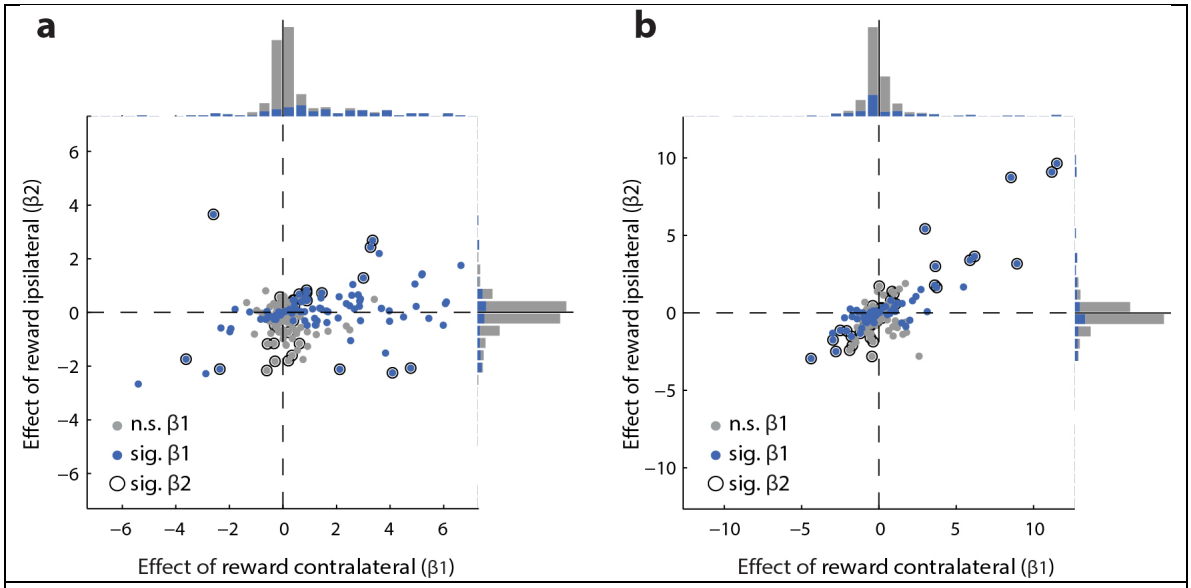

Figure 3.2. Effects of reward at locations contralateral and ipsilateral to amygdala neurons. Joint and marginal distributions of regression coefficients across all recorded units (n=268). (**a**) Cue epoch (0-600 ms after cue onset). (**b**) Gabor epoch (0-500 ms after Gabor onset). Symbol style denotes significance for individual data points ($p<0.05$). Colored shading in marginal histograms indicates significance for individual data points ($p<0.05$). In both epochs (**a,b**), results are similar. Contralateral and ipsilateral rewards are generally associated with the same sign of modulation (χ2-tests, $p<0.005$). Effects of contralateral and ipsilateral rewards are correlated across units (cue epoch: $r= 0.27$, $p< 10^{-5}$; Gabor epoch: $r=0.82$, $p<10^{-10}$), and effects are larger for contralateral than ipsilateral rewards (WSR, $p<10^{-7}$).

In both epochs, the effect size of contralateral and ipsilateral reward was correlated across neurons (**Figure 3.2a**, cue epoch: r= 0.27, $p<10^{-5}$; **Figure 3.2b**, Gabor epoch: r=0.82, $p<10^{-10}$). Finally, the magnitude of reward effects was larger for contralateral than ipsilateral locations (**Figure 3.2a**, cue epoch: Wilcoxon signed-rank test [WSR], $p<10^{-7}$; **Figure 3.2b**, Gabor epoch: WSR, $p<10^{-7}$).

Therefore, amygdala neurons were more responsive to contralateral than ipsilateral rewards, and thus selective for the spatial configuration of reward. However, in contrast to relative value modulation observed in the oculomotor system, contralateral and ipsilateral rewards were associated with the same sign of modulation in the amygdala.

Coherence of amygdala and V4 sites

Functional connectivity between brain areas is often inferred from coherence of the local field potential in two brain areas. To determine whether the amygdala and visual area V4 exhibit these signatures of functional connectivity, we examined the coherence of the LFP in the two areas, in each of three epochs: prior to the presentation of reward cues (**Figure 3.3a**), during the reward cue presentation (**Figure 3.3b**) and during the perceptual discrimination (**Figure 3.3c**).

In preliminary analyses, we noted two prominent results. First, in all conditions, coherence in the alpha (8-16 Hz) and beta (18-30 Hz) bands was elevated upon presentation of reward cues **(Figure 3.3a,b**; WSR, $p<10^{-10}$ for all conditions considered together). Second, gamma band (25-60 Hz) coherence during the perceptual discrimination epoch was elevated in LS compared to SL trials (**Figure 3.3c**, WSR, $p<10^{-10}$). These findings may reflect changes in functional connectivity between the amygdala and V4 during performance of an attentionally demanding task.

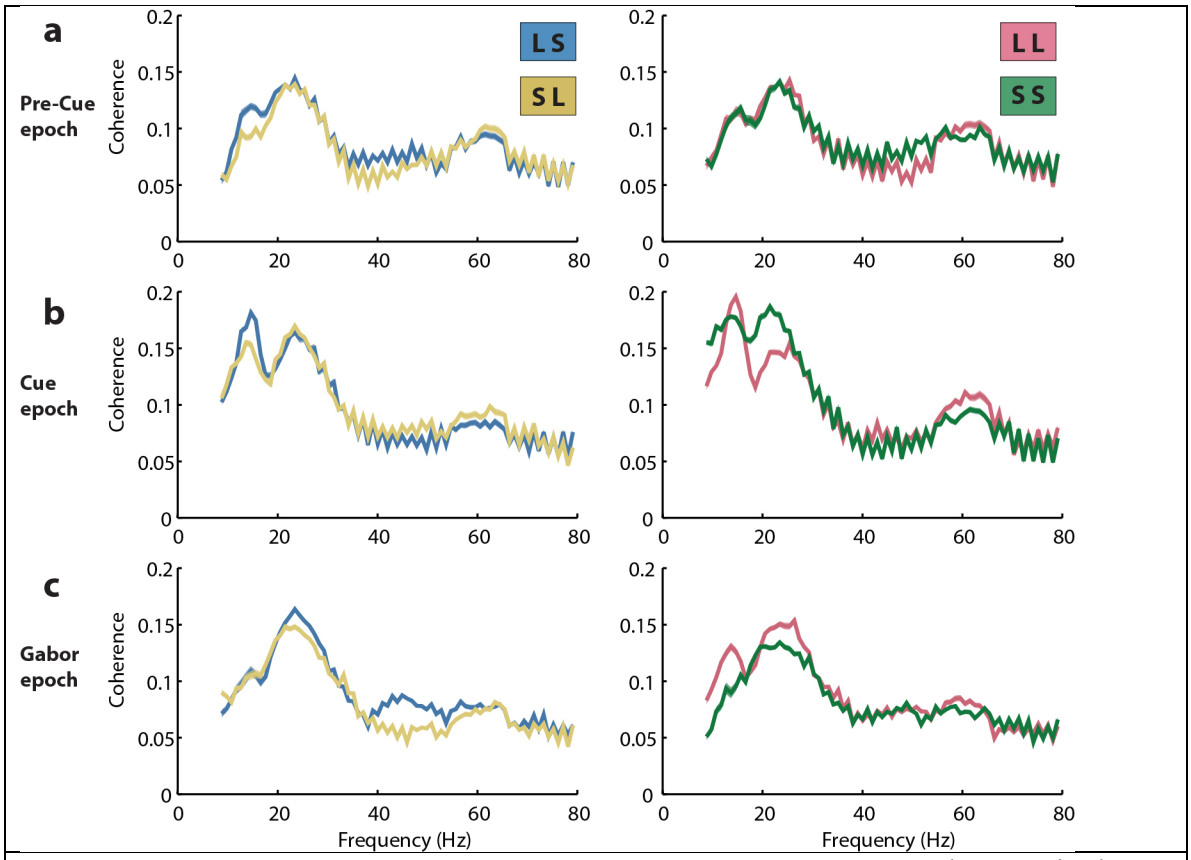

Figure 3.3. Field-field coherence between amygdala and V4 sites. Coherence is shown for each condition, averaged across all inter-area sites (n= 192 paired sites). Line thickness exceeds +/- 1 SEM. (**a**) Pre-cue epoch (400 ms before - 100 ms after reward cue onset). (**b**) In the cue epoch (100-600 ms after reward cue onset), coherence in the alpha (8-16 Hz) and beta (18-30 Hz) bands is significantly elevated with respect to the pre-cue epoch (WSR, $p<10^{-10}$). (**c**) In the Gabor epoch (0-500 ms after Gabor onset), coherence in gamma band (25-60 Hz) is significantly higher in LS than SL trials (WSR, $p<10^{-10}$).

3.3 Discussion

Brain areas known to be involved in the control of attention share several attributes. Anatomically, they are connected to visual cortex, where activity modulation is thought to underlie the perceptual benefit of attention. Electrophysiologically, firing rates and in some cases functional connectivity with visual cortex are modulated by attentional state. Finally, causal activation and inactivation of attentional source areas affects behavioral and neural correlates of attention. The primate amygdala, although certainly distinctive among candidate attentional source areas, displays many of these attributes. The amygdala projects directly to visual cortex, neurons in the amygdala signal the spatial configuration of reward, and perturbations of amygdala activity affect behaviors perhaps related to attention. Here, we describe two additional findings related to the amygdala's potential role in the control of attention.

First, consistent with prior results, we find that amygdala neurons are modulated both by overall reward expectation and the spatial configuration of reward. Interestingly, we find that reward modulation in the amygdala differs from the relative value modulation observed in other candidate attentional source areas. In oculomotor areas like the lateral intraparietal area, rewards inside and outside the RF have opposing effects on firing rate (Louie et al., 2011; Platt and Glimcher, 1999; Rorie et al., 2010; Sugrue et al., 2004). By contrast, amygdala firing rates display the same sign of modulation for rewards both contralateral and ipsilateral. Contralateral reward responses are larger than ipsilateral rewards, and thus firing rates signal the spatial location (hemifield) of reward. Relative value modulation in frontal and parietal cortices have been interpreted as reflecting competition between action plans and attentional priorities (Bisley

and Goldberg, 2010; Cisek, 2006; Louie et al., 2011), which apparently does not occur in the amygdala.

A key concern in characterizing amygdala responses to the spatial configuration of reward is that response field properties in the amygdala have not been characterized. Most physiological studies of the primate amygdala employ large visual stimuli and do not enforce tight fixation windows (Mosher et al., 2014; Paton et al., 2006). However, there may be unaccounted for spatial structure to amygdala response fields. Visual inputs to the amygdala come from inferotemporal cortex, where receptive fields are not strictly large and foveal (Op De Beeck and Vogels, 2000; DiCarlo and Maunsell, 2003), and it is possible that amygdala neurons inherit receptive field structure from their inputs. Further complicating matters, the spatial structure of amygdala response fields may be task dependent (Peck et al., 2013, 2014). Here, we consider reward modulation for ipsilateral and contralateral visual fields. While this is not justified on the basis of detailed response field mapping in the amygdala, it does reflect the anatomy linking the amygdala to visual cortex. Connections between the amygdala and visual cortex are almost exclusively ipsilateral (Iwai and Yukie, 1987). Thus, any modulatory influence of the amygdala would be primarily directed to visual cortical neurons with receptive fields contralateral to the amygdala.

To directly probe the interaction between the amygdala and visual cortex, we simultaneously recorded neural activity in the amygdala and V4. Preliminary data analyses revealed two salient findings. First, presentation of the cues indicating the spatial configuration of reward was associated with elevated alpha and beta coherence between the amygdala and V4. Notably, while the mechanistic import of coherent LFP oscillations is disputed, alpha (van Kerkoerle et al., 2014) and beta (Bastos et al., 2014) oscillations have recently been noted as

signatures of feedback processing in visual cortex. If generally true, this would suggest that information about spatial configuration of reward is fed back from the amygdala to visual cortex during reward cue presentation. Feedforward influences are frequently characterized by elevated gamma coherence (Bastos et al., 2014; Jia et al., 2013; van Kerkoerle et al., 2014; Zandvakili and Kohn, 2015), with especially prominent findings noting increased gamma coherence between the FEF and V4 with attention (Gregoriou et al., 2009b). Here, we find that during the perceptual discrimination phase of the task, gamma coherence is elevated in LS (attended) compared to SL (unattended) trials. Notably, V4 does not project directly to the amygdala, thus any feedforward coupling between the amygdala and V4 would have to be indirect.

Several key questions remain unaddressed in the preliminary analysis of functional connectivity presented here. For example, the mapping of coherence in particular frequency bands to feedback and feedforward processing would be bolstered by an analysis of directed coherence (i.e. Granger causality). Additionally, it will be important to determine whether spiking activity displays similarly coherent modulation to LFP activity and whether coherence between sites depends on response properties at each site. For example, in FEF, 'visual' neurons, but not 'movement' or 'visuomovement' neurons display elevated coherence with V4 during an attention task (Gregoriou et al., 2012). The analysis presented here considers all sites, agnostic to response properties at each site. These results are thus quite preliminary, but suggestive that the amygdala may play some role in linking reward related activity to the control of spatial attention.

3.4 Methods

Animals and implantation.

Two male rhesus monkeys (*Macaca mulatta*, 8–13 kg, 7-8 years old) were used in these experiments. All experimental procedures complied with US National Institutes of Health guidelines and were approved by the Institutional Animal Care and Use Committees at the New York State Psychiatric Institute and Columbia University. Prior to training, we implanted a plastic head post secured to the skull using ceramic bone screws. Surgery was conducted using aseptic techniques under isoflurane anesthesia, and analgesics and antibiotics were administered postsurgically. After the monkeys were behaviorally trained, we acquired T1-weighted MRIs with fiducial markers attached to the head post. In a second surgery, we implanted one plastic recording chamber over dorsal visual area V4 and another over the amygdala, guided by a neuronavigation system (Brainsight, Rogue Research, Quebec, Canada) registered to the MRI for each monkey. V4 Recordings targeted the lunate gyrus posterior to the junction of the superior temporal sulcus and the sylvian fissure. Amygdala recordings targeted the basal nuclei.

Data acquisition.

Monkeys were seated and head-restrained in a darkened sound-attenuating booth. Eye position and pupil diameter were monitored using an infrared camera sampled at 1000 Hz (Eyelink, SR Research, Ontario, Canada). Visual stimuli were generated using EXPO (Center for Neural Science, New York University) and were displayed on a CRT monitor positioned 57 cm away from the monkey. We recorded from the right dorsal V4 and right amygdala of each monkey using electrodes lowered with a multiple-electrode microdrive (NaN Instruments, Nazareth, Israel). In V4, extracellular activity was recorded using epoxylite-insulated tungsten electrodes (8-10 MΩ impedance at 1kHz; FHC Inc., Bowdoinham, Maine) or glass-coated

tungsten electrodes (0.5-2.0 MΩ impedance at 1kHz; Alpha Omega, Alpharetta, Georgia). Extracellular activity in the amygdala was recorded using 24-channel Plexon U-probes (275 kΩ impedance at 1kHz; Plexon, Dallas, TX) or epoxylite-insulated tungsten electrodes (2 MΩ impedance at 1kHz; FHC Inc., Bowdoinham, Maine). Analog signals were amplified, band-pass filtered (250–7500 Hz) and sampled (30 kHz) for unit isolation (Blackrock Microsystems, Salt Lake City, Utah). Units were isolated using manual clustering on the basis of several waveform parameters including principal components, peak and trough amplitudes, as well as the presence of a refractory period (Plexon Offline Sorter, Plexon, Dallas, TX). LFPs were filtered between 0.3 and 500 Hz and sampled at 1 kHz.

Behavioral task and visual stimuli.

The behavioral task is detailed in Chapter 2.

Data analysis

Preliminary data analysis presented in this chapter incorporated the data from only one of two monkeys used in these experiments. All statistical tests were two-sided. Data analysis methods common to Chapter 2 are detailed in Chapter 2.

Regression. We used multiple, linear regression to quantify how the reward contingency at each location affected neuronal activity and behavior across the population. The regression was performed on spike rates in two epochs. Responses to reward cues were assessed in a 600 ms window beginning at cue onset and ending at onset of streaming Gabor stimulus. Responses during the perceptual discrimination phase of the task were assessed in the first 500 ms of the streaming Gabor stimulus. For each neuron, we regressed the firing rate in this epoch onto two predictors and a constant term:

$$FR = \beta_0 + \beta_1 * x_1 + \beta_2 * x_2 ,$$

where x1 is a categorical predictor indicating whether the contralateral location is associated with large reward (x1=1 for LS and LL trials, x1=0 for SL and SS trials), and x2 is a categorical predictor indicating whether the ipsilateral location is associated with large reward (x2=1 for SL and LL trials, x2=0 for SS and LS trials). To assess the statistical significance of differences in regression coefficients across the population, we used two-tailed Wilcoxon signed-rank tests.

Spectral analysis. We estimated the coherence of the LFP in amygdala and V4 sites using a multi-taper algorithm (Mitra and Bokil, 2007) implemented in the Chronux toolbox (www.chronux.org), using 5 tapers and a time-bandwidth product of 3. Coherence was estimated in 3 trial epochs: prior to the presentatation of reward cues (400 ms before - 100 ms after cue onset), during the reward cue presentation (100 -600 ms after reward cue onset) and during the perceptual discrimination (0 - 500 ms after Gabor onset). Coherence was analyzed for each inter-area pair of sites recorded, and averaged across pairs in **Figure 3.3**. To assess statistical significance in defined frequency bands, we used two-tailed Wilcoxon signed-rank tests.

3.5 Author contributions

Brian Lau developed the task. Jalal Baruni and Brian Lau collected the data. Jalal Baruni performed the analysis, with assistance from Brian Lau. C. Daniel Salzman supervised all aspects of the project. Jalal Baruni wrote the chapter.

Chapter 4. Conclusions

The beauty of visual attention as an experimental paradigm is that it dramatically influences perception, produces measurable effects on behavior, and is readily instantiated in experimental animals. For these reasons, visual attention has attracted vigorous investigation from the neuroscience community. We know a tremendous amount about the perceptual and behavioral correlates of attention (Carrasco, 2011; Posner, 1980), as well as the associated neural correlates in the primate brain (Desimone and Duncan, 1995; Maunsell and Cook, 2002). However, perhaps the most interesting systems-level question remains largely mysterious. How do the observed neural correlates of attention endow attended stimuli with such disproportionate leverage over perception? What is the mechanism by which relatively slight modulations in visual cortex render certain stimuli perceptible and others invisible? We hope that the research presented in this thesis contributes to our understanding of these brain-to-behavior mechanisms, but, of course, a substantial explanatory gap remains.

How do we move towards an understanding of how neural correlates of attention confer perceptual enhancement? The facile (and yet probably correct) response is that causal experiments will be critical to progress. Especially if freed from the constraint of considering only that which is feasible with current technology, one readily imagines hugely informative experiments. For example, attention is associated with a host of correlates in sensory cortex, but it is unknown which (if any) are important for behavior. If it were possible to observe and manipulate the activity of large numbers of neurons in sensory cortex, each aspect of attentional modulation could be assessed independently. For example, rate effects could be added independently of noise correlation effects, and the effect on behavior assayed. These types of

experiments, for which the enabling technology was unimaginable 15 years ago, are increasingly within reach.

Even absent sophisticated causal techniques, further insight into the mechanisms of attention might arrive from clever behavioral task design in animal and human experiments. One potentially interesting research direction concerns the role of noise correlations. In detection tasks, attention decreases noise correlations (Cohen and Maunsell, 2009; Mitchell et al., 2009). However, in discrimination tasks, attention apparently increases noise correlations for neurons in different decision pools (Ruff and Cohen, 2014a). Thus, the effects of attention on noise correlations, but not firing rate, are task-specific, potentially allowing the relative role of firing rate and noise correlations to be teased apart. Broadly sketched, if alterations in the structure of noise correlations are critical for the behavioral benefit of attention, then situations may exist where "attending for detection" would potentially decrease discrimination performance (and vice versa). By contrast, because firing rate modulation is similar in detection and discrimination tasks, mechanisms of attention that depend upon firing rate should generalize across tasks.

Characterization of the role of the amygdala in the control of attention is still in its infancy. In Chapter 3, we presented preliminary analysis of functional connectivity between the amygdala and visual cortex. Perhaps the more compelling experiment, however, would be to directly stimulate the amygdalar inputs to V4 and assess the effect on V4 neural activity. These experiments would be analogous to the series of FEF microstimulation experiments performed by Katherine Armstrong and Tirin Moore (Armstrong and Moore, 2007; Armstrong et al., 2006; Moore and Armstrong, 2003), in which they microstimulated FEF while recording from V4 neurons with retinotopically aligned receptive fields. In contrast to the FEF, the amygdala has no known retinotopy. Projections to visual cortex from the amygdala originate largely from the

basal nucleus (Amaral and Price, 1984; Freese and Amaral, 2005; Iwai and Yukie, 1987), which is fairly large, but not resolved in structural MRIs, and not identifiable by physiological response properties. Thus, finding connected sites in the amygdala and V4 is an unlikely proposition for even the most dogged physiologist. Optogenetic stimulation of terminals, however, may be a viable workaround. Transfecting amygdala neurons with channelrhodopsin and stimulating locally in visual cortex obviates the need to place electrodes in connected sites and may allow a direct examination of how the amygdala modulates visual processing.

It is currently unknown how amygdala inputs affect visual responses in V4. FEF microstimulation leads to enhanced responses that are multiplicative in the orientation domain (Moore and Armstrong, 2003), but there are several key differences between the amygdala and FEF. First, amygdala neurons display mixed selectivity for visual stimuli, and reward expectation is associated with increased responses in some neurons and decreased responses in others (Mosher et al., 2014; Paton et al., 2006). Whether the subset of neurons that project to visual cortex are more homogenous in their response properties is not known. Moreover, the laminar distribution of amygdala terminals in V4 differs from that of FEF. Whereas FEF terminals are found in all layers (Anderson et al., 2011b), amygdala inputs are largely restricted to the upper layers (Amaral and Price, 1984; Freese and Amaral, 2005). Thus, it may be that the amygdala modulates visual cortex in a manner quite distinct from known attentional source areas in the oculomotor system.

Finally, it is worth noting that attention as studied in awake, behaving primates is quite different from the colloquial notion of attention (as in: “Jalal, we are almost a hundred pages deep at this point. It is unreasonable to expect that anybody is still paying attention.”). Possibly, spatial attention in primate physiology experiments shares underlying neural processes with the

myriad richer phenomena encompassed under the colloquial notion of attention. But we are far from extending our understanding of visual attention to what it means to, for example, pay attention in a lecture or have attention deficit hyperactivity disorder. Even further afield, visual attention is a powerful 'switch' that controls perception and awareness. Perception of visual stimuli is dramatically enhanced when attention is directed towards them, and suppressed when attention is directed elsewhere. Is it possible that similar mechanisms control the switching between thoughts that occurs in internal mental processes? We don't yet know.

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