REPRESENTATION OF VALUE AND SALIENCE IN THE PRIMATE BRAIN

by

Marvin Lionel Leathers, Jr.

B.S. Biochemistry, B.A. Classics, Samford University, 2005

Submitted to the Graduate Faculty of

The Dietrich School of Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2015

UNIVERSITY OF PITTSBURGH

THE DIETRICH SCHOOL OF ARTS AND SCIENCES

This dissertation was presented

by

Marvin Lionel Leathers, Jr.

It was defended on

July 23, 2015

and approved by

Tai Sing Lee, Ph.D., Professor, Department of Computer Science and the Center for the Neural Basis of Cognition

Beatriz Luna, Ph.D., Professor, Department of Psychiatry and Pediatrics

Chair: Susan Sesack, Ph.D., Professor, Department of Neuroscience

Robert S. Turner, Ph.D., Associate Professor, Department of Neurobiology and the Center for the Neural Basis of Cognition

Steve Chase, Ph.D., Assistant Professor, Department of Biomedical Engineering and the Center for the Neural Basis of Cognition, Carnegie Mellon University

Dissertation Advisor: Carl Olson, Ph.D., Professor, Center for the Neural Basis of Cognition

REPRESENTATION OF VALUE AND SALIENCE IN THE PRIMATE BRAIN

Marvin Lionel Leathers, Jr., Ph.D.

University of Pittsburgh, 2015

Most times, we choose goods and avoid evils. Sometimes, goods and evils choose us, which quickly grabs our attention. How do our brains represent our values so that we can choose? How do things we love or loathe automatically capture our attention? To investigate these two cognitive processes, we performed two experiments to study neuronal representations of value (worth) and salience (importance) in the primate brain.

First, we tested whether neurons in LIP and amygdala encode the value or salience of choice-options early during value-based decision-making. To dissociate value from salience, we recorded neurons from LIP and the amygdala in monkeys making value-based decisions among options promising different reward-sizes and options threatening different penalty-sizes. Value increases with promised-reward but decreases with threatened-penalty. Salience increases with the intensity of both promises and threats.

LIP neurons fired more for options promising more reward and also fired more for options threatening more penalty. Amygdala neurons fired more for options promising more reward but fired less for options threatening more penalty. Whereas LIP encoded salience early during decision-making, reflecting automatic capture of attention by the more important options, the amygdala encoded value early during the decision-making process.

Second, we tested whether early reward-effects in neurons in LIP and amygdala depended on early automatic capture of visual attention by a more rewarding option. We dissociated cue-reward from cue-salience in LIP and amygdala using choice-options that could

not acquire salience. The near-identical physical appearance of these precluded early automatic capture of attention by the large-reward option but not the monkeys' ability to make optimal value-based decisions.

LIP did not encode reward early during decision-making, only later and weakly. The number of LIP neurons with reward-effects was no greater than expected by chance. In amygdala, reward-effects were stronger and earlier than in LIP. Significant numbers of single amygdala neurons signaled the reward-size of the choice-option. Early reward-effects depend upon cue-salience in LIP but not the amygdala.

The results from both experiments are consistent with the view that, early during value-based decision-making, neurons in LIP encode cue-salience whereas neurons in amygdala encode cue-value.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

PREFACE

Parts of this dissertation contain material that has been published in some form.

- Chapter 2.1 Reward-Penalty in LIP features peer-reviewed content published in 2012. Permission to reproduce this content for this dissertation was granted by AAAS.
- Chapter 4.1 Response to Newsome et al. features peer-reviewed content published in 2013. Permission to reproduce this content for this dissertation was granted by AAAS.
- Chapter 2.2 Reward-Penalty in amygdala: results from one monkey were described in a non-peer-reviewed abstract for the Society for Neuroscience Annual Meeting in 2014.
- Chapter 3 Morph in LIP and amygdala: results from both monkeys were described in a non-peer-reviewed abstract for the Society for Neuroscience Annual Meeting in 2015.

The citations below correspond to the bullets above.

Leathers, M. L., & Olson, C. R. (2012). In monkeys making value-based decisions, LIP neurons encode cue salience and not action value. *Science, 338*(6103), 132-135. doi: 10.1126/science.1226405

Leathers, M. L., & Olson, C. R. (2013). Response to comment on "In monkeys making value-based decisions, LIP neurons encode cue salience and not action value". *Science, 340*(6131), 430. doi: 10.1126/science.1233367

Leathers, M. L., & Olson, C. R. (2014). "Neuronal encoding of rewards and penalties in the primate amygdala: strong and consistent reward signals versus weak and inconsistent penalty signals". Program No. 206.12, Society for Neuroscience Abstract.

Leathers, M. L., & Olson, C. R. (2015). "Early reward-related activity depends on cue salience in LIP but not in the amygdala". (Accepted), Society for Neuroscience Abstract.

Acknowledgements

First, I thank my advisor Carl Olson for teaching me how to be a neuroscientist. The very first time we met, during my graduate school interview, Carl and I immediately hit it off and began planning experiments. I had never done research in neuroscience, but Carl took a chance on me. Carl began training me to think like a neuroscientist, even before I arrived in Pittsburgh. He corresponded with me via email, teaching me how to read and critique papers on the neural basis of value and decision-making and discussed designs for my own first experiments. Because of Carl's leadership, I was able to hit the ground running upon arrival in Pittsburgh. Carl even trained me how to program in C. Over the years, Carl always had an open door to answer any questions that I had. Many meetings and discussions with Carl were exhilarating to me. I appreciate the patience Carl showed me. He guided me in designing novel tasks to explore our topic of shared interest. Two of these experiments are found in this dissertation. If I have a successful career, it will be because I trained with Carl Olson. I am forever grateful.

Second, I thank my thesis committee members, Beatriz Luna, Committee Chair Susan Sesack, Rob Turner, and Tai Sing Lee who gave me excellent feedback on this project over the course of many meetings. Thank you for being patient with me and for encouraging me to persevere. Thank you Steve Chase for being my outside examiner.

Third, I would like to thank all the members of the Olson, Colby, Lee, Smith, Ghandi, Sommer, Cohen labs, and others who met each Tuesday to discuss the latest papers in "Brain Group." I have learned so much from your different perspectives. Olson lab member Arun Sripati, who now runs his own lab in India, deserves extra thanks for patiently answering my questions when I was at the "What is Matlab?" stage of my work. Trinity Crapse, a graduate from the Sommer lab, is a good neuroscientist, whom I'm thankful to have as my friend. Jan

Kalkus, a former undergraduate member of the Olson lab, deserves special thanks for his help with coding and monkey training.

Fourth, I thank the CNUP administrators, particularly Joan Blaney and Marlene Nieri, who keep the wheels turning smoothly in the Department of Neuroscience. I also thank Patti Argenzio, Lisa Bopp, and Mary Spanoudakis. From the Mellon Institute CNBC offices, I thank Barb Dorney, Rebecca Clark, Melissa Stupka, Anna Hegedus, and David Pane. Thanks for the great tea times! Karen McCracken has my special appreciation for giving excellent, special care to the monkeys, especially when I was juggling several at once (metaphorically speaking).

Fifth, Carol Colby deserves my special gratitude. She accepted me as a rotation student so that I could learn how to conduct electrophysiological recordings from lateral intraparietal cortex (LIP). Carol began a wonderful "LIP History Club," where her guidance through many classic LIP papers gave me context for my own experiments and challenged me to think critically about how to interpret neuronal activity in LIP.

Sixth, I would like to thank Wayne Wu for encouraging me to consider my results in the broader context of cognitive science and philosophy of mind, which expanded my outlook.

Seventh, I thank Kym Jordan-Simmons and the dissertation support group.

Finally, I would like to thank my greyhound Orwell (recently departed) and my wife Sally Caine (alive and well) for their love and support.

1.0 GENERAL INTRODUCTION

Imagine you and a friend sit down for breakfast at a diner. Each of you has an empty coffee cup and juice glass. “Coffee, juice?” you hear the waitress ask your friend. You, a coffee-addict, gaze repeatedly between the full coffee-pot in the waitress’ hand, your empty cup, your friend’s empty cup and back again, as if your eyes are magnets for coffee-objects. Your friend declines coffee for juice. The waitress asks to remove his coffee cup. To your surprise and amusement, your friend searches all around the table before seeing, for the first time, his coffee cup sitting right in front of him. You smirk at your friend. “Coffee, juice?” the waitress asks you. Your eyes widen with surprise. Now you see, for the first time, the giant carafe of orange juice that she has been holding in her other hand. For some reason, your friend is smirking at you. You are not amused. You order coffee and juice. These are poured. Easily, you decide to reach around your now bright-orange glass of juice and, grasping your full coffee cup, take your long-awaited first sip.

This dissertation is an investigation into the two cognitive processes evident in the imaginary breakfast example above. How are values for coffee and juice represented by neurons in your brain? How do these neurons mediate your decision to sip coffee before drinking juice? How do coffee-associated objects capture your attention but not your friend’s? To answer these questions, we trained rhesus monkeys to make value-based decisions similar to those we make at breakfast. As the monkeys decided between objects promising liquids of different values, we eavesdropped on this process going on live inside their brains. We did this by making electrical

recordings from single neurons in two areas of the primate brain, lateral intraparietal cortex (LIP) and the amygdala (Figure 1). Previously, neuroscientists have claimed that neurons in each of these areas 1) encode the values of choice-options for value-based decision-making and 2) encode the salience of valuable options so that these quickly and automatically capture visual attention. The bulk of this dissertation contains the results from two experiments in which we put these two claims to the test.

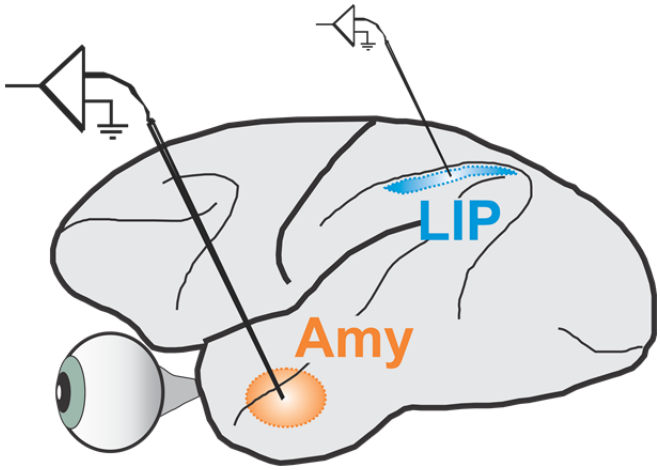


Figure 1. Rhesus Monkey Brain: LIP and Amygdala
Cartoon showing recording electrodes in lateral intraparietal cortex (LIP) and amygdala (Amy).

First, we define value (Section 1.1) and report on previous efforts made by neuroscientists to localize value representation in LIP and amygdala (Section 1.2). Next, we stress that neurons responsive to choice-options, such as coffee-cups and juice-glasses, might not be encoding their values for decision-making (Section 1.3) but instead be reflecting their salience (Section 1.4). We then report on previous efforts made by neuroscientists to localize salience processes in LIP and amygdala (Section 1.5). Finally, we state the specific aims for our two experiments during which we recorded from LIP and amygdala neurons (Section 1.6), present our results (Sections 2 and 3), and discuss whether or not we successfully dissociated representations of value and salience in the primate brain (Section 4).

1.1 VALUE

Value is how much something is worth. Economists may speak of value as utility, inferred by the preferences we reveal in our choice behavior (Samuelson, 1938). If your friend prefers to order juice instead coffee, then an economist might say he chooses "as if" he has an internal representation of value that is greater for juice than coffee. But economists stop there. Neuroeconomists, however, go beyond "as if," explanations. The goal of neuroeconomics is to determine how the activity of neurons in the brain encode the values that result in observable economic choices (P. W. Glimcher, 2010). In this dissertation, we assume that when monkeys choose an object more often than another, then they are revealing that they value it more. Identifying neuronal activity that is linearly correlated with value as revealed by choice behavior is the "central linking hypothesis of neuroeconomics" (P. W. Glimcher, 2010). Therefore, one major goal of this dissertation is to create experimental conditions that test whether or not neurons really do encode value that could be used for the process of economic decision-making.

1.2 LOCALIZING VALUE IN THE AMYGDALA AND LIP

There have been many previous attempts to localize value in the amygdala and LIP. Humans that have suffered brain damage to the amygdala are impaired at making value-based decisions (Gupta, Koscik, Bechara, & Tranel, 2011). When choosing between two decks of cards, one leading to net monetary reward and the other leading to net monetary loss, most people earn money by drawing more cards from the rewarding deck, but patients with bilateral amygdala lesions go into debt by drawing cards from the losing deck (Gupta et al., 2011). However, studies

of human and non-human primates with amygdala lesions are hard to interpret, as both value and emotion could play a role. The amygdala is necessary for rodents to acquire fear responses to a tone that predicts electrical shock (Moscarello & LeDoux, 2014). Monkeys with bi-lateral amygdala damage lose fear of strangers (KlÜVer & Bucy, 1939), begin to eat feces (Aggleton & Passingham, 1981), show impaired emotional reactivity upon seeing a potential reward, such as food (Braesicke et al., 2005), or a potential threat, such as a fake snake (Izquierdo, Suda, & Murray, 2005), and yet can easily make value-based decisions between reward-associated objects (Murray, 2007; Wellman, Gale, & Malkova, 2005). Thus, the amygdala might function for emotion instead of representing the learned economic-value of objects. However, finer-grained observations made with single-unit recordings suggest that amygdala neurons encode value for decision-making.

Some amygdala neurons fire more for a cue promising reward, while others fire more for a cue promising penalty (Belova, Paton, & Salzman, 2008; Paton, Belova, Morrison, & Salzman, 2006; Peck & Salzman, 2014b). Based on these results, it has been claimed that amygdala neurons encode the values of goods and evils in separate circuits for purposes of value-based decision-making (Morrison & Salzman, 2010; Zhang et al., 2013). However, no previous study has put to the test the claim that amygdala neurons encode value, instead of some other process such as emotional-intensity. This includes the only experiment that has recorded amygdala neurons in monkeys making value-based decisions (Grabenhorst, Hernadi, & Schultz, 2012; Hernadi, Grabenhorst, & Schultz, 2015). The reason that value-encoding has not been demonstrated in amygdala neurons is because no previous study recorded amygdala neurons in monkeys making value-based decisions with options that vary in the intensity of reward they

promise as well as options that vary in the intensity of penalty they threaten (as discussed in section 1.3).

As is the case with amygdala-damaged monkeys, monkeys with inactivated LIP neurons can still make value-based decisions between visual cues. Specifically, in LIP-inactivated monkeys performing reward choice tasks, responses to stimuli located in contralesional space are reduced in number and increased in latency but these spatial effects show no interaction effect with the value of the contralesional reward (Balan & Gottlieb, 2009). However, as with amygdala neurons, single-unit recordings suggest that LIP neurons encode value for decision-making. In fact, the view that reward-related activity in areas outside the limbic system represents value was first put forward on the basis of studies of parietal area LIP (Platt & Glimcher, 1999). Value-related modulation in LIP neurons has been observed during experiments that either directly manipulate the amount (Bendiksby & Platt, 2006; Coe, Tomihara, Matsuzawa, & Hikosaka, 2002; Klein, Deaner, & Platt, 2008; Platt & Glimcher, 1999; Rorie, Gao, McClelland, & Newsome, 2010), probability (Platt & Glimcher, 1999; Sugrue, Corrado, & Newsome, 2004; Yang & Shadlen, 2007), and delay (Louie & Glimcher, 2010) of rewards associated with visual cues, or indirectly manipulate reward probability by making the cues themselves more or less hard to see (Kiani & Shadlen, 2009; Roitman & Shadlen, 2002; Shadlen & Newsome, 1996, 2001). Value-related modulation occurs in LIP during choices made freely (Coe et al., 2002; Klein et al., 2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Sugrue et al., 2004) or by instruction (Platt & Glimcher, 1999; Rorie et al., 2010), even when value-associations are not needed to choose correctly (Rorie et al., 2010). These value-related modulations have been interpreted as biological instantiations of economic value represented by the activity of neurons in LIP (Bendiksby & Platt, 2006; Dorris & Glimcher, 2004; Klein et al.,

2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Rorie et al., 2010; Seo, Barraclough, & Lee, 2009; Sugrue et al., 2004). The dominant neuroeconomic claim is that LIP neurons represent action-value: the subjective relative value of a potential saccadic eye-movement into the neuronal response field (RF) (Dorris & Glimcher, 2004; P. Glimcher, 2013, 2014; Klein et al., 2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Seo et al., 2009; Sugrue et al., 2004). The same LIP neurons that are correlated with the action-value of RF saccades are even correlated with the action-value of RF saccades that rhesus monkeys made to pictures of the hind-parts of female monkeys and the faces of dominant male monkeys (Klein et al., 2008). Therefore, a neuroeconomic hypothesis of LIP function is that, regardless of the type of visual cue (non-social or social) or value manipulation (reward-probability, reward-amount, or reward-discounted by time or effort required to obtain it), LIP neuronal firing rates put these diverse value-determinants into a "common currency" of economic value that mediates the action-based decision of where next to move the eyes (Dorris & Glimcher, 2004; P. Glimcher, 2013; Kable & Glimcher, 2009; Klein et al., 2008).

1.3 ALL THAT GLITTERS IS NOT VALUE

Amygdala neurons may very well encode value. Also, the neuroeconomic view that economic choices are mediated by action-values embedded in motor-related circuits, like LIP, is a reasonable answer to the important question of how the brain represents economic value. However, there are equally plausible alternative explanations of value-related modulations observed in LIP and amygdala. As first pointed out in our laboratory by Roesch and Olson (2003), neurons whose firing rates increase when value increases might be involved in some

other process. In the brain, all that glitters is not value. For example, value-related activity could just as likely reflect neuronal processes that are not encoding value *per se*, such as enhanced action-preparation to obtain a more valuable outcome or increased visual attention to a more valuable object. As value increases, so too does motivation, so too does attention, so too does neuronal activity. Which of the three is encoded by such neurons? Interestingly, action-value correlations are strongest in neurons from premotor areas and are even present in some muscles (Roesch & Olson, 2003, 2004). Nevertheless, just as it does not logically follow that these muscles are making economic decisions, the same caveat applies to any neuron in the brain with value-related modulation (Roesch & Olson, 2007), including neurons in LIP that represent saccadic actions and neurons in the amygdala involved in emotion.

Value increases with the promise of reward but decreases with the threat of penalty. Accordingly, we expect value-coding neurons to fire more for the greater of two goods but to fire less for the greater of two evils. Roesch and Olson (2004) recorded neurons from orbitofrontal cortex and premotor cortex in monkeys making decisions among not only cues that promised different sizes of reward but also other cues that threatened different sizes of penalty. At the time, neuroeconomists were varying rewards but not penalties while recording from action-related neurons. Using the reward-penalty task, Roesch and Olson found that orbitofrontal neurons increased activity for larger rewards but decreased activity for larger penalties. Thus, orbitofrontal neurons encoded value. However, premotor neurons fired more for larger rewards and for larger penalties. Thus, premotor neurons reflected the higher importance of motor plans to obtain larger rewards and avoid larger penalties (Roesch & Olson, 2007). This was an important result. It established the reward-penalty task as a tool that could be used to separate neurons in the brain that encode value from those that do not. The first experiment in this

dissertation uses the reward-penalty task while recording from neurons in amygdala and LIP to dissociate value representation from salience.

1.4 SALIENCE

Salience is conspicuity. Salience is the form of attention by which a visual stimulus automatically captures your attention and orients your eyes to look in its direction (Itti & Koch, 2001). Bright lights steal your attention automatically due to their physical salience. No matter what goal you are trying to achieve, physically salient stimuli can automatically capture your attention so that you redirect it to earn rewards or avoid penalties to which you would otherwise have been oblivious. However, in this dissertation, the salience that we are interested in is salience by association. As we refer to it, salience is the associative-importance acquired by well-learned visual stimuli that predict intense outcomes. Recently, it has been demonstrated that once-neutral stimuli, when repeatedly associated with reward can come to automatically capture visual attention, even when these stimuli are irrelevant to decision-making (Anderson, 2013). This salience is like an attention habit. When such stimuli appear, they automatically capture attention not because they are brighter but because they have been associated with larger reward. Salience increases with the intensity of promises as well as threats. We expect salience-coding neurons to fire more for the greater of two goods and the greater of two evils. This is what we mean by salience in this dissertation.

Because this type of salience (reward-driven attentional capture) occurs early during decision-making, it too can masquerade in neuronal activity as a value-representation in the service of an economic decision process. If different looking stimuli associated with different

levels of reward acquire different levels of salience (Anderson, 2013), then similar looking stimuli associated with different levels of reward might acquire similar levels of salience. Neurons encoding value should differentiate similar looking but differentially preferred choice-options (to reflect their different value), but neurons encoding cue-salience should not (to reflect their similar salience). The second experiment in this dissertation uses this method to dissociate value representations for decision-making from early neuronal reflections of automatic attentional capture, or salience, in the brain.

1.5 LOCALIZING SALIENCE IN LIP AND THE AMYGDALA

Following Roesch and Olson, Maunsell (2004) cautioned that neuronal correlates in LIP like action-value might really be attention, or vice versa. Indeed, the traditional view of LIP function is to orient attention (Colby & Goldberg, 1999) and saccadic eye-movements (Snyder, Batista, & Andersen, 2000) via an internal representation of visual space. In monkeys, inactivation of LIP impairs localization and discrimination of targets in the contralesional visual hemifield (Wardak, Olivier, & Duhamel, 2002, 2004). Microstimulation of LIP at low current elicits saccades in the absence of other body movements (Thier & Andersen, 1998). Humans with posterior parietal lesions exhibit profound spatial deficits, such as neglecting to attend or move the eyes toward stimuli located in the spatial hemifield contralateral to the lesioned-hemisphere (Mesulam, 1999). The signature effect of posterior parietal damage is hemispatial neglect, which is the lack of spatial awareness in the contralesional visual hemifield. Patients with neglect often look more often and fixate longer in the ipsilesional than contralesional hemifield (Bartolomeo, 2007). In

extinction, a severe form of neglect, a single object in the impaired hemifield can be seen but not when another object is presented in the unimpaired hemifield (Bartolomeo, 2006).

LIP neurons fire most vigorously to small objects flashed in their contralateral receptive field (RF) (J. Gottlieb, Balan, Oristaglio, & Suzuki, 2009). LIP has RFs that often cover about one quadrant of visual space, but RF-size scales roughly with RF-eccentricity in the contralateral visual field (Ben Hamed, Duhamel, Bremmer, & Graf, 2001). LIP in each hemisphere provides a complete representation of its contralateral visual hemifield. LIP neurons are modulated by visual stimuli (Andersen, Essick, & Siegel, 1985; Colby & Duhamel, 1996), manipulations of behavioral relevance or salience (Colby & Duhamel, 1996; Goldberg, Bisley, Powell, & Gottlieb, 2006), eye-position (Andersen et al., 1985), and before goal-directed saccades in the absence of visual stimulation (Colby & Duhamel, 1996). That LIP neurons can show enhanced activity even when an RF saccade is not being made is strong evidence that enhanced LIP activity reflects allocation of visuospatial attention (Colby & Goldberg, 1999). Neuronal activity in LIP not only reflects the salience of visual stimuli that are not saccade goals (J. P. Gottlieb, Kusunoki, & Goldberg, 1998) but also of cues that interfere with the action-value of a required saccade (Peck, Jangraw, Suzuki, Efem, & Gottlieb, 2009). A synthetic proposal has been offered that LIP binds motor-intentional and visuospatial information together into a topographically organized map of behavioral salience that prioritizes locations in space for the purpose of attentional allocation (J. Gottlieb, 2007). Indeed, LIP may orient both oculomotor intention (Snyder et al., 2000) and visuospatial attention (Colby & Goldberg, 1999) by representing locations in visual space prioritized by their importance, or salience.

Though LIP is the apex of the dorsal stream of primate visual processing, or the 'where' pathway for locating objects in space, it is highly connected to the oculomotor network,

specifically the frontal eye fields and superior colliculus, which generate saccadic eye movements (Andersen, Asanuma, Essick, & Siegel, 1990; Lynch, Graybiel, & Lobeck, 1985). Clearly, LIP is well placed anatomically to associate information about the location of specific objects in visual space with commands to move the eyes.

Moreover, LIP may be well placed anatomically to acquire salience for visual features of reward-associated objects. LIP also receives information from the ventral 'what' stream concerning the identity of visual objects (Medalla & Barbas, 2006). LIP itself can be divided into a densely myelinated ventral area, which receives heavy input from motion area MT and has neurons that respond more to objects in the visual periphery, and a dorsal area, which is strongly connected to the ventral stream and responds more to objects in the center of the visual field (Ben Hamed et al., 2001; Lewis & Van Essen, 2000a, 2000b). Importantly, Gottlieb and colleagues have shown that early reward-effects in LIP develop over time as monkeys learn the differential rewards associated with distinct looking objects (Peck et al., 2009).

As with LIP, some claim that amygdala directs attention to reward cues (Peck, Lau, & Salzman, 2013). Amygdala is claimed to encode salience for penalty-cues in the same way it does for reward-cues (Peck & Salzman, 2014a). The amygdala is a subcortical collection of over twelve nuclei buried medially in the anterior temporal lobe (Swanson & Petrovich, 1998). It can be viewed as a three part structure consisting of superficial, basolateral, and centromedial and nuclear groups, with distinct structures, connectivities, and functions (McDonald, 1998). Significantly, the basolateral and centromedial groups are positioned, as if by anatomical strategy, to associate environmental stimuli with representations of value or prioritize them by salience and then broadcast these signals to other areas of the brain.

First, the "cortex-like" cells of the basolateral group, on one hand, receive almost exclusively in the lateral nucleus highly processed visual information about objects from area TE (Tanaka, 1996) the apex of the ventral visual or 'what' pathway in temporal cortex. On the other hand, the basal nucleus receives information about affect from areas of ventral prefrontal cortex, especially orbitofrontal cortex (Stefanacci & Amaral, 2002), a limbic cortical area in which neurons represent the abstract economic value of visual cues (Padoa-Schioppa & Assad, 2006; Roesch & Olson, 2004). Thus, the basolateral nuclei give amygdala a panoramic view of objects in the visual scene and the emotional or value-based information with which to associate them. Importantly, the basal nucleus, which in general projects to the striatum and cortex, can control visual processing of these value-associated objects via its reciprocal synapses at TE, the ventral stream output, and at ventral stream areas all the way back to V1, the fountainhead for both the ventral 'what' pathway that identifies objects and the dorsal 'where' pathway that locates objects in visual space (Freese & Amaral, 2005). LIP sits atop this dorsal pathway. Second, the "striatum-like" cells of the centromedial group, like the basolateral group, receive visual information from the temporal lobe and emotion- or value-related signals from limbic prefrontal cortex, especially the medial portion (McDonald, 1998). The centromedial nuclei also strongly modulate the cholinergic and GABA-ergic neurons in the basal forebrain that project diffusely across much of the cortical mantle to promote processes related to attention and salience in visual cortex (Peck & Salzman, 2014a; Pessoa, 2010). Therefore, despite the lack of direct connections between amygdala and LIP, value or salience signals from the basolateral and central nuclei of amygdala may be able to affect visual processing of visual cues in LIP via multi-synaptic pathways.

1.6 EXPERIMENTAL AIMS

There are two goals for the two experiments in this dissertation. (1) Determine whether neurons in LIP and amygdala encode the worth (value) or importance (salience) of choice-options early during value-based decision-making. (2) Determine whether early reward-effects in neurons in LIP and amygdala depend on early automatic capture of visual attention by the option promising larger reward.

Aim 1: Do neurons encode the value or salience of choice-options?

The goal of the first experiment (Chapter 2) is to determine whether neurons in LIP and amygdala encode the value or salience of choice-options, early during decision-making. Previous studies have claimed both value and salience functions for LIP and amygdala. However, these studies varied only the intensity of rewards associated with cues. Increasing the intensity of the reward promised by a cue not only increases its value but also increases its salience. Thus, these studies confound value with salience and cannot say which of these are encoded by neurons in LIP and amygdala.

We enable the dissociation of value from salience in LIP and amygdala by having monkeys making decisions not only among options promising different intensities of reward but also among options threatening different intensities of penalty. *Value* increases with the promise of reward but decreases with the threat of penalty. *Salience* increases with the intensity of promises as well as threats. Accordingly, we expect value-coding neurons to fire more for the greater of two goods but to fire less for the greater of two evils. We expect salience-coding neurons to fire more for the greater of two goods and the greater of two evils.

Neurons encoding the value of choice options—early during decision-making—could be involved in the decision-making process *based on the values of goods and evils* that the monkeys use to choose the greater of two goods, avoid the greater of two evils, and choose goods over evils. Neurons encoding the salience of choice options—early during decision-making—could be involved in a prioritizing process *based on the intensities of goods and evils* that directs covert attention to the most important option in visual space. Therefore, the goal of Chapter 2 is to disentangle value- from salience-based coding in neurons in LIP and amygdala, early during decision-making.

Aim 2: Do early reward-signals depend on an option's acquired-salience?

The goal of the second experiment (Chapter 3) is to determine whether early reward-effects in LIP and amygdala require early automatic capture of visual attention by the option promising more reward. Recent studies in humans show that repeated association with reward allows a visually distinct cue to acquire salience as the ability to automatically capture attention. LIP and amygdala neurons show early reward-effects for visually distinct cues. No one has yet tested whether these early reward-effects simply reflect early automatic capture of attention by the visually distinct large reward cue.

We enabled the dissociation of cue-reward from cue-salience in LIP and amygdala by having monkeys make decisions involving similar looking but differentially valued choice-options. The near identical physical appearance of the cues precluded early automatic capture of attention by the option associated with larger reward—but not the monkeys' ability to make value-based decisions involving these similar looking options. Accordingly, we expect value-

coding neurons to increase firing rates for options promising greater reward, but we expect salience-coding neurons to have their reward-effects attenuated or even eliminated.

Neurons that differentiate between differentially valued but similar looking choice-options—early during decision-making—could be involved in a decision-making process *based on the values of goods* to choose the greater of two goods. Neurons that fail to differentiate between differentially rewarding but similar looking choice options—early during decision-making—could be involved in a visual-reward associative process for cue-salience acquisition that can be thwarted by ambiguous looking options. Therefore, the goal of Chapter 3 is to disentangle visually independent (value) from visually dependent (salience) reward-effects in neurons in LIP and amygdala, early during decision-making.

2.0 REWARD-PENALTY

2.1 LIP

2.1.1 INTRODUCTION

In monkeys deciding between alternative saccadic eye movements, lateral intraparietal (LIP) neurons representing each saccade fire at a rate proportional to the value of the reward expected upon its completion. This observation has been interpreted as indicating that LIP neurons encode saccadic value and that they mediate value-based decisions between saccades. Here we show that LIP neurons representing a given saccade fire strongly not only if it will yield a large reward but also if it will incur a large penalty. This finding indicates that LIP neurons are sensitive to the motivational salience of cues. It is compatible neither with the idea that LIP neurons represent action value nor with the idea that value-based decisions take place in LIP.

Each of us makes hundreds of value-based decisions every day. Deciding whether to take a drink of juice or a sip of coffee at breakfast is a process driven by the subjective value of each outcome. So is deciding whether to go to graduate school or medical school. There has been debate in recent years concerning the neural mechanisms of such decisions. This debate has pitted a goods-based account against an action-based account. The goods-based account holds that limbic areas such as orbitofrontal cortex mediate a choice between goods (juice or coffee)

based on their respective values and that the choice is translated into an appropriate motor command (reach for the glass or the cup) in parietal and dorsal frontal cortex (Padoa-Schioppa & Assad, 2006; Padoa-Schioppa & Cai, 2011; Roesch & Olson, 2004). The action-based account holds that the values of juice and coffee are computed in orbitofrontal cortex and transmitted to parietal and dorsal frontal cortex, where neurons involved in planning to reach for the glass and the cup become active in proportion to the values of juice and coffee. The decision then evolves through competition between neuronal populations representing the opposed action plans (Gold & Shadlen, 2007; Kable & Glimcher, 2009; Platt, 2002; Rangel & Hare, 2010; Sugrue, Corrado, & Newsome, 2005).

> "At the first stage, a value transformation takes the input…and abstracts from it a representation of the value of available options. At the second stage, a decision transformation maps this value representation onto the probability of alternative courses of action. A final processing stage transforms this continuous probability into discrete choice among these alternatives (Sugrue et al., 2005)."

The goods-based model is intuitive and fits with the assumption underlying classic behavioral economics that decisions concern anticipated outcomes as distinct from motor plans. However, the action-based model has received apparent support from single-neuron recording studies of LIP. In monkeys making value-based decisions between saccade targets, LIP neurons representing each saccade fire early in the trial at a rate proportional to the reward expected upon its completion (Coe et al., 2002; Klein et al., 2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Sugrue et al., 2004). This observation is compatible with the idea that LIP neurons represent action value in the service of an action-based decision process. However, there is another possible interpretation. Emotionally potent stimuli are salient in the sense that they

automatically capture attention (Berridge, 2003; Brosch, Pourtois, Sander, & Vuilleumier, 2011). This is true in particular of stimuli associated with rewards and penalties (Anderson, Laurent, & Yantis, 2011; Lim, Padmala, & Pessoa, 2009; O'Brien & Raymond, 2012). LIP neurons fire at an enhanced rate when attention is directed into their response fields (Bisley & Goldberg, 2010). Thus LIP neurons might fire strongly when a valued target is in the response field simply because the target is motivationally salient (Maunsell, 2004; Peck et al., 2009).

2.1.2 MATERIALS AND METHODS

2.1.2.1 SUBJECTS

Two adult male rhesus macaque monkeys participated in the experiments (monkey 1, laboratory designation Eg, and monkey 2, laboratory designation Je). All experimental procedures were approved by the Carnegie Mellon University Institutional Animal Care and Use Committee (IACUC) and the University of Pittsburgh IACUC, and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals. In each monkey, a surgically implanted plastic cranial cap held a post for head restraint and a cylindrical recording chamber 2 cm in diameter oriented flush to the skull with its base centered at approximately posterior 5 mm and lateral 12 mm relative to the Horsley-Clarke reference frame. Electrodes could be advanced along tracks forming a square grid with 1 mm spacing. The chambers overlay the right hemisphere in monkey 1 and the left hemisphere in monkey 2.

2.1.2.2 REWARD-PENALTY TASK

On each trial, cues presented to the left and right of fixation predicted the outcomes that would result from leftward and rightward saccades later in the trial. The cues were selected from two sets of four digitized images. In each set, one image predicted a small reward (0.06 cc of water in monkey 1 and 0.12 cc in monkey 2), one predicted a large reward (0.18 cc in monkey 1 and 0.36 cc in monkey 2), one predicted a small penalty (1000 ms of enforced eccentric fixation in monkey 1 and 400 ms in monkey 2) and one predicted a large penalty (8000 ms in monkey 1 and 3200 ms in monkey 2). These amounts were the product of adjustments made during training of each monkey to induce engagement with the task and consistent choice behavior. Trials conformed to twelve conditions comprising all possible arrangements in which targets of unequal value could be placed inside and opposite the response field. A single session consisted of 96 successfully completed trials using image set 1 followed by 96 successfully completed trials using image set 2. A trial was judged to be successful if the monkey completed it regardless of whether he made an optimal or suboptimal choice. The sequence of conditions was random except for two constraints. First, within each block of 24 trials each condition had to be imposed twice. Second, following a fixation break, the identical condition was imposed again.

At the outset of each trial, the monkey fixated a central white square subtending 0.1º for 300 ms. Then two cues, each associated with a reward or a penalty of a particular size, appeared for 500 ms at diametrically opposed locations 12 º to the left and right of fixation. The cues were digitized images of objects against a transparent background. Each image subtended 7° along whichever dimension, horizontal or vertical, was greater. After the disappearance of the cues, the monkey had to maintain central fixation for a duration selected at random within the range 1000-1200 ms. At the end of the delay period, the fixation spot vanished and two white square targets

subtending 0.2° appeared at locations 12° to the left and right of fixation. The monkey was required to launch a saccade to one of the targets within 300 ms and to reach the target within 100 ms after launch. The sequence of events that ensued depended on whether the target was at a location marked earlier in the trial by a reward-predicting or penalty-predicting cue. 1) If the target was at a location marked by a reward-predicting cue, then the monkey was required to maintain fixation on it for 100 ms. At that point, the unselected target disappeared and the selected target was replaced by a version of the reward-predicting cue minified to 24% of its former size so as to render it suitable as an object of fixation. Reward was delivered after an interval selected at random within the range 300-450 ms. 2) If the target was at a location marked earlier in the trial by a penalty-predicting cue, then it was immediately replaced by a minified version of this cue. The monkey was required to fixate the image for a long or short period of time according to whether the penalty was large or small. While the monkey maintained fixation, the cue flashed on and off to the accompaniment of a periodic sound. If the monkey broke fixation, then the cue remained steadily on. When the monkey renewed fixation, it again flashed on and off to the accompaniment of the sound. This continued until the cumulative fixation time matched the required duration. We chose to require that the monkey fixate a minified version of the image that had predicted the penalty so as to strengthen the association between the image and the outcome.

The consequences of the monkey's prematurely breaking fixation depended on the stage of the trial at which the break occurred and the outcome options available on the trial. In general, if the options included one penalty, then that penalty was imposed and, if the options included two penalties, then the larger penalty was imposed. The use of penalties to punish fixation breaks ensured that the monkeys, even if they chose penalties rarely, had ongoing experience of them.

The following rules determined the consequences of a fixation break. 1) If the monkey failed to attain fixation on the central target or attained it but broke fixation before the outcome-predicting cues had appeared, then the trial simply terminated. 2) If, after the onset of the cues, the monkey broke central fixation, failed to launch a saccade in time or failed to reach a target in time, then (a) if the two options were both rewards, the trial simply terminated, (b) if one option was a penalty, this penalty was imposed, or (c) if both options were penalties, the larger penalty was imposed. 3) If the monkey made a saccade to a target at a location marked by a reward-predicting cue but broke eccentric fixation before delivery of reward, then (a) if the two options were both rewards, the trial simply terminated or (b) if the other option was a penalty, this penalty was imposed.

2.1.2.3 MEMORY-GUIDED SACCADE TASK

In the reward-penalty task, the monkey chose between two targets located 12° to the left and right of fixation. Accordingly, we selected for study neurons that fired differentially in conjunction with the performance of memory-guided saccades to those locations. As we advanced the microelectrode, we monitored neuronal activity while the monkey performed a memory-guided saccade task. At the outset of each trial, the monkey fixated a central spot 0.1º in diameter for 300 ms. Then two targets subtending 0.2º appeared to the left and right of fixation at an eccentricity of 12 º. After a delay of 300 ms, a cue subtending 0.8° appeared for 250 ms in superimposition on one of the targets. A delay of duration 400-500 ms ensued. At the end of the delay period, offset of the fixation spot signaled the monkey to make a saccade to the target previously marked by the cue. We inspected on-line raster and histogram displays to determine whether the neuron exhibited task-related activity and, if so, whether this was spatially selective.

We proceeded to run the reward-penalty task only if the neuron exhibited a clear contralateral spatial preference during the cue, delay or saccade period.

2.1.2.4 RECORDING SITES

To determine the location of recording sites relative to gross morphological landmarks, we extrapolated from frontoparallel MR images containing the brain and fiducial markers placed at known locations within the chamber. The recording sites occupied the lateral bank of the intraparietal sulcus at levels 4-6 mm posterior to the splenial limit of the corpus callosum. In Monkey 1 (Eg), recording sites extended 1 mm anterior, 1 mm posterior, 1 mm medial and 0 mm lateral relative to the central recording point whose coordinates were 4 mm posterior and 8 mm lateral in the Horsley-Clarke reference frame. In Monkey 2 (Je), recording sites extended 2 mm anterior, 0 mm posterior, 1 mm medial and 2 mm lateral relative to the central recording point whose coordinates were 7 mm posterior and 8 mm lateral in the Horsley-Clarke reference frame. At the beginning of each day's session, we lowered a varnish-coated tungsten microelectrode with an initial impedance of several megaohms at 1 KHz through the dura into the underlying cortex. Action potentials of single neurons were isolated from the multi-neuronal trace by use of a commercially available spike-sorting system. All waveforms were recorded during the experiments and spike sorting was performed offline using commercially available spike-sorting software.

2.1.2.5 ANALYSIS OF BEHAVIOR

(a) Reward and Penalty Effects

We characterized the impact of predicted reward and penalty on the behavior of each monkey during each recording session with three measures: percent correct, fixation break rate and reaction time. We based the calculation on the eight trial conditions in which the monkey was given a choice between a reward and a penalty (Figure 3). Across these conditions, reward size was fully counterbalanced against penalty size. For each measure in each monkey, we carried out an ANOVA with reward size (large or small), penalty size (large or small) and reward location (right or left) as factors and with n equal to the number of sessions (16 in M1; 20 in M2). Inclusion of reward location as a factor buffered any variance that might have arisen from a spatial bias.

Percent correct. We defined percent correct as the number of trials on which the monkey chose the preferred target expressed as a percentage of all trials on which either target was chosen.

Fixation-break rate. We defined the fixation-break rate as the number of trials on which the monkey broke fixation expressed as a percentage of all trials completed at least up to the point of the appearance of the cues.

Reaction time. We defined reaction time as the interval between the imperative cue (offset of the central fixation spot) and initiation of the saccade on trials which the monkey completed after having made an optimal choice.

(b) Generalization Test Using Unfamiliar Combinations of Images

Extensive training on the reward-penalty task might have induced a form of habitual behavior in which each combination of cues, acting as a single compound stimulus, elicited a particular response. This would have obviated the need for the monkeys to evaluate the individual cues on each trial. If this were the basis for performing the task, then the monkeys would be thrown off by presenting the cues in combinations not previously experienced. To test for this possibility, we took advantage of the fact that the monkeys had been exposed to two sets of cues in separate blocks of trials throughout the period of training and neuronal data collection (Figure 2B). We will designate the first and second image sets as A_{LR}, A_{SR}, A_{SP}, A_{LP} and B_{LR}, B_{SR}, B_{SP}, B_{LP}, where the subscript indicates the predictive association of the image (large reward, small reward, small penalty and large penalty). At the end of the period of data collection, we tested each monkey in four 192-trial sessions: two sessions using the standard image sets followed by two sessions using image sets derived from the original ones by transposing some images. In transposition session 1, the small-penalty images were swapped to create sets A_{LR}, A_{SR}, B_{SP}, A_{LP} and B_{LR}, B_{SR}, A_{SP}, B_{LP}. Consequently, the combination of images was novel on any trial involving a small-penalty cue. In session 2, the small-reward images were swapped to create sets A_{LR}, B_{SR}, A_{SP}, A_{LP} and B_{LR}, A_{SR}, B_{SP}, B_{LP}. Consequently, the combination of images was novel on any trial involving a small-reward cue. For each of the six possible combinations of values, we compared the percentage of optimal choices in the standard sessions to the percentage of optimal choices in the transposition sessions.

2.1.2.6 ANALYSIS OF NEURONS

(a) Population-level Statistical Tests

(i) Reward and Penalty Effects

To compare neuronal activity between conditions, we inspected population histograms constructed by computing the average firing rate in each 1 ms bin and applying a Gaussian smoothing function (σ = 10 ms). To determine whether the average firing rate during a standard analysis epoch (0-250 ms following cue onset) differed significantly (α = 0.05) between conditions, we employed a two-tailed paired t-test with n equal to the number of neurons in the sample and with each neuron contributing one mean firing rate for each condition. In addition, we applied a t-test to each successive 10 ms bin (α = 0.01) so as to place, beneath population histograms, tick marks indicating time points at which the firing-rate difference between two conditions attained an arbitrary stringent statistical threshold. The role of this step was to provide a graphic indication of signal timing and not to serve as a test of effect significance.

(ii) Latency of Reward and Penalty Effects

To determine the latency of the reward and penalty signals relative to that of the earlier arrival of the raw visual information, we normalized the firing rate on the eight trial conditions in which the monkey was given a choice between a reward and a penalty (Figure 3). Latency was defined as time from zero to half-peak of the signal. Normalized signal strength was computed as (F-B)/(P-B) where F was instantaneous firing rate, B was firing rate at time zero and P was peak firing rate in the window 0-350 ms. For the effect of reward (Figure 3A) or penalty (Figure 3B) in the response field, firing rate was defined as the mean across neurons of the firing rate

associated with a large predicted outcome minus the firing rate associated with a small predicted outcome. For the visual responses, firing rate was defined as the mean population firing rate as computed across all neurons from the conditions used to calculated the reward (Figure 3A) or penalty (Figure 3B) normalized effect.

(b) Neuron-level Statistical Tests

(i) Reward and Penalty Effects

To determine whether individual neurons were significantly sensitive to reward size or penalty size as predicted by cues in or opposite the response field, we carried out a pair of two-factor ANOVAs. One ANOVA was based on a set of four conditions across which the size of the reward predicted by a cue in the response field was counterbalanced against the size of the penalty predicted by a cue opposite the response field. The second ANOVA was based on a set of four conditions across which the size of the penalty predicted by a cue in the response field was counterbalanced against the size of the reward predicted by a cue opposite the response field. In each ANOVA, the direction of the saccadic response was constant across all conditions and so did not contribute to the observed effects. When then assessed whether the number of neurons with significant effects was significantly greater than expected by chance using a χ^2 test with Yates-correction.

(ii) Correlation of Reward and Penalty Effects

We characterized the reward and penalty dependence of each neuron's firing with indices capturing the effect of reward and penalty cues presented in the response field. Each index had the form (L-S)/(L+S) where L and S were the firing rates associated with a large and small

prediction respectively. We then computed the Pearson's correlation across neurons between the reward and penalty indices.

2.1.3 RESULTS

To distinguish between value-based and salience-based signals in LIP, we employed a task incorporating rewards and penalties (Roesch & Olson, 2004). On each trial, the monkey chose between cues placed in and opposite the neuronal response field (Figure 2A). Each cue indicated that if the monkey made an eye movement to its location at the end of the trial a particular outcome would ensue (Figure 2B). The possible outcomes were large reward (several drops of water), small reward (one drop of water), small penalty (short period of eccentric fixation) and large penalty (long period of eccentric fixation). Other distinguishing features of the task included associating outcomes with cues regardless of their location, which ruled out the development of motor biases, and giving the cues fixed significance, which ruled out uncertainty.

2.1.3.1 BEHAVIOR

Confronted with two offers of different value, the monkeys consistently chose the better offer (Figure 2C, Table 1).

(a) Reward and Penalty Effects on Behavior

For the eight trial conditions in which the monkey was given a choice between a reward and a penalty (Figure 3), we computed the impact of predicted reward and penalty on the behavior of each monkey during each recording session for three measures: percent correct, fixation break rate and reaction time (Table 1).

Percent correct. The monkeys performed very close to ceiling on this measure. In M1, the percent correct did not depend significantly on the size of either the predicted reward or the predicted penalty. In M2, it was significantly greater when a large reward was at stake than when a small reward was at stake.

Fixation-break rate. This measure depended on reward size and penalty size in both monkeys. Monkey 1 broke fixation significantly less often when a large reward or a large penalty was at stake. Monkey 2 broke fixation significantly more often when a large reward was at stake and significantly less often when a large penalty was at stake.

Reaction time. In monkey 1, the reaction time was shorter on trials in which a large reward was at stake and longer on trials in which a large penalty was at stake. In monkey 2, both of these trends were present but only the effect of reward size attained significance.

Table 1. Behavior on reward-penalty task: LIP recording sessions

Monkey	Large Reward (mean)	Small Reward (mean)	p (ANOVA)		Large Penalty (mean)	Small Penalty (mean)	p (ANOVA)
Percent Correct							
M1	99.7	99.3	0.25		99.5	99.5	1
M2	99.9	99.3	0.002		99.7	99.6	.44
Percent Fixation Breaks							
M1	5.52	7.99	0.0072		5.57	7.93	0.0096
M2	49.6	46.1	0.011		43.7	52.0	<0.0001
Reaction Time (ms)							
M1	183	191	0.00065		191	183	0.00049
M2	143	176	<0.0001		160	158	0.46

Impact of predicted reward and penalty on three performance measures. Each p-value indicates the level of statistical significance of the difference between the two values immediately to its left.

(b) Monkeys Evaluated Each Image Not Image-pairs

For each of the six possible combinations of values, we compared the percentage of optimal choices in the standard sessions to the percentage of optimal choices in the transposition sessions. In no case was performance with transposed image sets worse than performance with the standard image sets (Table 2). We conclude that the monkeys were processing the cues as separate items rather than as a single composite item.

Table 2. Behavior on generalization test

	LR sr	**sp LP**	**LR LP**	**sr LP**	**sr sp**	**LR sp**
Standard	99.2%	92.2%	99.2%	96.9%	94.5%	100%
Transposed	100%	93.0%	100%	100%	95.3%	100%

Percent-correct scores under all six choice conditions during testing with the standard image sets and with image sets created by transposition of images between the standard sets. The nature of the choice is indicated in the heading of each column (LR = large reward, sr = small reward, LP = large penalty, sp = small penalty). The optimal decision is indicated by underlining. The percent-correct score indicates the percentage of trials on which the monkeys made the optimal choice expressed as a percentage of all trials on which they made either choice.

2.1.3.2 NEURONS

Confronted with two offers of different value, the monkeys consistently chose the better offer (Figure 2C, Table 1). A large penalty possesses lower value than a small penalty but is emotionally more potent. Consequently, value-based and salience-based models make opposite predictions with regard to the impact of predicted penalty size on neuronal activity (Bisley & Goldberg, 2010; Roesch & Olson, 2004; Wallis & Rich, 2011). To test the predictions, we collected data from 28 neurons in the right LIP of monkey 1 and 39 neurons in the left LIP of monkey 2.

(a) Data Combined from Both Monkeys

We first examined trials in which the monkey, offered a choice between a large and a small reward, chose the large reward. Population activity during the cue period (0-250 millisecond analysis window) was significantly stronger when the cue in the response field predicted a large reward (Figure 2D, blue fill). The enhancement could have depended on the cue's higher value, its greater motivational salience or the monkey's decision to look toward the response field. We next examined trials in which the monkey, offered a choice between a large penalty and a small penalty, chose the small penalty. Firing during the cue period was significantly stronger when the cue in the response field predicted a large penalty (Figure 2E, red fill). This enhancement must have depended on the greater motivational salience of the cue because its value was low and the monkey decided to look away from it.

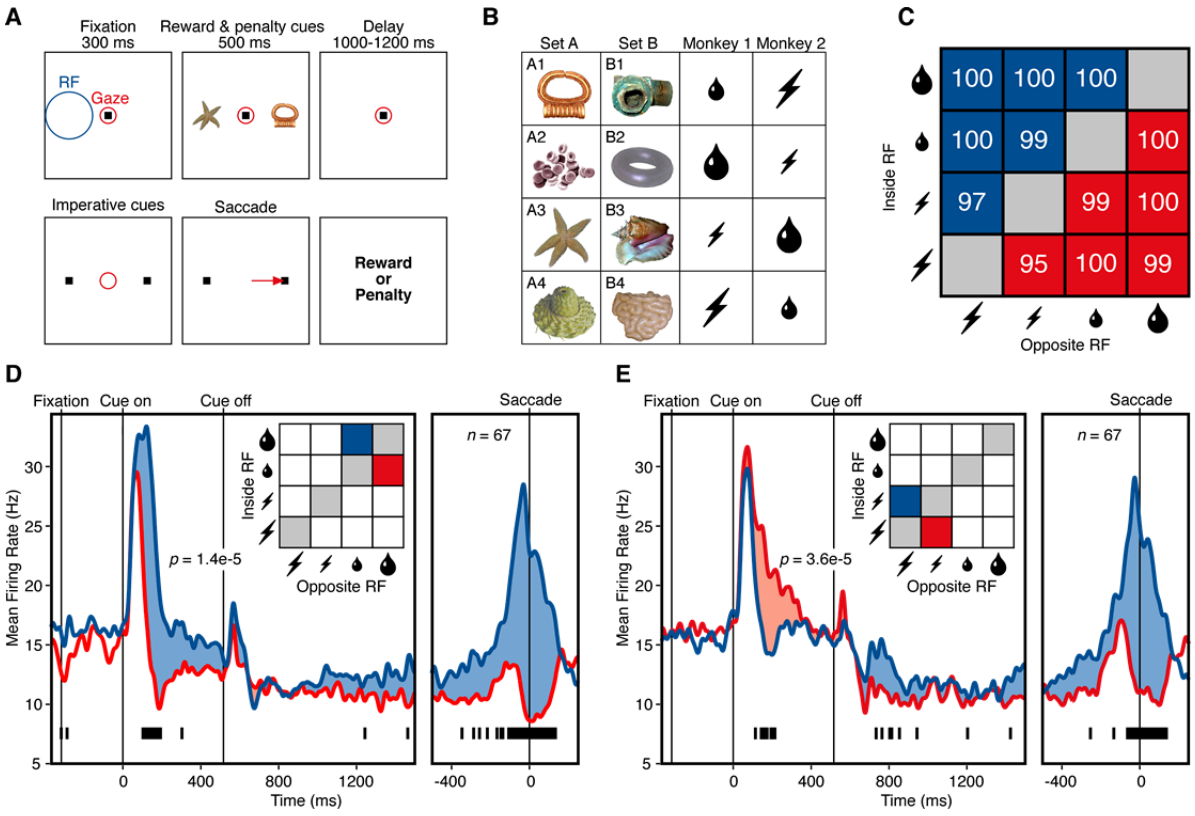


Figure 2. LIP: Reward-Penalty Task, Cue-Associations, Choice-Behavior and Two PSTHs
(A) Sequence of events in a single trial. The items in each panel were visible to the monkey with the exception of those depicting the response field (RF), gaze location and saccade. **(B)** Stimuli and their contingencies. The eight cues possessed different significance in the two monkeys. Large and small water drops: large and small reward. Large and small lightning bolts: large and small penalty. **(C)** The monkeys nearly always chose optimally. The numbers indicate the percentage of trials on which they chose the better outcome – either into the response field (blue) or away from it (red). **(D)** Population firing rate as a function of time during trials with a large-reward cue in the RF and a small-reward cue opposite (blue) or vice versa (red). The monkey chose large reward. **(E)** Population firing rate as a function of time during trials with a large-penalty cue in the RF and a small-penalty cue opposite (red) or vice versa (blue). The monkey chose small penalty. Tick marks indicate 10 ms bins in which the difference between red and blue curves crossed an arbitrary statistical threshold (two-tailed paired t-test, $n = 67$, $\alpha = 0.01$). In D-E, each pair of red and blue curves is based on conditions colored red and blue in the accompanying inset and each p value indicates the outcome of a two-tailed paired t-test ($n = 67$) applied to firing rates under red and blue conditions. All analyses concern 0 to 250 ms after the cue onset unless otherwise stated.

To factor out completely any effect of the saccadic decision, we constructed population plots based on subsets of conditions in which cue value varied but saccade direction did not. Population activity was stronger when a cue in the response field predicted a large as compared to a small reward (Figure 3A, blue fill) and also when it predicted a large as compared to a small penalty (Figure 3B, blue fill). The value of the cue opposite the response field exerted only a weak and inconsistent effect (Figures 3C-D, 9C-D, 10C-D). This pattern of location specificity could arise from enhanced spatial attention but not enhanced arousal, vigilance or general motivation.

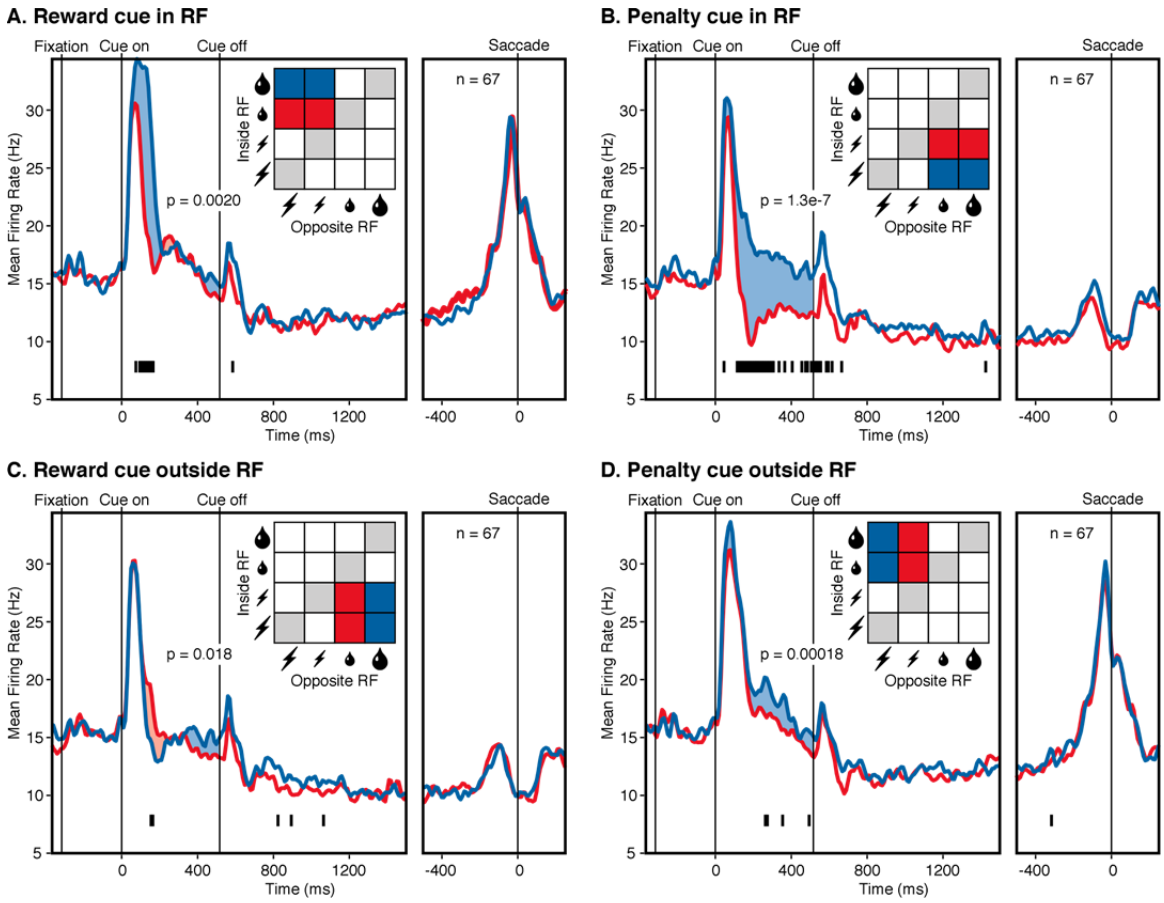


Figure 3. Reward & Penalty Effects PSTHs
(A) The cue in the response field predicted large (blue) or small (red) reward. **(B)** The cue in the response field predicted large (blue) or small (red) penalty. **(C)** The cue opposite the response field predicted large (blue) or small (red) reward. **(D)** The cue opposite the response field predicted large (blue) or small (red) penalty.

Neurons might have responded strongly to large-penalty cues because, by chance, they possessed a high degree of physical salience. Therefore we gave the images different significance in the two monkeys. Cues predicting a large penalty in monkey 1 predicted a small reward in monkey 2 and vice versa (Figure 2B). Nevertheless, in each monkey, cues predicting a large penalty elicited stronger firing than cues predicting a small reward (Figure 4A-B, blue fill). Thus neuronal activity depended on the images' associated outcomes and not their physical attributes.

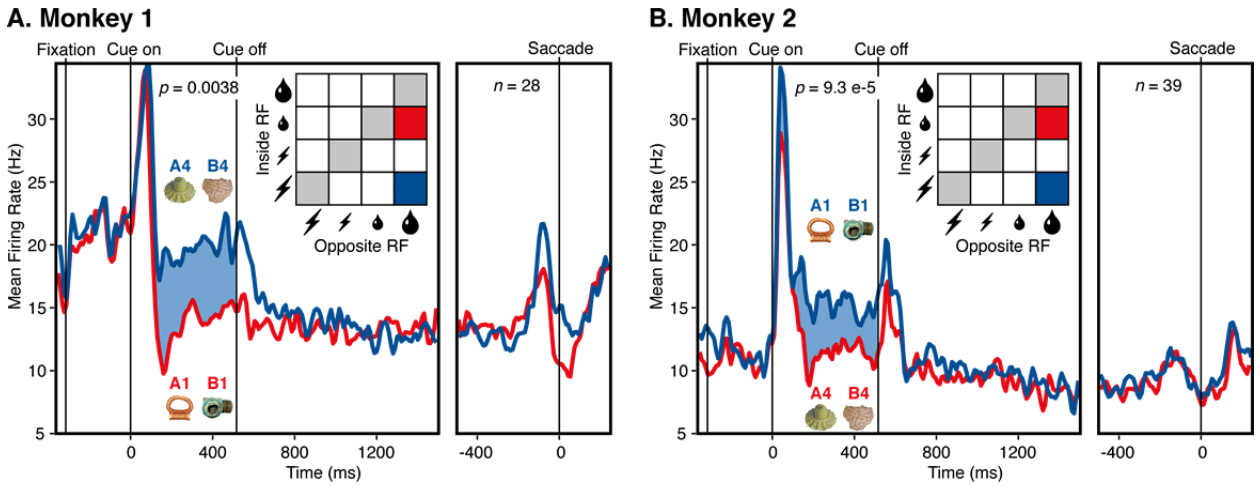


Figure 4. Effect of physical salience of images counter-balanced between monkeys
Population activity when a cue appearing in the response field predicted a large penalty (blue) or a small reward (red). On all trials, the cue opposite the response field predicted a large reward and the monkey chose it. **(A)** In monkey 1, images A4 and B4 predicted a large penalty and images A1 and B1 predicted small reward. **(B)** In monkey 2, the contingencies were reversed.

To characterize reward- and penalty-related activity at the level of individual neurons, we carried out two analyses. One analysis assessed the impact of reward cues inside and penalty cues opposite the response field (Figure 3A). Main effects of reward size in the response field predominated (red sector of Figure 5A). A second analysis assessed the impact of penalty cues inside and reward cues opposite the response field (Figure 3B). Main effects of penalty size in the response field predominated (green sector of Figure 5B). We next generated for each neuron a reward index and a penalty index based on responses to cues in the response field. Each index ranged from -1 (fired only in response to "small" cue) to +1 (fired only in response to "large" cue). Plotting the penalty against the reward index revealed that they were positively correlated across neurons (an effect driven by monkey 1, Figures 11 and 12) and that most points fell in the upper right quadrant (Figure 5C). These points represent neurons whose activity is best explained as encoding the motivational salience of the cues.

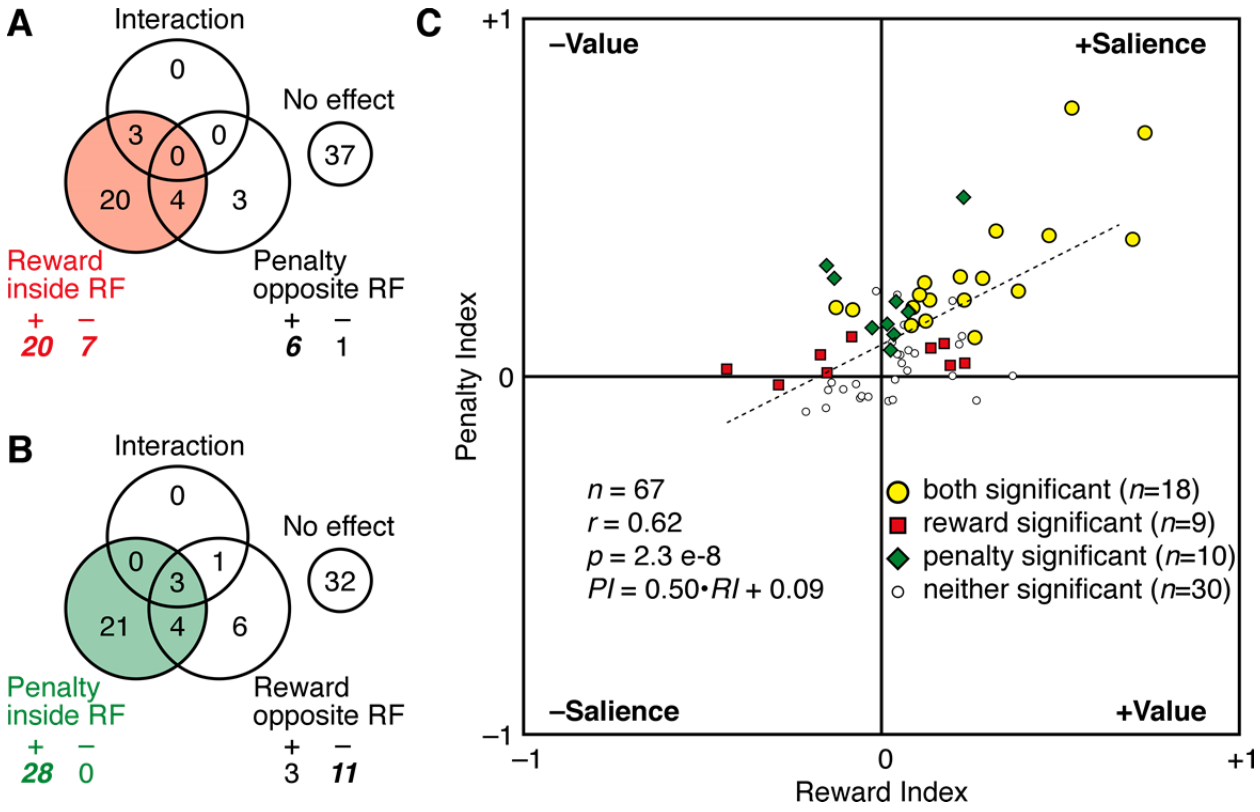


Figure 5. Single Neuron Effects & Correlation Analysis
Individual neurons exhibited significant sensitivity to reward size and penalty size for cues in the response field. **(A)** Counts of neurons exhibiting significant effects of reward size in the response field and penalty size opposite the response field (two factor ANOVA, $\alpha = 0.05$). The predominant outcome was a main effect of reward in the response field (27 neurons: red tinting). **(B)** Counts of neurons exhibiting significant effects of penalty size in the response field and reward size opposite the response field (two factor ANOVA, $\alpha = 0.05$). The predominant outcome was a main effect of penalty in the response field (28 neurons: green tinting). In A-B, "+" and "–" counts indicate numbers of neurons firing more strongly for the larger (+) or smaller (–) predicted outcome; counts in italic boldface are significantly greater than expected by chance (χ^2 test, Yates correction, $\alpha = 0.05$). **(C)** Penalty index vs. reward index for all 67 neurons. The quadrants are labeled according to the hypothesis most concordant with the corresponding pattern of activity: +salience = responds more strongly to more salient stimuli; -salience = responds more strongly to less salient stimuli; + value = responds more strongly to more valuable stimuli; -value = responds more strongly to less valuable stimuli.

Arcizet et al. (2011) reported on the rate of incidence, strength and latency of neuronal activity in LIP dependent on the physical salience of a stimulus. They report (a) that the firing rate was significantly affected by target salience in 48% of neurons, (b) that the firing rate was enhanced by 10% on average for salient as compared to non-salient stimuli and (c) that the visual response began 40 ms after stimulus onset whereas (d) salience-induced modulation of the firing rate began 75 ms following stimulus onset. These results are concordant with other results

described previously (Bisley & Goldberg, 2010). We have carried out comparable analyses on data from trials in which the cue in the receptive field predicted rewards of different sizes (Figure 3A) or penalties of different sizes (Figure 3B). With regard to reward-predicting cues, we find (a) that the firing rate was significantly affected by reward size in 40% of the sample (Figure 5A, 27/67 neurons), (b) that the firing rate was enhanced by 21% on average for large as compared to small reward (Figure 3A, 0-250 ms) and (c) that the visual response began 42 ms after stimulus onset whereas (d) reward-related modulation of the firing rate began 102 ms following stimulus onset (Figure 6A). With regard to penalty-predicting cues, we find (a) that the firing rate was significantly affected by reward size in 42% of the sample (Figure 5B, 28/67 neurons), (b) that the firing rate was enhanced by 31% on average for large as compared to small penalty (Figure 3B, 0-250 ms) and (c) that the visual response began 41 ms after stimulus onset whereas (d) penalty-related modulation of the firing rate began 107 ms following stimulus onset (Figure 6B). Thus manipulations of motivational salience (in the current study) and of physical salience (in previous studies) have produced roughly commensurate effects.

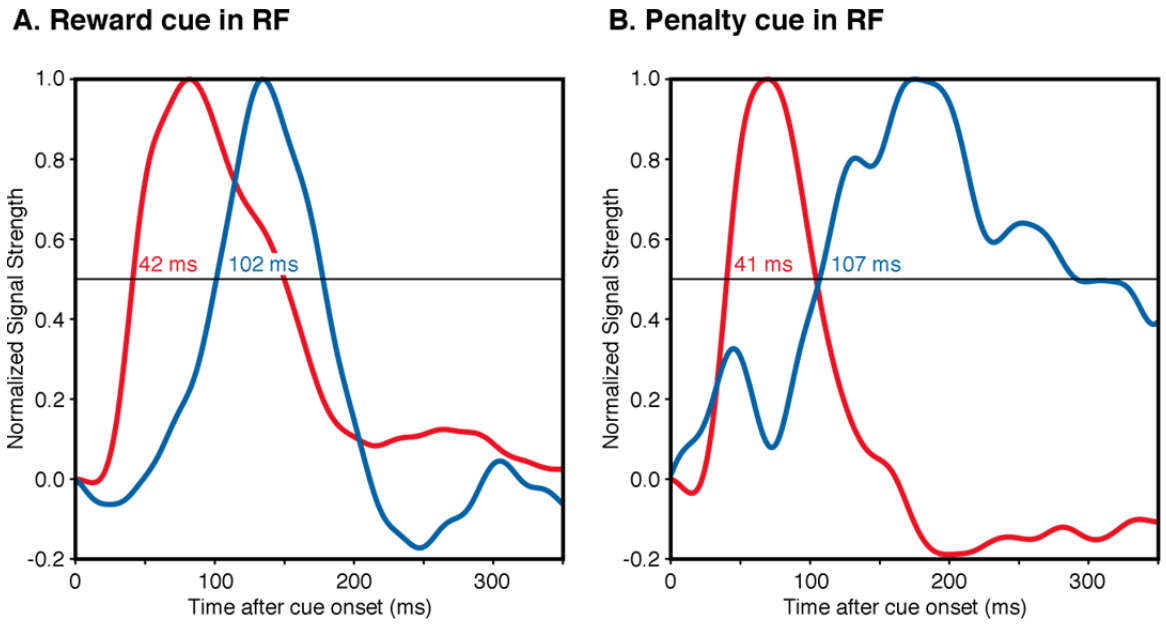


Figure 6. Latency Analysis

Firing dependent on predicted reward or penalty size (blue curves) began around 60 ms later than the visual response itself (red curves). **(A)** Data from trials in which the cue in the RF predicted either a large or a small reward (Figure 2A). **(B)** Data from trials in which the cue in the RF predicted either a large or a small penalty (Figure 2B). Normalized signal strength was computed as (F-B)/(P-B) where F was instantaneous firing rate, B was firing rate at time zero and P was peak firing rate in the window 0-350 ms. For each red curve, firing rate was defined as the mean population firing rate as computed across all neurons. For each blue curve, firing rate was defined as the mean across neurons of the firing rate associated with a large predicted outcome minus the firing rate associated with a small predicted outcome. The number juxtaposed to each curve indicates time to half height.

(b) Individual Monkey Data

Nearly all conclusions based on the combined data held up for monkeys 1 and 2 considered separately. a) On trials requiring a choice between a large reward and a small reward, cue-period firing was stronger when the cue in the response field predicted a large reward than when it predicted a small reward (Figures 7A and 8A, blue fill). b) On trials requiring a choice between a large penalty and a small penalty, cue-period firing was stronger when the cue in the response field predicted a large penalty than when it predicted a small penalty (Figures 7B and 8B, red fill). c) With the value of the reward cue in the response field counterbalanced against other factors that might influence neuronal firing, the response to a large-reward cue was greater than the response to a small-reward cue (Figures 9A and 10A, blue fill). d) With the value of the penalty cue in the response field counterbalanced against other factors that might influence neuronal firing, the response to a large-penalty cue was greater than the response to a small-penalty cue (Figures 9B and 10B, blue fill). e) More neurons were significantly affected by the value of the cue in the response field than by the value of the cue outside it (Figures 11A-B and 12A-B). f) Among these neurons, more fell in the "+" category, firing more strongly for the larger predicted outcome, than fell in the "–" category, firing more strongly for the smaller predicted outcome (Figures 11A-B and 12A-B). g) When the penalty index was plotted against the reward index, most points fell in the upper right quadrant in conformity with the hypothesis that the firing rate was proportional to the motivational salience of cues (Figures 11C and 12C).

Two differences between monkeys are worth noting although they do not affect the key conclusions of the study. a) For cues outside the response field, population activity in monkey 1 was significantly affected by reward size alone (Figure 9C-D) whereas population activity in monkey 2 was significantly affected by penalty size alone (Figure 10C-D). b) In monkey 1, there was a significant positive correlation across neurons between the penalty index and the reward index but, in monkey 2, there was not (Figures 11C and 12C).

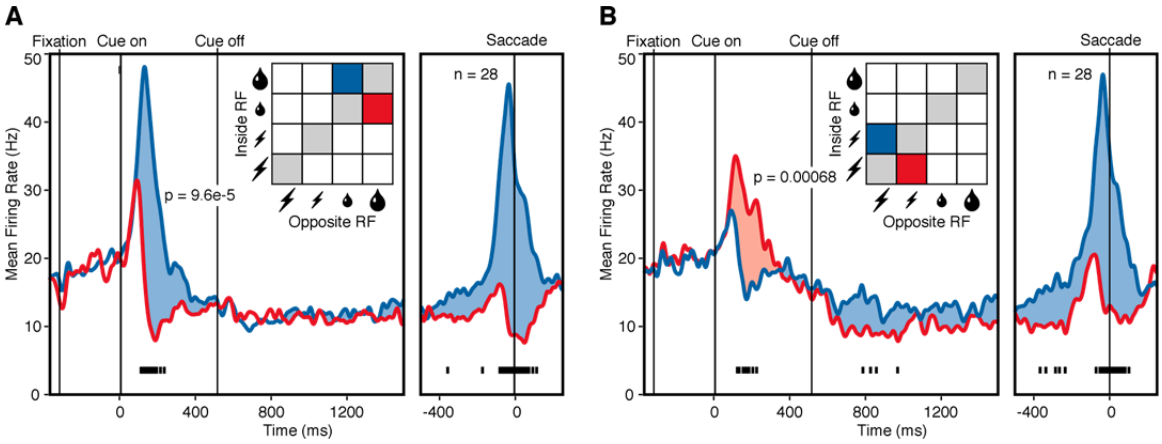


Figure 7. M1: Two PSTHs (n = 28)

Same conventions as Figure 2D-E.

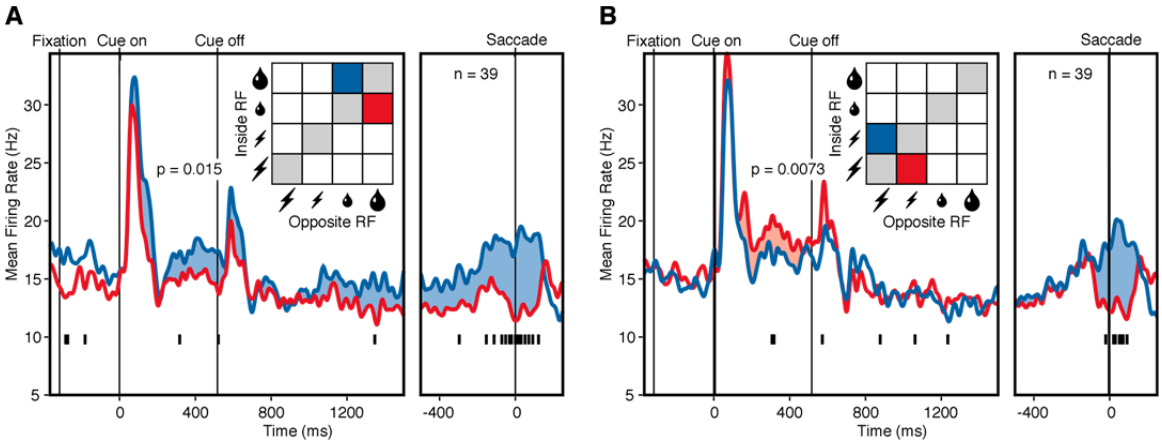


Figure 8. M2: Two PSTHs (n = 39)

Same conventions as Figure 2D-E.

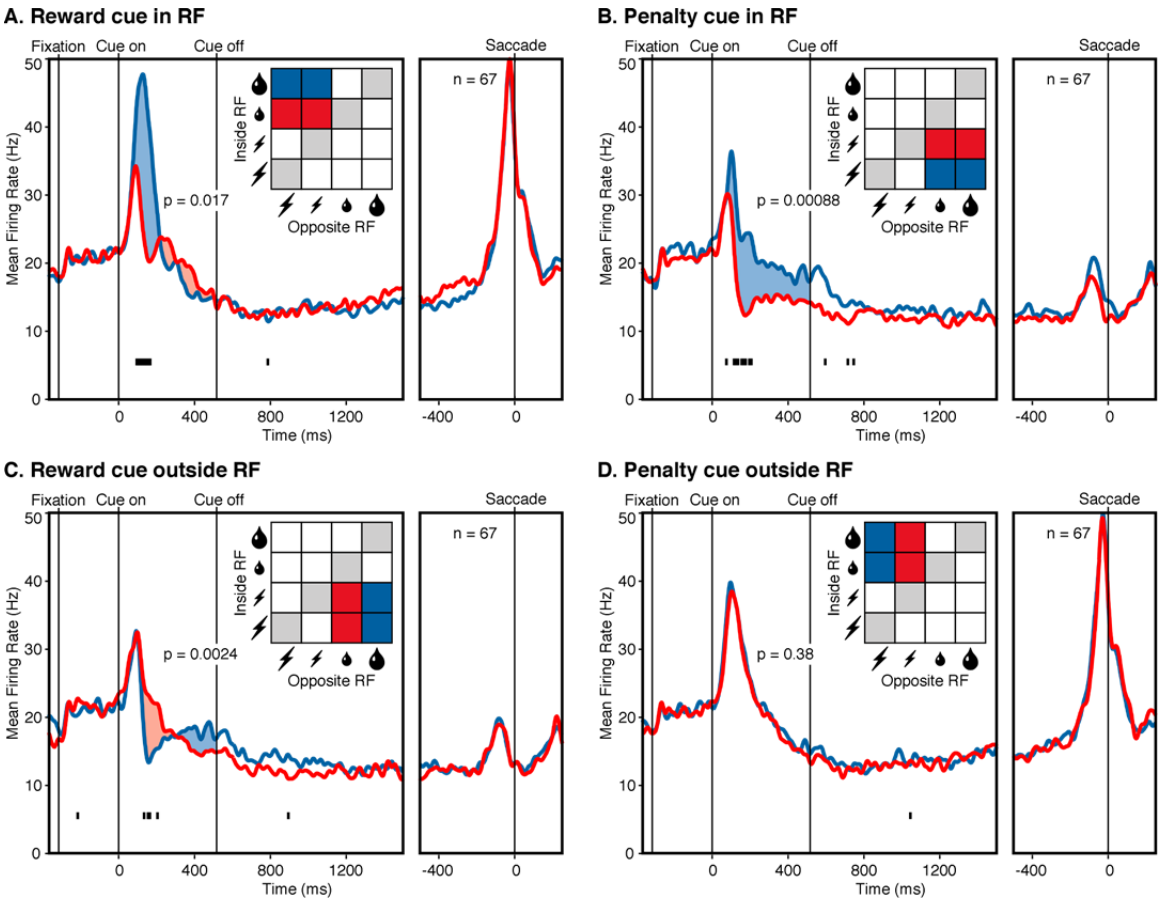


Figure 9. M1: Reward & Penalty Effects PSTHs (n = 28)

Same conventions as Figure 3.

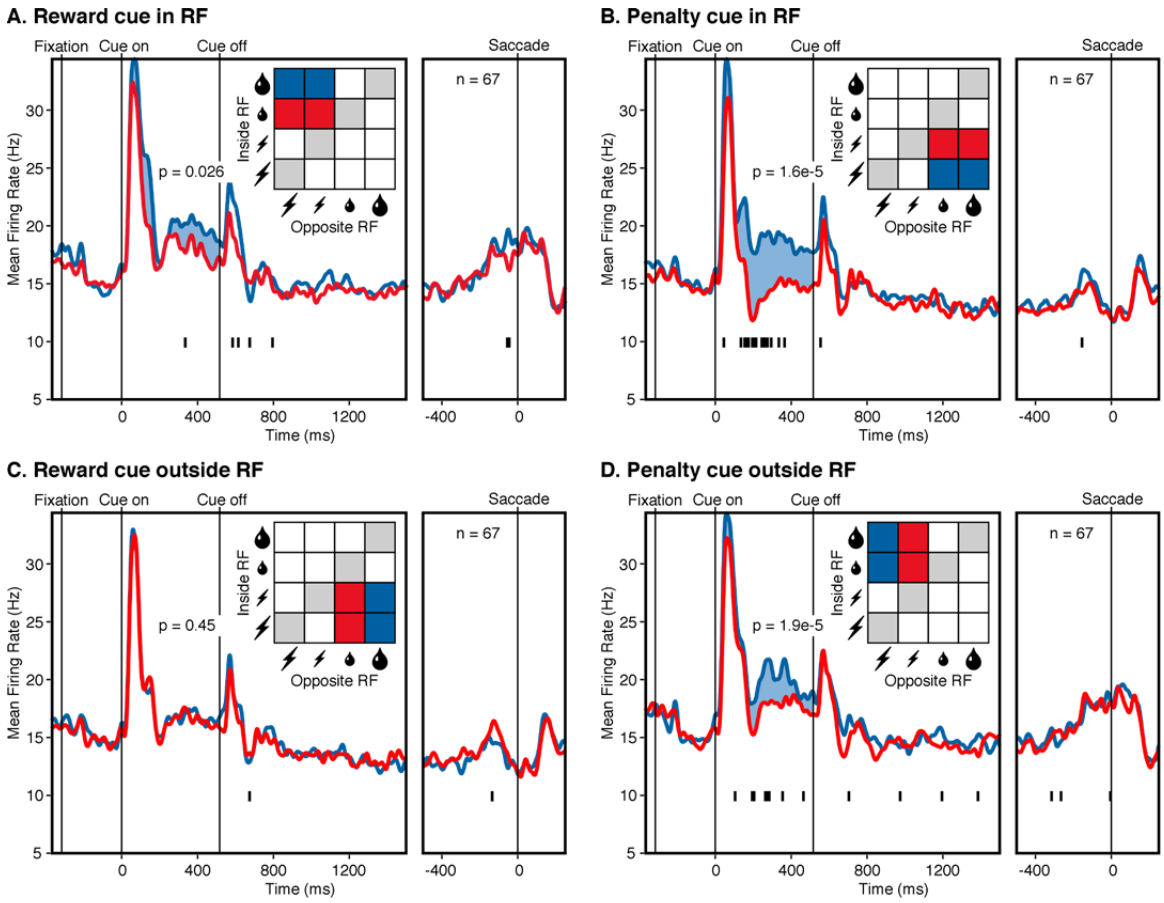


Figure 10. M2: Reward & Penalty Effects PSTHs (n = 39)

Same conventions as Figure 3.

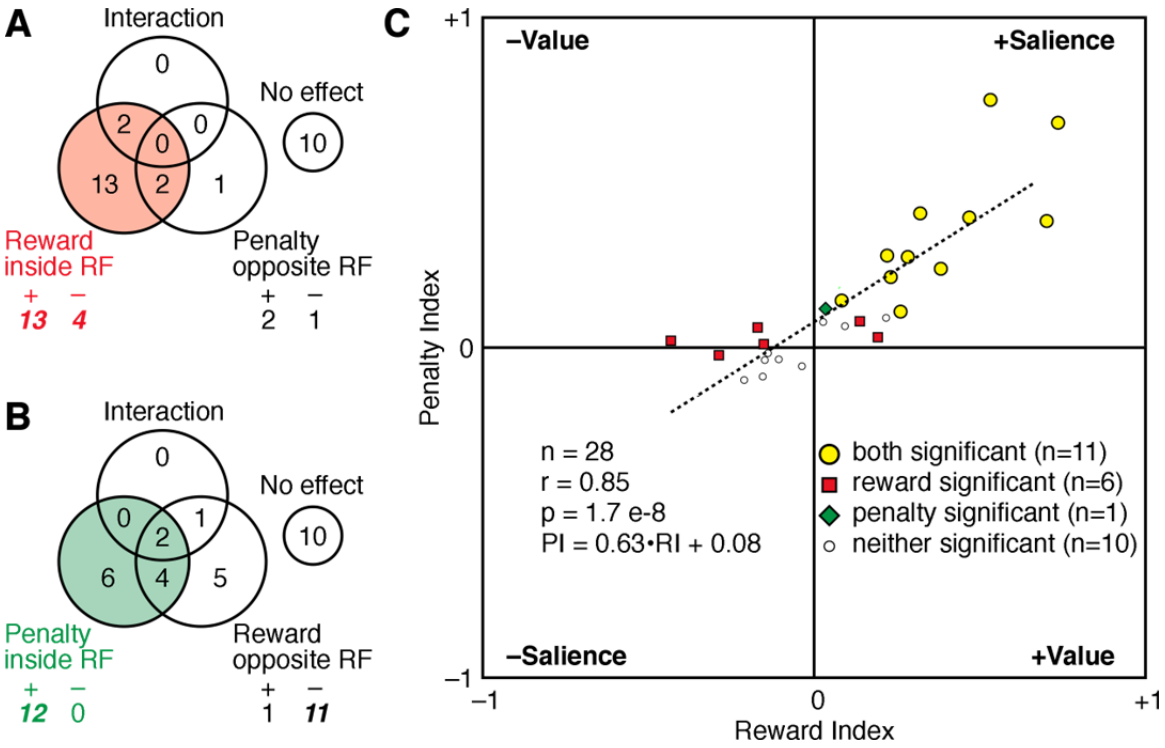


Figure 11. M1: Single Neuron Effects & Correlation Analysis (n = 28)
Same conventions as Figure 5.

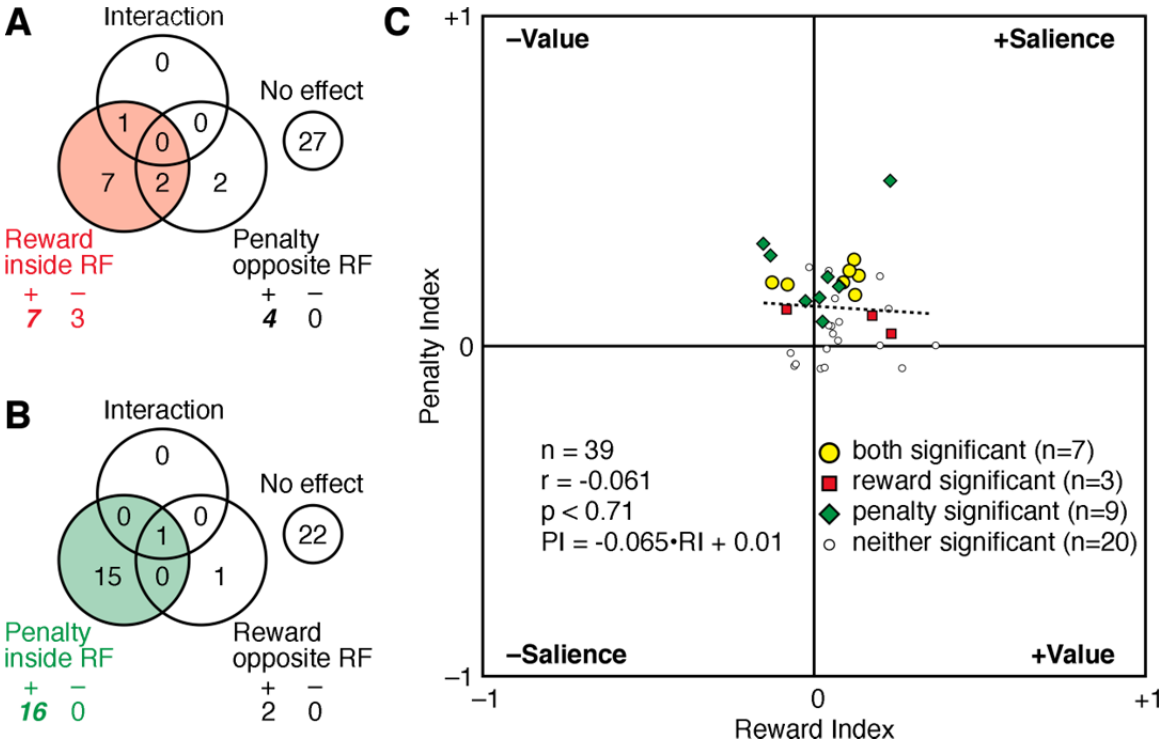


Figure 12. M2: Single Neuron Effects & Correlation Analysis (n = 39)
Same conventions as Figure 5.

(c) Omission of Repeat Trials

After a trial culminating in a fixation break of any kind, a penalty was imposed if a penalty was one of the options, and the identical condition was imposed on the following trial. The rate of fixation breaks varied slightly across conditions, as described in the preceding section. Therefore, any neural activity dependent on recent imposition of a penalty or on repetition of the same condition would have appeared as a difference between conditions. To be sure that the key findings were not an artifact of such an effect, we repeated all of the analyses after omitting repeat trials from the data set. This omission reduced the statistical power of the analyses by reducing the number of observations but left the trends intact and left all key trends highly significant. This statement applies to effects shown in Figure 2D ($p = 1.4$ e-5 before and 4.5 e-5 after omission), Figure 2E ($p = 3.6$ e-5 before and 2.4 e-6 after the omission), Figure 3A ($p = 0.0020$ before and 0.0019 after the omission), Figure 3B ($p = 1.3$ e-7 before and 2.3 e-6 after the omission), Figure 3C ($p = 0.018$ before and 0.0077 after omission), Figure 3D ($p = 0.00018$ before and 0.13 after omission), Figure 4A ($p = 0.0038$ before and 0.0014 after omission), Figure 4B ($p = 9.3$ e-5 before and 0.13 after omission) and Figure 5C ($p = 2.3$ e-8 before and 6.5 e-7 after omission). In two of these cases (Figures 3D and 4B), an effect significant upon analysis of the complete data set failed to achieve significance upon analysis of the reduced data set. Case 1: the difference between population activity elicited by a large-penalty cue and a small-penalty cue outside the response field (Figure 3D) ceased to be significant. This effect was anomalous to begin with because it occurred in only one monkey (Figure 9D vs. Figure 10D). It is irrelevant to our main argument. Case 2: the difference between population activity elicited in monkey 2 by a large-penalty cue and a small-reward cue in the response field (Figure 4B) ceased to be significant. The effect remained evident in population firing rate curves but dipped below the

threshold of statistical significance. This is not surprising because the rate of fixation breaks was much higher and therefore the number of omitted trials, with consequent reduction in statistical power, was much greater in monkey 2 than in monkey 1 (Table 1). Critically, after omission of repeat trials, the mean response to images A4 and B4 minus the mean response to images A1 and B1 was still of opposite sign in the two monkeys (m1: 4.6 Hz; m2: –1.1 Hz) and the difference in this measure between the monkeys was still significant (two-tailed t-test, $p = 0.00016$).

2.1.4 DISCUSSION

That images with greater motivational salience elicit stronger activity in LIP fits with the idea that LIP constitutes a priority map in which neurons representing a given visual-field location fire at a rate proportional to that location's current draw on attention (Bisley & Goldberg, 2010). Neurons in LIP respond strongly to physically salient images (Arcizet, Mirpour, & Bisley, 2011; Buschman & Miller, 2007). Whether they respond strongly to motivationally salient images has been unclear. Cues with greater incentive salience elicit stronger firing (Peck et al., 2009) but this effect is difficult to disentangle from the encoding of value (Louie, Grattan, & Glimcher, 2011; Rorie et al., 2010). The current finding that cues with greater aversive salience likewise elicit stronger firing establishes that LIP neurons are indeed sensitive to motivational salience. Incentive and aversive salience refer to the control of cues over behavior and do not necessarily denote an ability to capture attention (Berridge, 2003; Brosch et al., 2011). Note, however, that the monkeys were faster to look toward locations marked by big-reward than by small-reward cues and slower to look away from locations marked by large-penalty than by small-penalty cues (Table 1) as expected from attentional capture.

We have shown that monkeys can make value-based saccadic decisions under circumstances in which the early firing of LIP neurons does not signal action value. This finding jibes with prior reports indicating that neuronal activity in LIP is poorly correlated with target value in a visual foraging task (Mirpour & Bisley, 2012), that inactivation of LIP leaves intact the ability of monkeys to make value-based saccadic decisions (Balan & Gottlieb, 2009) and that neural activity indicating which reward a subject will choose can develop even if the subject does not yet know which action will be required to obtain it (Padoa-Schioppa & Cai, 2014; Wunderlich, Rangel, & O'Doherty, 2010). These observations provide collective support for the idea that value-based decisions do not depend on LIP and may instead depend on limbic areas, including orbitofrontal cortex, where neurons signal goods value beginning around 100 ms after cue onset (Padoa-Schioppa & Assad, 2006; Roesch & Olson, 2004).

2.2 AMYGDALA

2.2.1 INTRODUCTION

In monkeys presented with cues that promise reward or threaten penalty, some amygdala neurons fire more for reward cues, but others fire more for penalty cues. This observation has been interpreted as indicating that some amygdala neurons encode the value of goods, others encode the value of evils, and that amygdala neurons could mediate value-based decisions between such cues. Nevertheless, when reward or penalty cues are presented in the periphery, firing rates in amygdala neurons are modulated in the same direction for these cues of opposite value. This observation has been interpreted as indicating that amygdala neurons encode the emotional intensity, or salience, associated with a cue, irrespective of its value, as a basis for directing visual attention to it. However, whether amygdala neurons encode value or salience has not been put to the test by using cues of opposite value that also vary in intensity. Here we show that amygdala neurons fire more for cues promising greater goods but fire less for cues promising greater evils. This negative correlation indicates that amygdala neurons encode the value of cues. It is incompatible with the idea that these amygdala neurons encode salience for directing attention but supports the idea that amygdala neurons encode value for decision-making.

The amygdala is a small brain area that gives emotional meaning to the world's promises of reward and threats of penalty, enabling animals to react appropriately and survive (Moscarello & LeDoux, 2014; Murray, 2007). Primates with amygdala lesions have intact general vision but have long been known to appear "emotionally" blind (KlÜVer & Bucy, 1939). They fail to increase cardiovascular responses upon seeing a potential good, such as food (Braesicke et al., 2005), and show decreased fear responses upon seeing a potential evil, such as a fake snake

(Izquierdo et al., 2005). Emotional meaning, or affect, has two dimensions: value (either reward or penalty) and salience (intensity). That the amygdala is involved in both value and salience processes has received apparent support from single-neuron recording studies in the amygdala of awake-behaving primates. On the one hand, some amygdala neurons fire more for cues promising reward, while others fire more for cues threatening penalty (Belova et al., 2008; Paton et al., 2006; Peck & Salzman, 2014b). Based on these results, it has been claimed that amygdala neurons encode the values of goods and evils in separate circuits (Morrison & Salzman, 2010; Zhang et al., 2013). On the other hand, neuronal activity in amygdala is correlated with increased allocation of visual attention to the spatial location of reward cues as well as penalty cues (Peck et al., 2013; Peck & Salzman, 2014a). Based on these results, it has been claimed that amygdala neurons direct visual attention based on the salience of cues, as opposed to their value (Peck & Salzman, 2014a). However, these claims have not been put to the test because no study has varied reward-intensity as well as penalty-intensity while recording from amygdala neurons. This includes the only experiment that has recorded amygdala neurons in monkeys making value-based decisions (Grabenhorst et al., 2012; Hernadi et al., 2015). Previously, our group dissociated value from salience in the primate brain by recording neurons in monkeys making value-based decisions among cues that promised different sizes of reward as well as cues that threatened different sizes of penalty. We found that neurons in LIP, which is not directly connected to the amygdala (Amaral & Price, 1984; Baizer, Desimone, & Ungerleider, 1993), encoded salience not value (Leathers & Olson, 2012), but neurons in orbitofrontal cortex, which is strongly and reciprocally connected with the amygdala (Amaral & Price, 1984; Barbas & De Olmos, 1990), encoded value not salience (Roesch & Olson, 2004). Therefore, we conducted single-neuron recordings from the amygdala of monkeys performing this same reward-penalty

task to determine whether neurons in the primate amygdala encode value (like OFC) or salience (like LIP) early during decision-making.

2.2.2 MATERIALS AND METHODS

2.2.2.1 SUBJECTS

Two adult rhesus macaque monkeys participated in the experiments (monkey 1, female, laboratory designation Ju and monkey 2, male, laboratory designation Je). All experimental procedures were approved by the Carnegie Mellon University Institutional Animal Care and Use Committee (IACUC) and the University of Pittsburgh IACUC, and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals. In each monkey, a surgically implanted plastic cranial cap held a post for head restraint and a cylindrical recording chamber 2 cm in diameter oriented flush to the skull with its base centered approximately over the amygdala. Electrodes could be advanced along tracks forming a square grid with 1 mm spacing. The chambers overlay the right hemisphere in monkey 1 and the left hemisphere in monkey 2.

2.2.2.2 REWARD-PENALTY TASK

The reward-penalty task for amygdala sessions was the same as that for the LIP sessions with six exceptions: nature of reward fluid (monkey 1's reward was 1/3 dilution of apple juice but monkey 2's reward remained plain water); size of rewards (small reward was 0.20 cc in monkey 1 and 0.04 cc in monkey 2, and large reward was 0.30 cc in monkey 1 and 0.12 cc in monkey 2); duration of penalties (small penalty was 400 ms and large penalty was 3200 ms for both monkeys); monkey 1 was given 600 ms to launch her saccade; monkey 2 was given a short fixed

delay period (500 ms post-cue offset); and monkey 2 was not required to maintain fixation upon the saccade target after reaching it nor fixate a subsequent minified version of a chosen reward cue presented before delivery of reward.

2.2.2.3 RECORDING SITES

To determine the location of recording sites relative to gross morphological landmarks, we extrapolated from frontoparallel MR images containing the brain and fiducial markers placed at known locations within the chamber. The recording sites allowed for recording from the amygdala. In Monkey 1 (Ju), recording sites extended 0 mm anterior, 0 mm posterior, 0 mm medial and 2 mm lateral relative to the central recording point whose coordinates were 16 mm anterior and 10 mm lateral in the Horsley-Clarke reference frame. In Monkey 2 (Je), recording sites extended 0 mm anterior, 0 mm posterior, 0 mm medial and 1 mm lateral relative to the central recording point whose coordinates were 16 mm anterior and 10 mm lateral in the Horsley-Clarke reference frame. We selected neurons, not by running the memory guided saccade task, but by having the monkey perform the reward-penalty task until amygdala neurons could be found. Then we restarted the task. We included in our data set any well-isolated neuron that could be held for the duration of the full reward-penalty task. Other factors of single electrode recording were the same for the amygdala recording sessions as those described for the LIP recording sessions.

2.2.2.4 ANALYSIS OF BEHAVIOR

As we did for the LIP recording sessions, we characterized the impact of predicted reward and penalty on the behavior of each monkey during each amygdala recording session with three measures: percent correct, fixation break rate and reaction time. We based the calculation on the

eight trial conditions in which the monkey was given a choice between a reward and a penalty (Figures 20 and 21). Across these conditions, reward size was fully counterbalanced against penalty size. For each measure in each monkey, we carried out an ANOVA with reward size (large or small), penalty size (large or small) and reward location (right or left) as factors and with n equal to the number of sessions (12 in M1; 19 in M2). Inclusion of reward location as a factor buffered any variance that might have arisen from a spatial bias.

2.2.2.5 ANALYSIS OF NEURONS

(a) Population-level Statistical Tests

(i) Reward and Penalty Effects

As we did for LIP recording sessions, to compare neuronal activity between conditions, we inspected population histograms constructed by computing the average firing rate in each 1 ms bin and applying a Gaussian smoothing function (σ = 10 ms). Again, as was done for the LIP data, we determined whether the average firing rate during a standard analysis epoch (0-250 ms following cue onset) differed significantly (α = 0.05) between conditions.

However, for the main conditions—the eight trial conditions in which the monkey was given a choice between a reward and a penalty and across which reward size was fully counterbalanced against penalty size (Figures 14, 20 and 21)—we performed more sensitive analyses on the amygdala data than we did on the LIP data in our published study (Leathers & Olson, 2012). Specifically, instead of using two-tailed paired t-tests as we did for the LIP data on these conditions (Figures 3, 9, and 10), here we employed two three-factor ANOVAs, each with four of the eight trial conditions. One three-factor ANOVA was performed on the four conditions

in which reward was in the RF and penalty was opposite the RF (Figures 14A & D, 20A & D, and 21A & D). The other three-factor ANOVA was performed on the four conditions in which penalty was in the RF and reward was opposite the RF (Figures 14B-C, 20B-C, and 21B-C). The three factors were reward size (large or small), penalty size (large or small) and neuron identity (1,2…n) with n equal to the number of amygdala neurons in the sample and with each neuron contributing one mean firing rate for each condition.

We made this switch from two-tailed paired t-tests (Leathers & Olson, 2012) to three-factor ANOVAs for three reasons. First, using ANOVA allowed us to test the statistical significance of the two main effects (reward or penalty) as well as their interaction (reward x penalty). Second, inclusion of neuron identity served to "pair" the ANOVA, in that the firing rates being compared for the large and small outcomes came from the same neuron. Thus, these ANOVA analyses were more sensitive because they tested not only for main effects but also for interactions), and inclusion of reward identity as a factor buffered any variance that might have arisen from overall firing rate differences between neurons. Third, the neuron-level statistical tests already used ANOVAs for these conditions (for both the LIP and amygdala data), so the population-level statistical tests should as well. In addition, we applied the appropriate sliding three-factor ANOVA to each successive 50 ms bins ($\alpha = 0.01$) stepped every 1 ms so as to place, beneath population histograms, tick marks indicating time points at which the firing-rate difference *for the main effect of interest* attained an arbitrary stringent statistical threshold. The role of this step was to provide a graphic indication of signal timing and not to serve as a test of effect significance.

As we did for LIP recording sessions, to determine whether the average firing rate during the analysis window differed significantly between two conditions, we employed a two-tailed

paired t-test with n equal to the number of neurons in the sample and with each neuron contributing one mean firing rate for each condition. In addition, we applied a t-test to each successive 10 ms bin so as to place, beneath population histograms, tick marks indicating time points at which the firing-rate difference between two conditions attained an arbitrary stringent statistical threshold. Note that we used $\alpha = 0.05$ for the sliding t-test for these comparisons with amygdala data (Figures 13, 15, 18, and 19), unlike both the sliding three-factor ANOVAs described above for the main amygdala comparisons and also the sliding t-tests for LIP comparisons where $\alpha = 0.01$. Again, the role of the sliding tests was to provide a graphic indication of signal timing and not to serve as a test of effect significance.

(ii) Latency of Reward and Penalty Effects

These were calculated for the amygdala data just as they were for the LIP data. In addition, we report the latency of the effect of the reward cue located outside the response field.

(b) Neuron-level Statistical Tests

(i) Reward and Penalty Effects

These were calculated for the amygdala data just as they were for the LIP data.

(ii) Correlation of Reward and Penalty Effects

These were calculated for the amygdala data just as they were for the LIP data.

2.2.3 RESULTS

To distinguish between value-based and salience-based signals in amygdala, we employed the task (Figure 2A-B) incorporating rewards and penalties that we used during LIP sessions (Leathers & Olson, 2012).

2.2.3.1 BEHAVIOR

As during LIP sessions, confronted with two offers of different value, the monkeys consistently chose the better offer (Figure 13A, Table 3).

As during LIP sessions, reward and penalty had independent effects on behavior during amygdala sessions. For the eight trial conditions in which the monkey was given a choice between a reward and a penalty (Figure 14), we computed the impact of predicted reward and penalty on the behavior of each monkey during each recording session for three measures: percent correct, fixation break rate and reaction time (Table 3).

Percent correct. The monkeys performed very close to ceiling on this measure. Still, this measure depended on reward size and penalty size in both monkeys. For each monkeys, percent correct was significantly greater not only when a large rather than small reward was at stake but also when a when a large rather than small penalty was at stake. Thus, during amygdala sessions, reward and penalty had independent effects on behavior in each monkey.

Fixation-break rate. Monkey 2 broke fixation significantly less often when a large rather than small reward was at stake, but this trend was not present in monkey 1. Penalty effects on fixation-break rate were not significant in either monkey.

Reaction time. For each monkey, the reaction time was significantly shorter on trials in which a large rather than small reward was at stake. For each monkey, reaction time was shorter

on trials in which a large rather than small penalty was at stake, but this trend attained significance in monkey 2 alone.

Table 3. Behavior on reward-penalty task: amygdala recording sessions

Monkey (#sessions)	Large Reward (mean)	Small Reward (mean)	p (ANOVA)		Large Penalty (mean)	Small Penalty (mean)	p (ANOVA)
Percent Correct							
M1	100	97.7	0.00052		99.7	97.9	0.0062
M2	99.8	93.8	<0.0001		99.3	94.3	<0.0001
Percent Fixation Breaks							
M1	11.9	12.0	0.97		11.7	12.2	0.72
M2	13.4	21.9	<0.0001		18.1	17.2	0.54
Reaction Time (ms)							
M1	224	234	0.0017		227	231	0.10
M2	186	197	<0.0001		189	194	0.0087

Impact of predicted reward and penalty on three performance measures. Each p-value indicates the level of statistical significance of the difference between the two values immediately to its left.

2.2.3.2 NEURONS

Confronted with two offers of different value, the monkeys consistently chose the better offer (Figure 13A, Table 3). A large penalty possesses lower value than a small penalty but is emotionally more potent. Consequently, value-based and salience-based models make opposite predictions with regard to the impact of predicted penalty size on neuronal activity (Bisley & Goldberg, 2010; Roesch & Olson, 2004; Wallis & Rich, 2011). To test the predictions, we

collected data from 20 neurons in the right amygdala of monkey 1 and 30 neurons in the left amygdala of monkey 2.

(a) Data Combined from Both Monkeys

We first examined trials in which the monkey, offered a choice between a large and a small reward, chose the large reward. Population activity during the cue period (0-250 millisecond analysis window) was significantly stronger when the cue in the response field predicted a large reward (Figure 13B, blue fill). The enhancement could have depended on the cue's higher value, its greater motivational salience or the monkey's decision to look toward the response field. We next examined trials in which the monkey, offered a choice between a large penalty and a small penalty, chose the small penalty. Firing during the cue period was similar for large- and small-penalty (Figure 13C). This absence of a penalty-size effect could not have depended the large-penalty cue's lower value, its greater motivational salience, or the monkey's decision to look away from it.

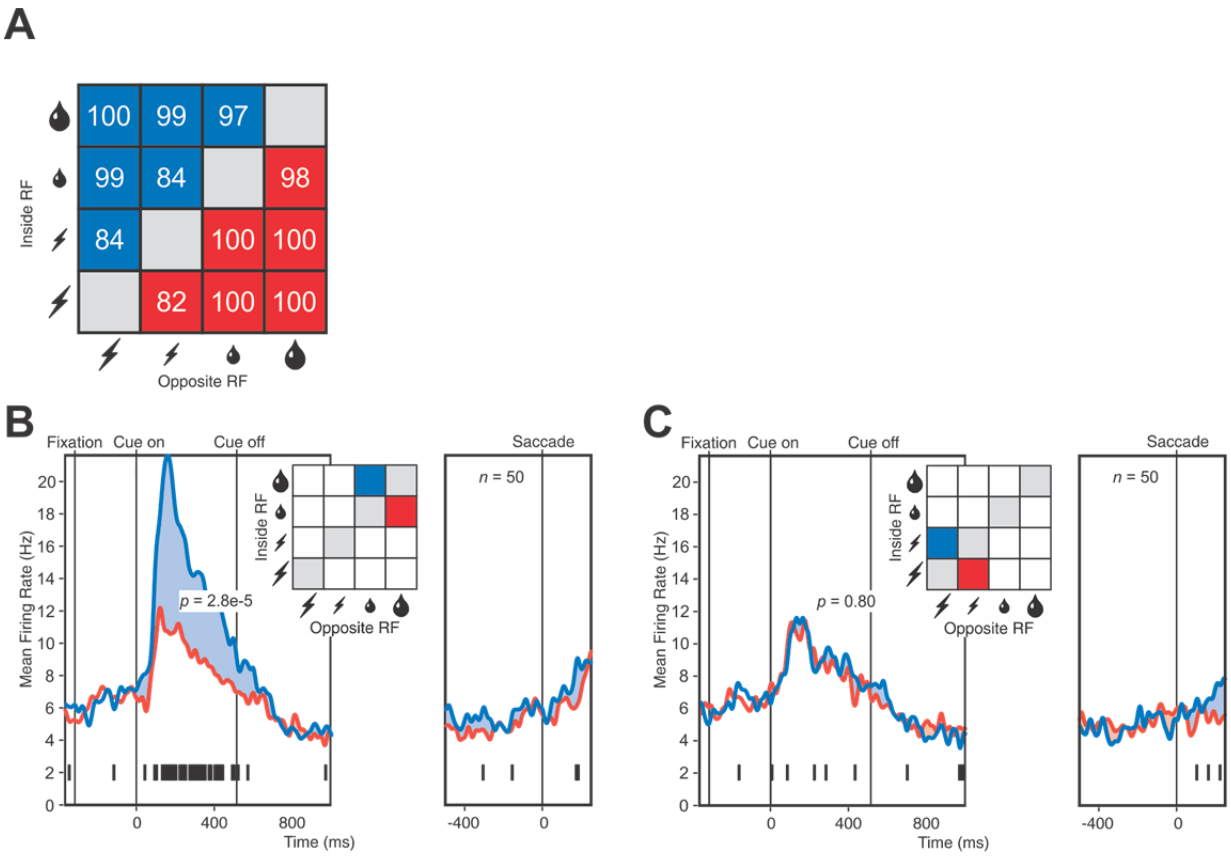


Figure 13. Amygdala: Reward-Penalty Choice-Behavior and Two PSTHs
(A) The monkeys nearly always chose optimally. The numbers indicate the percentage of trials on which they chose the better outcome – either into the response field (blue) or away from it (red). **(B)** Population firing rate as a function of time during trials with a large-reward cue in the RF and a small-reward cue opposite (blue) or vice versa (red). The monkey chose large reward. **(C)** Population firing rate as a function of time during trials with a large-penalty cue in the RF and a small-penalty cue opposite (red) or vice versa (blue). The monkey chose small penalty. Tick marks indicate 10 ms bins in which the difference between red and blue curves crossed an arbitrary statistical threshold (two-tailed paired t-test, n = 50, $\alpha = 0.05$). In B-C, each pair of red and blue curves is based on conditions colored red and blue in the accompanying inset and each p value indicates the outcome of a two-tailed paired t-test (n = 50) applied to firing rates under red and blue conditions.

To factor out completely any effect of the saccadic decision, we constructed population plots based on subsets of conditions in which cue value varied but saccade direction did not. Population activity was stronger when a cue in the response field predicted a large as compared to a small reward (Figure 14A, blue fill) but was similar when the cue predicted a large as compared to a small penalty (Figure 14B). The value of cues opposite the response field had no significant main effects (Figure 14C-D) nor did they significantly interact with the value of cues

inside the response field ($p > 0.20$). This pattern of location specificity for a reward-effect (but not a penalty-effect) could not arise from enhanced spatial attention, arousal, vigilance or general motivation.

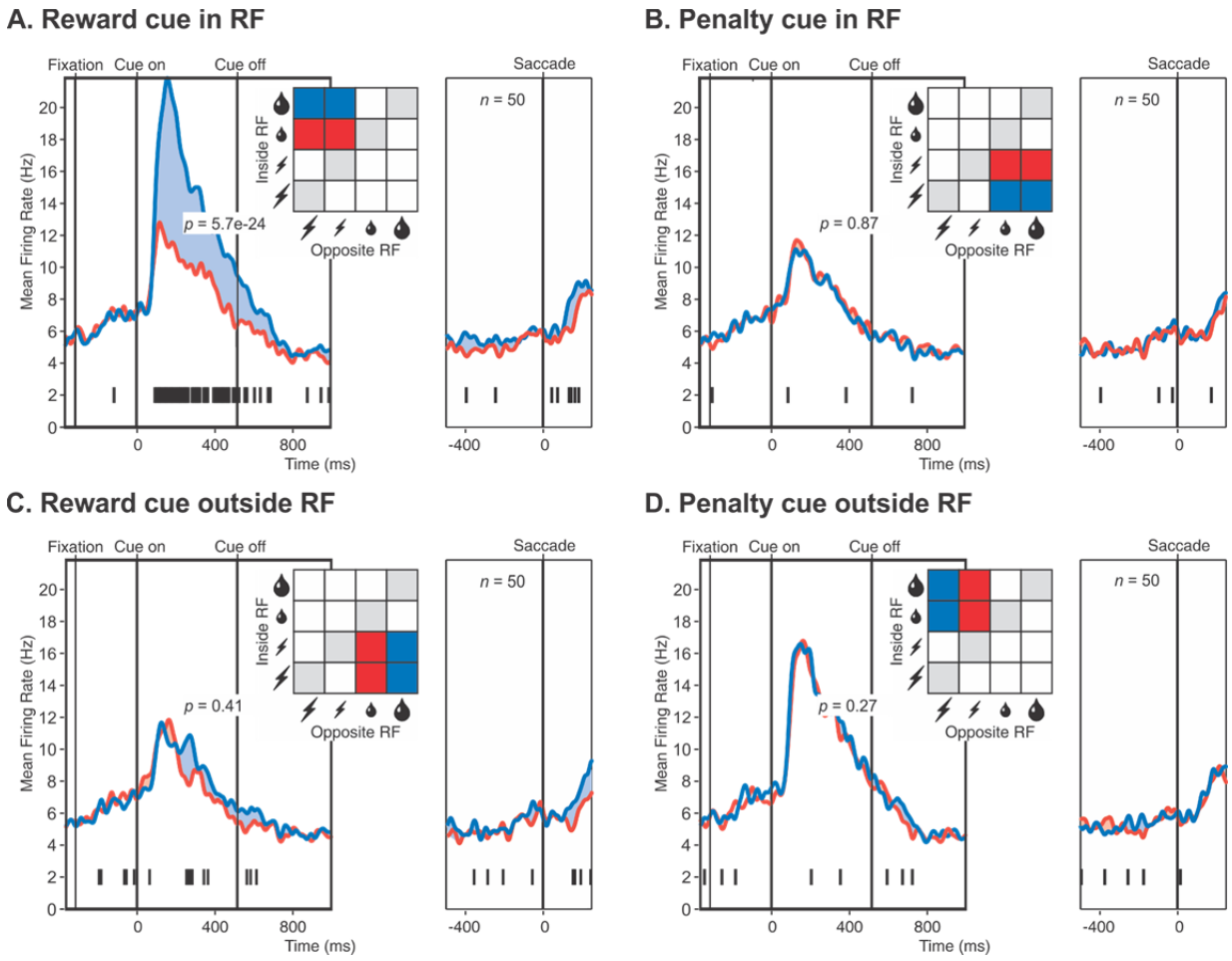


Figure 14. Reward & Penalty Effects PSTHs
Population firing rate under selected conditions. **(A)** The cue in the response field predicted large (blue) or small (red) reward. **(B)** The cue in the response field predicted large (blue) or small (red) penalty. **(C)** The cue opposite the response field predicted large (blue) or small (red) reward. **(D)** The cue opposite the response field predicted large (blue) or small (red) penalty. Tick marks indicate 50 ms bins stepped every 1 ms in which the difference between red and blue curves crossed an arbitrary statistical threshold (three-factor ANOVA, n = 50, $\alpha = 0.01$). In A-D, each pair of red and blue curves is based on conditions colored red and blue in the accompanying inset and each p value indicates the outcome of a three-factor ANOVA (n = 50) applied to firing rates under red and blue conditions.

Neurons might have responded strongly to large-reward cues because, by chance, they possessed a high degree of physical salience. Therefore we gave the images different significance in the two monkeys. Cues predicting a large reward in monkey 1 predicted a small

penalty in monkey 2 and vice versa (Figure 2B). Nevertheless, in each monkey, cues predicting a large reward elicited stronger firing than cues predicting a small penalty (Figure 15A-B, blue fill). Thus neuronal activity depended on the images' associated outcomes and not their physical attributes.

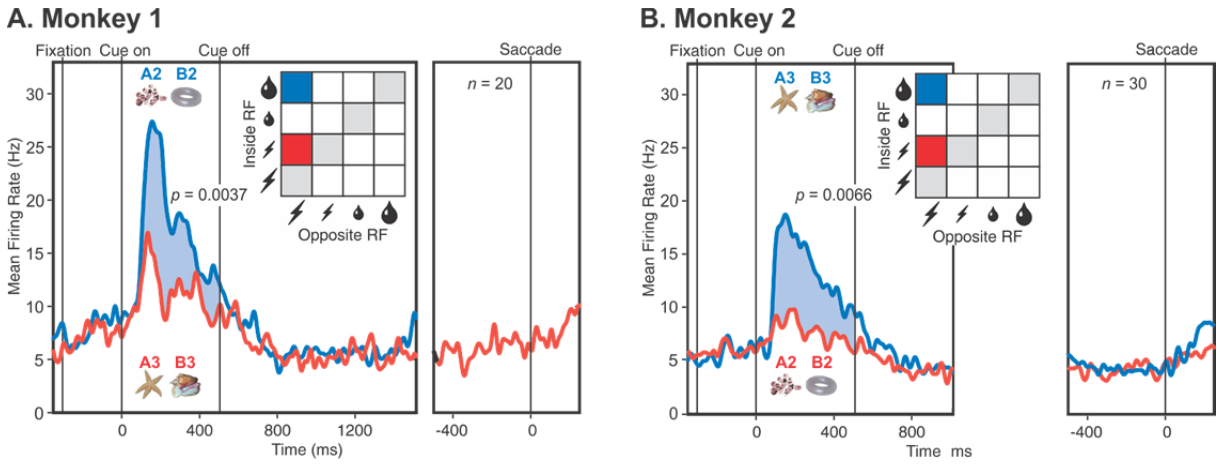


Figure 15. Effect of physical salience of images counter-balanced between monkeys
Population activity when a cue appearing in the response field predicted a large reward (blue) or a small penalty (red). On all trials, the cue opposite the response field predicted a large penalty and the monkey avoided it. **(A)** In monkey 1, images A2 and B2 predicted a large reward and images A3 and B3 predicted small penalty. **(B)** In monkey 2, the contingencies were reversed.

To characterize reward- and penalty-related activity at the level of individual neurons, we carried out two analyses. One analysis assessed the impact of reward cues inside and penalty cues opposite the response field (Figure 14A). Main effects of reward size in the response field predominated (red sector of Figure 16A). A second analysis assessed the impact of penalty cues inside and reward cues opposite the response field (Figure 14B). Main effects of penalty size in the response field predominated (green sector of Figure 16B). We next generated for each neuron a reward index and a penalty index based on responses to cues in the response field. Each index ranged from -1 (fired only in response to "small" cue) to +1 (fired only in response to "large" cue). Plotting the penalty against the reward index revealed that they were negatively correlated

across neurons (an effect driven by trends present in each monkey, Figures 22 and 23). This negative correlation is a representation of value across the population of amygdala neurons (Figure 16C).

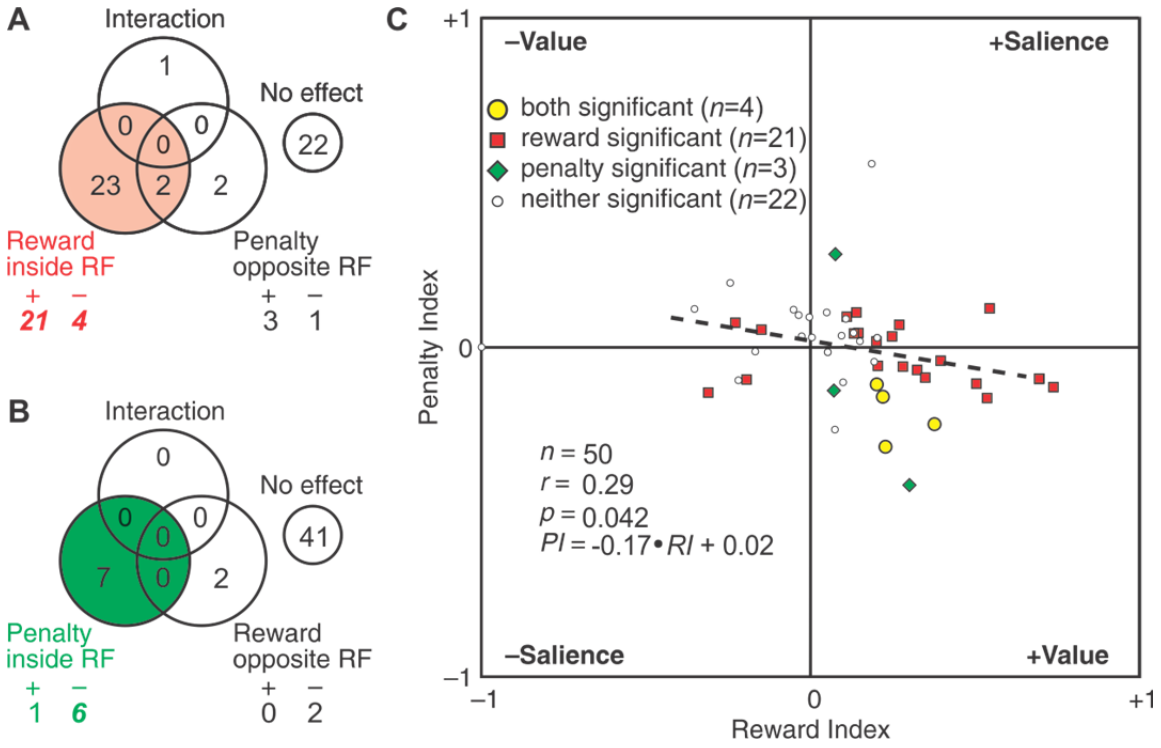


Figure 16. Single Neuron Effects & Correlation Analysis
Individual neurons exhibited significant sensitivity to reward size and penalty size for cues in the response field. **(A)** Counts of neurons exhibiting significant effects of reward size in the response field and penalty size opposite the response field (three-factor ANOVA, $\alpha = 0.05$). The predominant outcome was a main effect of reward in the response field (25 neurons: red tinting). **(B)** Counts of neurons exhibiting significant effects of penalty size in the response field and reward size opposite the response field (three-factor ANOVA, $\alpha = 0.05$). The predominant outcome was a main effect of penalty in the response field (7 neurons: green tinting). In A-B, "+" and "–" counts indicate numbers of neurons firing more strongly for the larger (+) or smaller (–) predicted outcome; counts in italic boldface are significantly greater than expected by chance (χ^2 test, Yates correction, $\alpha = 0.05$). **(C)** Penalty index vs. reward index for all 50 neurons. The quadrants are labeled according to the hypothesis most concordant with the corresponding pattern of activity: +salience = responds more strongly to more salient stimuli; -salience = responds more strongly to less salient stimuli; + value = responds more strongly to more valuable stimuli; -value = responds more strongly to less valuable stimuli.

We have carried out analyses on data from trials in which the cue in the receptive field predicted rewards of different sizes (Figure 14A) or penalties of different sizes (Figure 14B). With regard to reward-predicting cues, we find (a) that the firing rate was significantly affected

by reward size in 50% of the sample (Figure 16A, 25/50 neurons), (b) that the firing rate was enhanced by 47% on average for large as compared to small reward (Figure 14A, 0-250 ms) and (c) that the visual response began 92 ms after stimulus onset whereas (d) reward-related modulation of the firing rate began 112 ms following stimulus onset (Figure 17A). With regard to penalty-predicting cues, we find (a) that the firing rate was significantly affected by penalty size in 14% of the sample (Figure 16B, 7/50 neurons), (b) that the firing rate was reduced insignificantly by -0.40% on average for large as compared to small penalty (Figure 14B, 0-250 ms) and (c) that the visual response began 89 ms after stimulus onset whereas (d) penalty-related modulation of the firing rate showed no peak and was thus not estimable by our time-to-half-peak latency analysis. Instead, we note that the effect of the reward-cue out of the response field (Figure 17B) appeared 123 ms later than the effect of the reward-cue in the response field (Figure 17A). Peck et al. (2013) reported a contra minus ipsi lag of 44 ms for normalized encoding of reward size during a task that did not require value-based decision-making. Thus, manipulations of reward-size during decision-making (in the current study) and in non-decision-making tasks (Peck et al., 2013) result in faster contralateral than ipsilateral reward signaling in the amygdala.

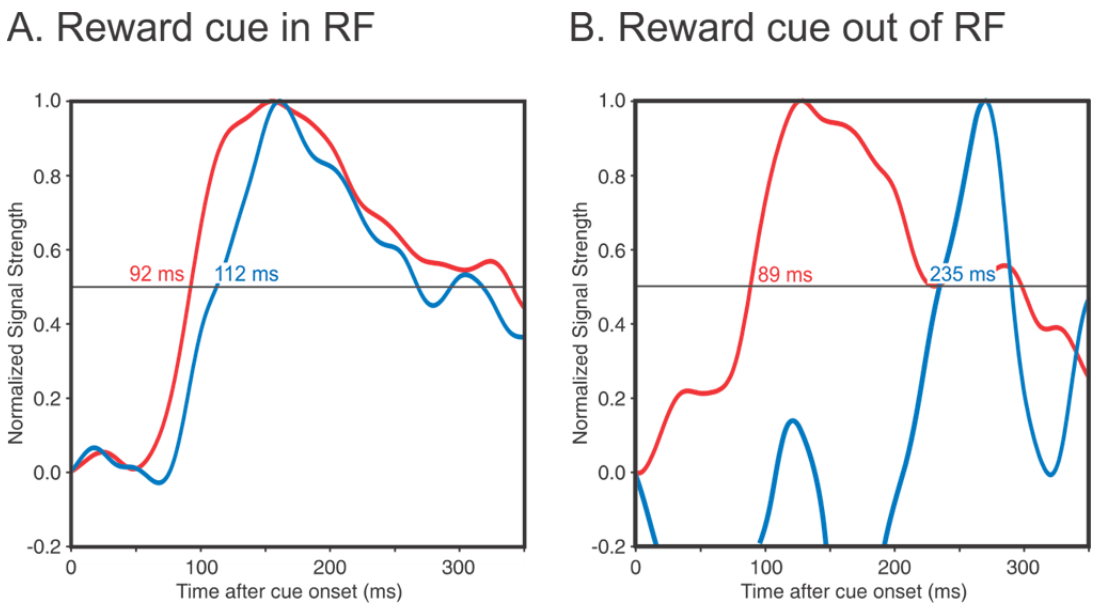


Figure 17. Latency Analysis
Firing dependent on predicted reward (blue curves) began as early as 20 ms or as late as 150 ms after than the visual response itself (red curves) depending upon the spatial location of the reward cue. **(A)** Data from trials in which the cue in the RF predicted either a large or a small reward (Figure 2A). **(B)** Data from trials in which the cue out of the RF predicted either a large or a small reward (Figure 2B). Normalized signal strength was computed as (F-B)/(P-B) where F was instantaneous firing rate, B was firing rate at time zero and P was peak firing rate in the window 0-350 ms. For each red curve, firing rate was defined as the mean population firing rate as computed across all neurons. For each blue curve, firing rate was defined as the mean across neurons of the firing rate associated with a large predicted reward minus the firing rate associated with a small predicted reward. The number juxtaposed to each curve indicates time to half height.

(b) Individual Monkey Data

Nearly all conclusions based on the combined data held up for monkeys 1 and 2 considered separately. a) On trials requiring a choice between a large reward and a small reward, cue-period firing was stronger when the cue in the response field predicted a large reward than when it predicted a small reward (Figures 18A and 19A, blue fill). b) On trials requiring a choice between a large penalty and a small penalty, cue-period firing was similar when the cue in the response field predicted a large penalty than when it predicted a small penalty (Figures 18B and 19B). c) With the value of the reward cue in the response field counterbalanced against other factors that might influence neuronal firing, the response to a large-reward cue was greater than

the response to a small-reward cue (Figures 20A and 21A, blue fill) with no significant interactions with the value of penalty opposite the response field. d) With the value of the penalty cue in the response field counterbalanced against other factors that might influence neuronal firing, the response to a large-penalty cue was similar to the response to a small-penalty cue (Figures 20B and 21B) with no significant interactions with the value of reward opposite the response field. e) More neurons were significantly affected by the value of the reward cue in the response field than by the value of the penalty cue outside it (Figures 22A and 23A). f) Among these neurons, more fell in the "+" category, firing more strongly for the larger predicted reward, than fell in the "–" category, firing more strongly for the smaller predicted reward (Figures 22A and 23A). g) When the penalty index was plotted against the reward index, trends toward negative correlations were observed in each monkey (Figures 22C and 23C). Though these did not reach the $p < 0.05$ level of statistical significance in either monkey considered separately, we note that the slopes and r-values for these trends were comparable to those found for the significant negative correlation that resulted from these data combined across monkeys (Figure 16C). This is in conformity with the hypothesis that the firing rate was proportional to the value of the cues.

Three differences between monkeys are worth noting although they do not affect the key conclusions of the study. a) For cues inside the response field, a significant number of neurons with negatively-signed effects were found for penalty size in monkey 2 alone (Figure 23B, number beneath bold green negative sign) and for reward size in monkey 1 alone (Figure 22A, number beneath bold red negative sign). b) For cues outside the response field, population activity in monkey 1 was significantly affected by reward size alone (Figure 20C-D) whereas population activity in monkey 2 was not significantly affected by either reward size or penalty

size (Figure 21C-D). c) Monkey 1 alone showed a trend for an interaction effect between reward-size in the response field and penalty-size out of the response field (p = 0.089).

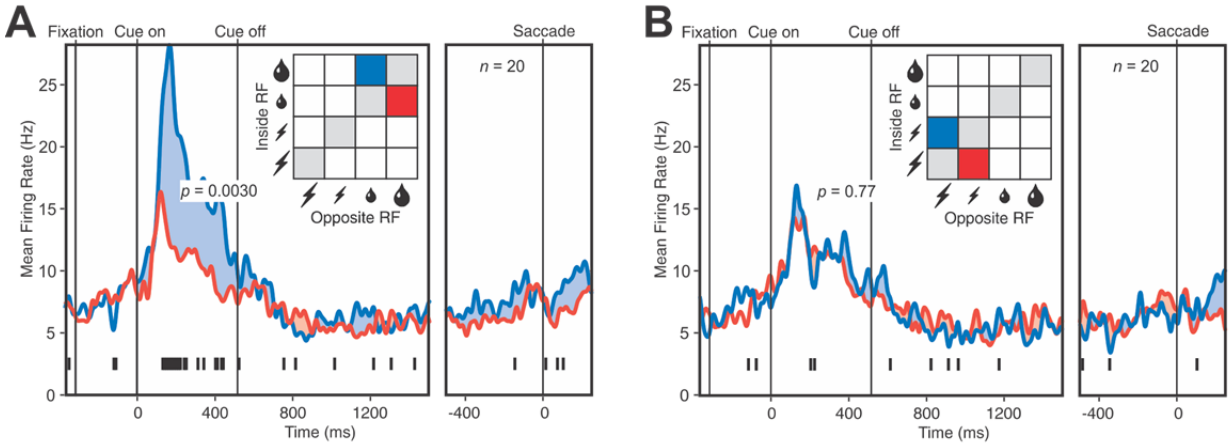


Figure 18. M1: Two PSTHs (n = 20)

Same conventions as Figure 2D-E.

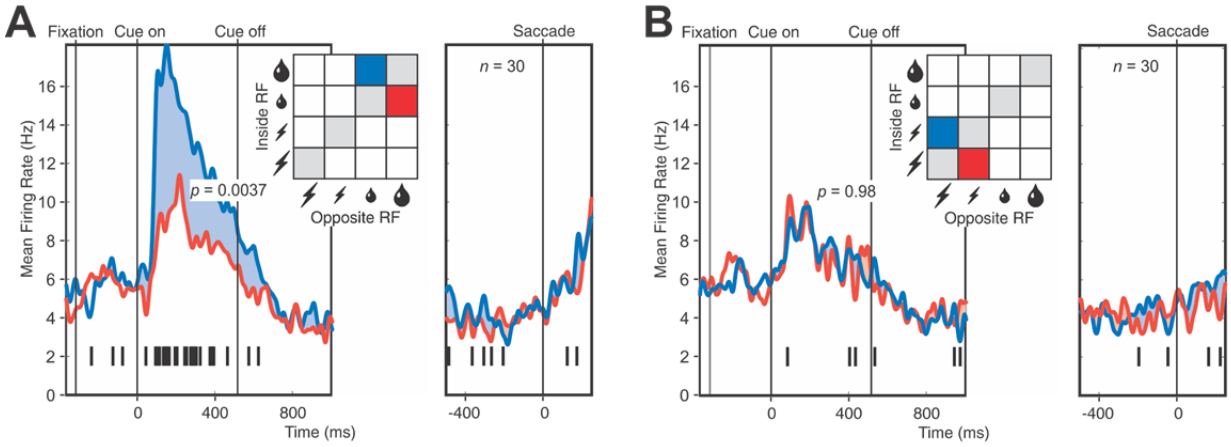


Figure 19. M2: Two PSTHs (n = 30)

Same conventions as Figure 2D-E.

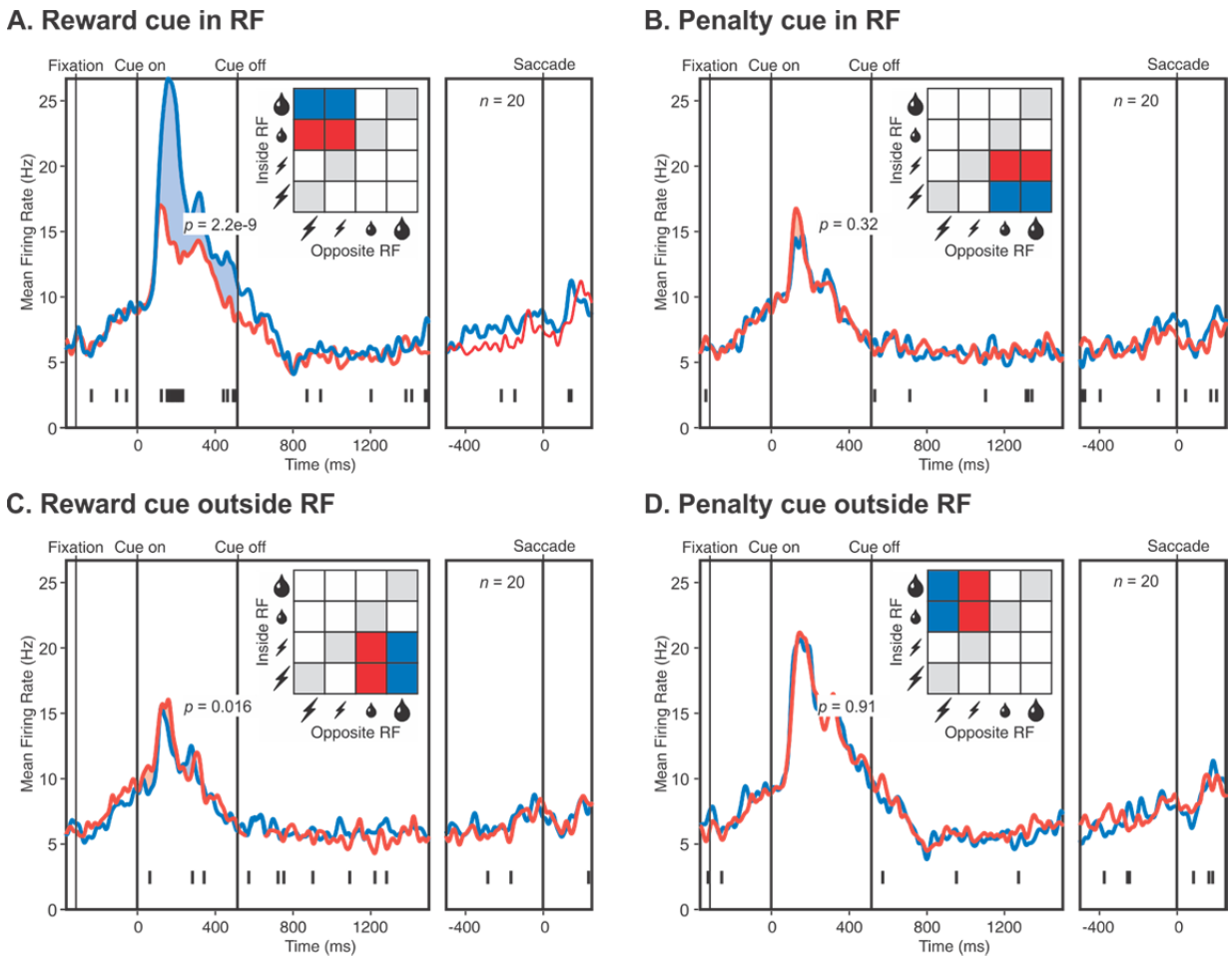


Figure 20. M1: Reward & Penalty Effects PSTHs (n = 20)

Same conventions as Figure 3.

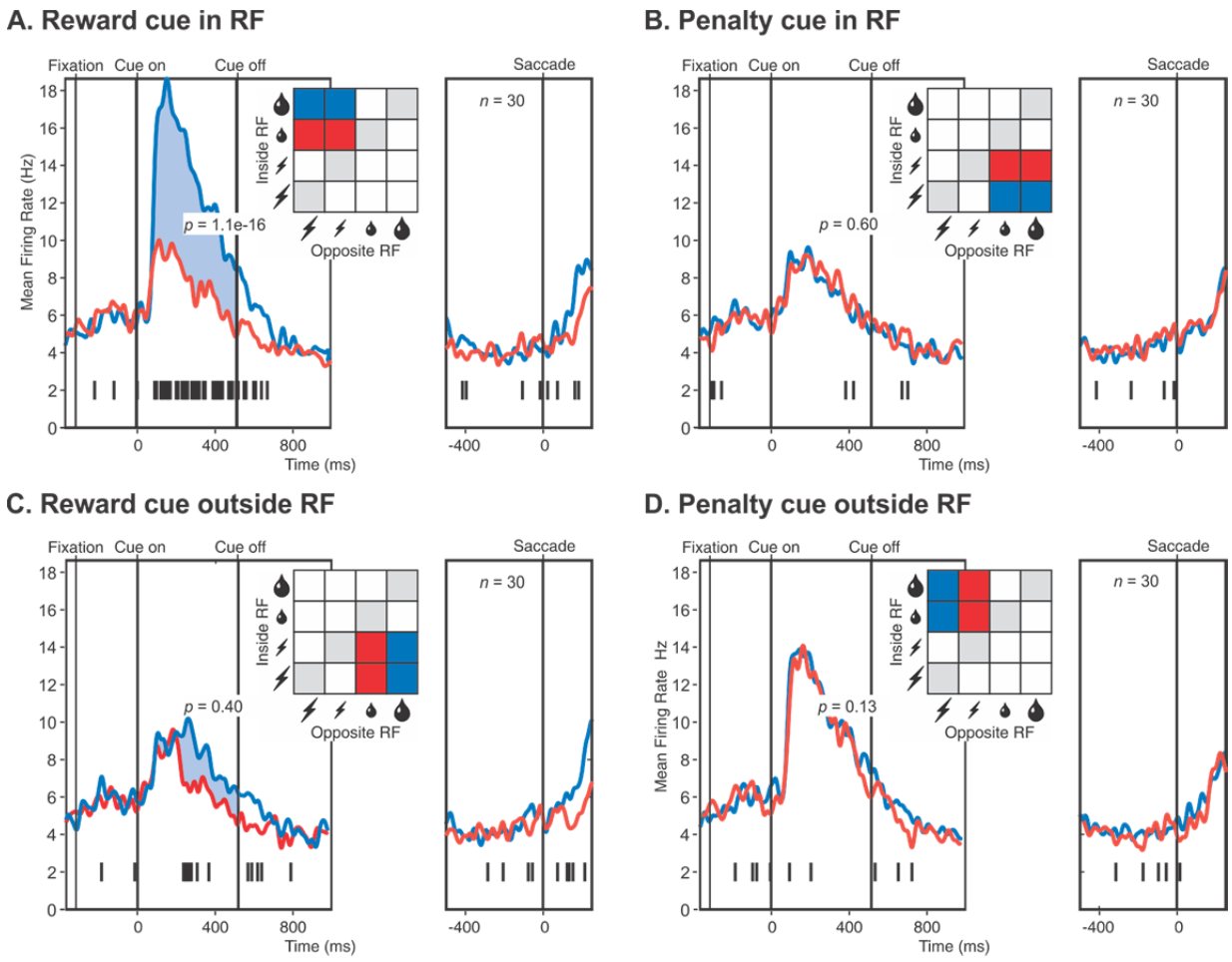


Figure 21. M2: Reward and Penalty Effects PSTHs (n = 30)
Same conventions as Figure 3.

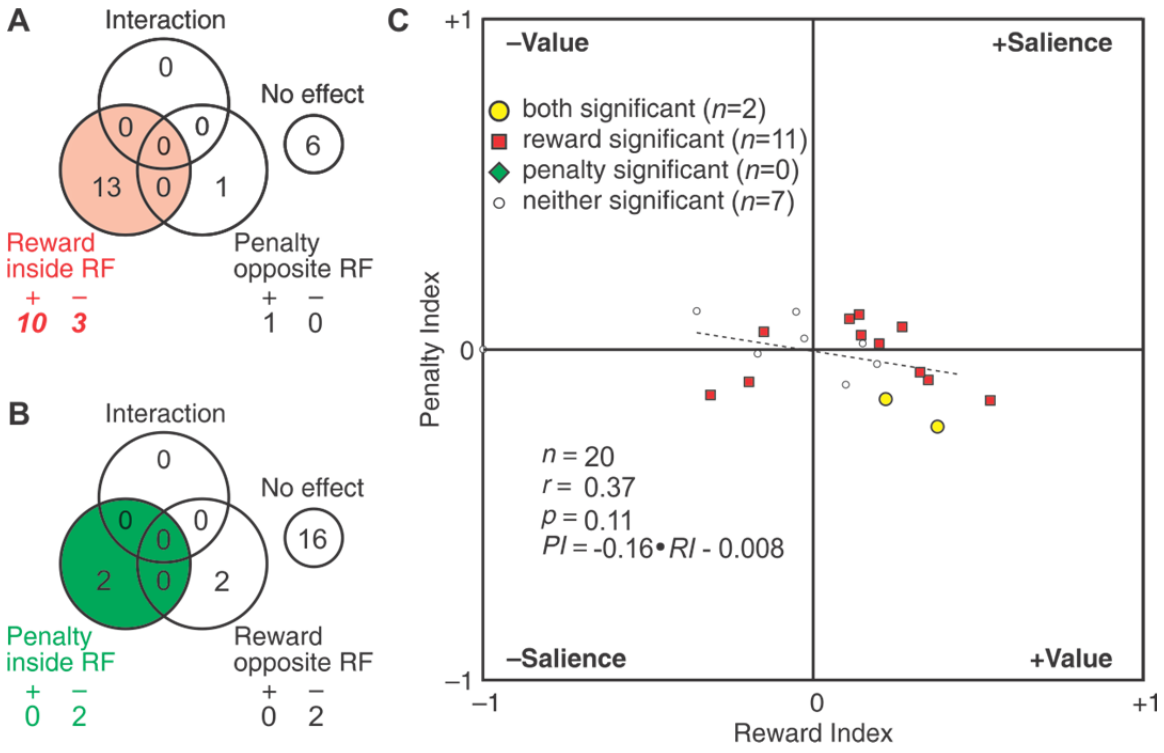


Figure 22. M1: Single Neuron Effects & Correlation Analysis (n = 20)
Same conventions as Figure 5.

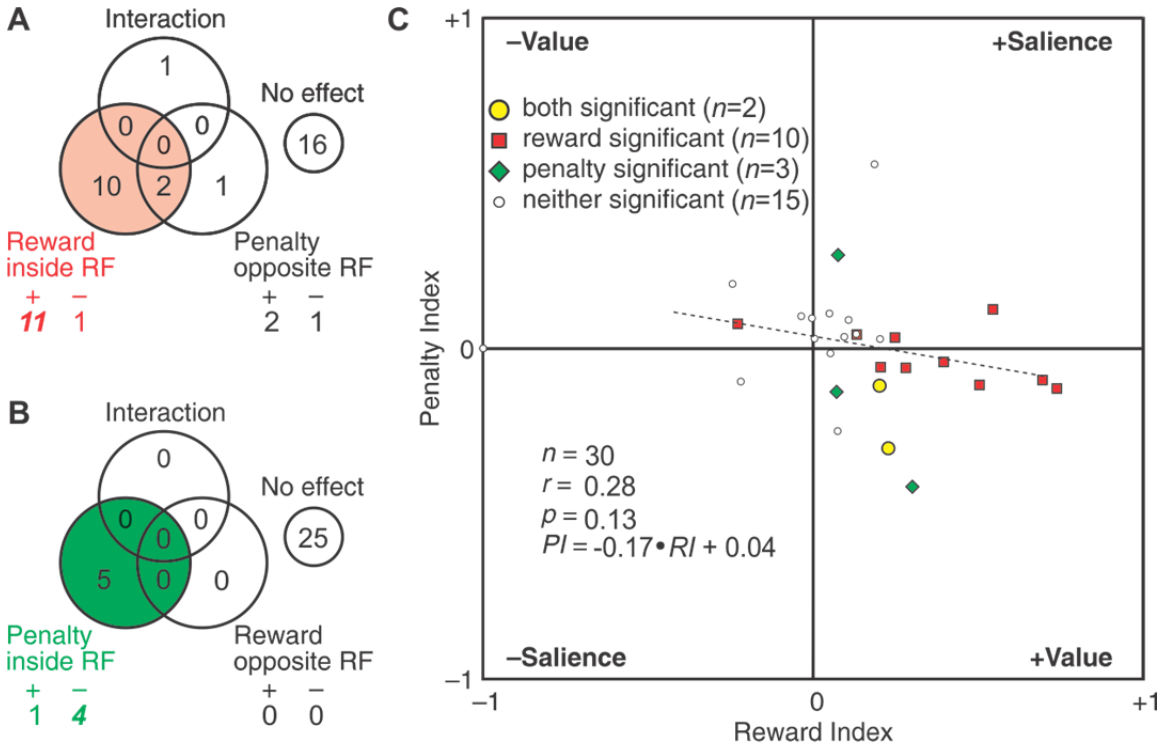


Figure 23. M2: Single Neurons Effects & Correlation Analysis (n = 30)
Same conventions as Figure 5.

(c) Omission of Repeat Trials

After a trial culminating in a fixation break of any kind, a penalty was imposed if a penalty was one of the options, and the identical condition was imposed on the following trial. The rate of fixation breaks varied slightly across conditions, as previously described. Therefore, any neural activity dependent on recent imposition of a penalty or on repetition of the same condition would have appeared as a difference between conditions. To be sure that the key findings were not an artifact of such an effect, we repeated all of the analyses after omitting repeat trials from the data set. This omission reduced the statistical power of the analyses by reducing the number of observations but left the trends intact and left all but one key trend highly significant. (As before, no interaction effects were significant.) This statement applies to effects shown in Figure 13B ($p = 2.8$ e-5 before and 3.4 e-5 after omission), Figure 13C ($p = 0.80$ before and 0.060 after the omission), Figure 14A ($p = 5.7$ e-24 before and 2.6 e-23 after the omission), Figure 14B ($p = 0.87$ before and 0.95 after the omission), Figure 14C ($p = 0.41$ before and 0.24 after omission), Figure 14D ($p = 0.27$ before and 0.43 after omission), Figure 15A ($p = 0.0037$ before and 0.0022 after omission), Figure 15B ($p = 0.0066$ before and 0.0046 after omission) and Figure 16C ($p = 0.042$ before and 0.22 after omission). In one of these cases (Figure 16C), an effect significant upon analysis of the complete data set failed to achieve significance upon analysis of the reduced data set. The negative correlation between the reward and penalty indices across the population of amygdala neurons (Figure 16C) ceased to be significant. The effect remained evident in the form of a negative trend ($r = 0.29$ before and 0.18 after omission) but dipped below the threshold of statistical significance. This is to be expected given that the p-value was already just below that threshold and omitting repeat trials reduced statistical power. Importantly, with repeat trials omitted, the slope of the line (slope = -0.17 before and -0.13 after omission) was negative across

the population of amygdala neurons' reward- and penalty-indices and comparable to the slope of the significant negative correlation observed in the full dataset with greater statistical power (Figure 16C). This is in conformity with the hypothesis that the firing rate was proportional to the value of the cues.

2.2.4 DISCUSSION

That images with greater value elicit stronger activity in amygdala fits with the idea that amygdala neurons encode cue-value (Morrison & Salzman, 2010). Amygdala neurons fire differentially for cues predicting different magnitudes of reward (Belova et al., 2008; Peck et al., 2013), and some fire more for reward cues while others fire more for penalty cues (Belova et al., 2008; Paton et al., 2006). Whether these are value or salience signals has been unclear. Our study is the first to record amygdala neurons while outcome magnitude varies not only along the reward-axis but also along the penalty-axis. The current finding of a negative correlation between firing rates to differential reward and penalty sizes establishes that amygdala neurons are indeed sensitive to value, as opposed to salience.

We have shown that when monkeys make value-based decisions the early firing of amygdala neurons encodes value instead of cue-salience. Could this signal be used to direct attention or make value-based decisions? Amygdala neurons are hypothesized to direct visual spatial attention by increasing their firing rates to contralateral reward and penalty cues as their associative salience, or emotional intensity, increases (Peck & Salzman, 2014a). Our result that amygdala encodes value but not salience suggests that early activity in amygdala does not direct visual attention based on the associative salience of reward and penalty cues. However, it does not rule out the amygdala's involvement in attention in some other way.

Prior to our study, only one experiment had recorded amygdala neurons in monkeys making value-based decisions. The authors suggest that amygdala neurons not only encode cue value but also could mediate the value-based decision process *per se* (Grabenhorst et al., 2012) by transforming abstract value plans into concrete actions (Hernadi et al., 2015). While our results do not speak to their suggested role for the amygdala in updating plans to accumulate value over many trials, we do note that causal studies and latency results appear to argue against the idea that amygdala neurons carry out the process of value-based decision making. First, while their baslolateral amygdala is inactivated, primates can make value-based decisions between objects with recently updated outcome-value associations, but without a functioning orbitofrontal cortex, primates are impaired at making such value-based decisions (Murray & Rudebeck, 2013; Wellman et al., 2005). Second, we show that the amygdala rapidly signals contralateral reward-size by 112 ms after cue onset, but it takes 235 ms after cue onset for the amygdala population to signal the reward-size associated with the ipsilateral option. Results from a different oculomotor delayed saccade task with peripheral decision cues show that orbitofrontal neurons signal the outcome of the decision around 100 ms after cue onset (Padoa-Schioppa & Assad, 2006). Thus, each amygdalae may not "see" the option ipsilateral to it before orbitofrontal cortex has mediated the value-based decision process *per se*, at least not in our task. Instead, our results suggest a role for the amygdala in facilitating value-based decision-making in orbitofrontal cortex. Complete bilateral amygdala lesions made using fiber-sparing excitotoxins increase the latency of cue-reward size signals in orbitofrontal cortex and decrease the prevalence of reward-size coding among orbitofrontal neurons by roughly one-third (Rudebeck, Mitz, Chacko, & Murray, 2013). Neurons in orbitofrontal cortex, like amygdala neurons, encode value instead of salience (Roesch & Olson, 2004), but in addition signal the value of the chosen option, regardless of its spatial

location, beginning around 100 ms after cue onset (Padoa-Schioppa & Assad, 2006; Roesch & Olson, 2004). Our result that amygdala neurons encode cue-value and not salience early during decision-making opens up the possibility that each amygdalae sends a contralateral cue-value signal to its ipsilateral orbitofrontal cortex where the value-based decision process appears to occur (Padoa-Schioppa, 2011).

3.0 MORPH

3.1 INTRODUCTION

Reward-associated stimuli can quickly and automatically capture our attention. Studies in humans have recently demonstrated that once-neutral stimuli, when repeatedly associated with reward, come to automatically capture visual attention, even when these stimuli are irrelevant to decision-making (Anderson, 2013). Learned reward-associations endow visually distinct and differentially rewarding stimuli with salience, or conspicuity.

Both LIP and the amygdala have been implicated in two distinct processes: value-representation for decision-making and salience for attention. The view that reward-related activity in areas outside the limbic system represents value was first put forward on the basis of studies of parietal area LIP (Platt & Glimcher, 1999). Value-related modulation in LIP neurons has been observed during experiments that associate differential rewards with visually distinct cues during saccade tasks requiring value-based decision-making (Klein et al., 2008; Rorie et al., 2010; Sugrue et al., 2004; Yang & Shadlen, 2007) and perceptual-decision making (Kiani & Shadlen, 2009; Roitman & Shadlen, 2002; Shadlen & Newsome, 1996, 2001). However, causal evidence supports the traditional view that LIP functions to orient spatial attention and plan saccades (Bisley & Goldberg, 2010) as opposed to the neuroeconomic view that LIP encodes value for value-based decision-making. In monkeys performing reward choice tasks, LIP-

inactivation leads to fewer and slower contralesional saccades but these spatial effects show no interaction effect with the value of the contralesional reward (Balan & Gottlieb, 2009). Thus, LIP might not be necessary for value-based decision-making with rewards. At the single neuron level, neuronal activity in LIP not only reflects the physical salience of visual stimuli that are not saccade goals (J. P. Gottlieb et al., 1998) but also the acquired salience of reward-associated cues that, as distractors, interfere with the action-value of a required saccade (Peck et al., 2009). Importantly, early reward-effects develop in LIP neurons as visually distinct stimuli are repeatedly associated with differential reward-values (Peck et al., 2009). In Chapter 2.1, we showed that LIP neurons encode cue-salience for visually distinct stimuli that were repeatedly associated with differential reward-sizes and penalty-sizes (Leathers & Olson, 2012). It is possible that the early-reward effects in LIP (Figure. 3A) reflect early automatic capture of attention by those cues, a form of salience acquired by visual-associative learning.

That the amygdala is involved in both value and salience processes has received support from single-neuron recording studies in the amygdala of awake-behaving primates. On the one hand, some amygdala neurons fire more for a cue promising reward, while others fire more for a cue promising penalties (Belova et al., 2008; Paton et al., 2006; Peck & Salzman, 2014b). Based on these results, it has been claimed that amygdala neurons encode the values of goods and evils in separate circuits (Morrison & Salzman, 2010; Zhang et al., 2013). On the other hand, neuronal activity in amygdala is correlated with increased allocation of visual attention to the spatial location of reward cues as well as penalty cues (Peck et al., 2013; Peck & Salzman, 2014a). Based on these results, it has been claimed that amygdala neurons direct visual attention based on the salience of cues, as opposed to their value (Peck & Salzman, 2014a). However, none of these experiments varied reward-size and penalty-size to determine whether or not early reward

effects in amygdala are value-representations or salience-reflections. In Chapter 2.2, we showed that amygdala neurons encode the value but not the salience of visually distinct stimuli that had been repeatedly associated with differential reward-sizes and penalty-sizes. It is possible that early-reward effects in amygdala neurons (Figure 14A) do not depend upon early automatic capture of attention by visually distinct yet differentially rewarding cues.

In this chapter, we present results from neuronal recordings made from LIP and amygdala in monkeys making value-based decisions between cues that could not acquire differential associative salience because, though differentially rewarding, these cues possessed near-identical visual properties. We predict that, under these conditions, early reward-effects would be attenuated in LIP but not in the amygdala.

3.2 LIP

To determine whether or not reward-effects in LIP neurons depended on the ability of visually distinctive cues to acquire differential salience by virtue of their differential associated values, we employed a task using cues that could not acquire differential associative salience. On each trial, the monkey chose, with a delayed saccade, between a "safety" cue that guaranteed a small certain reward and a perceptually ambiguous cue that predicted either large reward or no reward (Figure 24A). The ambiguous cue was a morph that was a transparency of two parent images (Figure 24B). The "good" morph contained a slightly greater proportion of the parent image promising large reward. The "bad" morph contained a slightly greater proportion of the parent image promising no reward. (The physical identities of the "good" and "bad" morphs were reversed between the two monkeys in which we recorded single-unit data.) These morph-

proportions were equal and opposite between the two morphs (Figure 24B) and held constant during each recording session. The discriminability of the morph was adjusted so that the monkey would choose the more valuable option ("good" morph over safety but safety over "bad" morph) on average 75% of the time during a session. The near-identical physical appearance of the morphs precluded automatic capture of attention by the more valuable morph—not the monkeys' ability to make perceptual decisions based on morph-value. If early reward-effects in LIP (Figure 3A) are actually reflections of visual salience acquired by value-associated cues, then we predict that our manipulation could possibly eliminate the ability of LIP neurons to signal action-value early during decision making.

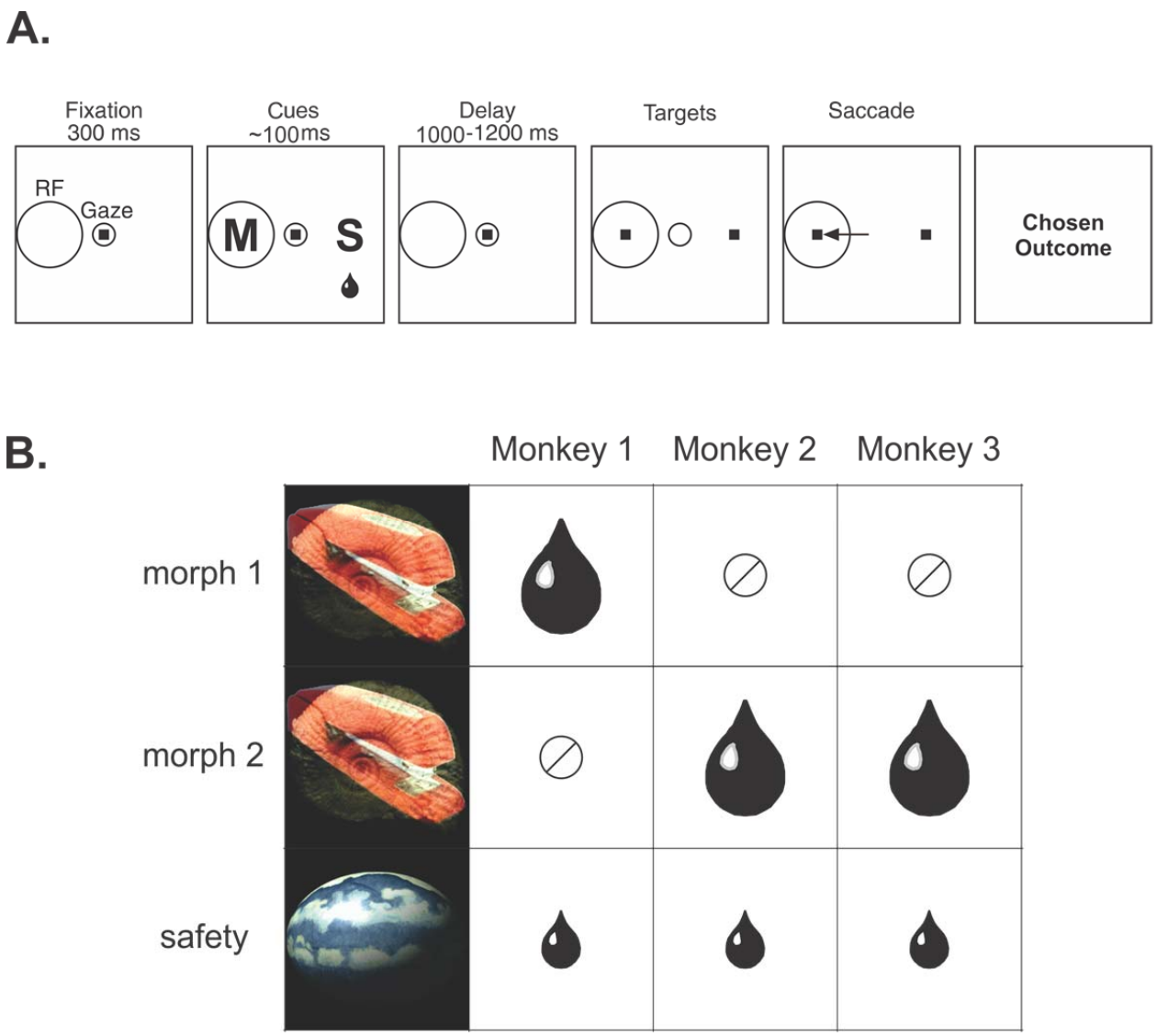


Figure 24. Morph: Task and Cue-Associations
(A) Sequence of events in a single trial. The items in each panel were visible to the monkey with the exception of those depicting the response field (RF), gaze location and saccade. M = morph cue, in this case the "bad" or no-reward morph. S = safety. **(B)** The two morphs possessed different significance in the two monkeys. The safety cue promised moderate reward for all monkeys. Large and small water drops: large and small reward. Barred-circle: no reward. Morph 1 = 55 % stapler, 45 % fossil. Morph 2 = 55 % fossil, 45 % stapler.

3.2.1 MATERIALS AND METHODS

3.2.1.1 SUBJECTS

Three adult rhesus macaque monkeys participated in the experiments (monkey 1, female, laboratory designation Ju; monkey 2, male, laboratory designation Eg; monkey 3, male,

laboratory designation Je). All experimental procedures were approved by the Carnegie Mellon University Institutional Animal Care and Use Committee (IACUC) and the University of Pittsburgh IACUC, and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals. In each monkey, a surgically implanted plastic cranial cap held a post for head restraint and a cylindrical recording chamber 2 cm in diameter oriented flush to the skull with its base centered to allow for recordings from the lateral bank of the intraparietal sulcus. Electrodes could be advanced along tracks forming a square grid with 1 mm spacing. The chambers overlay the left hemisphere in all three monkeys.

3.2.1.2 MORPH TASK

The sequence of events in each trial of the morph task (Figure 24A) were similar to that of the reward-penalty task (Figure 2A). On each trial, cues presented to the left and right of fixation predicted the outcomes that would result from leftward and rightward saccades later in the trial. However, no cues threatened penalty, the morph cues were associated with either reward or no reward, the morph cues were perceptually ambiguous, a morph cue presented on the left appeared as its mirror reflection when presented on the right, the duration of the cues was shorter (around 100 ms) and varied according to a stair-case procedure dependent upon the outcome of the monkeys choice the previous trial so as to hold the monkeys' percentages of choices for the more valuable option (morph or safety) around 75 % across the entire recording session.

The "safety" cue was always, and for all monkeys, the digitized image of a watermelon. It promised a small certain reward (0.09 cc of 1/3 dilution of apple juice for Monkey 1, 0.09 cc of plain water for Monkey 2 and 0.04 cc of plain water for Monkey 3). The "morph" cues were always, for all monkeys, an ambiguous transparent composite containing subtly different

proportions of two parent images, a brown fossil and a red stapler. Thus, there were two morphs whose physical appearances were nearly identical. A morph's "signal" was its dominant parent image. A morph's "noise" was the parent image dominant in the other morph. These proportions of signal and noise were equal and opposite between the two morphs and invariant throughout a recording session. The "good" morph predicted reward twice as large as the safety (0.18 cc for Monkey 1, 0.18 cc for Monkey 2, and 0.08 cc for Monkey 3). The "bad" morph predicted no reward. These amounts were the product of adjustments made during training of each monkey to induce engagement with the task and consistent choice behavior. Trials conformed to four conditions comprising all possible arrangements in which targets of unequal value could be placed inside and opposite the response field. A single session consisted of 72 successfully completed trials. A trial was judged to be successful if the monkey completed it regardless of whether he made an optimal or suboptimal choice. The sequence of conditions was random except for two constraints. First, for Monkey 1 and Monkey 2, within each block of 8 trials, each of the four conditions was imposed twice. For Monkey 3, within each block of 12 trials, the two "good" morph conditions were imposed twice, but the two "bad" morph conditions were imposed four times. (In training, Monkey 3 alone tended to always choose morph. To encourage him to make value-based decisions based on perceptually discriminating the morph, we made "bad" morph trials twice as likely per block as "good" morph trials for Monkey 3 alone.) Second, for all monkeys, following a fixation break, the next condition was selected pseudo-randomly from the remaining conditions in that block.

At the outset of each trial, the monkey fixated a central white square subtending 0.1º for 300 ms. Then two cues, an ambiguous "morph" predicting either large or no reward and a watermelon "safety" predicting small certain reward, appeared for about 100 ms at diametrically

opposed locations 12 º to the left and right of fixation. The cues were digitized images of objects against a transparent background. Each image subtended 7° along whichever dimension, horizontal or vertical, was greater. After the disappearance of the cues, Monkey 1 and Monkey 2 had to maintain central fixation for a duration selected at random within the range 1000-1200 ms, but Monkey 3 had to maintain central fixation for a shorter, fixed duration of 500 ms. At the end of the delay period, the fixation spot vanished and two white square targets subtending 0.2° appeared at locations 12° to the left and right of fixation. The monkey was required to launch a saccade to one of the targets within 300 ms and to reach the target within 100 ms after launch. The sequence of events that ensued depended on whether the target was at a location marked earlier in the trial by a reward-predicting cue. 1) If the target was at a location marked by a reward-predicting cue (either "safety" or "good" morph), then Monkeys 1 and 2 were required to maintain fixation on it for 100 ms. At that point, the unselected target disappeared and the selected target was replaced by a version of the chosen morph's dominant parent image or the chosen safety image minified to 24% of its former size so as to render it suitable as an object for fixation. Reward was delivered after an interval selected at random within the range 300-450 ms. 2) If the target was at a location marked earlier in the trial by the "bad" morph cue, Monkeys 1 and 2 were required to maintain fixation on it for 100 ms. At that point, it was immediately replaced by a minified version of the bad morph's parent image. The monkeys were not required to fixate this while no reward was delivered. Unlike Monkey 1 and Monkey 2, Monkey 3 alone was neither required to maintain fixation upon the saccade target after reaching it nor fixate a subsequent minified version of a chosen reward cue (either the "safety" or "good" morph parent image) presented before delivery of reward.

The consequences for the monkeys prematurely breaking fixation depended on the stage of the trial at which the break occurred and the outcome options available on the trial. The following rules determined the consequences of a fixation break. 1) If any monkey failed to attain fixation on the central target or attained it but broke fixation before the outcome-predicting cues had appeared, then the trial simply terminated. 2) If, after the onset of the cues, any monkey broke central fixation, failed to launch a saccade in time or failed to reach a target in time, then the trial terminated, and a remaining trial was pseudo-randomly imposed. 3) If Monkey 1 or Monkey 2 made a saccade to a target at a location marked by any type of cue but broke eccentric fixation of the target dot before 100 ms had expired, then the trial terminated, and a remaining trial was pseudo-randomly imposed. Rule three ensured that, if the ambiguous morph was chosen, its minified parent image did not appear to reveal whether the "good" or "bad" morph had been chosen. 4) If Monkey 1 or Monkey 2 made a saccade to a target at a location marked by a reward-predicting cue (either "safety" or "good" morph) but broke eccentric fixation before delivery of reward, then the trial terminated, and a remaining trial was pseudo-randomly imposed. Monkey 3, did not experience the consequences of fixation break stipulated here by rules three and four because, as indicated above, he did not have to maintain target- and feedback-fixation after indicating his choice via saccade.

3.2.1.3 MEMORY-GUIDED SACCADE TASK

In the morph task, the monkey chose between two targets located 12° to the left and right of fixation. Accordingly, we selected for study neurons that fired differentially in conjunction with the performance of memory-guided saccades to those locations. As we advanced the microelectrode, we monitored neuronal activity while the monkey performed a memory-guided saccade task. At the outset of each trial, the monkey fixated a central spot 0.1º in diameter for

300 ms. Then two targets subtending 0.2º appeared to the left and right of fixation at an eccentricity of 12 º. After a delay of 300 ms, a cue subtending 0.8° appeared for 250 ms in superimposition on one of the targets. A delay of duration 400-500 ms ensued. At the end of the delay period, offset of the fixation spot signaled the monkey to make a saccade to the target previously marked by the cue. We inspected on-line raster and histogram displays to determine whether the neuron exhibited task-related activity and, if so, whether this was spatially selective. We proceeded to run the morph task only if the neuron exhibited a clear contralateral spatial preference during the cue, delay or saccade period. These statements apply only to Monkey 1 and Monkey 2. For Monkey 3, who refused to perform the memory-guided saccade task, we used the same procedures indicated above but ran trials of the morph-task to select spatially selective multi-units.

3.2.1.4 RECORDING SITES

To determine the location of recording sites relative to gross morphological landmarks, we extrapolated from frontoparallel MR images containing the brain and fiducial markers placed at known locations within the chamber. The recording sites occupied the lateral bank of the intraparietal sulcus. In Monkey 1 (Ju), recording sites extended 1 mm anterior, 1 mm posterior, 0 mm medial and 2 mm lateral relative to the central recording point whose coordinates were 8 mm posterior and 8 mm lateral in the Horsley-Clarke reference frame. In Monkey 2 (Eg), recording sites extended 2 mm anterior, 2 mm posterior, 1 mm medial and 2 mm lateral relative to the central recording point whose coordinates were 6 mm posterior and 7 mm lateral in the Horsley-Clarke reference frame. In Monkey 3 (Je), recording sites extended 2 mm anterior, 1 mm posterior, 1 mm medial and 3 mm lateral relative to the central recording point whose

coordinates were 7 mm posterior and 7 mm lateral in the Horsley-Clarke reference frame. At the beginning of each day's session, we lowered a varnish-coated tungsten microelectrode with an initial impedance of several megaohms at 1 KHz through the dura into the underlying cortex. Action potentials of single neurons were isolated from the multi-neuronal trace by use of a commercially available spike-sorting system. All waveforms were recorded during the experiments and spike sorting was performed offline using commercially available spike-sorting software.

3.2.1.5 ANALYSIS OF BEHAVIOR

We used three measures to characterize the impact of predicted morph value on the behavior of each monkey during each LIP recording session: percent chosen, fixation break rate and reaction time. Morph proportions were fixed within each session, but morph difficulty could have varied within a session as we varied cue duration according to our staircase procedure. So, we also tested whether the ratio of morph choices to morph rejections varied across each cue-duration. The statistical tests and conditions involved are described in detail below. We performed these tests on data combined from 25 sessions involving monkeys 1 and 2 and also separately for each individual monkey's sessions (14 in M1; 11 in M2; 41 in M3). The criterion for statistical significance was $\alpha = 0.05$ for all behavioral analyses.

Percent chosen. We defined percent chosen as the number of trials on which the monkey chose the "good" or "bad" morph target expressed as a percentage of all trials on which either target was chosen.

Fixation-break rate. We defined the fixation-break rate as the number of trials on which the monkey broke fixation expressed as a percentage of all trials completed at least up to the point of the appearance of the cues.

Reaction time. We defined reaction time as the interval between the imperative cue (offset of the central fixation spot) and initiation of the saccade on trials which the monkey completed after having made a choice.

(a) Morph Value Effects

To test for morph value effects, we calculated the above three behavioral measures for good morph and bad morph trial types and tested for statistically significant differences between them (Figures 27-30A-C). In two ways, we expressed these data and tested them for differences. First, for each measure, we calculated the distributions of counts of the session-averages of each measure, separately for good and bad morph trial types (Figures 27-30A-C Top). We tested whether the means of these distributions of session counts differed significantly using a two-tailed paired t-test, which assumes normality. Second, for each measure, we expressed the cumulative distribution functions for the frequencies of observed values for each measure, separately for good and bad morph trials (Figures 27-30A-C Bottom). We tested whether the cumulative distribution functions observed for good and bad morph trials differed significantly using a k-s test, which makes no normality assumption.

(b) Reaction Time: Morph Chosen v. Rejected

To test for reaction time differences between trials when the morph was chosen or rejected, we used data only from completed bad morph trials (Figures 27-30E). We could not perform this test for data from good morph trials because the monkeys rarely rejected the good morph (Figures 27-30A). First, we performed a two-tailed paired t-test on the difference between the means of the distributions of session counts observed for reaction times on all bad morph chosen and bad morph rejected trials (Figures 27-30 E Top). Second, we performed a k-s test for difference in

the cumulative distribution functions for the reactions times on all bad morph chosen and bad morph rejected trials (Figures 27-30E Bottom)

(c) Morph Duration Effects on Choice

To test if the duration of the morph cue differentially affected the decision to choose or reject the morph, we again used data only from bad morph trials (Figures 27-30D), as there were too few trials in which the monkeys rejected the good morph (Figures 27-30A). We grouped the bad morph chosen and bad morph rejected trials by the duration the cues were on the screen. First, we tested whether the difference in counts between bad morph chosen and bad morph rejected trials varied across cue durations using a χ^2 test with degrees of freedom equal to the number of cue durations minus one (Figures 27-30D Top). Second, we performed a k-s test for a difference in the cumulative distribution functions for the frequencies of bad morph chosen and bad morph rejected trials observed across all cue durations (Figures 27-30D Bottom).

3.2.1.6 ANALYSIS OF NEURONS

We provide a visual guide to the eight effects we tested at the population-level and single neuron-level and for which we constructed histograms of neuronal firing rate indices so that we could, at the end of this chapter, test for significant differences in these effects between LIP and amygdala. These eight effects can be grouped into four primary effects of interest (Figure 25) and four other effects that we could test for in our data (Figure 26). Six effects are spatial in nature (RF-relative). Two effects are non-spatial ("global"). Details of statistical tests will be explained in the next section. This is an overview of the eight effects tested for in neuronal activity recorded during the morph task.

Spatial Decision to Saccade. This is the main effect of saccade direction chosen (either into or out of the RF), regardless of the spatial location of the bad morph and whether or not it or safety was chosen (Figure 25A). It is the first primary effect of interest.

Spatial Attention to Morph. This is the main effect of the bad morph location (either into or out of the RF), regardless of the saccade direction chosen and whether or not bad morph or safety was chosen (Figure 25B). It is the second primary effect of interest.

Value of Morph in the RF. This is the difference in firing rate when choosing to saccade to either a "good" morph (high value) or "bad" morph (low value) target located in the RF (Figure 25C). Only the value of the RF target differs between these two conditions. Safety value is constant and located out of the RF. It is the third primary effect of interest.

Value of Morph out of the RF. This is the difference in firing rate when choosing to saccade to either a "good" morph (high value) or "bad" morph (low value) target located out of the RF (Figure 25D). Only the value of the RF-out target differs between these two conditions. Safety value is constant and located in the RF. It is the fourth primary effect of interest.

Spatial Decision. This is the main effect of choosing a morph target (in or out of the RF), independent of morph value (Figure 26A).

Global Value. This is the main effect of choosing the "good" morph (high value) versus "bad" morph (low value), regardless of these morphs' locations or the saccade direction to their targets (Figure 26B). "Global Value" reflects the non-spatial difference in reward expectation for good and bad morph choices.

Action-Value. This is the interaction effect between the value of the morph ("good" morph = high value and "bad" morph = low value) and the direction of the saccade that obtains (Figure 26C) and is independent of the main effects of "Global Value" and "Spatial Decision."

Global Decision. This is the interaction effect of choosing versus rejecting the bad morph, regardless of the bad morph's spatial location and the saccade's spatial direction (hence "global"). This non-spatial signal is independent of the main effects of "Spatial Decision to Saccade" and "Spatial Attention to Morph" (Figure 26D).

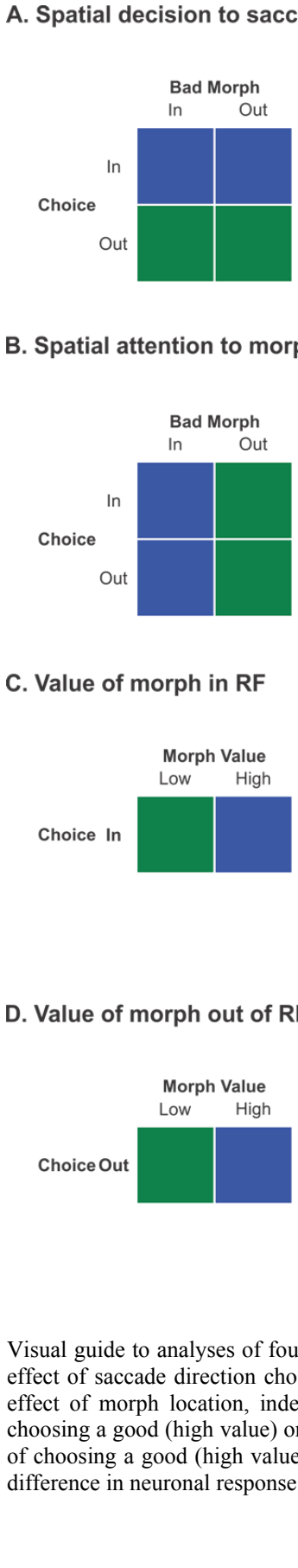


Figure 25. Primary Effects: Analyses Matrices

Visual guide to analyses of four primary effects on neuronal firing rate. **(A)** Spatial decision to saccade is the main effect of saccade direction chosen, independent of bad morph location. **(B)** Spatial attention to morph is the main effect of morph location, independent of saccade direction chosen. **(C)** Value of morph in RF is the effect of choosing a good (high value) or bad (low value) morph in the response field. **(D)** Value of morph in RF is the effect of choosing a good (high value) or bad (low value) morph out of the response field. All effects are quantified as a difference in neuronal response between select conditions: blue minus green.

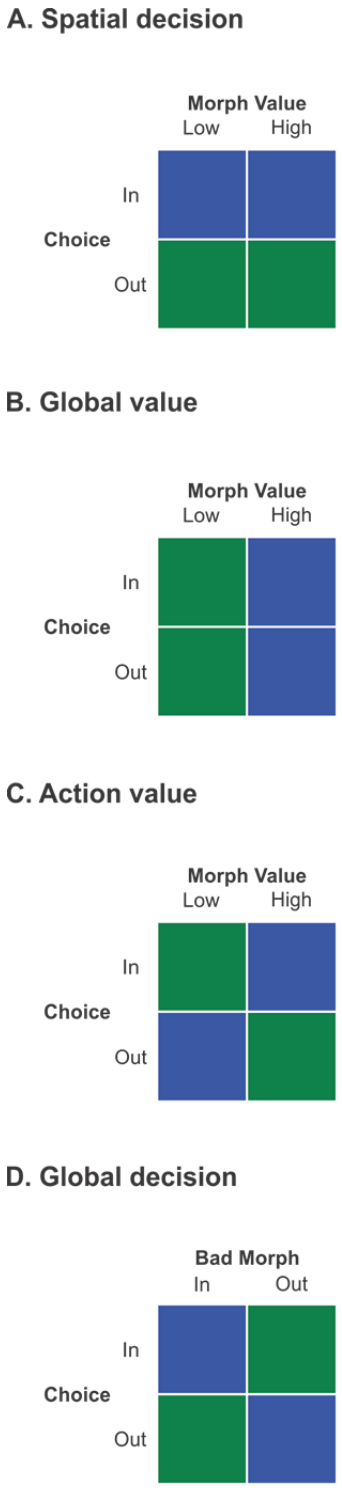


Figure 26. Secondary Effects: Analyses Matrices

Visual guide to analyses of the four secondary effects on neuronal firing rate. **(A)** Spatial decision is the main effect of choosing morph in or opposite the RF, independent of morph value (good or bad). **(B)** Global value is the main effect of choosing the high value morph, independent of its spatial location. **(C)** Action value is the interaction effect between the value of the morph and the spatial location at which it is chosen. **(D)** Global decision is the interaction effect of choosing versus rejecting the bad morph, regardless of spatial location. Secondary effects **(B)** and **(D)** are the only non-spatial (global) effects in the experiment.

(a) Population-level Statistical Tests

The criterion for statistical significance was $\alpha = 0.05$ for all neuronal analyses.

(i) Tests for Eight Effects

To compare neuronal activity between conditions, we inspected population histograms constructed by computing the average firing rate in each 1 ms bin and applying a Gaussian smoothing function (σ = 10 ms). We determined whether the average firing rate differed significantly ($\alpha = 0.05$) between conditions during each of four standard analysis epochs: 1st half (0-250 ms following cue onset), 2nd half (250-500 ms following cue onset), whole (0-500 ms from cue onset to end of shortest delay period), saccade (from 200 ms prior to saccade to 100 ms post-saccade).

To determine whether the average firing rate during an analysis window showed significant effects involving four conditions, we used two three-factor ANOVAs on firing rates within each window separately. One three-factor ANOVA was used for the bad morph conditions matrix (Figures. 25A-B and 25D). The three factors were spatial direction of the saccadic choice (RFin or RFout), spatial location of the bad morph cue (RFin or RFout), and neuron identity (1,2…n) with n equal to the number of amygdala neurons in the sample and with each neuron contributing one mean firing rate for each condition. A separate three-factor ANOVA was used for the morph chosen conditions matrix (Figures. 26A-C). The three factors were spatial location of the chosen-morph (RFin or RFout), value of the chosen-morph ("good" morph = high value or "bad" morph = low value), and neuron identity (1,2…n) with n equal to the number of amygdala neurons in the sample and with each neuron contributing one mean

firing rate for each condition. In addition, we applied the appropriate sliding three-factor ANOVA to each successive 50 ms bin ($\alpha = 0.05$) stepped every 1 ms so as to place, beneath population histograms, tick marks indicating time points at which the firing-rate difference *for the main effect of interest* attained an arbitrary stringent statistical threshold ($\alpha = 0.05$). The role of this step was to provide a graphic indication of signal timing and not to serve as a test of effect significance.

To determine whether the average firing rate during an analysis window differed significantly between two conditions, we employed a two-tailed paired t-test with n equal to the number of neurons in the sample and with each neuron contributing one mean firing rate for each condition for each window (Figure 25C-D). In addition, we applied a two-tailed sliding paired t-test to each successive 50 ms bin ($\alpha = 0.05$) stepped every 1 ms so as to place, beneath population histograms, tick marks indicating time points at which the firing-rate difference between two conditions attained an arbitrary stringent statistical threshold ($\alpha = 0.05$).

(ii) Negative Log of P-values

To visualize the strength of statistical significance of each effect as it evolved over the course of these trials, we computed the negative logarithm of the p-values that resulted from the corresponding sliding statistical test for that effect (performed as described above on each successive 50 ms bins stepped every 1 ms).

(b) Neuron-level Statistical Tests

Neuron-level statistical tests mirrored the population-level statistical tests.

(i) Tests for Eight Effects

To determine whether individual neurons were significantly sensitive to an effect involving four conditions, we carried out two different two-factor ANOVAs. One ANOVA was based on a set of four conditions comprising the bad morph conditions matrix (Figures 25A-B and 26D). A separate two-factor ANOVA was based on a set of four conditions comprising the morph-chosen conditions matrix (Figure 26A-C). To determine whether individual neurons were significantly sensitive to an effect involving two conditions, we carried a two-tailed paired t-test (Figure 25C-D). Finally, for all neuron-level effects analyses, we assessed whether the number of neurons with significant effects was significantly greater than expected by chance using a χ^2 test with Yates-correction.

(ii) Indices for Eight Effects

For each epoch, for each effect, we characterized the strength of each effect present in each neuron's firing rate with indices capturing the raw difference in firing rates observed during the relevant conditions for calculating each effect (Figures. 25 & 26, blue versus green conditions) For effects involving four conditions, we averaged the mean firing rates for each neuron within each of the two appropriate conditions (within each blue square) separately then took the mean across those two averages (across the two blue squares). We did likewise for the two opponent conditions (green squares). For effects involving two conditions, we averaged the mean firing rates for each neuron within one condition (within one blue square). Then did likewise for its opponent condition (green square). Each effect index had the form B-G where B and G were the mean firing rates, calculated as just described, associated with the blue and green conditions respectively. Then, for each epoch, for each effect, we created histograms to plot a distribution of the counts of neurons by the size and sign of their effect index grouped in 1 Hz bins. Finally, we

tested for differences in the means of LIP and amygdala effect indices using two-tailed unpaired t-tests separately for each epoch, for each effect.

3.2.2 RESULTS

3.2.2.1 BEHAVIOR

Confronted with two offers of different value (morph vs. safety), the monkeys consistently chose the better offer. This was true in the data combined from both monkeys and for each monkey individually.

(a) Data Combined from Both Monkeys

Behavioral data from Monkey 1 (Ju) and Monkey 2 (Eg) were combined. All LIP single-units were recorded from these two monkeys. Only LIP multi-units were recorded from Monkey 3 (Je).

(i) Morph Value Effects

During the 25 LIP recording sessions combined across both monkeys (14 from M1; 11 from M2), the monkeys chose the better offer (the good morph over safety but safety over the bad morph) for 72.0 % of all choices, on average. We computed the impact of predicted morph-value on behavior of with three measures: percent better chosen, fixation break rate and reaction time (Figure 27A-C).

Percent better chosen. The monkeys made a significantly greater fraction (44 %) of good than bad morph choices (Figure 27A Top). Thus, the monkeys could perceive the difference between the two morphs and made their decisions based on morph-value.

Fixation-break rate. The monkeys aborted a significantly greater percentage (5 %) of trials that offered a bad rather than good morph (Figure 27B Top). Thus, the monkeys' willingness to make the decision reflected the value of the morph offered.

Reaction time. The monkeys' reaction times did not differ significantly for choices made to good or bad morph targets (Figure 27C Top). Thus, morph-value did not motivate saccadic reaction time. However, this effect was inconsistent between monkeys.

(ii) Reaction Time: Morph Chosen v. Rejected

The monkeys' reaction times were significantly slower (16 ms) when rejecting versus accepting the morph (Figure 27E Top). Thus, the monkeys allocated attention to the morph cue location. When they decided to reject the morph at that location, this slowed their saccadic reaction time to the safety target in the opposite hemifield.

(iii) Morph Duration Effects on Choice

The monkeys' proportion of choices for accepting versus rejecting the bad morph did not vary significantly as a function of the duration the cues were displayed (Figure 27D Top). Thus, perceptual difficulty did not vary as cue duration varied according to the stair-casing procedure used to hold the monkeys' correct performance ("percent better chosen") around 75%.

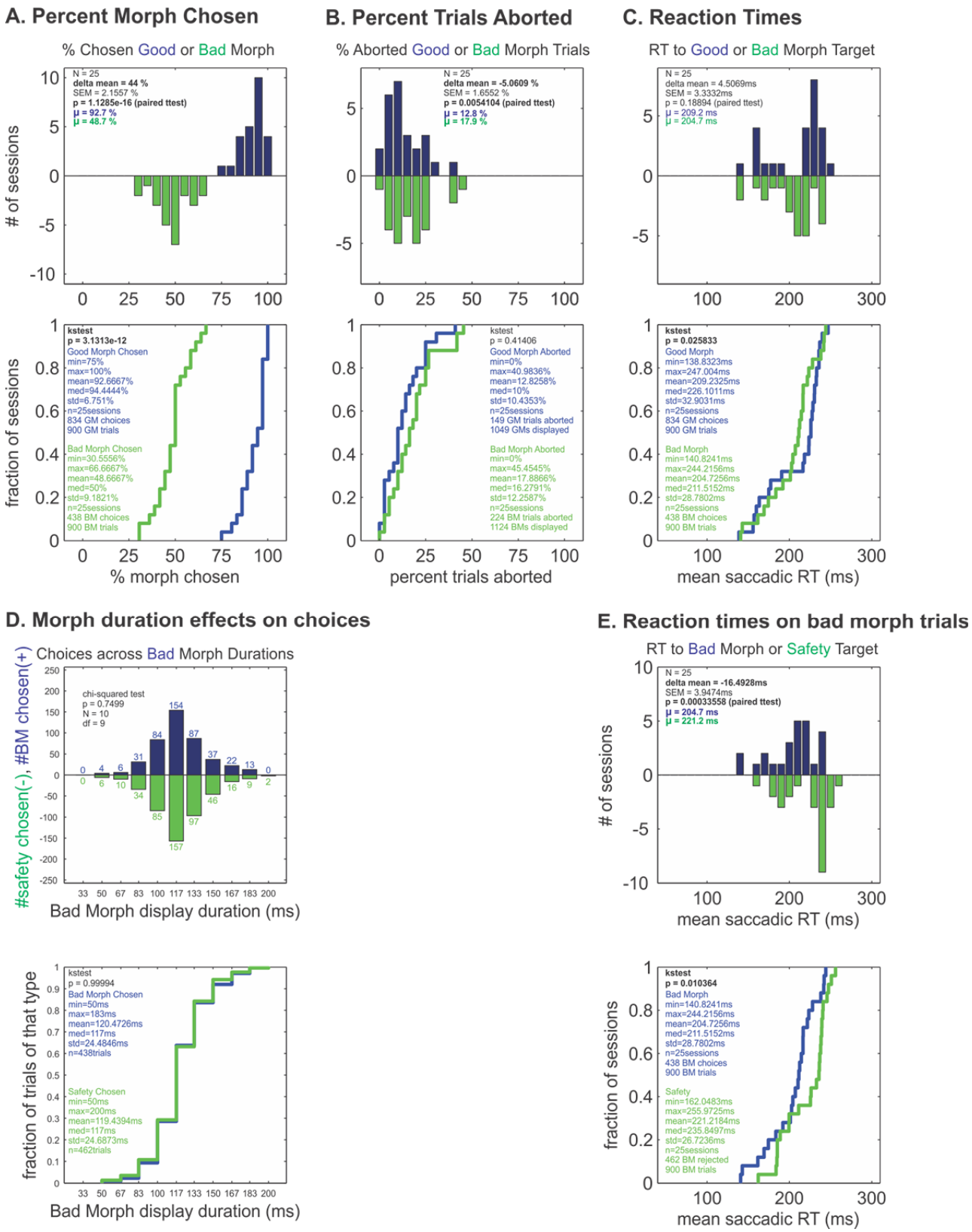


Figure 27. Behavior: LIP Recording Sessions

Behavioral measures across sessions (n = 25), expressed as distributions of counts (top panels) and cumulative fractional distributions (bottom panels). **(A)** Percentage of choices made to the good (blue) or bad (green) morph. **(B)** Percentage of trials aborted after display of either the good (blue) or bad (green) morph. **(C)** Reaction times when good (blue) or bad (morph) is chosen via saccade. **(D)** Bad morph chosen (blue) or rejected for safety (green) as a function of cue duration. **(E)** Reaction times when bad morph is chosen (blue) or rejected for safety (green). In all top panels except in **(D)**, we tested whether the difference between the blue and green distribution means (delta mean) differed significantly using a two-tailed paired t-test. In **(D)** top panel, we tested whether the difference in blue and green counts varied across each cue duration using a χ^2 test. In all bottom panels, we tested for a significant difference in the blue and green cumulative distribution functions using a k-s test. P values in bold reached statistical significance ($\alpha = 0.05$).

(b) Individual Monkey Data

(i) Morph Value Effects

The fraction of choices made for the better offer was 72.7 % for Monkey 1 (14 sessions), 71.1% for Monkey 2 (11 sessions), and 76.0 % for Monkey 3 (42 sessions). We computed the impact of predicted morph-value on behavior of with three measures: percent better chosen, fixation break rate and reaction time (Figures 28-30A-C Top).

Percent better chosen. Each of the three monkeys made a significantly higher percentage (M1: 45 %, M2: 42 %, M3: 52 %) of good than bad morph choices (Figures 28-30A Top). Thus, each individual monkey perceived the difference between the two morphs and decided based on morph-value.

Fixation-break rate. All three monkeys aborted a higher percentage of trials (M1: 3 %, M2: 7 %, M3: 4 %) that offered the bad morph rather than the good morph (Figures 28-30B Top). For Monkey 1 and Monkey 3, this effect was significant. Monkey 2 showed a similar trend ($p < 0.10$). Thus, each individual monkey's willingness to perform the task increased with morph-value.

Reaction time. This measure was inconsistent between monkeys (Figures 28-30C Top). We observed mean reaction times that significantly increased (M1: 12 ms) and significantly

decreased (M3: 9 ms) with morph-value. Monkey 2 made shorter latency saccades to good rather than bad morph targets (5 ms), but this effect did not attain significance. Thus, morph-value motivated saccadic reaction time differently for different monkeys.

(ii) Reaction Time: Morph Chosen v. Rejected

Each monkey's reaction times were slower (M1: 22 ms, M2: 10 ms, M3: 34 ms) when rejecting versus accepting the morph (Figures 28-30E Top). Thus, the monkeys allocated attention to the morph's location, which slowed their reaction time when rejecting morph for safety. For Monkeys 1 and 3, this effect was significant.

(iii) Morph Duration Effects on Choice

For each of the three monkeys, the proportion of choices accepting versus rejecting the bad morph did not vary significantly as a function of the duration the cues were displayed (Figures 28-30D Top). Thus, for each monkey individually, perceptual difficulty did not vary, on average, as a function of cue duration.

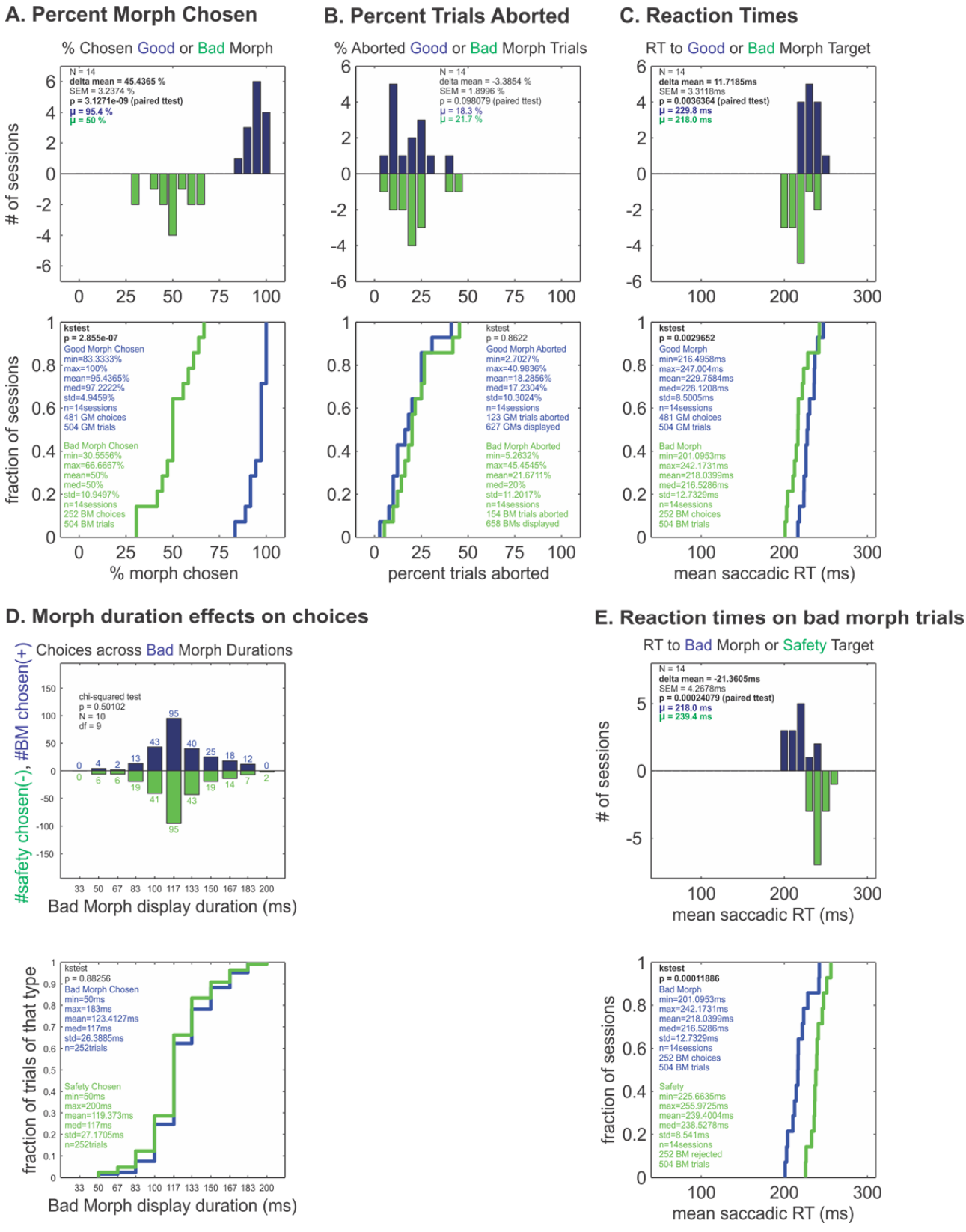


Figure 28. M1: Behavior (n = 14)

Same conventions as Figure 27.

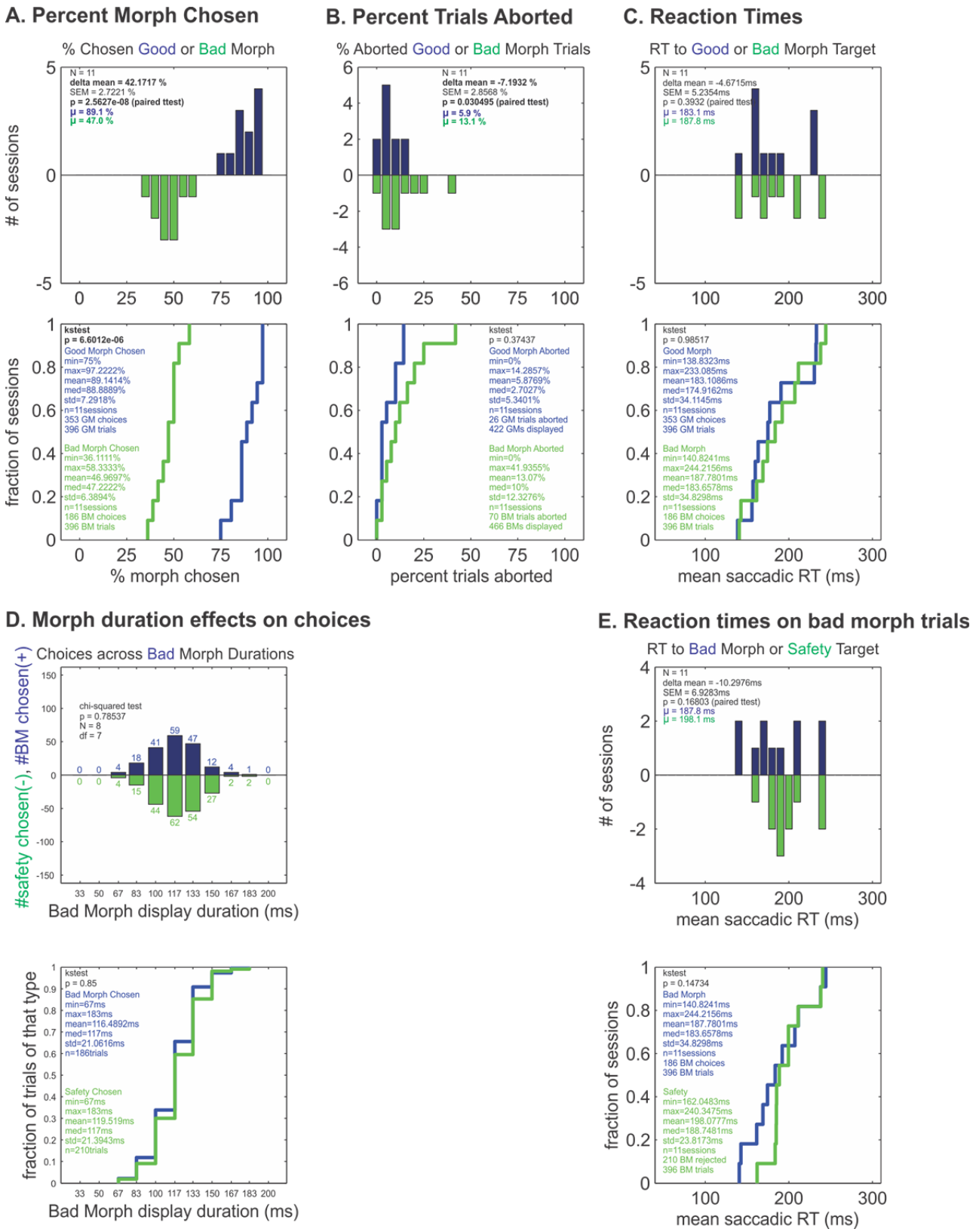


Figure 29. M2: Behavior (n = 11)

Same conventions as Figure 27.

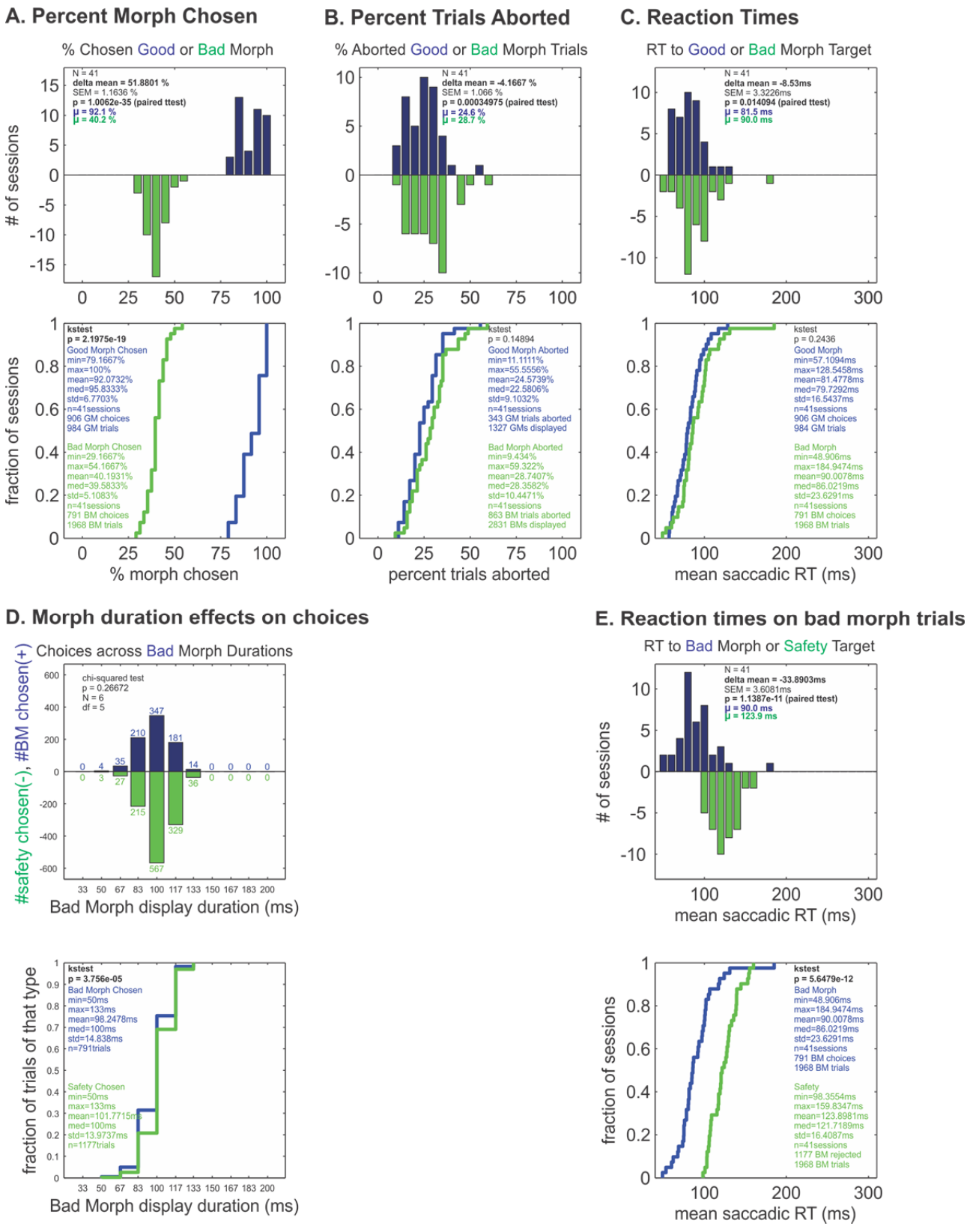


Figure 30. M3: Behavior (n = 41)

Same conventions as Figure 27.

3.2.2.2 NEURONS

Confronted with two offers of different value (morph vs. safety), the monkeys consistently chose the better offer. On average, 72.0 % of choices were made for good morph over safety and safety over bad morph. More importantly, these decisions were based on morph-value. Though the two morphs were of near-identical physical appearance, the monkeys made a significantly greater percentage (44 %) of good-morph than bad-morph choices (Figure 27A Top). Monkeys allocated attention to the morph location while making the saccadic decision to choose morph or safety (Figure 27E Top). LIP neuronal activity reflects not only the locus of visual spatial attention (Bisley & Goldberg, 2010) but also the direction of the saccadic decision during tasks requiring perceptual (Shadlen & Kiani, 2013) or value-based decision-making (Kable & Glimcher, 2009; Sugrue et al., 2005).

Early during value-based decisions, LIP neurons appear to reflect the value of reward associated with the saccade. However, we have shown that LIP encodes cue-salience and not action-value (Leathers & Olson, 2012). This result was contentious (Leathers & Olson, 2013; Newsome, Glimcher, Gottlieb, Lee, & Platt, 2013). If the early reward-effect in LIP (Figure 3A) is truly a reflection of visual salience acquired by value-associated cues, then our morphing manipulation should reduce or even eliminate the reward-effect in LIP neurons early during decision making, while leaving attention and saccadic decision signals intact. To test these predictions, we collected data from 22 neurons in the left LIP of monkey 1, 19 neurons in the left LIP of monkey 2, and 45 multi-units in the left LIP of monkey 3.

(a) Data Combined from Both Monkeys

Neuronal data from Monkey 1 (Ju, n = 22) and Monkey 2 (Eg, n = 19) were combined. All LIP single-units were recorded from these two monkeys. We did not include LIP multi-units recorded

from Monkey 3 (Je, n = 45). Population-level results for the four value-effects and the four non-value effects are presented in Tables 4 and 5, respectively. Neuron-level results for the four value-effects and the four non-value effects are presented in Tables 6 and 7, respectively.

We first tested for four primary effects of interest: "Spatial Decision to Saccade," "Spatial Attention to Morph," "Value of Morph in RF," and "Value of Morph out of RF." We first examined trials in which the monkey chose or rejected the bad morph to test for independent effects of the saccadic decision (Figure 25A) and allocation of attention to the morph (Figure 25B). Population activity during the interval 0 – 250 ms following cue onset was not significantly different for decisions made into rather than out of the RF, increasing by only 5 % (Figure 31A). LIP began encoding the decision around 200 ms (Figure 31A, black tick-marks, rising red line). Population activity was significantly increased for saccadic decisions planned into the response field by 55 % during the delay period (250 – 500 ms, the longest delay encountered by all monkeys in these experiments), by 24 % when averaged across cue and delay periods (0 – 500 ms), and by 65 % around the time of saccade execution (200 ms pre-saccade to 100 ms post-saccade). The strength of significance of this decision signal first crossed statistical threshold around 200 ms and remained above it for almost the entire duration of the trial (Figure 32A). Thus, LIP encoded the decision robustly and persistently from the delay period until saccade execution.

LIP significantly encoded the allocation of spatial attention in the earliest analysis window (Figure 31B). Population activity during the interval 0 – 250 ms decreased by 17 % when the morph was located outside rather than inside the RF. The attention signal began to wane with the emergence of the decision signal, changed signs, and then disappeared after 500 ms. The strength of significance of the attention signal first crossed statistical threshold around

122 ms, the mean cue duration (Figure 32B, blue and green numbers). Thus, LIP encoded the allocation of spatial attention to the morph's location robustly, early during decision-making.

The above results established that our morphing manipulation left intact the ability of the LIP population to encode pre-decision and post-decision spatial signals: the allocation of spatial attention to the morph and the spatial decision to saccade. Would LIP likewise encode morph-value spatially early during the decision process? We therefore examined trials in which the monkey chose the good or bad morph inside or outside of the RF (Figure 25C-D). For choices into the RF, population activity increased with morph-value by 5% early during the decision (0 – 250 ms), but this effect did not attain significance (Figure 31C). The strength of this effect's significance first crossed statistical threshold transiently around 200 ms but remained below statistical threshold for most of the rest of the trial (Figure 32C). During the delay period (250 – 500 ms), firing increased with morph-value by 8 % and trended towards significance ($p = 0.087$). When population activity was averaged from cue onset to the end of the longest delay encountered by every monkey in these experiments (0 – 500 ms), LIP significantly encoded morph-value (Figure 31C). Thus, LIP did not significantly encode the value of the morph located in the RF early during decision-making but did so later and weakly. This result supports our hypothesis that early reward-effects in LIP are signals for cue-salience not action-value.

For choices out of the RF, population activity was weakly and insignificantly modulated by the value of the morph chosen out of the RF for all epochs (Figure 31D). As with morph-value located in the RF, firing rate increased with the value of the morph located out of the RF beginning around 200 ms after cue onset (Figure 31D, black tick marks, rising red line), and the strength of this effect's significance first crossed statistical threshold transiently around 200 ms but remained below statistical threshold for most of the rest of the trial (Figure 32D). Thus, LIP

did not significantly encode the value of the morph located out the RF early during decision-making. This result supports our hypothesis that early reward-effects in LIP are signals for cue-salience not action-value.

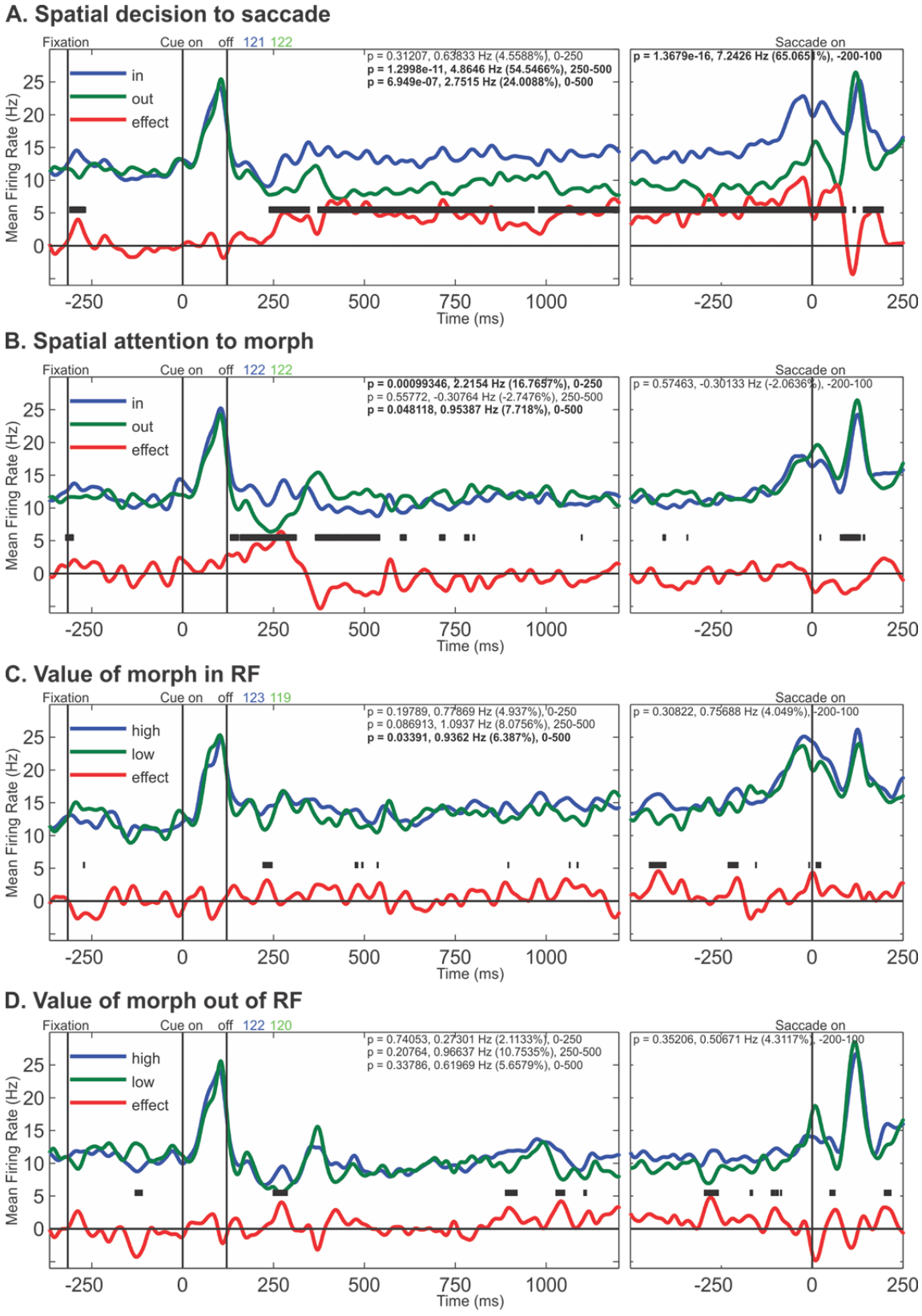


Figure 31. Primary Effects PSTHs (n = 41)

Mean population firing rates for the four primary effects. Data is from both monkeys (n = 41). **(A)** Spatial decision to saccade. **(B)** Spatial attention to morph. Tick marks indicate 50 ms bins in which the difference between red and blue curves crossed an arbitrary statistical threshold (three-factor ANOVA, n = 41, $\alpha = 0.05$). **(C)** Value of morph in RF. **(D)** Value of morph out of RF. Tick marks indicate 50 ms bins in which the difference between red and blue curves crossed an arbitrary statistical threshold (two-tailed paired t-test, n = 41, $\alpha = 0.05$). Effect significance (p-value), size and sign (+ or – Hz), and percentage change in firing rate (blue relative to green) are given for all four analysis epochs. In the first panel, in which neuronal activity is aligned to cue onset, analyses epochs from top to bottom are first half (0-250 ms), second half (250-500 ms), and whole (0 – 500 ms). In the second panel, in which neuronal activity is aligned to saccade onset, the analysis epoch is from 200 ms before to 100 ms after the saccade (-200-100).

We then tested for four other effects: "Spatial Decision," "Global Value," "Action Value," and "Global Decision." We first examined trials in which the monkey chose the morph target to test for independent effects of the spatial decision (Figure 26A), global value (Figure 26B), and the interaction effect of action-value (Figure 26C). Population activity encoded "Spatial Decision," in which attention to the morph location corresponded to the saccade direction being chosen. Activity increased significantly when spatial attention and the saccadic decision were both directed into rather than out of the RF by 24 % in the earliest epoch (0 – 250), by 49 % in the delay epoch (250 – 500), by 34 % across the cue and shortest delay period used in these experiments (0 – 500), and by 59 % around the time of the saccade (Figure 33A). Thus, when the location of spatial attention and the direction of the chosen saccade correspond, the spatial decision signal emerges earlier, around the time of cue offset (Figure 33A, black tick-marks, rising red line). The strength of significance of this decision signal first crossed statistical threshold around 100 ms and remained above it for almost the entire duration of the trial (Figure 34A). Thus, LIP encoded "Spatial Decision" robustly and persistently from the delay period until saccade execution.

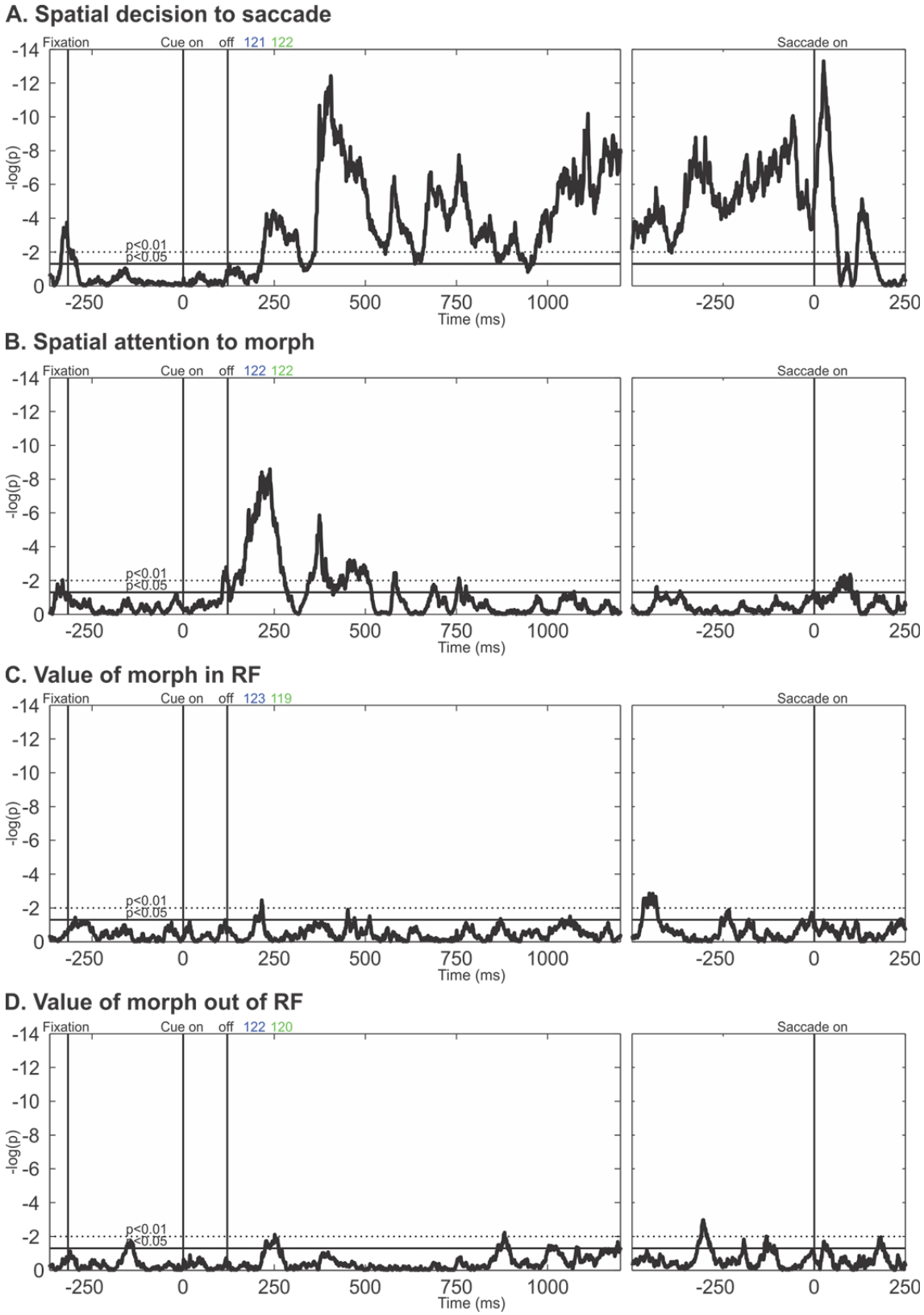


Figure 32. Primary Effects –log(p) (n = 41)

Negative log of p-values for the four primary effects. Data is from both monkeys (n = 41). **(A)** Spatial decision to saccade. **(B)** Spatial attention to morph. **(C)** Value of morph in RF. **(D)** Value of morph out of RF. P-values were calculated every 1 ms across a 50 ms sized bin using either a three-factor ANOVA **(A-B)** or two separate two-tailed paired t-test **(C)** and **(D)** ($\alpha = 0.05$). Solid line is $p = 0.05$. Dashed line is $p = 0.01$.

Global value is the non-spatial effect of morph-value (Figure 26B). Population firing rates in LIP increased significantly by 8 % (250 – 500) and 6% (0 – 500) as morph-value increased, regardless of the morph's spatial location or the direction of the saccade (Figure 33B). However, this effect was not seen in the earliest epoch (Figure 33B). Thus, LIP does not significantly encode morph-value either spatially (Figure 31C-D) or globally (Figure 33B), early during decision-making.

Action-value, fully defined, is the change in spatial selectivity for neurons representing potential motor plans as a function of the value those actions would earn. In LIP, action-value is proposed to push-up or pull-down firing rates in proportion to the relative value of the potential saccade plans into or out of the RF (P. Glimcher, 2013). When morph-value in the RF is higher relative to morph-value out of the RF (Figure 26C blue conditions, Figure 33C in>out) then spatial selectivity for saccade plans in LIP (firing rates) should be greater than when morph-value in the RF is lower relative to morph-value out of the RF (Figure 26C green conditions, Figure 33C out>in). We found that population firing rates in LIP do not significantly encode action-value early in the decision or in later epochs (Figure 33C). The strength of significance for action-value makes a blip above statistical threshold around 250 ms but remains well below it for most of the rest of the trial (Figure 34C). Thus, LIP did not significantly encode action-value. This result supports our hypothesis that early reward-effects in LIP are signals for cue-salience not action-value.

Finally, "Global Decision" is the non-spatial firing rate difference between morph-chosen and morph-rejected trials (Figure 26D). Population activity increased by 7 % during the saccade

period when morph was chosen over safety (Figure 33D), but this trend did not attain significance ($p = 0.09$). It is not clear what this effect means.

We tested the eight effects above at the single-neuron level. The numbers of LIP neurons with significant reward-effects was no greater than expected by chance for all three epochs prior to the saccade, for all four value-effects tested (Figure 35B "Value of morph in RF," 35C "Value of morph out of RF", 35D "Global Value" and "Action Value," and Table 6). This was true for data combined across two monkeys and for all three monkeys individually (Figures 48-50B-D). The only exception is the four multi-units from Monkey 3 that showed a reversed action-value effect in the earliest epoch. Thus, with that one exception, our morphing manipulation reduced the number of single-neurons with significant reward-effects in LIP to levels expected by chance alone (Table 6).

In contrast, our morphing manipulation left intact a significant number of LIP neurons that significantly encoded visual attention and saccadic decision signals (Figure 35A "Spatial Attention" and "Spatial Decision," 35D "Spatial Decision," and Table 7). This was true for data combined across two monkeys (Figure 35A, 35D and Table 7) and for all three monkeys individually (Figures 48-50A, 48-50B and Table 7). The number of LIP neurons encoding "Global Decision" and was no greater than expected by chance in data from both monkeys (Figures 35A and Table 7) combined and all three monkeys individually (Figures 48-50A and Table 7).

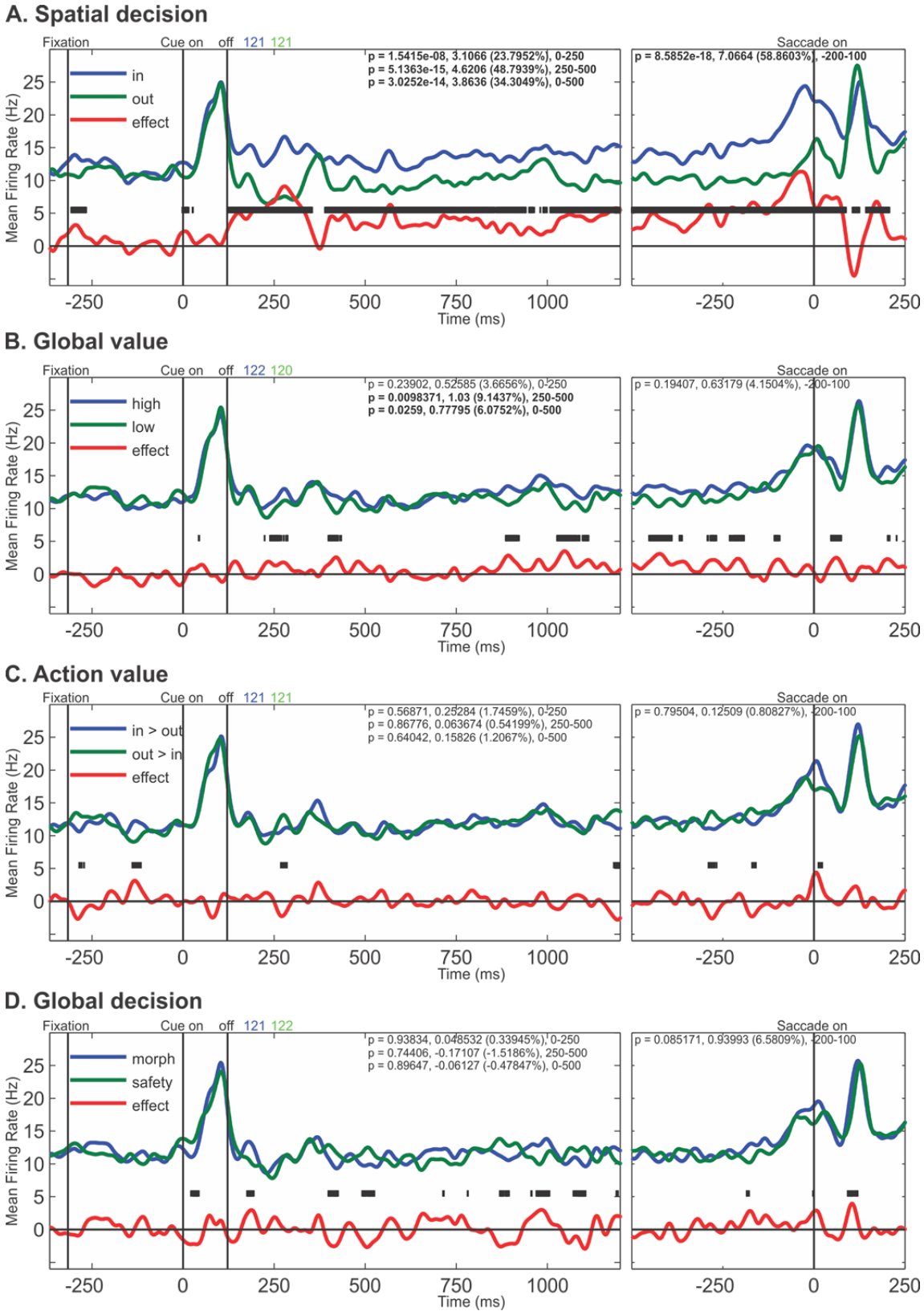


Figure 33. Secondary Effects PSTHs (n = 41)

Mean population firing rates for the four secondary effects. Data is from both monkeys (n = 41). **(A)** Spatial decision. **(B)** Global Value. **(C)** Action Value. **(D)** Global Decision. Tick marks indicate 50 ms bins in which the difference between red and blue curves crossed an arbitrary statistical threshold (three-factor ANOVA, n = 41, α = 0.05). All other conventions the same as in Figure 27.

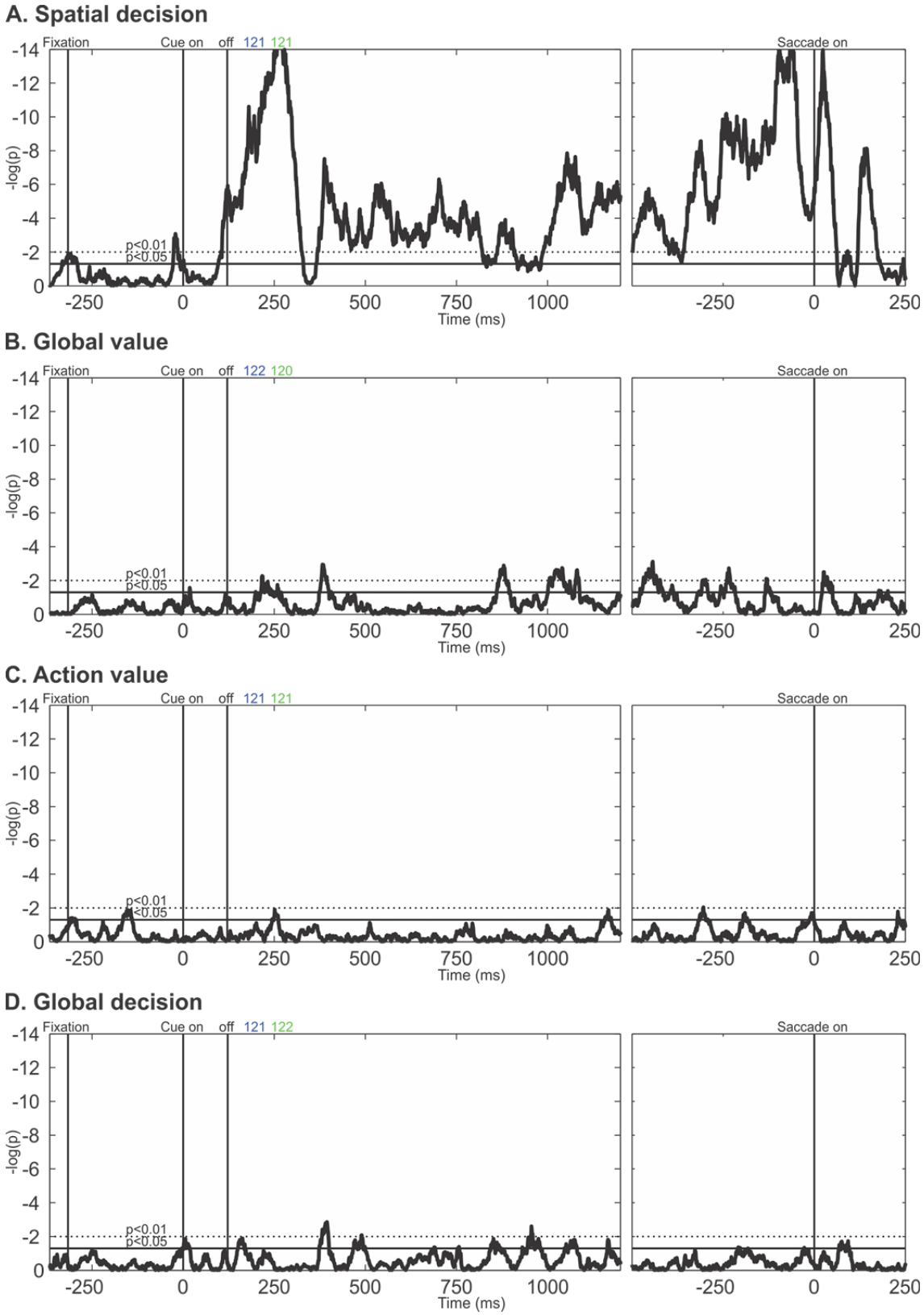


Figure 34. Secondary Effects –log(p) (n = 41)

Negative log of p values for the four secondary effects. Data is from both monkeys (n = 41). **(A)** Spatial decision. **(B)** Global Value. **(C)** Action Value. **(D)** Global Decision. P-values were calculated every 1 ms across a 50 ms sized bin using three-factor ANOVAs (α = 0.05). All other conventions the same as in Figure 27.

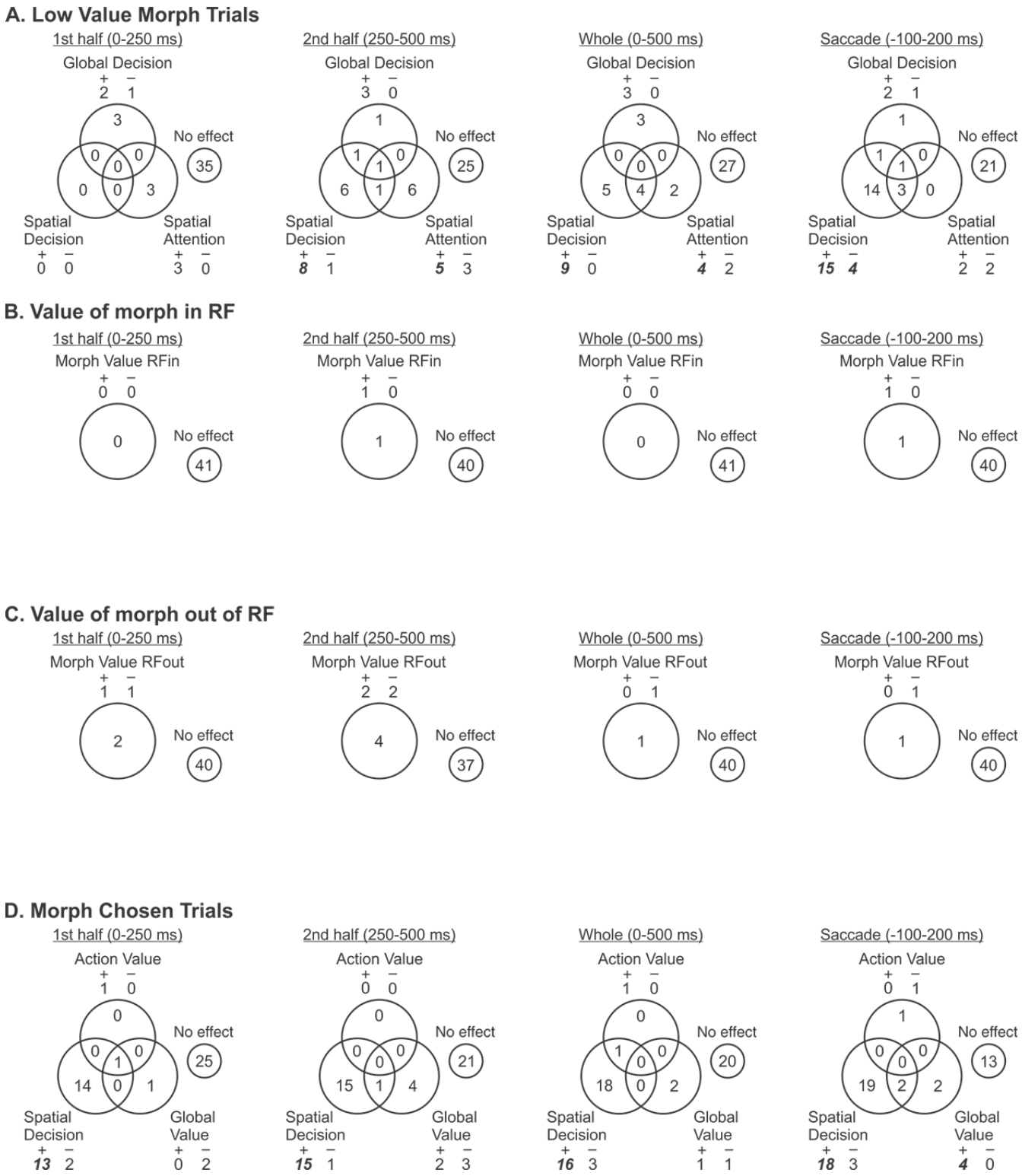


Figure 35. Single Neuron Effects (n = 41)

Individual neuronal effects for four analysis epochs. Data is from both monkeys (n = 41). **(A)** Counts of neurons exhibiting significant effects on bad morph trials for direction of spatial decision to saccade into or out of response field, spatial attention to morph location in or out of response field, and their non-spatial interaction (global decision to choose bad morph or reject it for safety (three-factor ANOVA, $\alpha = 0.05$). **(B)** Counts of neurons exhibiting significant effects of morph value in the response field (two-tailed paired t-test, $\alpha = 0.05$). **(C)** Counts of neurons exhibiting significant effects of morph value out of the response field (two-tailed paired t-test, $\alpha = 0.05$). **(D)** Counts of neurons exhibiting significant effects on morph chosen trials for direction of spatial decision to saccade to morph location into or out of response field, global value of morph chosen independent of spatial location, and their spatial interaction (action value), defined as value in > value out - value out > value in (three-factor ANOVA, $\alpha = 0.05$). In A-D, "+" and "–" counts indicate numbers of neurons firing more strongly for the larger (+) or smaller (–) predicted outcome; counts in italic boldface are significantly greater than expected by chance (χ^2 test, Yates correction, $\alpha = 0.05$).

Table 4. LIP Population-level Analysis Results: 4 Value Effects

Value of Morph in RF	1st	2nd	full	sac
Both (Ju & Eg):	+1 Hz (5 %)	+1 Hz (8 %)^	+1 Hz (6 %)*	+1 Hz (4 %)
Ju:	+2 Hz (11 %)^	+1 Hz (4 %)	+1 Hz (7 %)^	+1 Hz (4 %)
Eg:	-0 Hz (2 %)	+2 Hz (14 %)	+1 Hz (5 %)	+1 Hz (4 %)
Je:	-1 Hz (4 %)	+2 Hz (8 %)	+0 Hz (1 %)	+1 Hz (2 %)
Value of Morph out RF	1st	2nd	full	sac
Both (Ju & Eg):	+0 Hz (2 %)	+1 Hz (11 %)	+1 Hz (6 %)	+1 Hz (4 %)
Ju:	+0 Hz (2 %)	+0 Hz (3 %)	+0 Hz (2 %)	+1 Hz (9 %)
Eg:	-0 Hz (3 %)	+2 Hz (22 %)	+1 Hz (10 %)	-0 Hz (0 %)
Je:	-1 Hz (2 %)	-1 Hz (5 %)	-1 Hz (3%)	-1 Hz (2 %)
Global Value	1st	2nd	full	sac
Both (Ju & Eg):	+1 Hz (4 %)	+1 Hz (8 %)*	+1 Hz (6 %)*	+1 Hz (4 %)
Ju:	+1 Hz (7 %)	+0 Hz (4 %)	+1 Hz (5 %)	+1 Hz (6 %)
Eg:	+0 Hz (0 %)	+2 Hz (17 %)*	+1 Hz (7 %)*	+0 Hz (2 %)
Je:	-1 Hz (3 %)	+0 Hz (2 %)	+0 Hz (1 %)	+0 Hz (0 %)
Action Value	1st	2nd	full	sac
Both (Ju & Eg):	+0 Hz (2 %)	+0 Hz (1 %)	-0 Hz (1 %)	+0 Hz (1 %)
Ju:	+1 Hz (5 %)	+0 Hz (1 %)	+0 Hz (3 %)	-0 Hz (1 %)
Eg:	-0 Hz (2 %)	-0 Hz (0 %)	-0 Hz (1 %)	+0 Hz (3 %)
Je:	-0 Hz (1 %)	+2 Hz (6 %)*	+1 Hz (2 %)	+1 Hz (2 %)

Four effects, per epoch, per monkey. Sign and size of each effect given as raw firing rate difference in spikes/sec (Hz) and percentage firing rate change (%) due to effect, rounded to nearest integer. Effects significance were assessed with three-factor ANOVA or two-tailed paired t-test where appropriate. * = $p < 0.05$ and ^ = $p \leq 0.10$.

Table 5. LIP Population-level Analysis Results: 4 Non-Value Effects

Spatial Decision to Saccade	1st	2nd	full	sac
Both (Ju & Eg):	+1 Hz (5 %)	+5 Hz (55 %)*	+3 Hz (24 %)*	+7 Hz (65 %)*
Ju:	-0 Hz (0 %)	+6 Hz (56 %)*	+3 Hz (23 %)*	+9 Hz (81 %)*
Eg:	+1 Hz (10 %)^	+4 Hz (52 %)*	+3 Hz (26 %)*	+5 Hz (47 %)*
Je:	+2 Hz (6 %)*	+2 Hz (9 %)*	+2 Hz (8 %)*	+6 Hz (25 %)*
Spatial Attention to Morph	1st	2nd	full	sac
Both (Ju & Eg):	+2 Hz (17 %)*	-0 Hz (3 %)	+1 Hz (8 %)*	-0 Hz (2 %)
Ju:	+4 Hz (35 %)*	-0 Hz (3 %)	+2 Hz (15 %)*	-0 Hz (1 %)
Eg:	-0 Hz (1 %)	-0 Hz (2 %)	-0 Hz (2 %)	-1 Hz (4 %)
Je:	+4 Hz (18 %)*	+2 Hz (9 %)*	+3 Hz (14 %)*	-1 Hz (4 %)^
Spatial Decision	1st	2nd	full	sac
Both (Ju & Eg):	+3 Hz (24 %)*	+5 Hz (49 %)*	+4 Hz (34 %)*	+7 Hz (59 %)*
Ju:	+5 Hz (41 %)*	+5 Hz (53 %)*	+5 Hz (47 %)*	+9 Hz (73 %)*
Eg:	+1 Hz (7 %)^	+4 Hz (43 %)*	+2 Hz (21 %)*	+5 Hz (42 %)*
Je:	+6 Hz (24 %)*	+5 Hz (27 %)*	+5 Hz (25 %)*	+6 Hz (24 %)*
Global Decision	1st	2nd	full	sac
Both (Ju & Eg):	+0 Hz (0 %)	-0 Hz (2 %)	-0 Hz (0 %)	+1 Hz (7 %)^
Ju:	-1 Hz (4 %)	-0 Hz (4 %)	-1 Hz (4 %)	+1 Hz (6 %)
Eg:	+1 Hz (6 %)	+0 Hz (2 %)	+0 Hz (4 %)	+1 Hz (8 %)
Je:	+0 Hz (0 %)	-0 Hz (1 %)	-0 Hz (0 %)	-2 Hz (7 %)*

Four effects, per epoch, per monkey. Sign and size of each effect given as raw firing rate difference in spikes/sec (Hz) and percentage firing rate change (%) due to effect, rounded to nearest integer. Effects significance were assessed with three-factor ANOVA or two-tailed paired t-test where appropriate. * = $p < 0.05$ and ^ = $p \leq 0.10$.

Table 6. LIP Neuronal-level Analysis Results: 4 Value Effects

Value of Morph in RF	1st	2nd	full	sac
Both (Ju & Eg):	-	-	-	-
Ju:	-	-	-	-
Eg:	-	-	-	-
Je:	-	-	-	-
Value of Morph out RF	1st	2nd	full	sac
Both (Ju & Eg):	-	-	-	-
Ju:	-	-	-	-
Eg:	-	-	-	-
Je:	-	-	-	-
Global Value	1st	2nd	full	sac
Both (Ju & Eg):	-	-	-	4+
Ju:	-	-	-	-
Eg:	-	-	-	-
Je:	-	-	-	4-
Action Value	1st	2nd	full	sac
Both (Ju & Eg):	-	-	-	-
Ju:	-	-	-	-
Eg:	-	-	-	-
Je:	4-	-	-	-

Four effects, per epoch, per monkey. Counts of neurons with significant effects that were significantly more numerous than expected by chance alone, followed by sign of their effect. The - means the number of neurons observed with significant effects was no greater than chance expectation. Significant effects were assessed by either two-factor ANOVA or two-tailed paired t-test where appropriate. Significance of counts were assessed with chi-squared test with Yates-Correction.

Table 7. LIP Neuronal-level Analysis Results: 4 Non-Value Effects

Spatial Decision to Saccade	1st	2nd	full	sac
Both (Ju & Eg):	-	8+	9+	15+, 4-
Ju:	-	5+	5+	10+
Eg:	-	3+	4+	5+
Je:	4+	-	-	12+, 6-
Spatial Attention to Morph	1st	2nd	full	sac
Both (Ju & Eg):	-	5+	4+	-
Ju:	3+	-	-	-
Eg:	-	4+	3+	-
Je:	8+	4+	5+	-
Spatial Decision	1st	2nd	full	sac
Both (Ju & Eg):	13+	15+	16+	18+
Ju:	10+	9+	12+	11+
Eg:	3+	6+	4+	7+
Je:	7+	7+	9+	12+
Global Decision	1st	2nd	full	sac
Both (Ju & Eg):	-	-	-	-
Ju:	-	-	-	-
Eg:	-	-	-	-
Je:	-	-	-	-

Four effects, per epoch, per monkey. Counts of neurons with significant effects that were significantly more numerous than expected by chance alone, followed by sign of their effect. The - means the number of neurons observed with significant effects was no greater than chance expectation. Significant effects were assessed by either two-factor ANOVA or two-tailed paired t-test where appropriate. Significance of counts were assessed with chi-squared test with Yates-Correction.

(b) Individual Monkey Data

The main results from data combined from both monkeys are that our morphing manipulation all but eliminated early reward-effects in LIP during value-based decision-making at both the population-level and single-neuron level, while leaving spatial attention and saccadic decision signals intact. The neuron-level results in the data combined across two monkeys and in each individual monkey were reported above. Below we report each monkey's population-level results. We describe the four value effects followed by the four non-value effects.

Value of Morph in RF. Monkey 1 alone (Figure 36C) showed a trend toward significantly greater activity for the value of the morph in the RF early during the decision from 0 -250 ms ($p = 0.06$) and from 0 – 500 ms ($p = 0.06$). No other trends towards significance were present in each of the three monkeys, in each of the four epochs (Figures 36-38C).

Value of Morph out of RF. As with the data from the two monkeys combined, no individual monkey showed significant trends in any epoch (Figures 36-38D).

Global Value. This effect was significant in the second and full epochs in the data from both monkeys combined but reached significance in these two epochs in the individual data from Monkey 2 alone (Figure 43B). No other trends towards significance were present in each of the three monkeys, in each of the four epochs (Figures 42-44B).

Action Value. As with the data from the two monkeys combined, no individual monkey showed significant trends in any epoch, except for Monkey 3 in one epoch. The population of multi-units increased activity by 6% significantly during the second epoch for Monkey 3 (Figure 44C). No other trends towards significance were present in each of the three monkeys, in each of the four epochs (Figures. 42-44C).

Spatial Decision to Saccade. As with the data from the two monkeys combined, for all three monkeys individually, LIP significantly increased activity for saccadic decisions made into rather than out of the RF during the second, full, and saccade epochs (Figures 36-38A). Monkey 3 had a significant positive effect in the cue epoch (Figure 38A). Monkey 2 showed this trend ($p = 0.08$), but it did not reach significance (Figure 37A).

Spatial Attention. The effect of significantly increased firing rate during the first and full epochs for the morph located in rather than out of the RF was observed in the data combined across Monkey 1 and Monkey 2. However, this effect was driven by Monkey 1, who had significant effects in those two epochs (Figure 36B). Monkey 3 had significant effects in all three of the pre-saccade epochs (Figure 38B). Monkey 2 showed no significant population-level effect of attention in any epoch (Figure 37B).

Spatial Decision. This effect of increased activity before morph choices into rather than out of the RF was significant in all monkeys in all epochs, except for the first epoch where Monkey 2 showed a trend ($p = 0.06$) that did not attain significance (Figures. 42-44A).

Global Decision. This effect was not present in any epoch before the saccade epoch in the data from both monkeys combined or in any individual monkey (Figures. 42-44D).

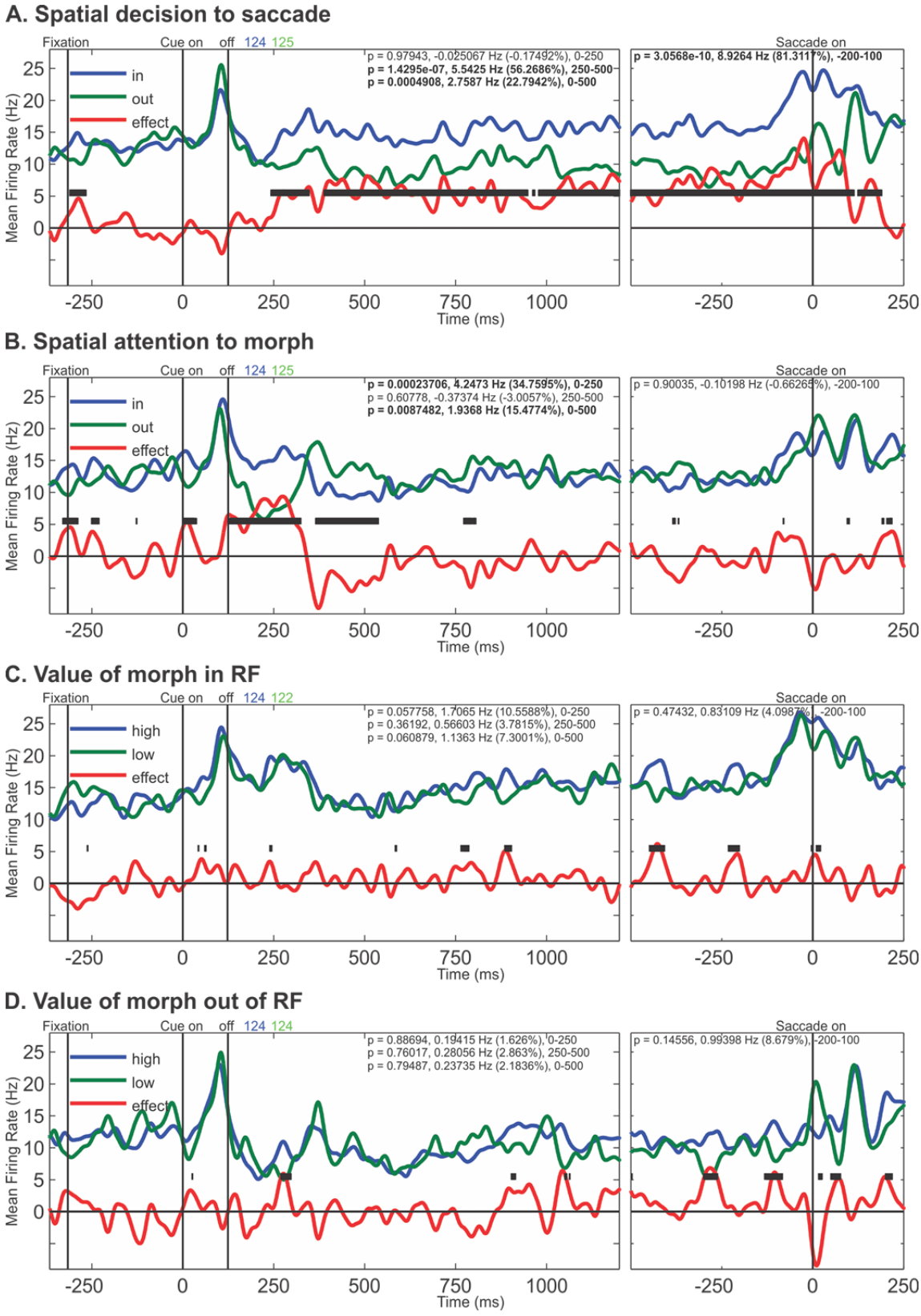


Figure 36. M1: Primary Effects PSTHs (n = 22)

Same conventions as Figure 31.

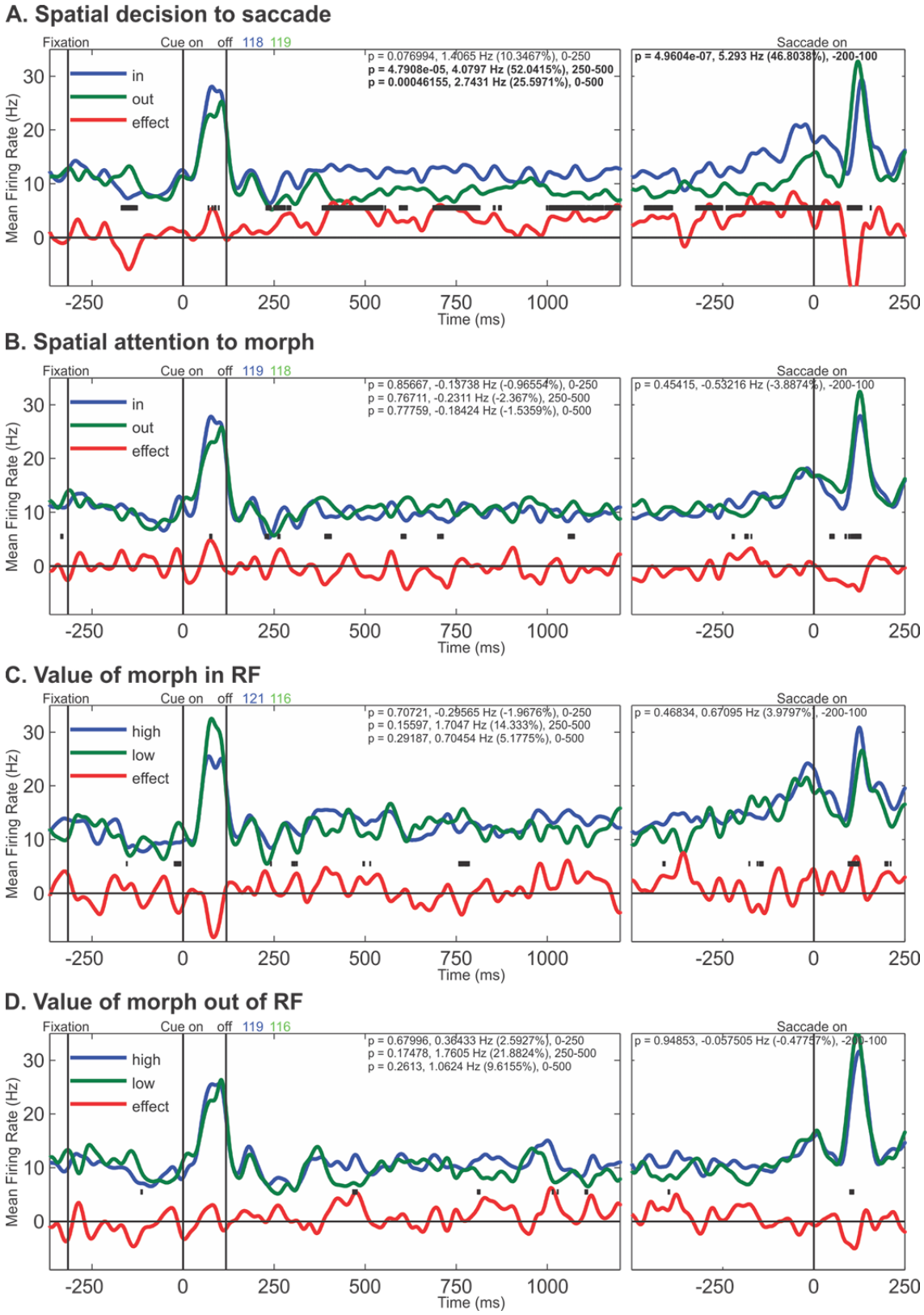


Figure 37. M2: Primary Effects PSTHs (n = 19)

Same conventions as Figure 31.

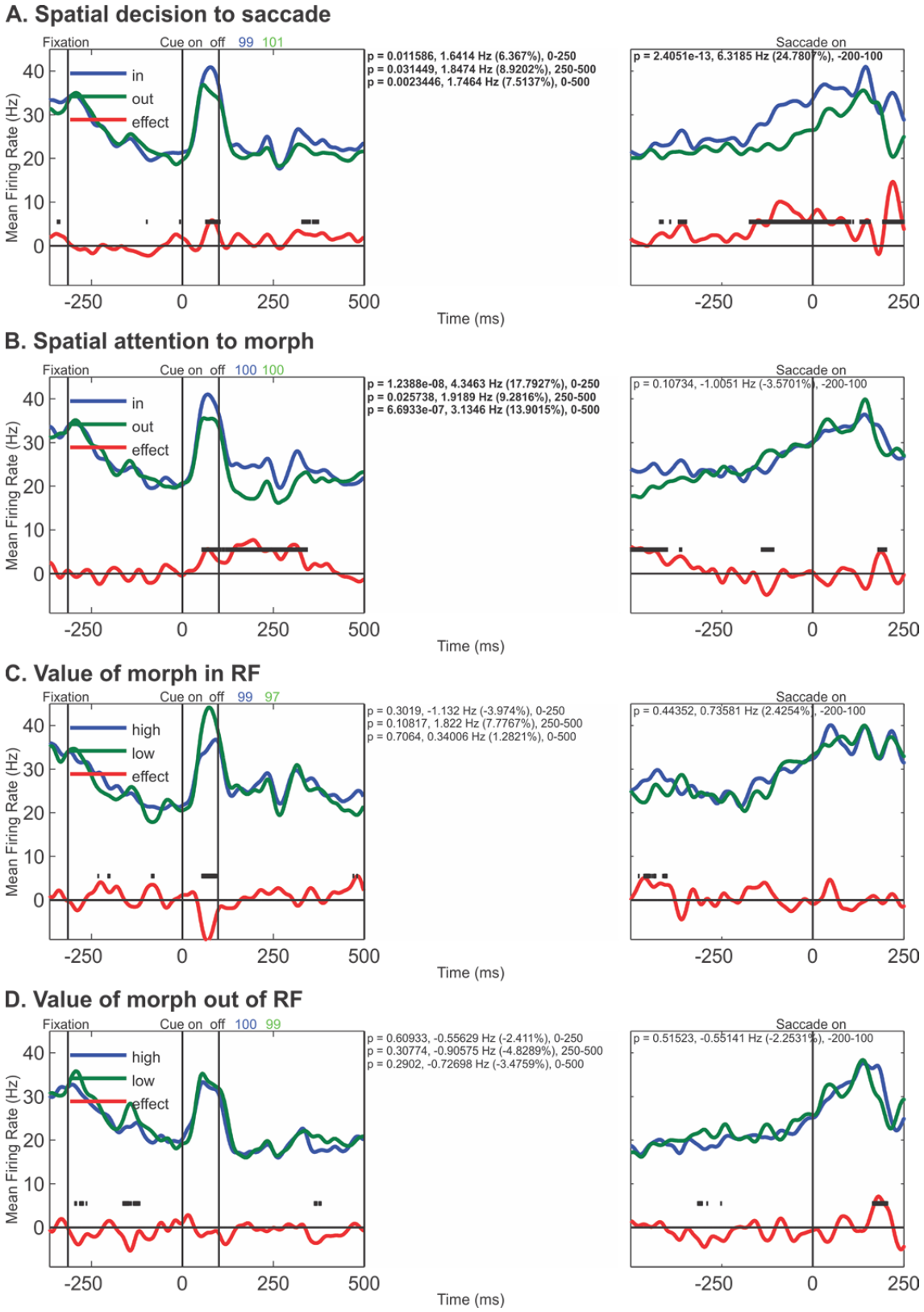


Figure 38. M3: Primary Effects PSTHs (n = 45)

Same conventions as Figure 31.

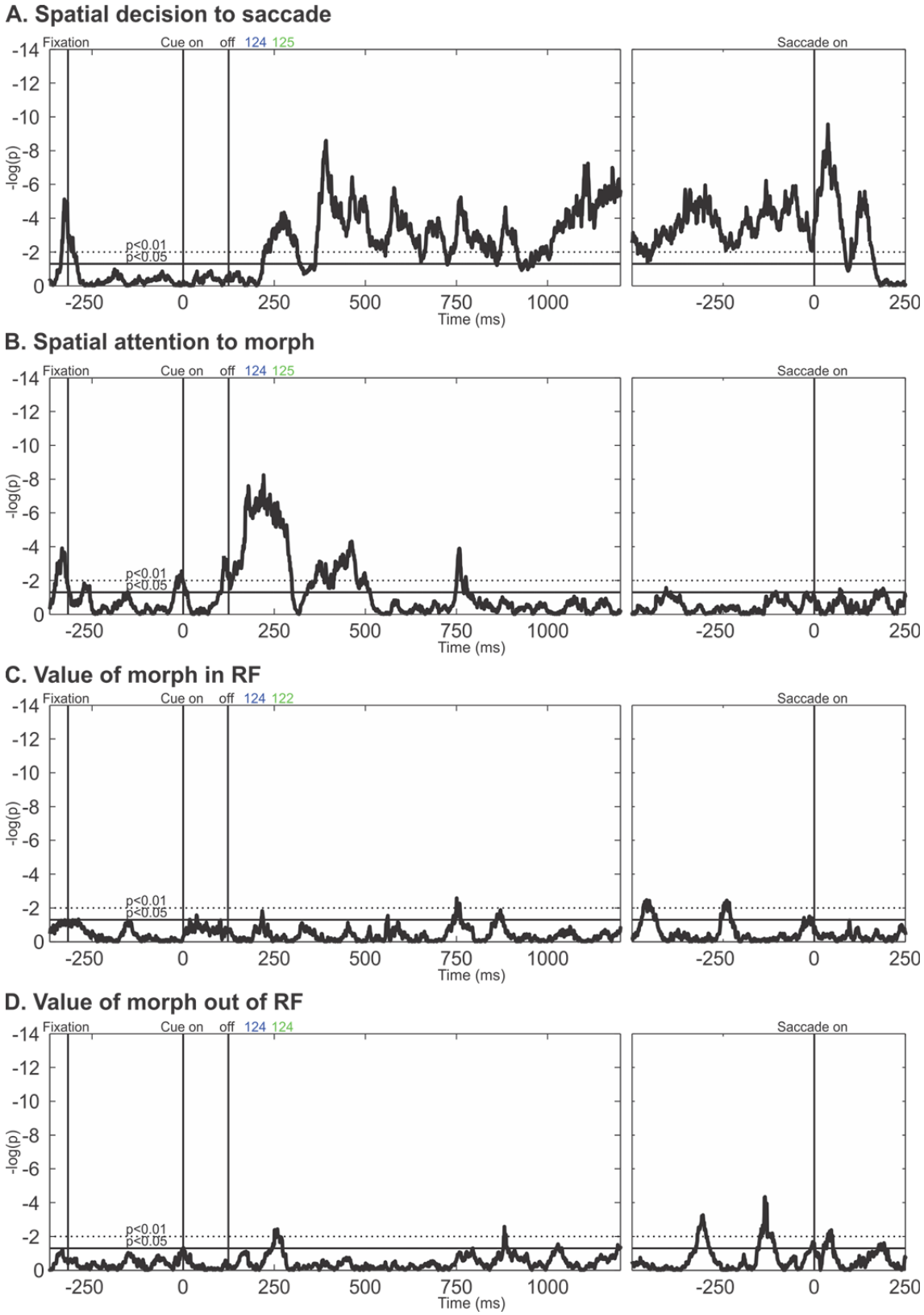


Figure 39. M1: Primary Effects –log(p) (n = 22)

Same conventions as Figure 32.

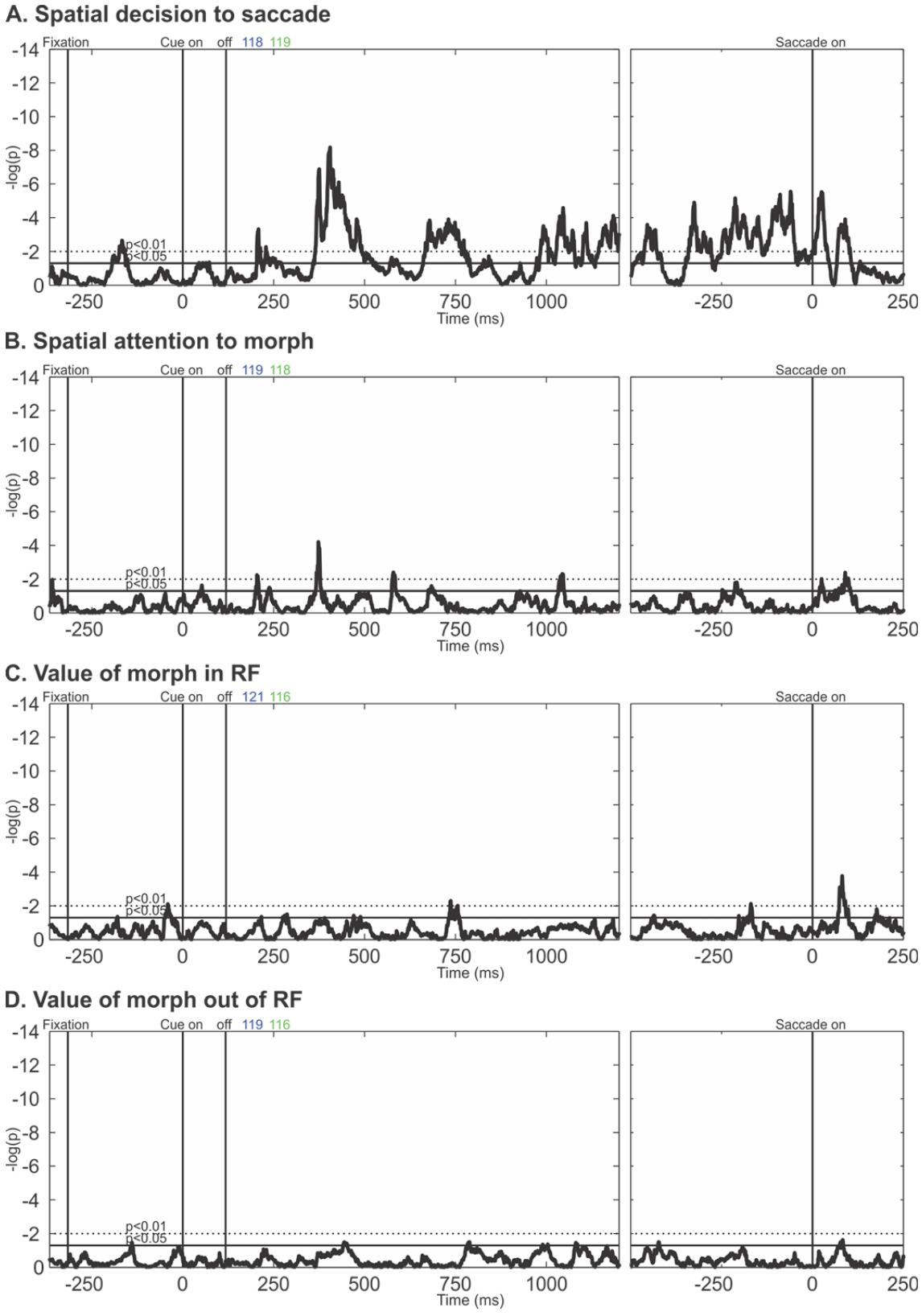


Figure 40. M2: Primary Effects –log(p) (n = 19)

Same conventions as Figure 32.

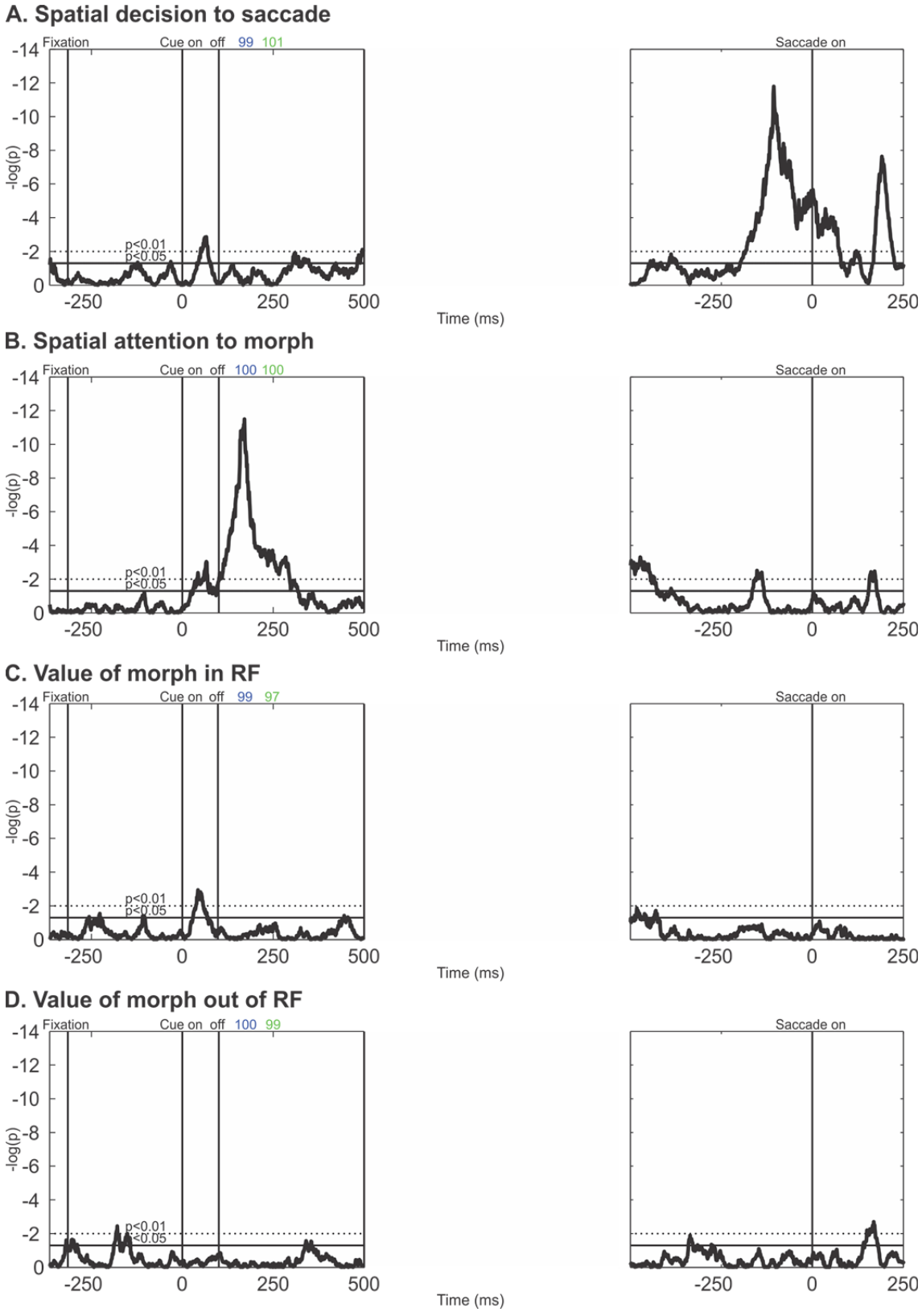


Figure 41. M3: Primary Effects –log(p) (n = 45)

Same conventions as Figure 32.

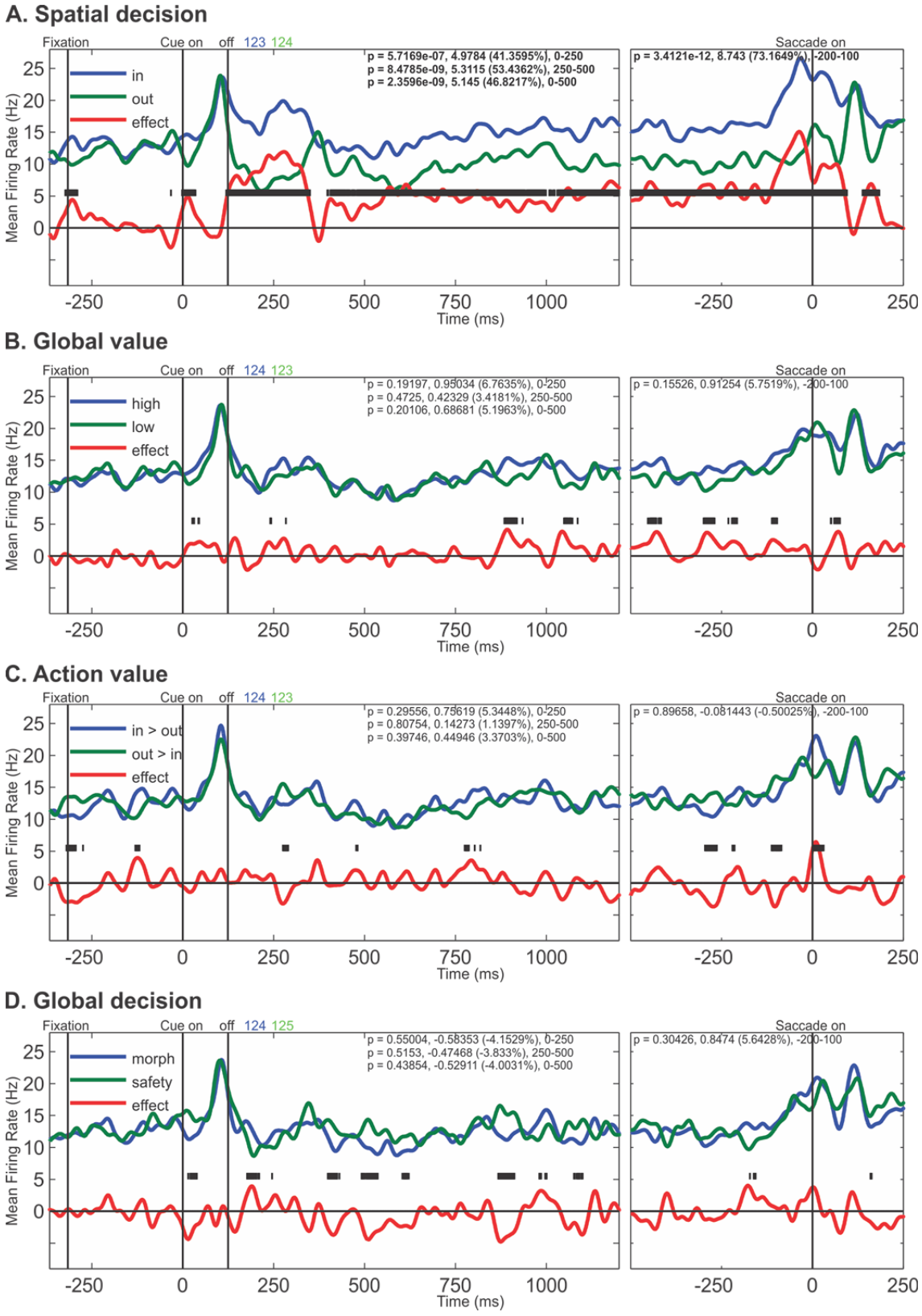


Figure 42. M1: Secondary Effects PSTHs (n = 22)

Same conventions as Figure 33.

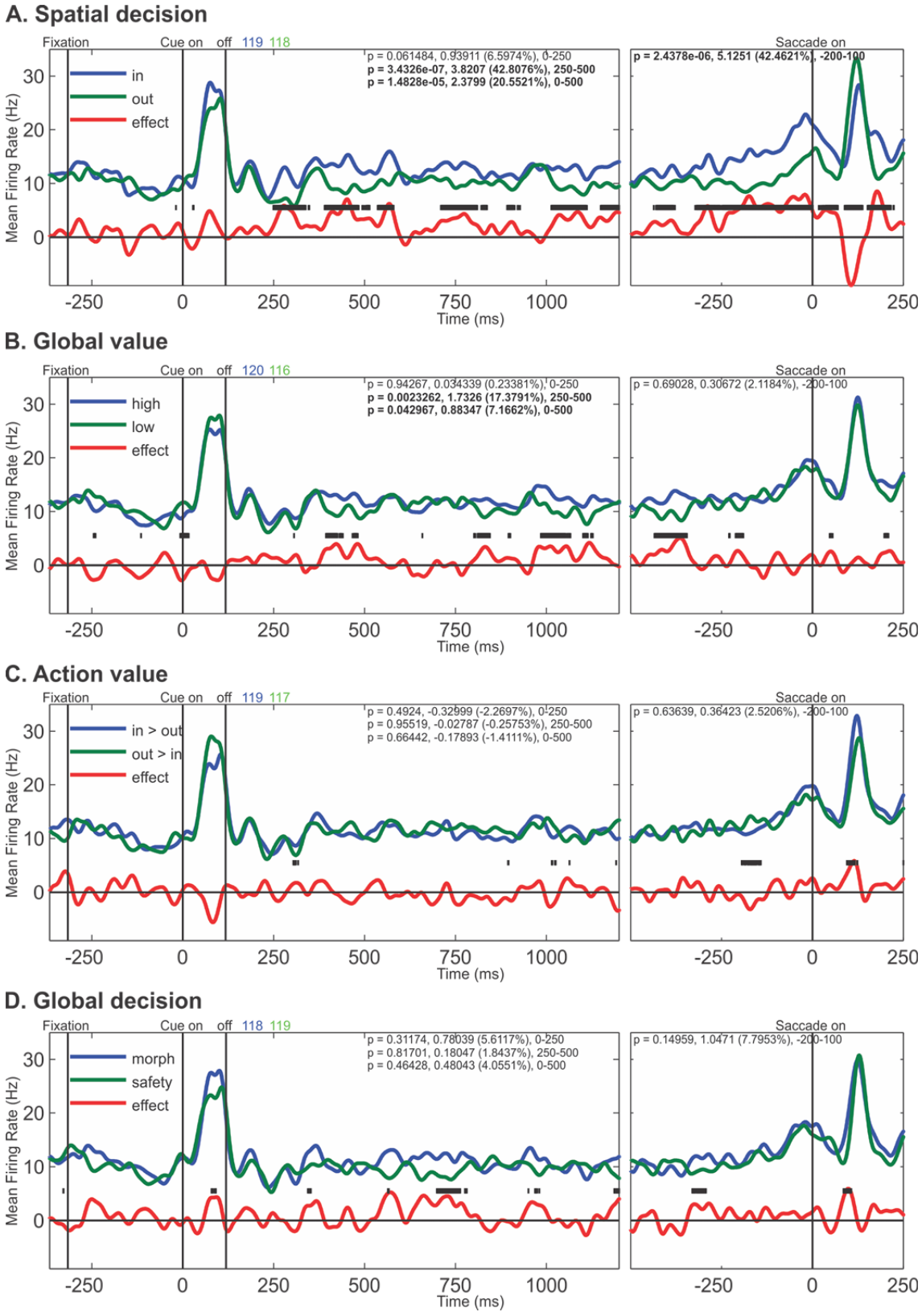


Figure 43. M2: Secondary Effects PSTHs (n = 19)

Same conventions as Figure 33.

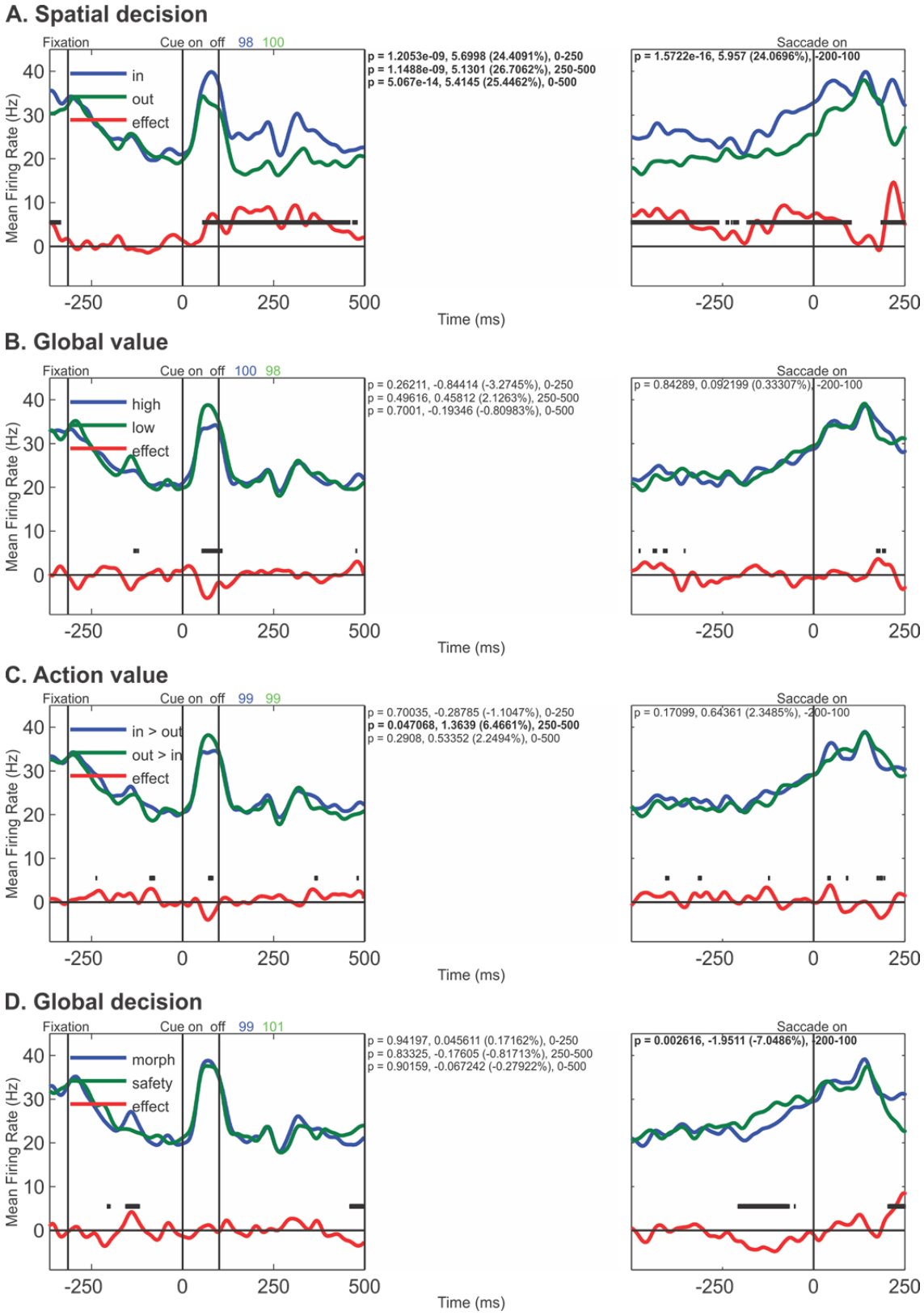


Figure 44. M3: Secondary Effects PSTHs (n = 45)

Same conventions as Figure 33.

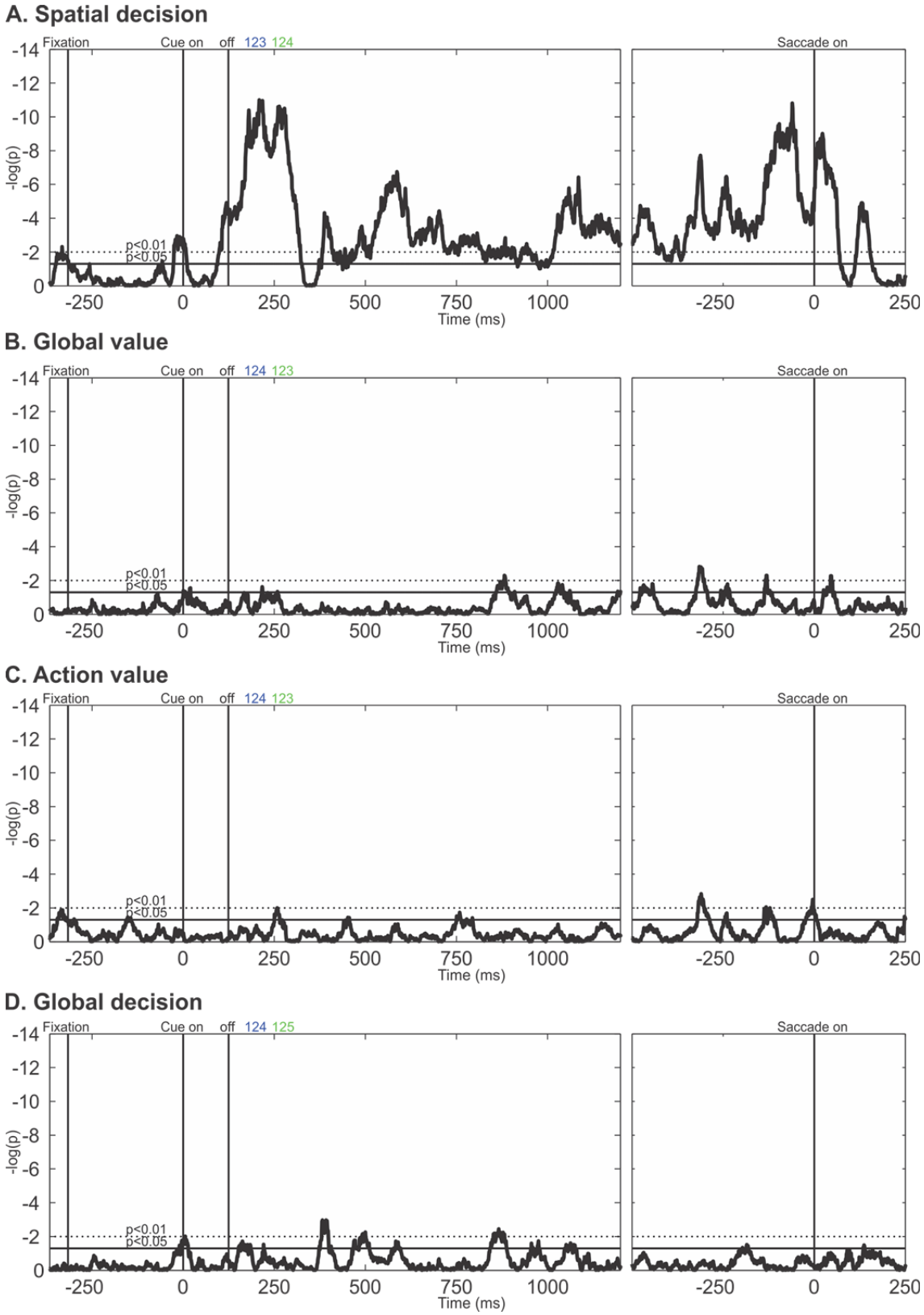


Figure 45. M1: Secondary Effects –log(p) (n = 22)

Same conventions as Figure 34.

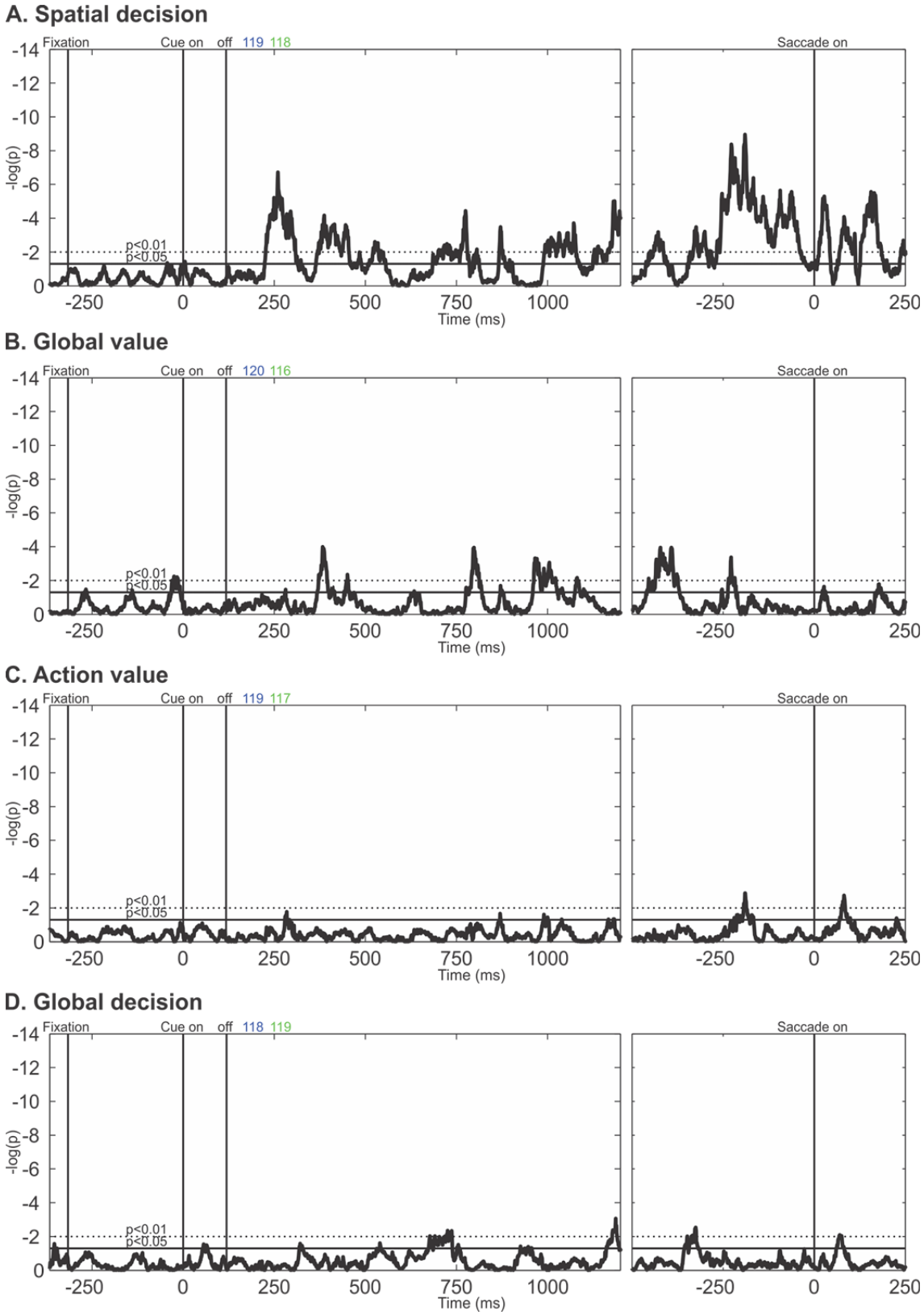


Figure 46. M2: Secondary Effects –log(p) (n = 19)

Same conventions as Figure 34.

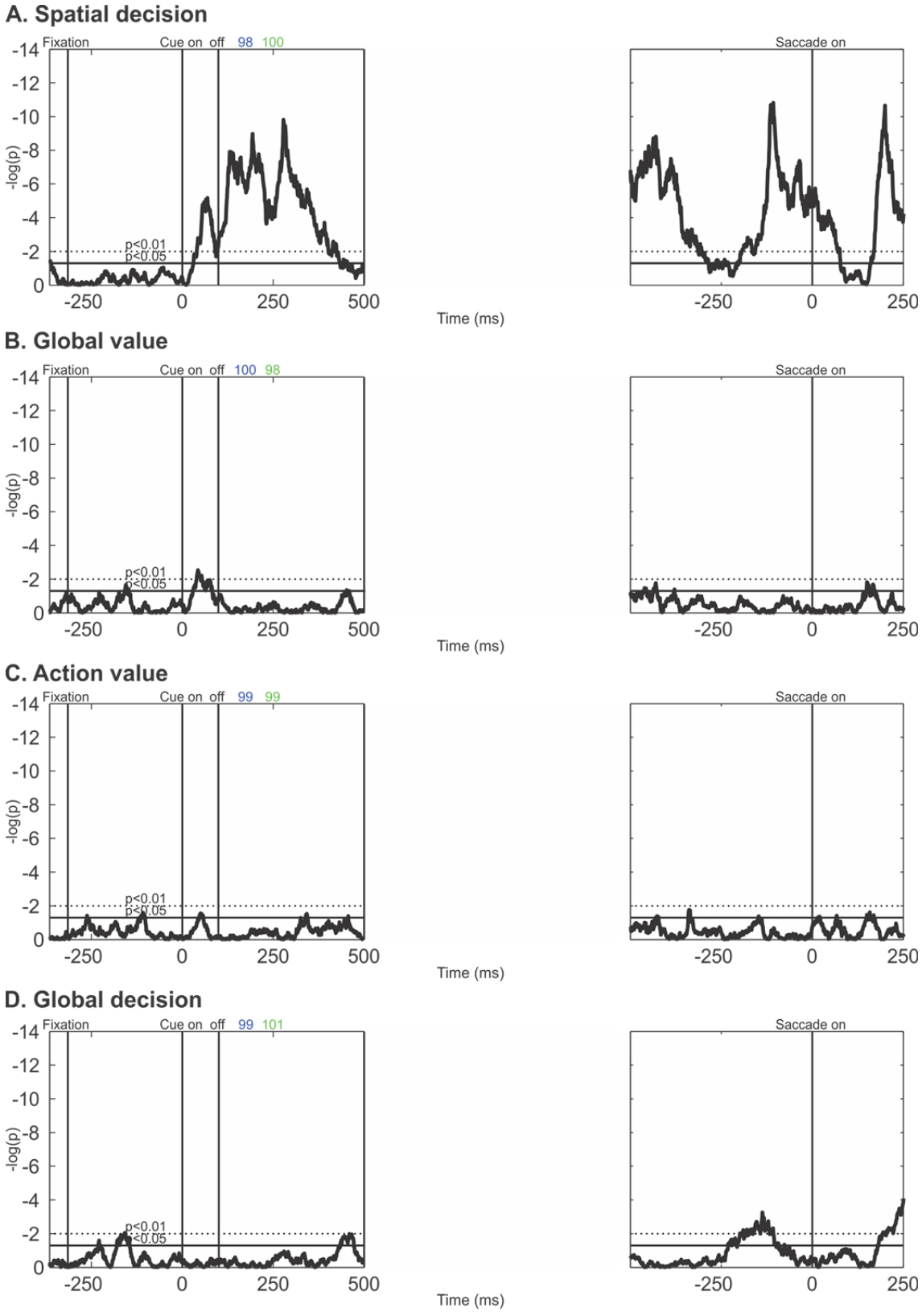


Figure 47. M3: Secondary Effects –log(p) (n = 45)

Same conventions as Figure 34.

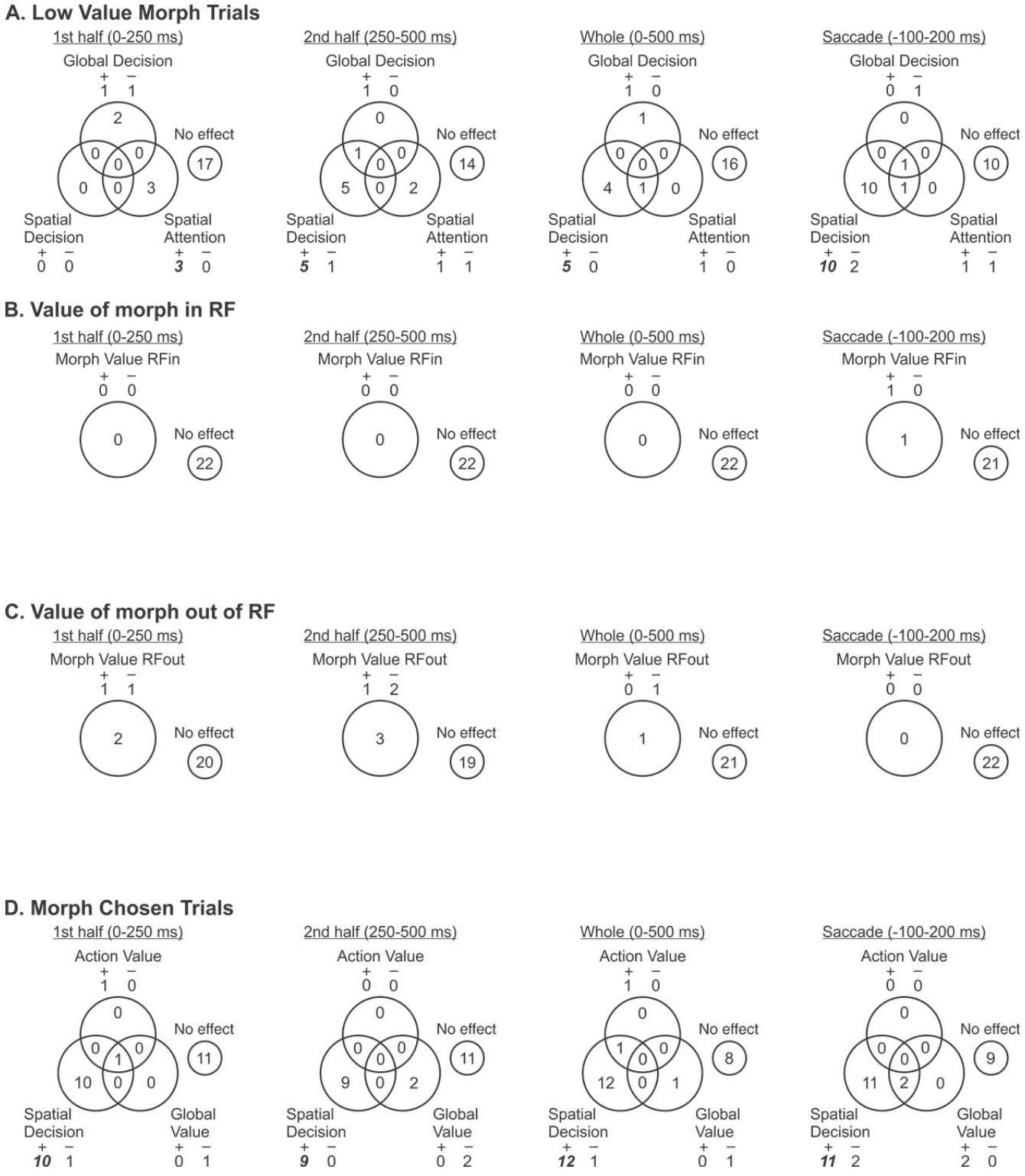


Figure 48. M1: Single Neuron Effects (n = 22)

Same conventions as Figure 35.

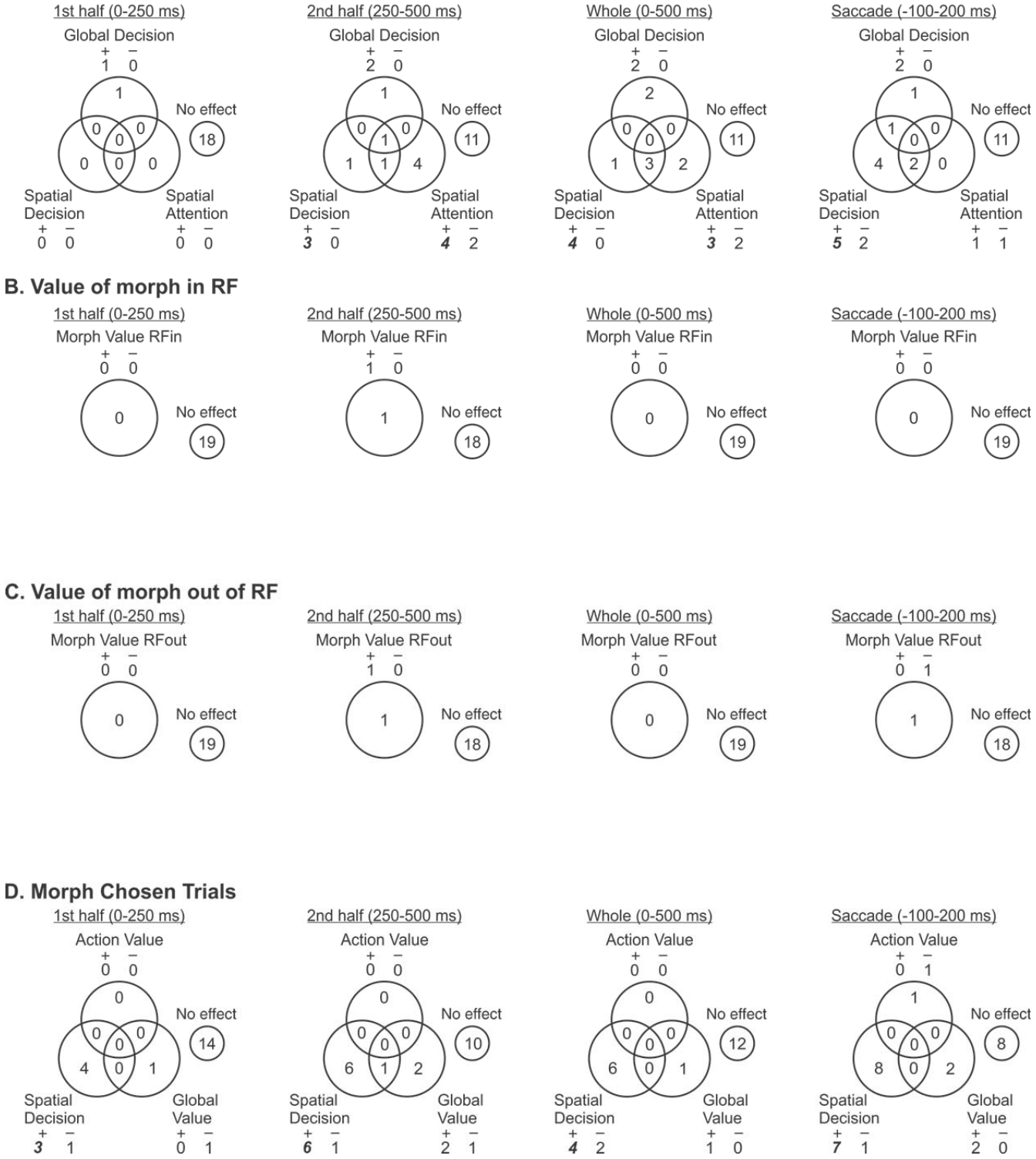


Figure 49. M2: Single Neuron Effects (n = 19)

Same conventions as Figure 35.

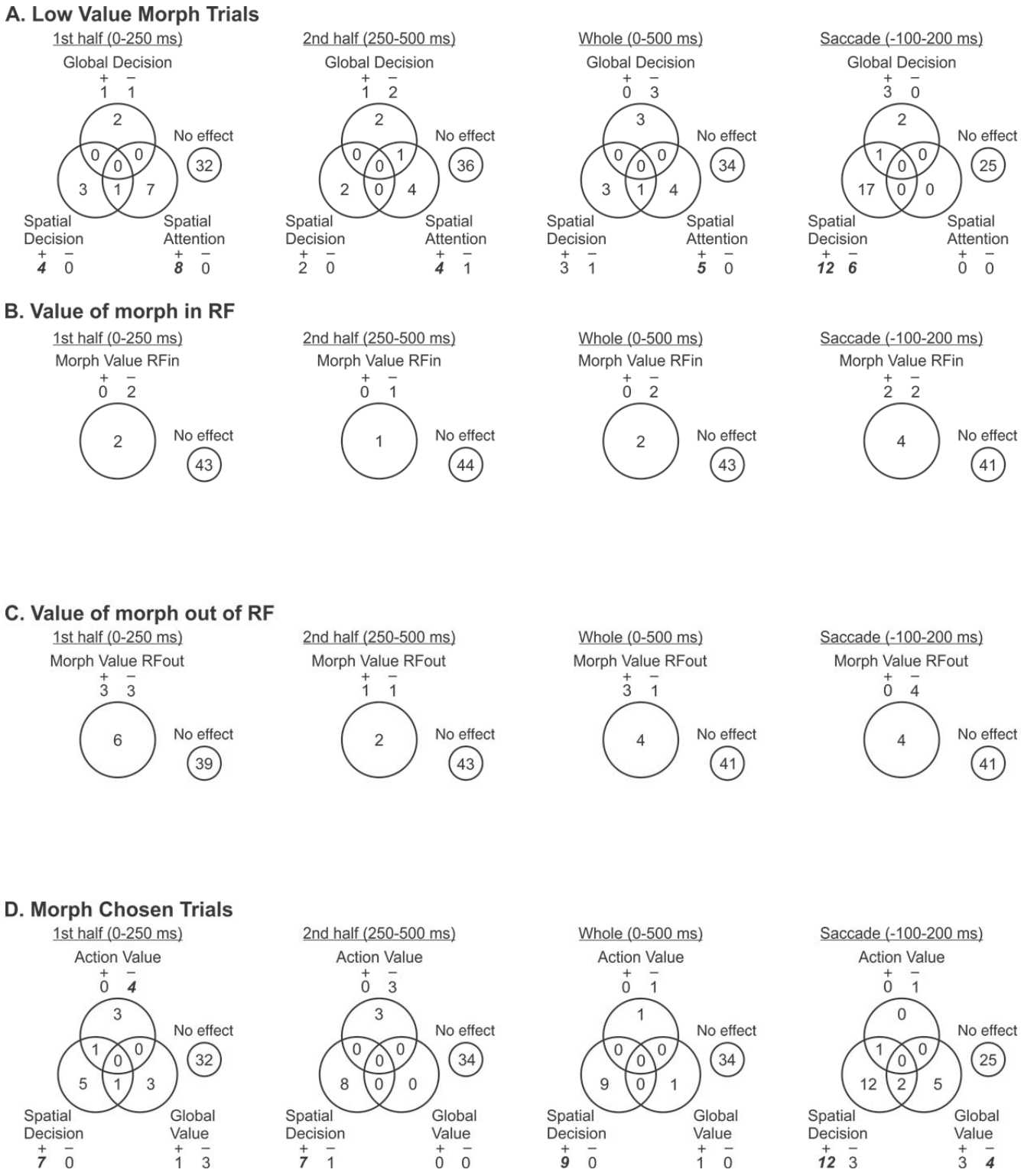


Figure 50. M3: Single Neuron Effects (n = 45)

Same conventions as Figure 35.

3.3 AMYGDALA

To determine whether or not early reward-effects in amygdala neurons depend on the ability of visually distinctive cues to acquire differential salience by virtue of their differential associated values, or instead signal cue-value, we employed a task using cues that could not acquire differential associative salience. On each trial, the monkey chose, with a delayed saccade, between a "safety" cue that guaranteed a small certain reward and a perceptually ambiguous cue that predicted either large reward or no reward (Figure 24A). The ambiguous cue was a morph that was a transparency of two parent images (Figure 24B). The "good" morph contained a slightly greater proportion of the parent image promising large reward. The "bad" morph contained a slightly greater proportion of the parent image promising no reward. (The physical identity of the "good" morph and "bad" morph were reversed between the two monkeys.) These morph-proportions were equal and opposite between the two morphs (Figure 24B) and held constant during each recording session. The discriminability of the morph was adjusted so that the monkey would choose the more valuable option ("good" morph over safety but safety over "bad" morph) on average 75% of the time during a session. The near-identical physical appearance of the morphs precluded stronger automatic capture of attention by the more valuable morph—not the monkeys' ability to make perceptual decisions based on morph-value. If early reward-effects in amygdala (Figure 14A) are actually value-representations instead of reflections of visual salience acquired by value-associated cues, then we predict that our manipulation would not eliminate the ability of amygdala neurons to signal value early during decision-making.

3.3.1 MATERIALS AND METHODS

All materials and methods used for amygdala recording sessions are identical to those used for LIP recording except for the subjects, recording sites, and selection of neurons while running the morph task not the memory-guided saccade task.

3.3.1.1 SUBJECTS

Two adult rhesus macaque monkeys participated in the experiments (monkey 1, female, laboratory designation Ju, and monkey 2, male, laboratory designation Je). All experimental procedures were approved by the Carnegie Mellon University Institutional Animal Care and Use Committee (IACUC) and the University of Pittsburgh IACUC, and were in compliance with the guidelines set forth in the United States Public Health Service Guide for the Care and Use of Laboratory Animals. In each monkey, a surgically implanted plastic cranial cap held a post for head restraint and a cylindrical recording chamber 2 cm in diameter oriented flush to the skull with its base centered at approximately over the amygdala. Electrodes could be advanced along tracks forming a square grid with 1 mm spacing. The chambers overlay the right hemisphere in monkey 1 and the left hemisphere in monkey 2.

3.3.1.2 MORPH TASK

This was the same as that used for LIP recording sessions.

3.3.1.3 RECORDING SITES

To determine the location of recording sites relative to gross morphological landmarks, we extrapolated from frontoparallel MR images containing the brain and fiducial markers placed at

known locations within the chamber. In Monkey 1 (Ju), recording sites extended 0 mm anterior, 1 mm posterior, 1 mm medial and 0 mm lateral relative to the central recording point whose coordinates were 16 mm anterior and 11 mm lateral in the Horsley-Clarke reference frame. In Monkey 2 (Je), recording sites extended 1 mm anterior, 0 mm posterior, 0 mm medial and 1 mm lateral relative to the central recording point whose coordinates were 16 mm anterior and 10 mm lateral in the Horsley-Clarke reference frame. We selected neurons, not by running the memory guided saccade task, but by having the monkey perform the morph task until neurons could be found. Then we restarted the task. We included in our data set any well-isolated amygdala neuron that could be held for the duration of the full morph task. Other factors of single electrode recording were the same for the amygdala recording sessions as those described for the LIP recording sessions.

3.3.1.4 ANALYSIS OF BEHAVIOR

These were the same as those performed on data from LIP recording sessions.

3.3.1.5 ANALYSIS OF NEURONS

These were the same as those performed on data from LIP recording sessions.

3.3.2 RESULTS

3.3.2.1 BEHAVIOR

As during LIP recording sessions, when confronted with two offers of different value (morph vs. safety) during amygdala recording, the monkeys consistently chose the better offer. This was true in the data combined from both monkeys and for each monkey individually.

(a) Data Combined from Both Monkeys

Behavioral data from Monkey 1 (Ju) and Monkey 2 (Je) were combined. All amygdala single-units were recorded from these two monkeys.

(i) Morph Value Effects

During the 45 amygdala-recording sessions combined across both monkeys (14 from M1; 31 from M2), the monkeys chose the better offer (the good morph over safety but safety over the bad morph) for 75.7 % of all choices, on average. We computed the impact of predicted morph-value on behavior of with three measures: percent better chosen, fixation break rate and reaction time (Figure 51A-C).

Percent better chosen. A significantly greater percentage (51 %) of good than bad morph choices were made (Figure 51A Top). Thus, the monkeys could perceive the difference between the two morphs and made their decisions based on morph-value.

Fixation-break rate. A significantly greater percentage (7 %) of trials were aborted after the bad morph rather than the good morph was offered (Figure 51B Top). Thus, the monkeys' willingness to make the decision reflected the value of the morph offered.

Reaction time. Reaction times were significantly shorter (11 ms) for choices made to good rather than bad morph targets (Figure 51C Top). Thus, morph-value motivated saccadic reaction time: as value increased, reaction time decreased.

(ii) Reaction Time: Morph Chosen v. Rejected

Reaction times were significantly slower (36 ms) when choosing to reject rather than accepting the morph target (Figure 51E Top). Thus, the monkeys allocated attention to the morph cue

location. When they decided to reject the morph at that location, this slowed their saccadic reaction time to the safety target in the opposite hemifield.

(iii) Morph Duration Effects on Choice

The proportion of choices to accept rather than reject the bad morph did not vary significantly as a function of the duration of time the cues were displayed (Figure 51D Top). Thus, perceptual difficulty did not vary as a function of cue duration, which varied according to the stair-casing procedure used to hold the monkeys' correct performance ("percent better chosen") around 75%.

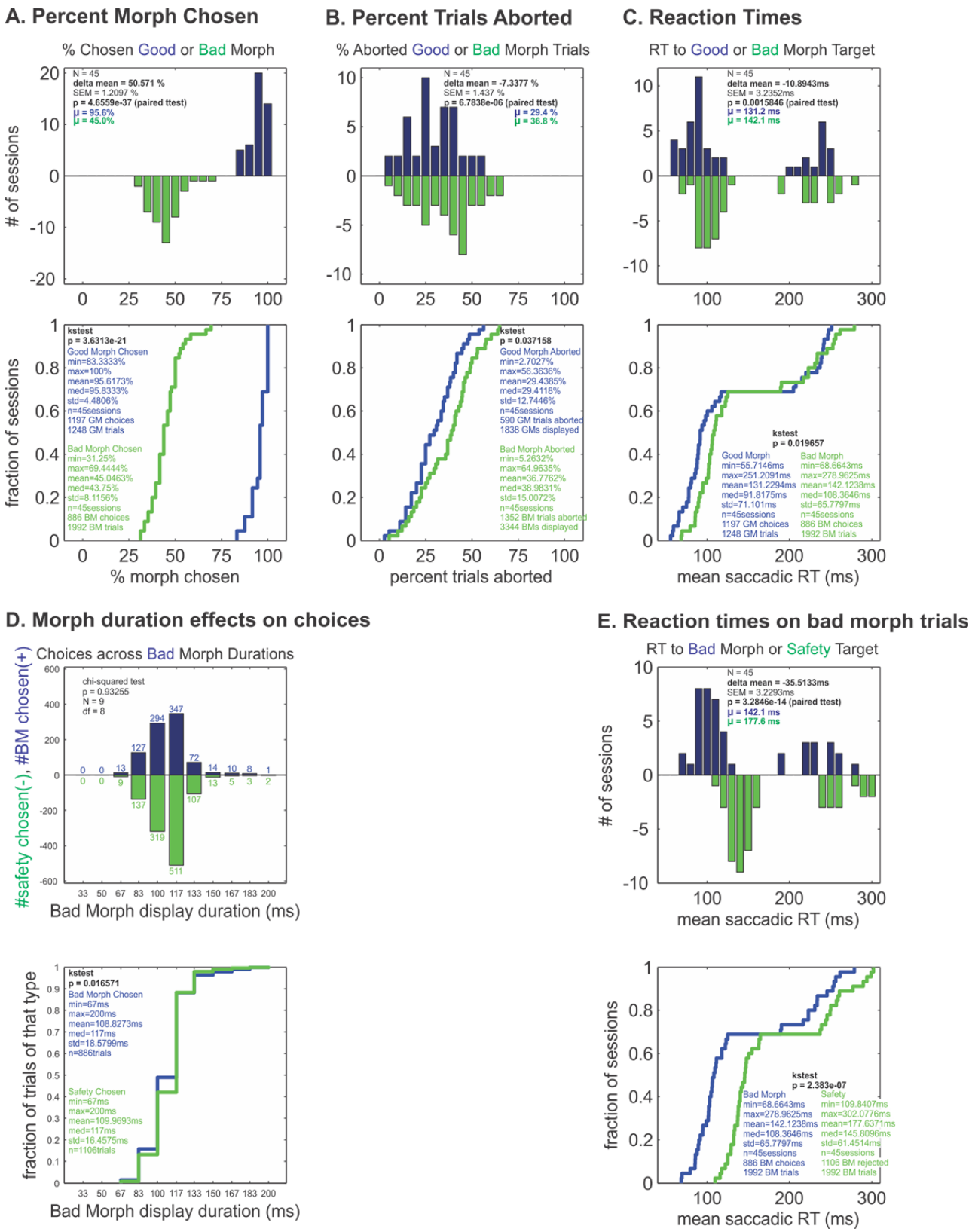


Figure 51. Behavior: Amygdala Sessions (n = 45)

Same conventions as Figure 27.

(b) Individual Monkey Data

(i) Morph Value Effects

The fraction of choices made for the better offer was 73.0 % for Monkey 1 (14 sessions) and 76.3% for Monkey 2 (31 sessions). We computed the impact of predicted morph-value on behavior of with three measures: percent better chosen, fixation break rate and reaction time (Figures 52-53A-C Top).

Percent better chosen. Each monkey made a significantly higher percentage (M1: 46 % and M2: 53 %) of good-morph rather than bad-morph choices (Figures 52- 53A Top). Thus, each individual monkey perceived the difference between the two morphs and decided based on morph-value.

Fixation-break rate. Each monkey aborted a significantly higher percentage of trials (M1: 5 % and M2: 9 %) that offered the bad morph rather than the good morph (Figures 52-53B Top). Thus, each individual monkey's willingness to perform the task increased significantly with morph-value.

Reaction time. This measure was inconsistent between the two monkeys (Figures 52-53C Top). Monkey 2 made significantly shorter latency saccades to good rather than bad morph targets (15 ms), but Monkey 1 did not. Thus, morph-value motivated faster saccadic reaction times for Monkey 1 but not for Monkey 2.

(ii) Reaction Time: Morph Chosen v. Rejected

Each monkey's reaction times were significantly slower (M1: 30 ms and M2: 38 ms) when rejecting versus accepting the morph (Figures 52-53E Top). Thus, each monkeys allocated

attention to the morph cue location, which significantly slowed their reaction time when rejecting morph for safety.

(iii) Morph Duration Effects on Choice

For each monkey, the proportion of choices for accepting versus rejecting the bad morph did not vary significantly as a function of the duration of time the cues were displayed (Figures 52-53D Top). Thus, for each monkey individually, perceptual difficulty did not vary, on average, as a function of cue duration.

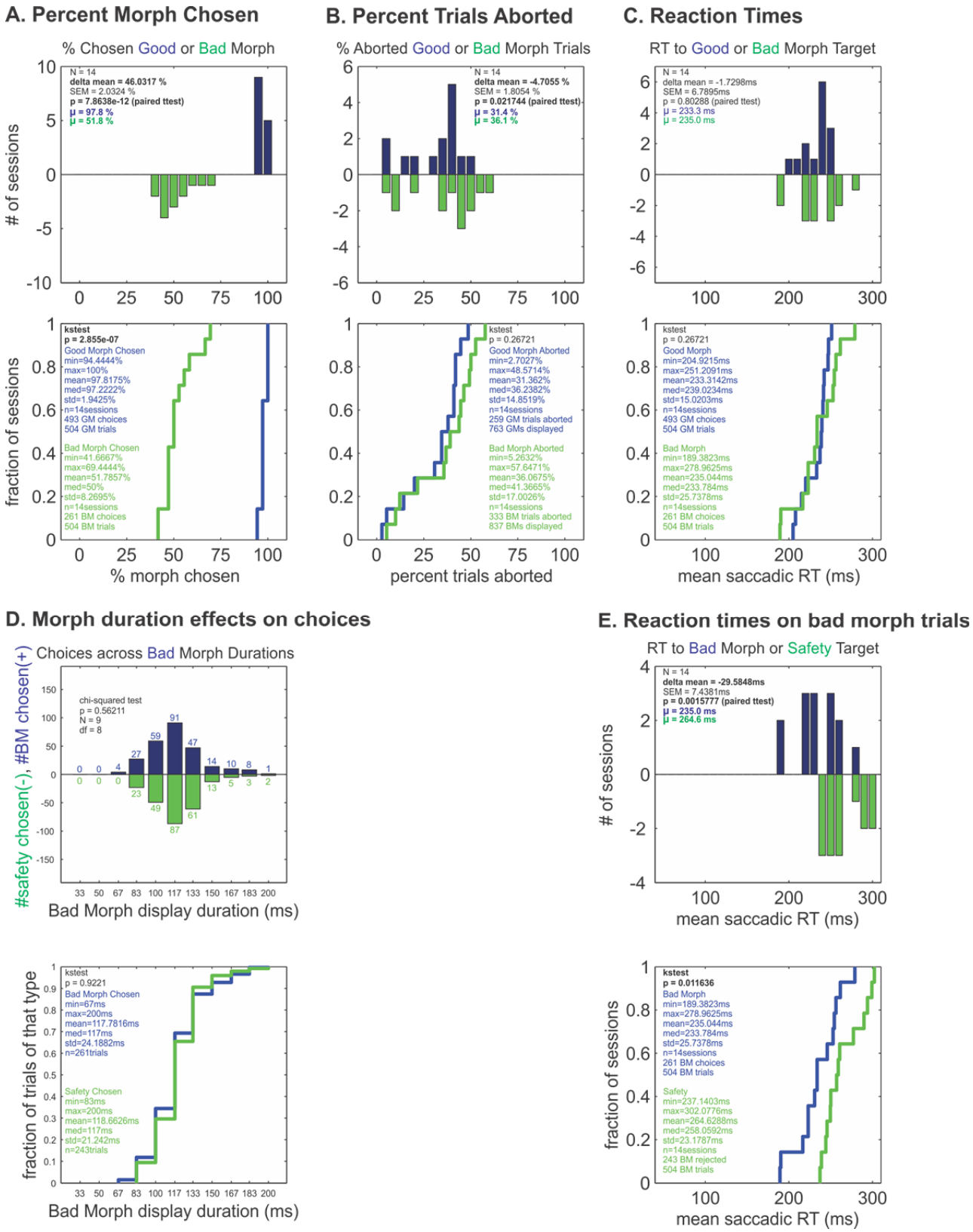


Figure 52. M1: Behavior (n = 14)

Same conventions as Figure 27.

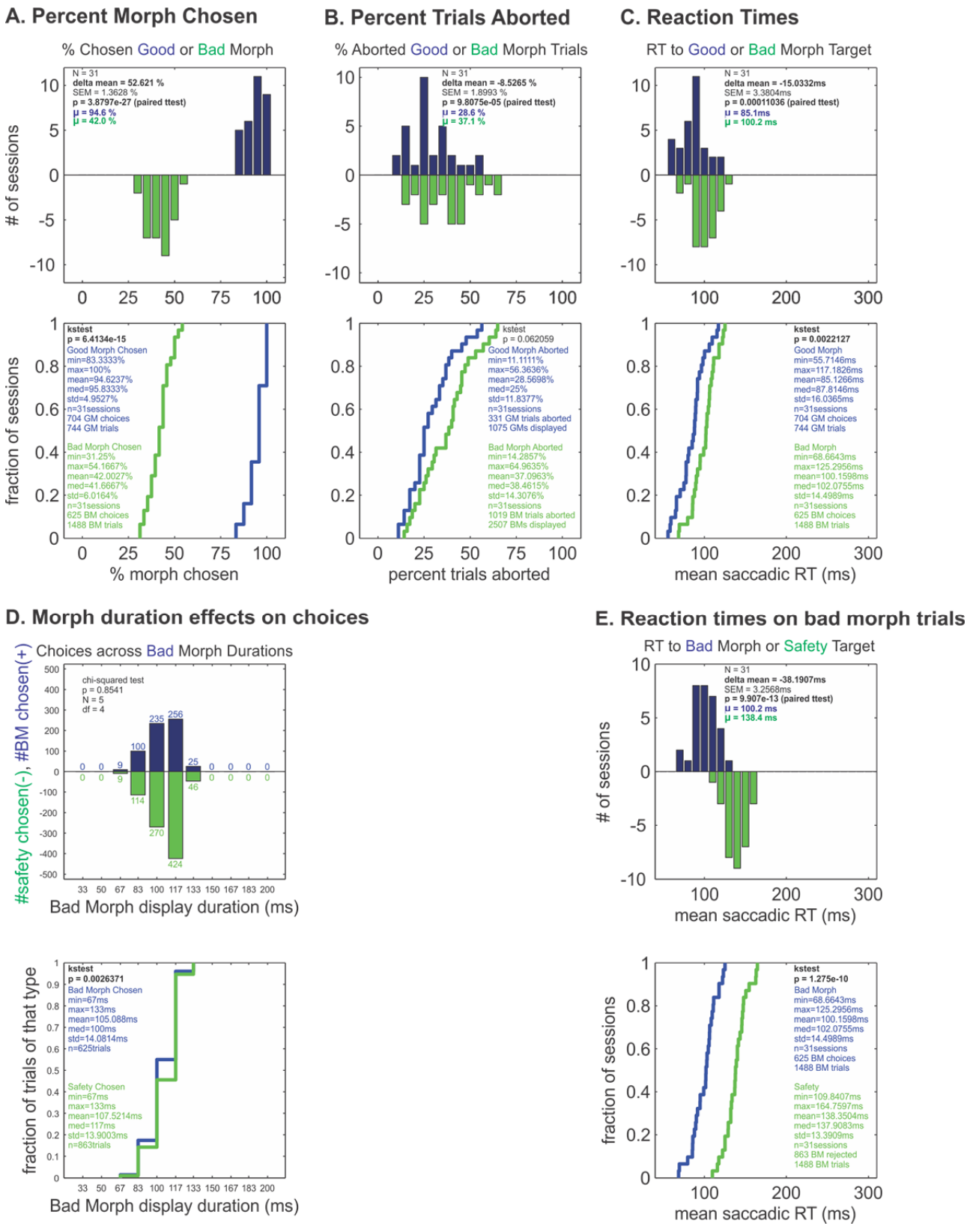


Figure 53. M2: Behavior (n = 31)

Same conventions as Figure 27.

3.3.2.2 NEURONS

(a) Data Combined from Both Monkeys

Single-unit amygdala data from Monkey 1 (Ju) and Monkey 2 (Je) were combined. Population-level results for the four value-effects and the four non-value effects are presented in Tables 8 and 9, respectively. Neuron-level results for the four value-effects and the four non-value effects are presented in Tables 10 and 11, respectively.

As we did for LIP, we first tested the amygdala population activity for four primary effects of interest: "Spatial Decision to Saccade," "Spatial Attention to Morph," "Value of Morph in RF," and "Value of Morph out of RF." We first examined trials in which the monkey chose or rejected the bad morph to test for independent effects of the saccadic decision (Figure 25A) and allocation of attention to the morph (Figure 25B). As in LIP, population activity during the interval 0 – 250 ms following cue onset was not significantly different for decisions made into rather than out of the RF, increasing by only 3 % (Figure 54A). However, a trend was present ($p < 0.10$). As in LIP, amygdala began encoding the decision around 200 ms (Figure 54A, black tick-marks, rising red line). Population activity was significantly increased for saccadic decisions planned into the response field by 9 % during the delay period (250 – 500 ms, the longest delay encountered by all monkeys in these experiments), by 6 % when averaged across cue and delay periods (0 – 500 ms) but not around the time of saccade execution (200 ms pre-saccade to 100 ms post-saccade). As in LIP, the strength of significance of this decision signal first crossed statistical threshold around 200 ms (Figure 55A). Unlike LIP, the decision signal was not persistent (Figure 54A) nor was the strength of its significance (Figure 55A). Thus, unlike LIP, amygdala encoded the decision weakly and transiently after cue offset.

Like LIP, the amygdala population significantly encoded the allocation of spatial attention in the earliest analysis window (Figure 54B). Population activity during the interval 0 – 250 ms increased by 20 % when the morph was located outside rather than inside the RF. As in LIP, the attention signal began to wane with the emergence of the decision signal and then disappeared around 500 ms (Figure 54B). Unlike LIP, the attention signal in the amygdala did not change signs mid-way through the delay period (Figure 54B). The strength of significance of the amygdala's attention signal crossed statistical threshold around 50 ms, about twice as fast as LIP's (Figure 55B, rising black line). Thus, like LIP, the amygdala population encoded the allocation of spatial attention to the morph's location robustly, early during decision-making.

The above results established that our morphing manipulation left intact the ability of the amygdala population to encode pre-decision and post-decision spatial signals: the allocation of spatial attention to the morph and the spatial decision to saccade. Would amygdala likewise encode morph-value spatially early during the decision process? We therefore examined trials in which the monkey chose the good or bad morph inside or outside of the RF (Figure 54C-D). For choices into the RF, unlike LIP, the amygdala population activity increased significantly with morph-value by 21% early during the decision (0 – 250 ms), by 28% during the delay period, and by 24 % when averaged across both periods (Figure 54C). The strength of this effect's significance first crossed statistical threshold around 100 ms, about twice as fast as LIP, and persisted until about 400 ms, unlike LIP (Figure 55C). Thus, the amygdala—but not LIP—significantly encoded the value of the morph located in the RF early during decision-making and did so strongly. This result supports our hypothesis that early reward-effects in amygdala are value signals.

For choices out of the RF, unlike LIP, the amygdala's population activity strongly and significantly increased by 16 % with morph-value in the second epoch (Figure 54D). Unlike amygdala's signal for morph-value located in the RF, which appeared around 100 ms (Figure 54C, black tick marks, rising red line), firing rate increased with the value of the morph located out of the RF at a later time, around 250 ms after cue onset (Figure 54D, black tick marks, rising red line). Likewise, unlike the effect of morph-value inside the RF (Figure 54C), the effect of morph-value outside the RF crossed statistical threshold later, around 250 ms (Figure 54D), and was more phasic. Its strength of significance quickly returned below statistical threshold for most of the rest of the trial (Figure 55D). Thus, unlike LIP, the amygdala significantly encoded the value of the morph located out the RF during decision-making but did so about 150 ms after signaling morph-value in the RF. This result supports our hypothesis that early reward-effects in amygdala are value signals. However, ipsilateral reward-effects in the amygdala may occur too late to be used for decision-making.

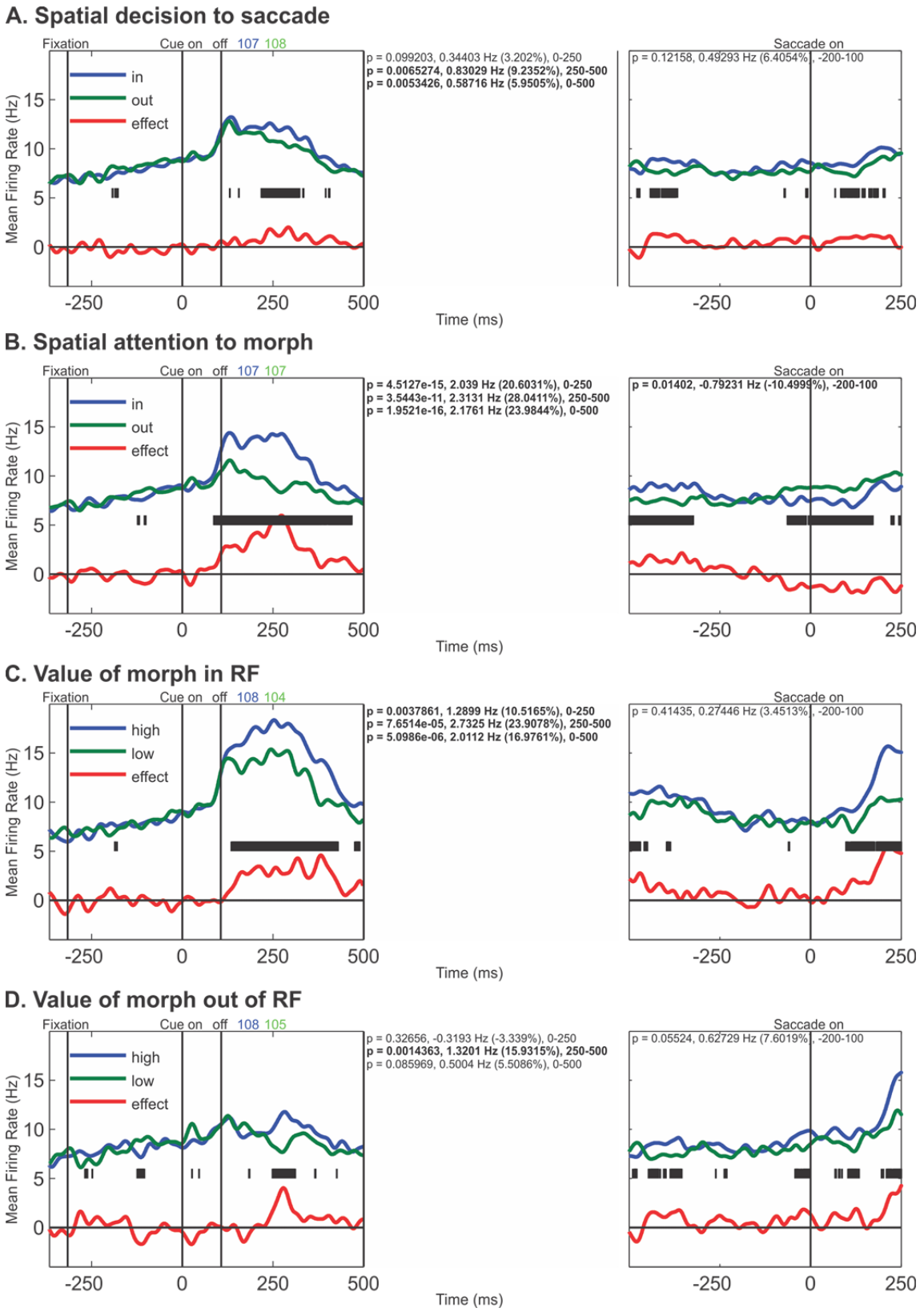


Figure 54. Primary Effects PSTHs (n = 73)

Same conventions as Figure 31.

As we did for LIP, we tested the amygdala population activity for four other effects: "Spatial Decision," "Global Value," "Action Value," and "Global Decision." We first examined trials in which the monkey chose the morph target to test for independent effects of the spatial decision (Figure 26A), global value (Figure 26B), and the interaction effect of action-value (Figure 26C). As in LIP, amygdala population activity encoded "Spatial Decision," in which attention to the morph location corresponded to the saccade direction being chosen. Like LIP, amygdala activity increased significantly when spatial attention and the saccadic decision were both directed into rather than out of the RF by 32 % in the earliest epoch (0 – 250), 43 % in the delay epoch (250 – 500) and 38 % in the full epoch (Figure 56A). Thus, as with LIP so with amygdala: when the location of spatial attention and the direction of the chosen saccade correspond, the spatial decision signal emerges earlier (Figure 56A, black tick-marks, rising red line). The strength of significance of the decision signal in the amygdala first crossed statistical threshold around 50 ms, about twice as fast as in LIP (Figure 57A, rising black line). Unlike LIP, the amygdala's decision signal returned to below statistical threshold around 500 ms (Figure 57A). Thus, like LIP, the amygdala encoded "Spatial Decision" robustly but, unlike LIP, the amygdala's decision signal did not persist to saccade execution.

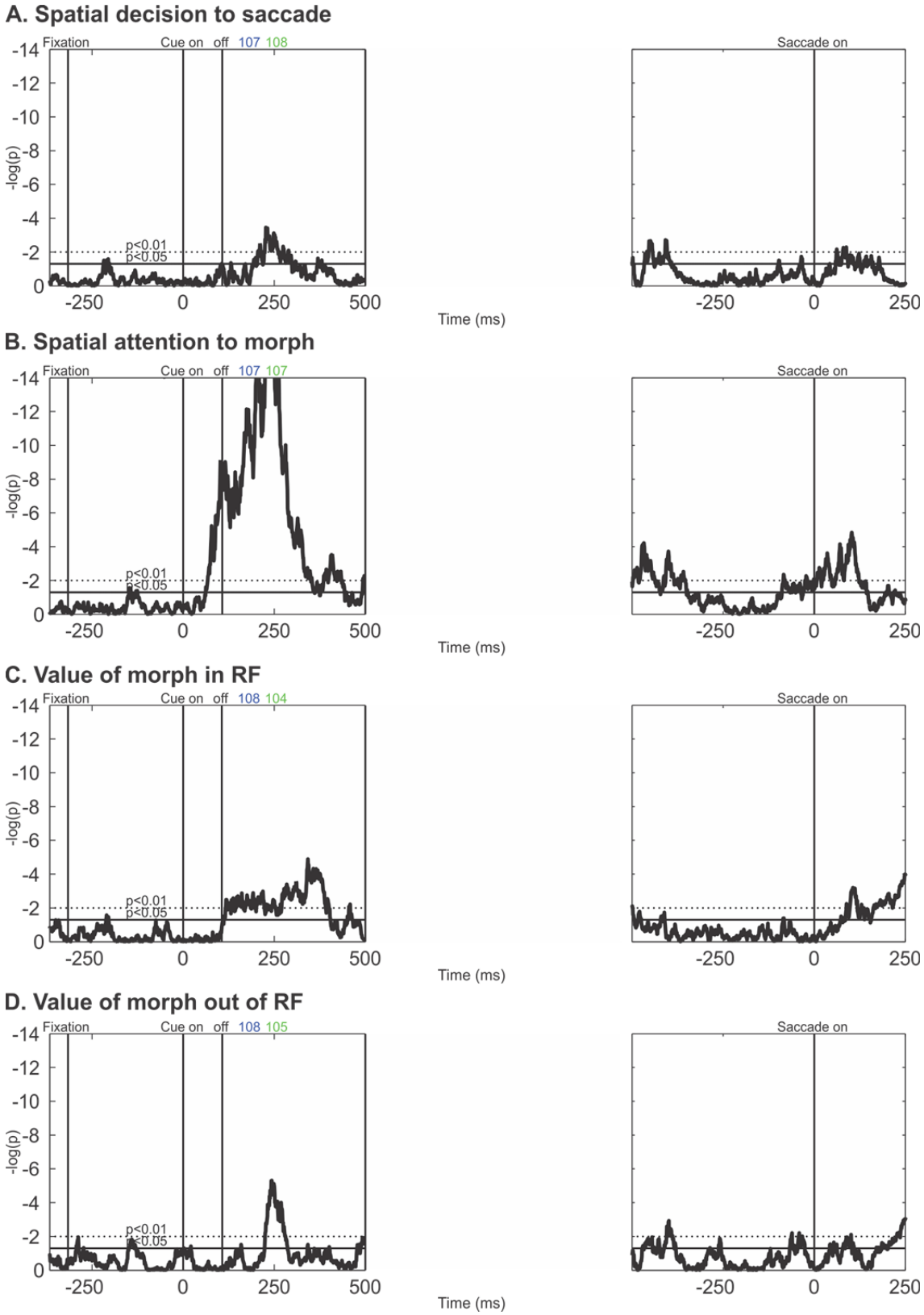


Figure 55. Primary Effects –log(p) (n = 73)

Same conventions as Figure 32.

Global value is the non-spatial effect of morph-value (Figure 26B). As in LIP, the amygdala's population firing rates increased significantly by 21 % (250 – 500) and 12% (0 – 500) as morph-value increased, regardless of the morph's spatial location or the direction of the saccade (Figure 56B). This trend was present in the earliest epoch ($p = 0.07$). Thus, like LIP, the amygdala has non-spatial reward-effects.

Action-value, fully defined, is the change in spatial selectivity for neurons representing potential motor plans as a function of the value those actions would obtain. However, amygdala neurons are not known to encode motor plans but could encode spatial-value in an action-free way. When morph-value in the RF is higher relative to morph-value out of the RF (Figure 26C blue conditions, Figure 56C in>out) then spatial selectivity for value in amygdala (firing rates) should be greater than when morph-value in the RF is lower relative to morph-value out of the RF (Figure 26C green conditions, Figure 56C out>in). We found that population firing rates in amygdala, unlike LIP, do significantly encode spatial-value early in the decision and in later epochs (Figure 56C). The time-course for both the effect of spatial-value and the strength of its significance for spatial-value (Figure 56-57C) look like those for morph-value in the RF (Figure 54-55C) but with a bite taken out of it by the effect of morph-value out of the RF at precisely the time the ipsilateral reward-effect emerges into significance. Thus, though LIP did not significantly encode action-value, amygdala does significantly encode spatial-value in the push-pull fashion proposed for action-value. This result supports our hypothesis that early reward-effects in amygdala are value signals.

Finally, "Global Decision" is the non-spatial firing rate difference between morph-chosen and morph-rejected trials (Figure 26D). Unlike LIP, the amygdala's population activity increased

significantly by 10 % during the delay period when morph was chosen over safety (Figure 56D). It is not clear what this effect means.

We tested the eight effects above at the single-neuron level. As opposed to the near absence of LIP neurons with significant reward effects, the numbers of amygdala neurons with significant reward-effects was greater than expected by chance for all reward-effects except morph-value out of the RF (Figure 58). Compare Tables 6 and 10. Most importantly, in the two monkeys combined, 6, 10, and 10 amygdala neurons significantly increased their activity during the first, second, and third epochs, respectively, with the value of the morph in the RF, which were greater numbers than expected by chance (Table 10). Thus, early during decision-making, and throughout the value-based decision process, single neurons in the amygdala, but not LIP, encoded the value of ambiguous cues that that could not acquire differential associative salience.

In addition, our morphing manipulation left intact a significant number of amygdala neurons that significantly encoded visual attention and decision signals (Figure 58A "Spatial Attention" and "Spatial Decision," 58D "Spatial Decision," and Table 11). This was true for all three pre-saccade epochs for data combined across two monkeys (Figure 58) and for each individual monkey (Figures 67-68). The sole exception to this was Monkey 1, who did not have a significant number of amygdala neurons encoding "spatial decision to saccade" in any epoch (Figure 67A). As in LIP, the number of amygdala neurons encoding "Global Decision" in any pre-saccade epoch was no greater than expected by chance in data from both monkeys (Figures 58A) combined and each individual monkeys (Figures 67-68).

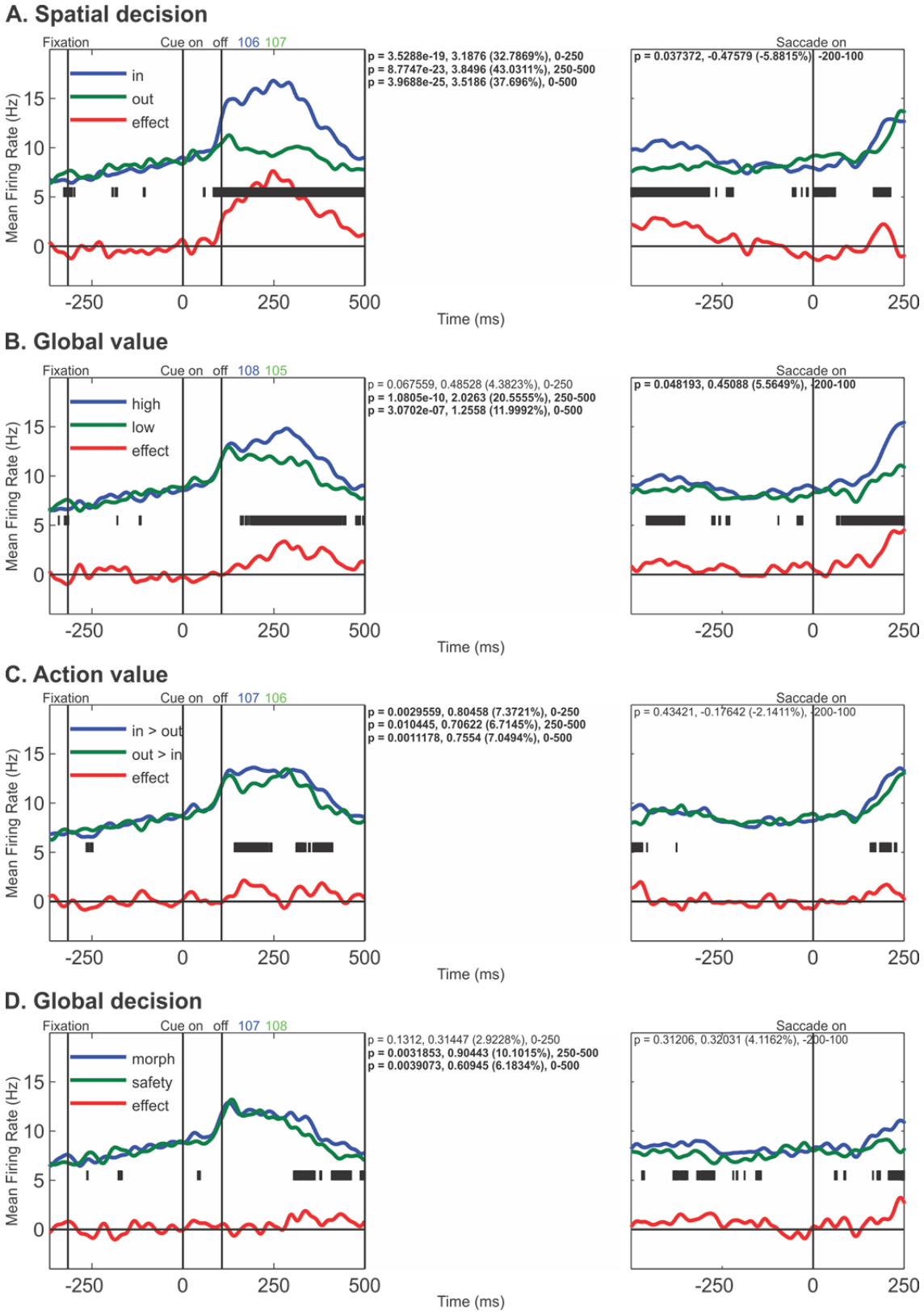


Figure 56. Secondary Effects PSTHs (n = 73)

Same conventions as Figure 33.

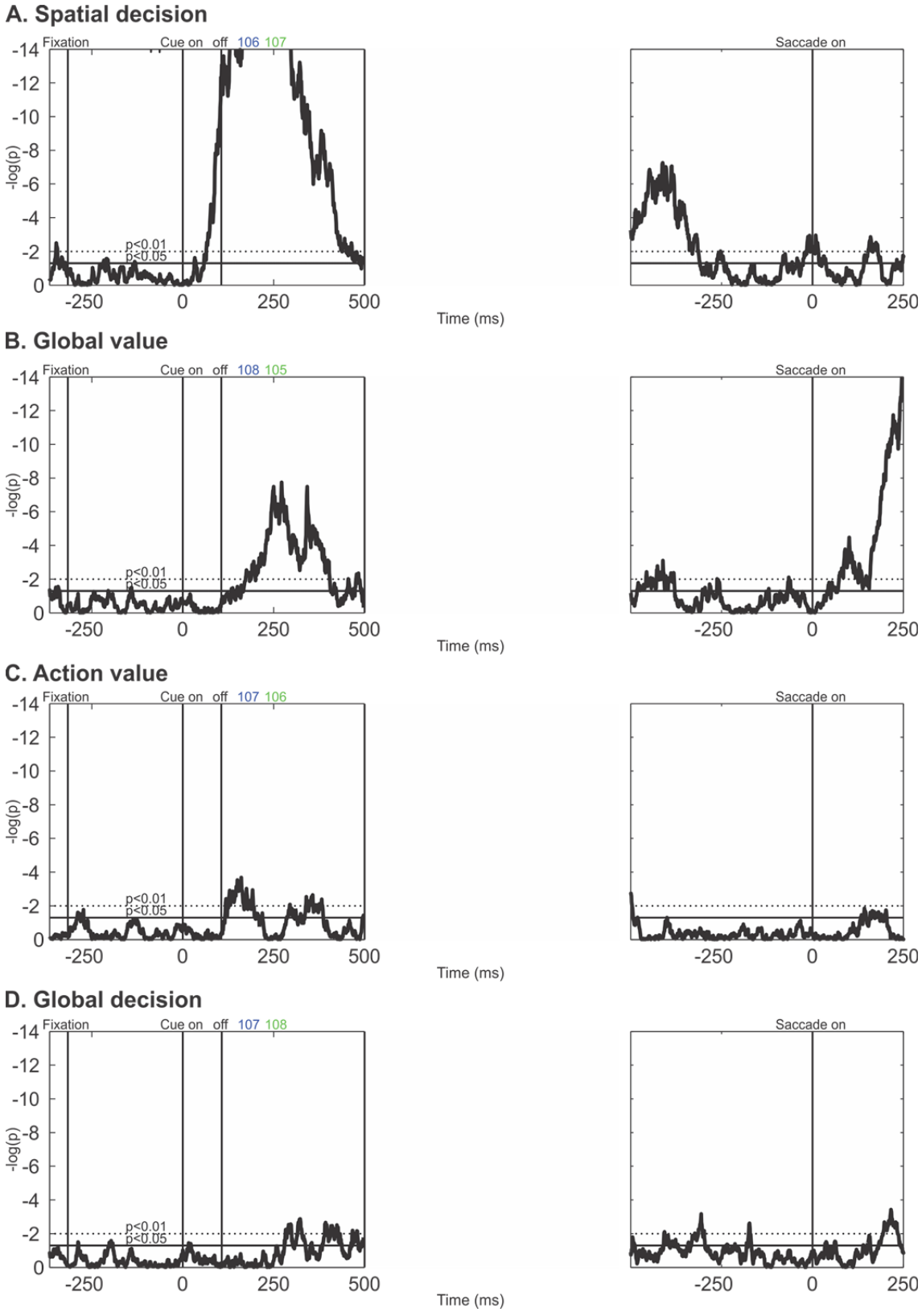


Figure 57. Secondary Effects –log(p) (n = 73)

Same conventions as Figure 34.

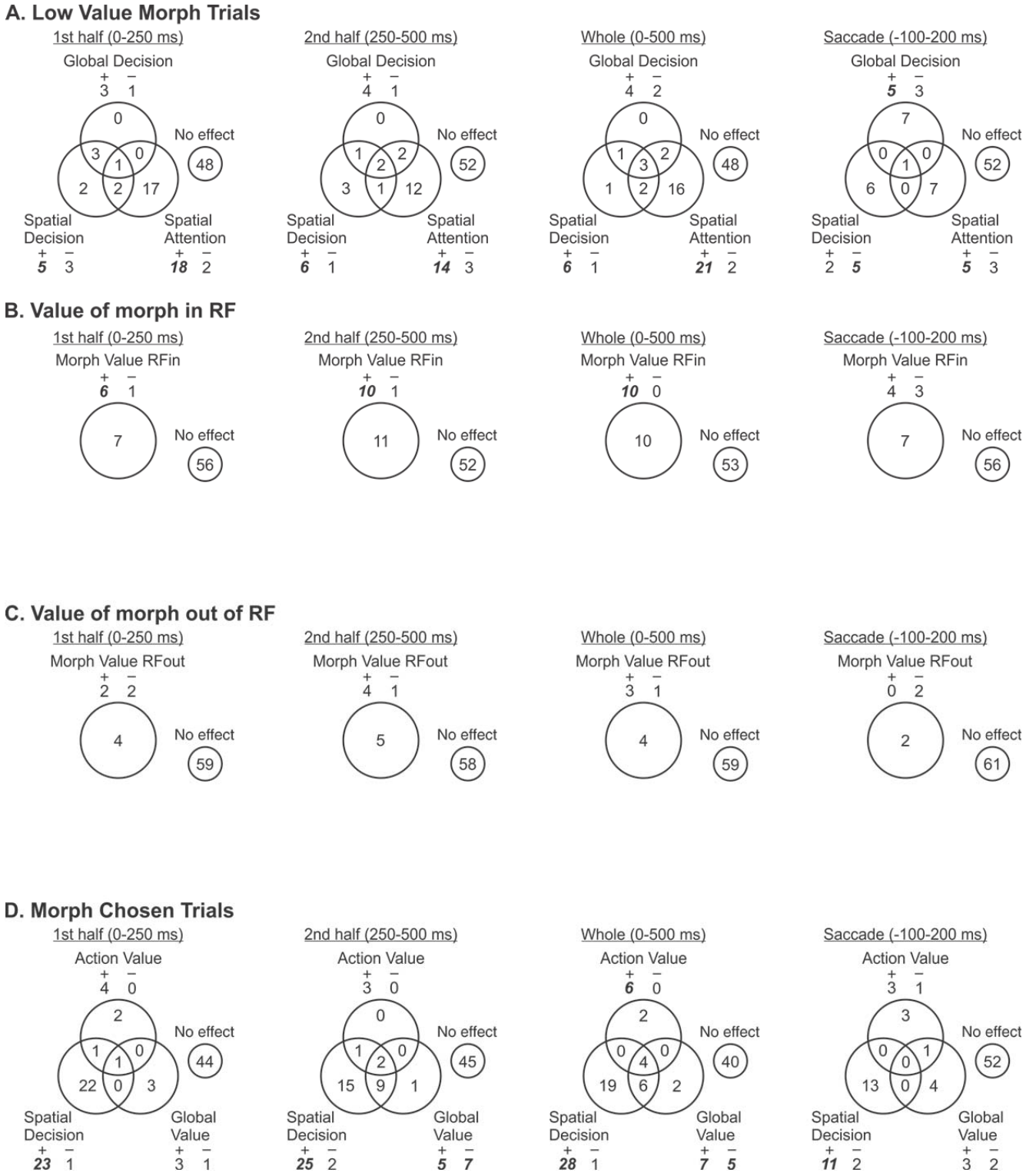


Figure 58. Single Neuron Effects (n = 73)

Same conventions as Figure 35.

Table 8. Amygdala Population-level Analysis Results: 4 Value Effects

Value of Morph in RF	1st	2nd	full	sac
Both (Ju & Je):	+1 Hz (11 %)*	+3 Hz (24 %)*	+2 Hz (17 %)*	+0 Hz (3 %)
Ju:	+2 Hz (7 %)^	+6 Hz (42 %)*	+4 Hz (21 %)*	-0 Hz (5 %)
Je:	+1 Hz (14 %)*	+1 Hz (14 %)*	+1 Hz (14 %)*	+1Hz (8 %)
Value of Morph out RF	1st	2nd	full	sac
Both (Ju & Je):	-0 Hz (3 %)	+1 Hz (16 %)*	+1 Hz (6 %)^	+1 Hz (8 %)^
Ju:	+0 Hz (2 %)	+3 Hz (34 %)*	+2 Hz (13 %)^	+2 Hz (15 %)*
Je:	-1 Hz (7 %)^	+1 Hz (9 %)*	+0 Hz (1 %)	+0 Hz (3 %)
Global Value	1st	2nd	full	sac
Both (Ju & Je):	+0 Hz (4 %)^	+2 Hz (21 %)*	+1 Hz (12 %)*	+0 Hz (6 %)*
Ju:	+1 Hz (5 %)	+5 Hz (39 %)*	+3 Hz (18 %)*	+1 Hz (6 %)
Je:	+0 Hz (4 %)	+1 Hz (12 %)*	+1 Hz (8 %)*	+0 Hz (6 %)^
Action Value	1st	2nd	full	sac
Both (Ju & Je):	+1 Hz (7 %)*	+1 Hz (7 %)*	+1 Hz (7 %)*	-0 Hz (2 %)
Ju:	+1 Hz (4 %)	+2 Hz (12 %)*	+1 Hz (7 %)^	-1 Hz (10 %)*
Je:	+1 Hz (11 %)*	+0 Hz (4 %)	+1 Hz (7 %)*	+0 Hz (2 %)

Four effects, per epoch, per monkey. Sign and size of each effect given as raw firing rate difference in spikes/sec (Hz) and percentage firing rate change (%) due to effect, rounded to nearest integer. Effects significance were assessed with three-factor ANOVA or two-tailed paired t-test where appropriate. * = $p < 0.05$ and ^ = $p \leq 0.10$.

Table 9. Amygdala Population-level Analysis Results: 4 Non-Value Effects

Spatial Decision to Saccade	1st	2nd	full	sac
Both (Ju & Je):	+0 Hz (3 %)^	+1 Hz (9 %)*	+1 Hz (6 %)*	+0 Hz (6 %)
Ju:	+1 Hz (5 %)^	+2 Hz (15 %)^	+1 Hz (9 %)*	+2 Hz (20 %)*
Je:	+0 Hz (1 %)	+1 Hz (7 %)^	+0 Hz (4 %)^	-0 Hz (1 %)
Spatial Attention to Morph	1st	2nd	full	sac
Both (Ju & Je):	+2 Hz (21 %)*	+2 Hz (28 %)*	+2 Hz (24 %)*	-1 Hz (10 %)*
Ju:	+6 Hz (37 %)*	+4 Hz (48 %)*	+5 Hz (41 %)*	-3 Hz (24 %)*
Je:	+1 Hz (8 %)*	+2 Hz (20 %)*	+1 Hz (14 %)*	-0 Hz (3 %)
Spatial Decision	1st	2nd	full	sac
Both (Ju & Je):	+3 Hz (33 %)*	+4 Hz (43 %)*	+4 Hz (38 %)*	-0 Hz (6 %)*
Ju:	+8 Hz (48 %)*	+8 Hz (72 %)*	+8 Hz (57 %)*	-1 Hz (14 %)*
Je:	+2 Hz (21 %)*	+2 Hz (30 %)*	+2 Hz (26 %)*	-0 Hz (2 %)
Global Decision	1st	2nd	full	sac
Both (Ju & Je):	+0 Hz (3 %)	+1 Hz (10 %)*	+1 Hz (6 %)*	+0 Hz (4 %)
Ju:	+1 Hz (3 %)	+2 Hz (11 %)	+1 Hz (6 %)	-1 Hz (6 %)
Je:	+0 Hz (3 %)	+1 Hz (10 %)*	+1 Hz (6 %)*	+1 Hz (11 %)*

Four effects, per epoch, per monkey. Sign and size of each effect given as raw firing rate difference in spikes/sec (Hz) and percentage firing rate change (%) due to effect, rounded to nearest integer. Effects significance were assessed with three-factor ANOVA or two-tailed paired t-test where appropriate. * = $p < 0.05$ and ^ = $p \leq 0.10$.

Table 10. Amygdala Neuron-level Analysis Results: 4 Value Effects

Value of Morph in RF	1st	2nd	full	sac
Both (Ju & Je):	6+	10+	10+	-
Ju:	3+	5+	6+	-
Je:	-	5+	-	-
Value of Morph out RF	**1st**	**2nd**	**full**	**sac**
Both (Ju & Je):	-	-	-	-
Ju:	-	4+	-	-
Je:	-	-	-	-
Global Value	**1st**	**2nd**	**full**	**sac**
Both (Ju & Je):	-	5+, 7-	7+, 5-	-
Ju:	-	5+, 3-	5+, 3-	-
Je:	-	-	-	-
Action Value	**1st**	**2nd**	**full**	**sac**
Both (Ju & Je):	-	-	6+	-
Ju:	-	-	4+	-
Je:	-	-	-	-

Four effects, per epoch, per monkey. Counts of neurons with significant effects that were significantly more numerous than expected by chance alone, followed by size of their effect. The - means the number of neurons observed with significant effects was no greater than chance expectation. Significant effects were assessed by either two-factor ANOVA or two-tailed paired t-test where appropriate. Significance of counts were assessed with chi-squared test with Yates-Correction.

Table 11. Amygdala Neuron-level Analysis Results: 4 Non-Value Effects

Spatial Decision to Saccade	1st	2nd	full	sac
Both (Ju & Je):	5+	6+	6+	5-
Ju:	-	-	-	-
Je:	5+	6+	6+	-
Spatial Attention to Morph	1st	2nd	full	sac
Both (Ju & Je):	18+	14+	21+	5+
Ju:	8+	7+	9+	-
Je:	10+	7+	12+	-
Spatial Decision	1st	2nd	full	sac
Both (Ju & Je):	23+	25+	28+	11+
Ju:	10+	14+	15+	6+
Je:	13+	11+	13+	5+
Global Decision	1st	2nd	full	sac
Both (Ju & Je):	-	-	-	5+
Ju:	-	-	-	-
Je:	-	-	-	-

Four effects, per epoch, per monkey. Counts of neurons with significant effects that were significantly more numerous than expected by chance alone, followed by size of their effect. The - means the number of neurons observed with significant effects was no greater than chance expectation. Significant effects were assessed by either two-factor ANOVA or two-tailed paired t-test where appropriate. Significance of counts were assessed with chi-squared test with Yates-Correction.

(b) Individual Monkey Data

The main results from data combined from both monkeys are that reward-effects were present in the amygdala early during value-based decision-making at both the population-level and single-neuron level, despite our morphing manipulation, along with attention and decision effects. The neuron-level results from data combined across two monkeys and for each individual monkey were described above. Here we report population-level results for each individual monkey. We describe the four value effects followed by the four non-value effects.

Value of Morph in RF. In data from each monkey individually and both monkeys combined, amygdala population activity increased with the value of the morph in the RF during the three pre-saccade epochs. All effects were significant with the sole exception of the trend ($p < 0.10$) in the first epoch for Monkey 1 (Figures 59-60C).

Value of Morph out of RF. As with the data from the two monkeys combined, each individual monkey significantly increased activity during the second epoch with the value of the morph out of the RF (Figures 59-60D).

Global Value. This effect of increased firing rate with increased value of the chosen morph was significant in the data from both monkeys combined and in their individual data for the second and full epochs (Figures. 63-64B).

Action Value. Whereas data combined across monkeys showed a significant increase with action-value (spatial-value) across all pre-saccade epochs, the timing of this effect differed between the two individual monkeys. In the first epoch, the increase was significant in Monkey 1 but not Monkey 2. In the second epoch, the increase was significant in Monkey 2 but not Monkey 1. In the full epoch, each monkey's data show increased activity with action-value (spatial-value) but this trend ($p = 0.10$) failed to reach significance in Monkey 1 (Figures 63-64C).

Spatial Decision to Saccade. Either trends ($p \leq 0.10$) or significant increases in activity for saccadic decisions into rather than out of the RF were observed during all pre-saccade epochs for the data combined from both monkeys and for each monkey individually with the sole exception that Monkey 2 showed no trend for this decision signal in the first epoch (Figures 59-60A).

Spatial Attention. Significant increases in activity for the morph located in rather than out of the RF were observed during all pre-saccade epochs for data combined from both monkeys and for each monkey individually (Figures 59-60B).

Spatial Decision. This effect of increased activity before morph choices into rather than out of the RF was significant in all monkeys in all epochs (Figures 63-64A).

Global Decision. This effect was present in the second epoch for all monkeys in the form of a 10-11 % increase in activity for morph choices over morph rejections (Figures 63-64D). However, this effect reached significance only in Monkey 1.

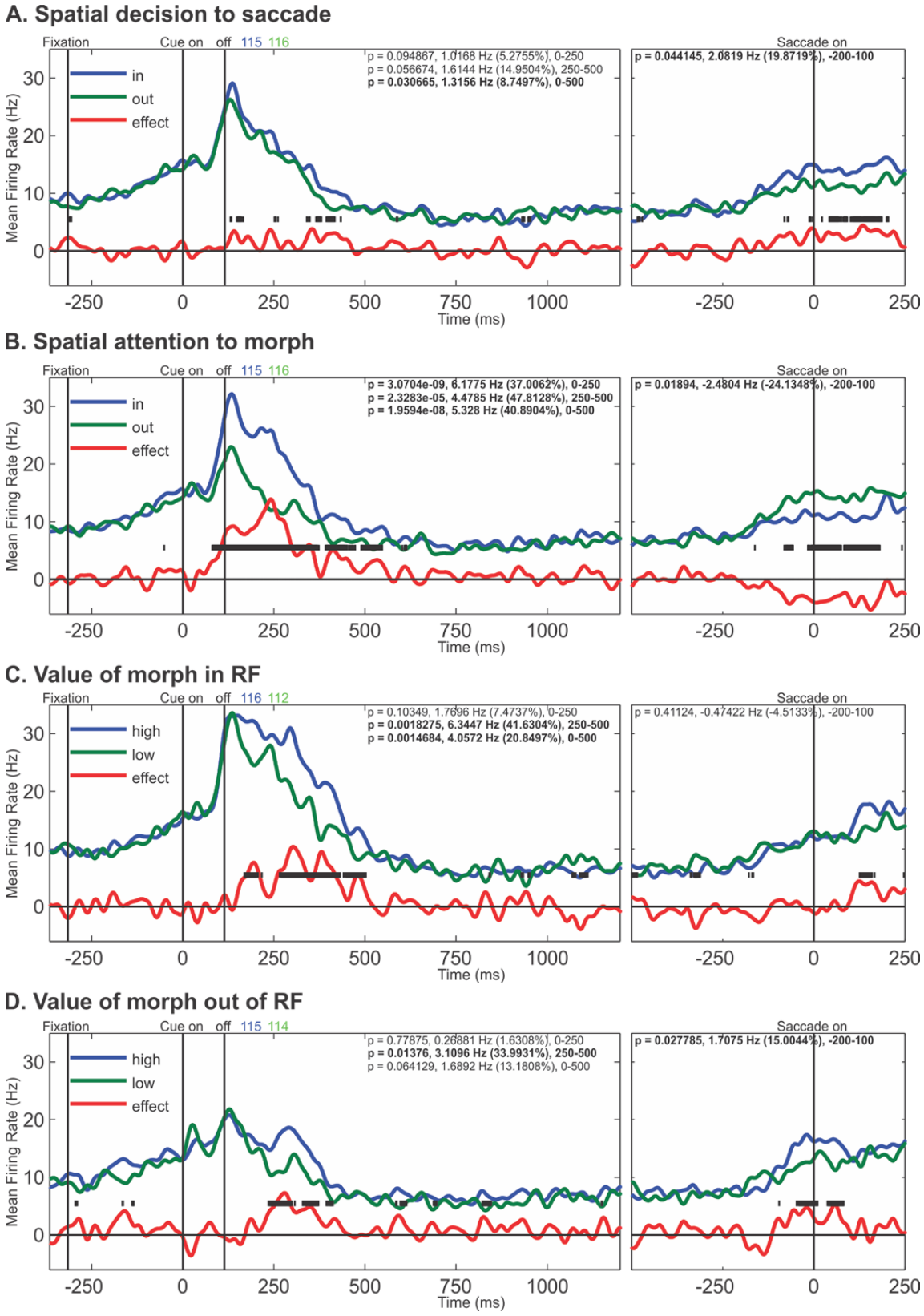


Figure 59. M1: Primary Effects PSTHs (n = 19)

Same conventions as Figure 31.

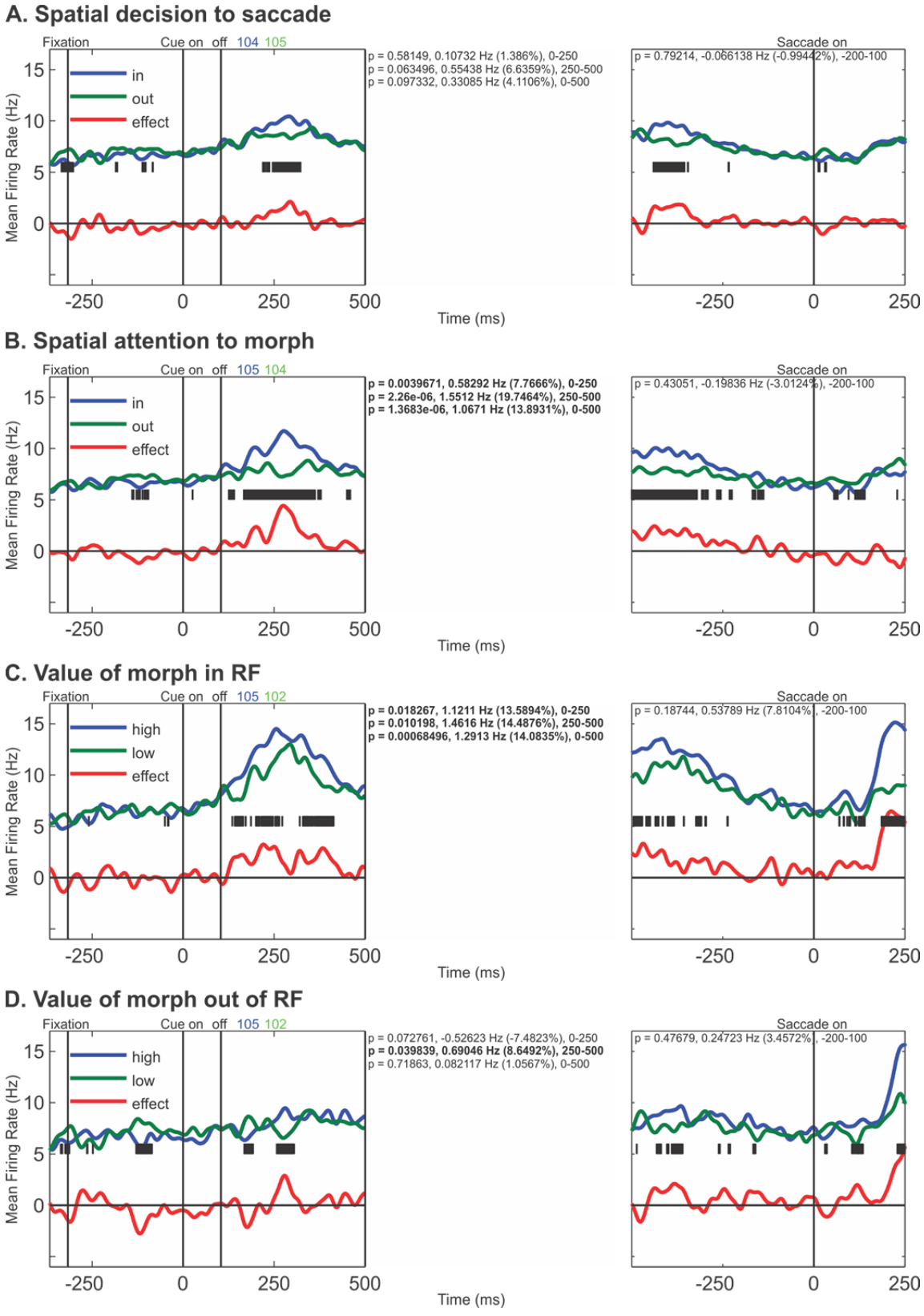


Figure 60. M2: Primary Effects PSTHs (n = 54)

Same conventions as Figure 31.

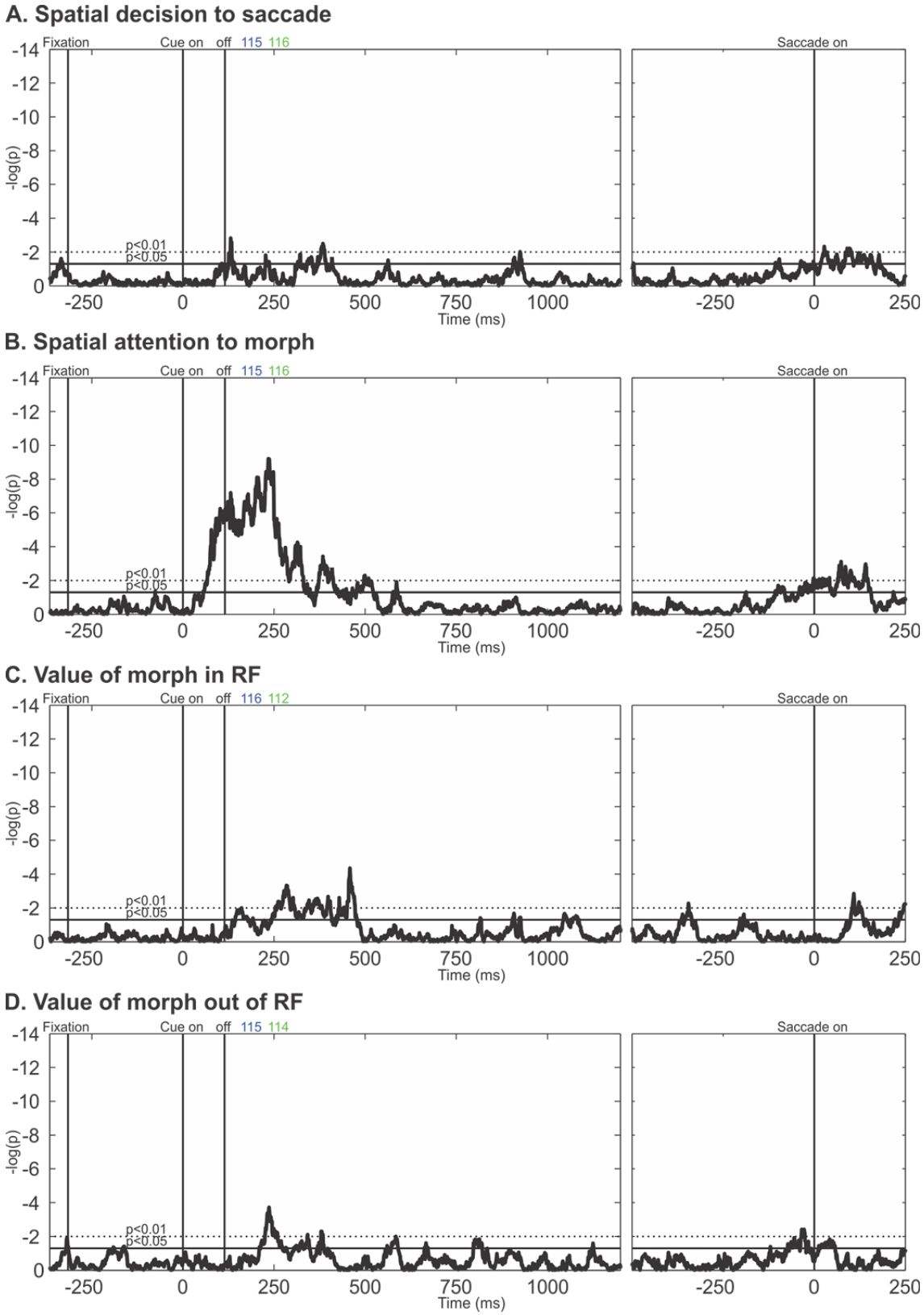


Figure 61. M1: Primary Effects –log(p) (n = 19)

Same conventions as Figure 32.

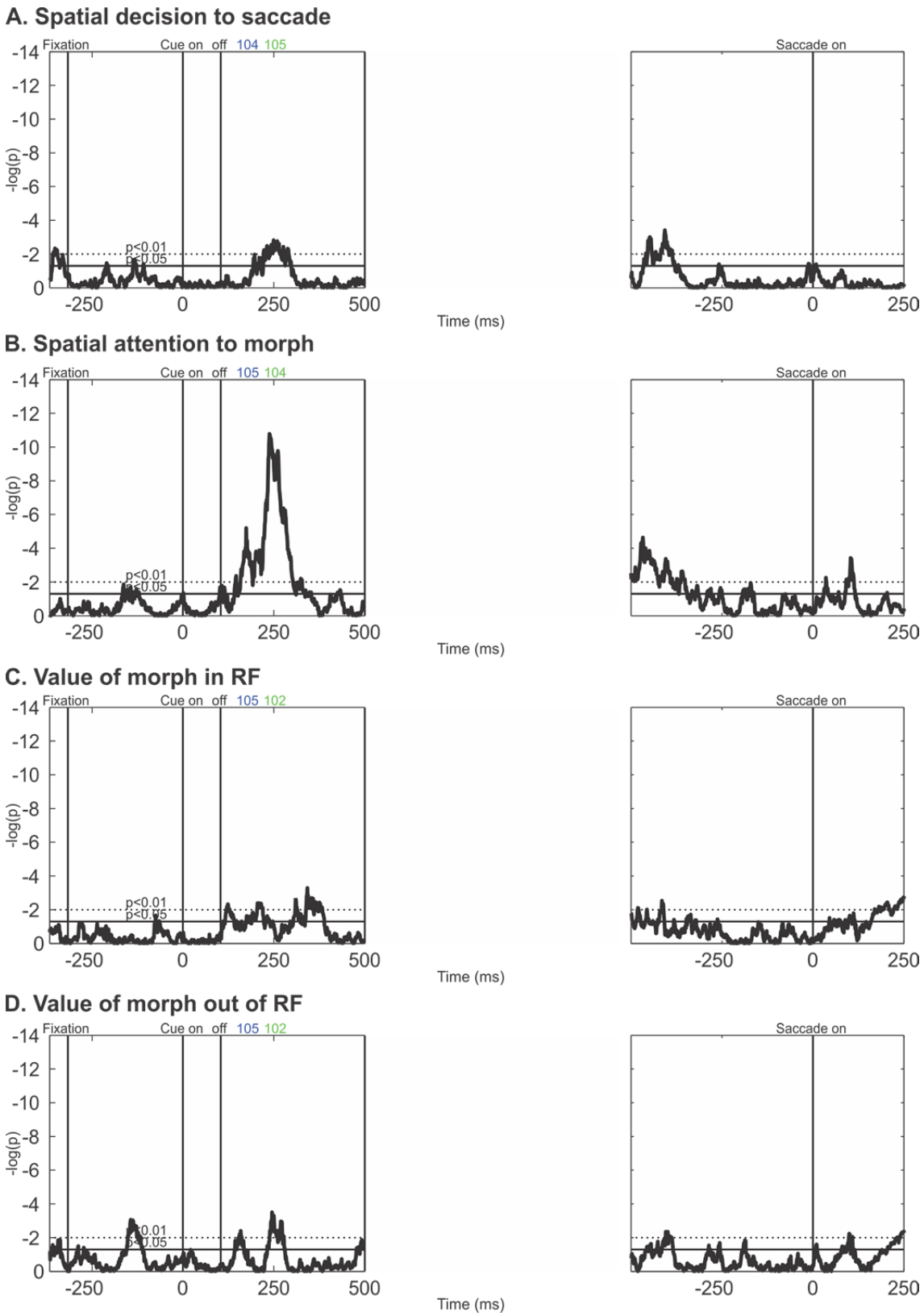


Figure 62. M2: Primary Effects –log(p) (n = 54)

Same conventions as Figure 32.

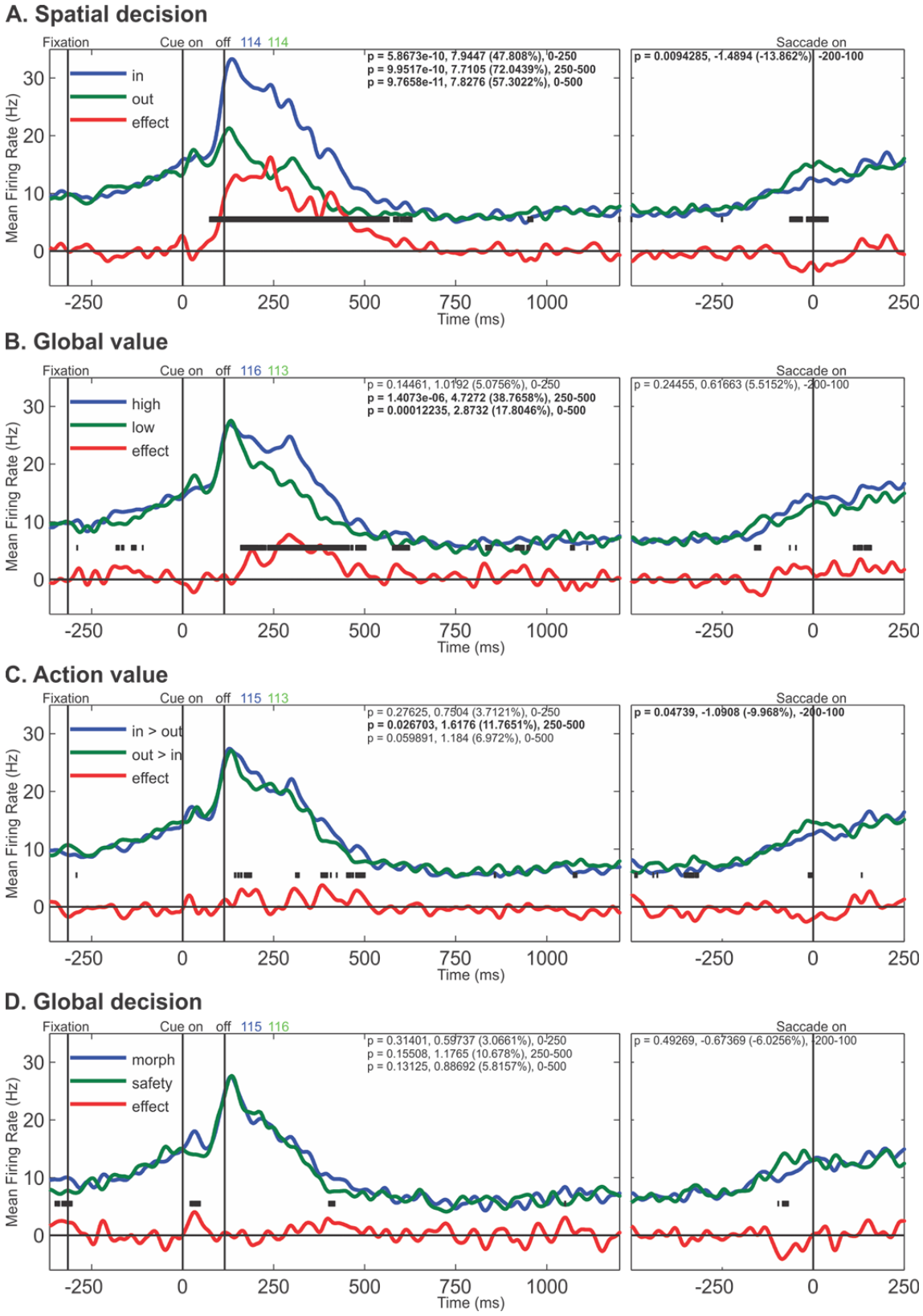


Figure 63. M1: Secondary Effects PSTHs (n = 19)

Same conventions as Figure 33.

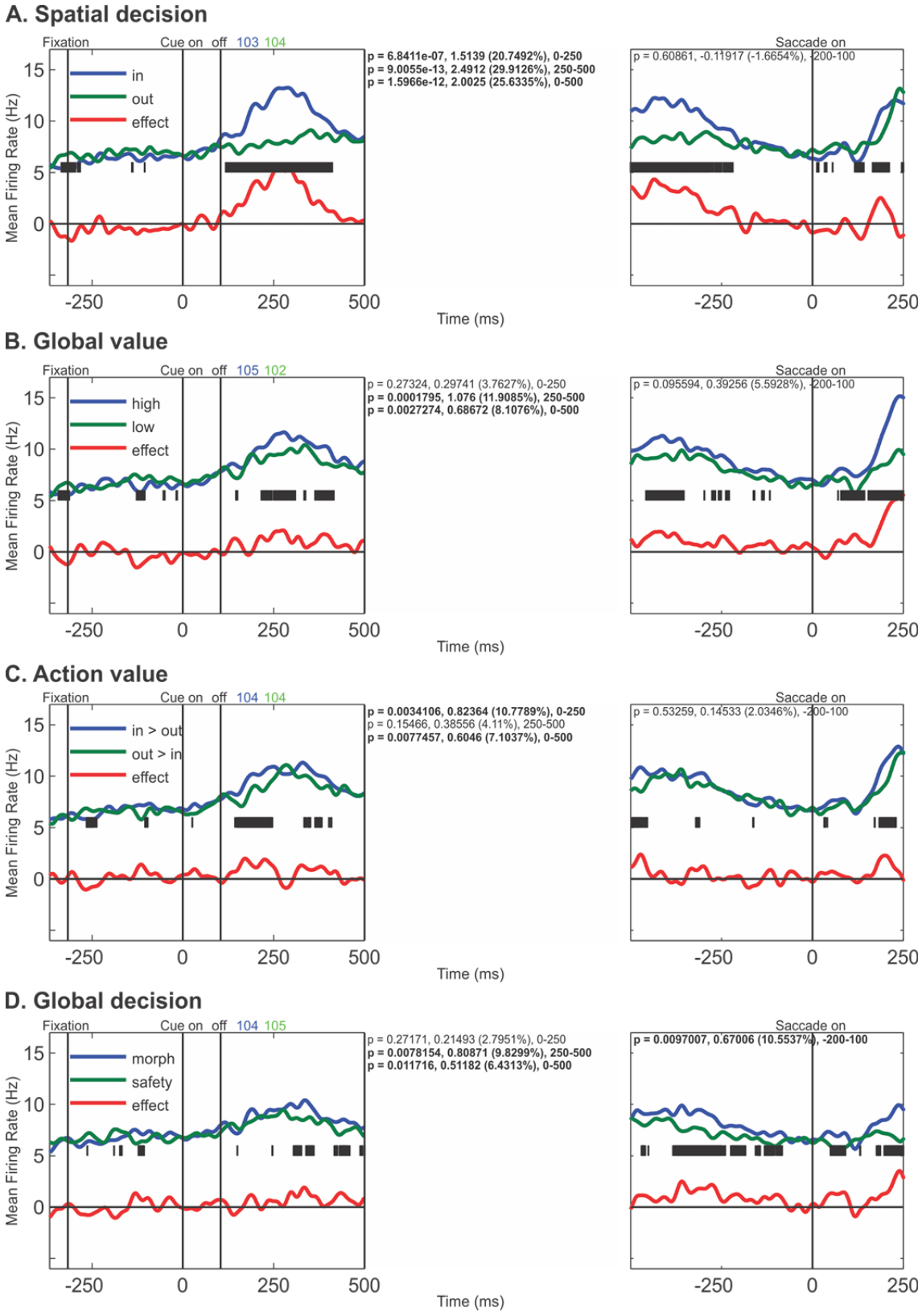


Figure 64. M2: Secondary Effects PSTHs (n = 54)

Same conventions as Figure 33.

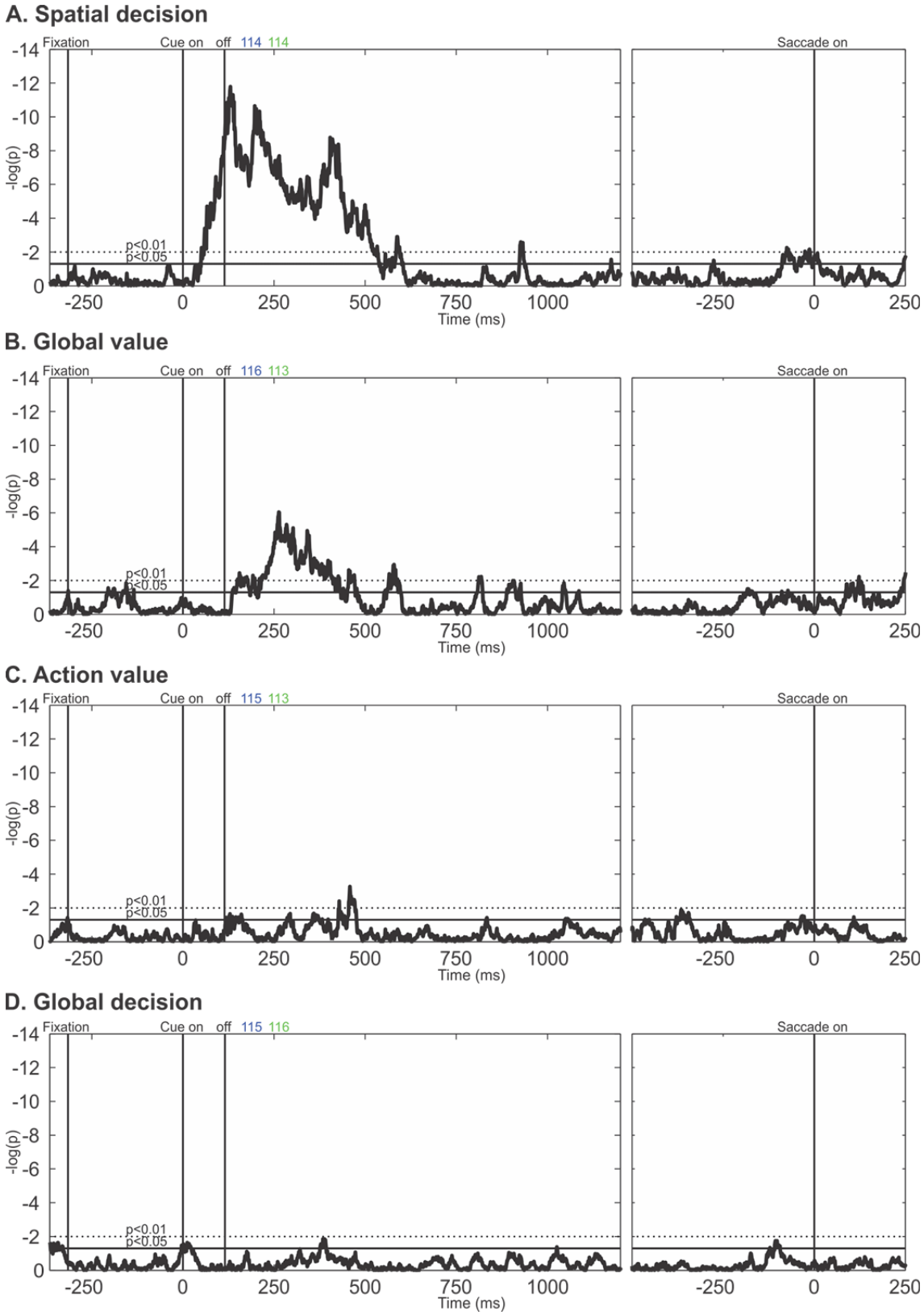


Figure 65. M1: Secondary Effects –log(p) (n = 19)

Same conventions as Figure 34.

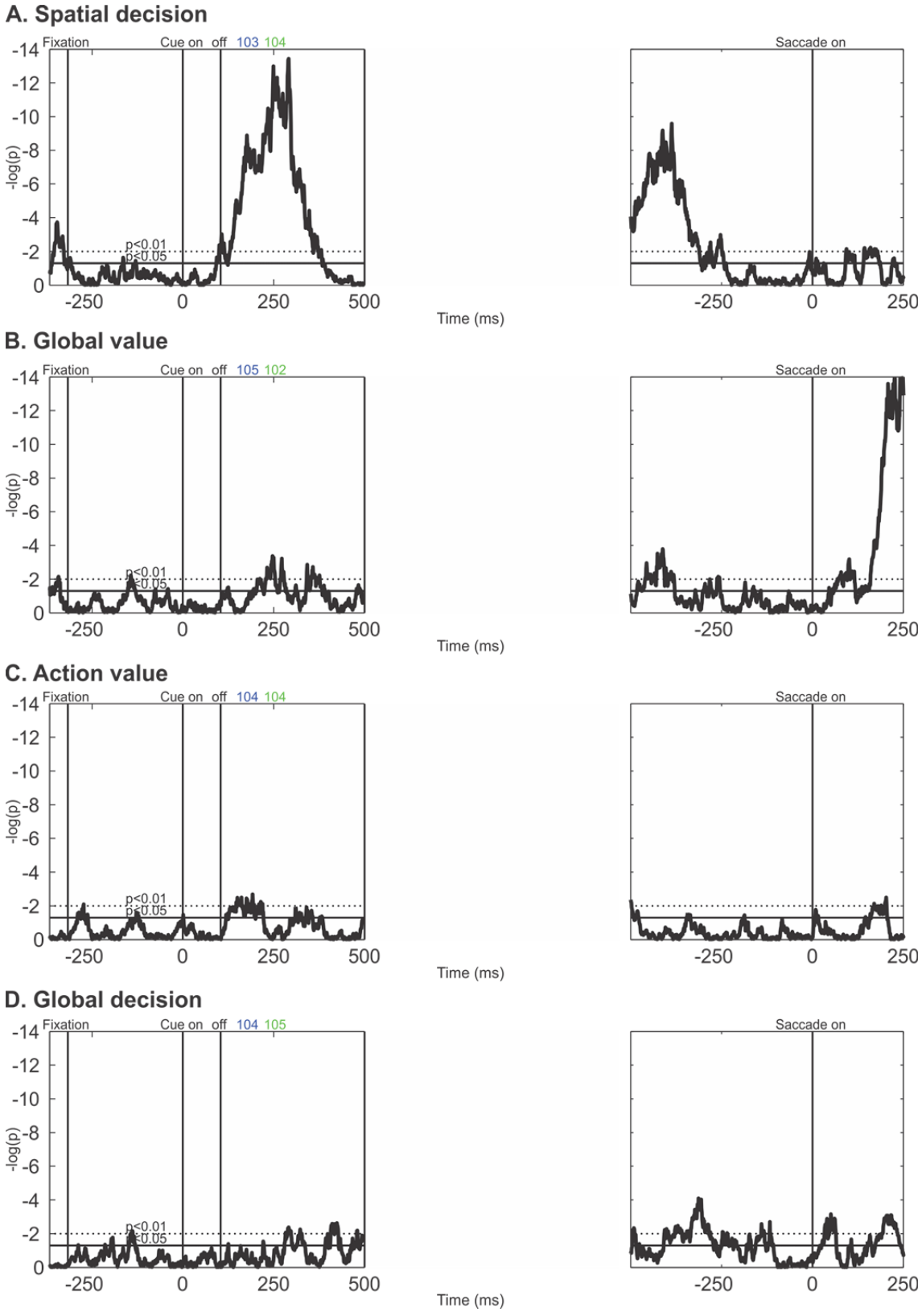


Figure 66. M2: Secondary Effects –log(p) (n = 54)

Same conventions as Figure 34.

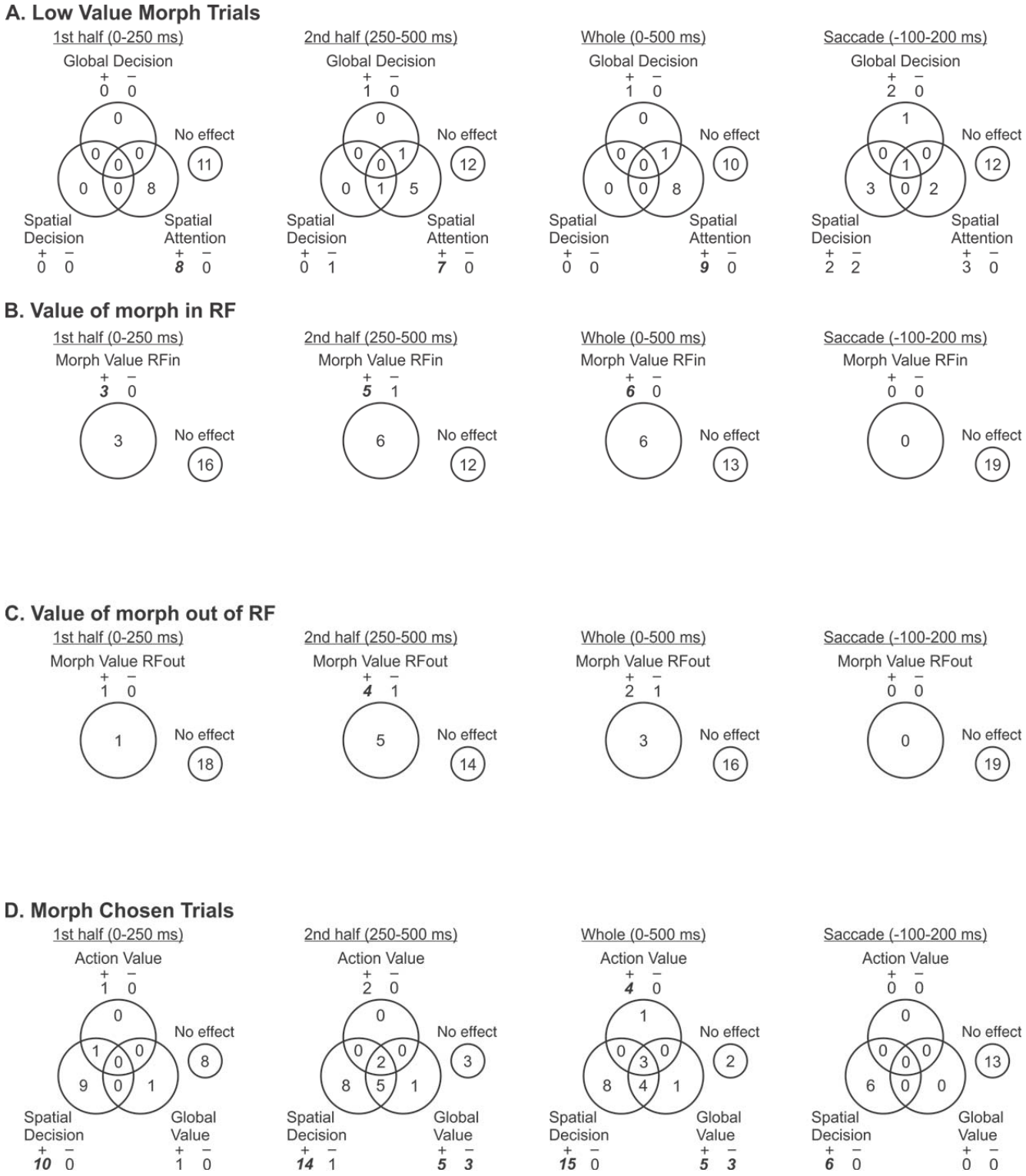


Figure 67. M1: Single Neuron Effects (n = 19)

Same conventions as Figure 35.

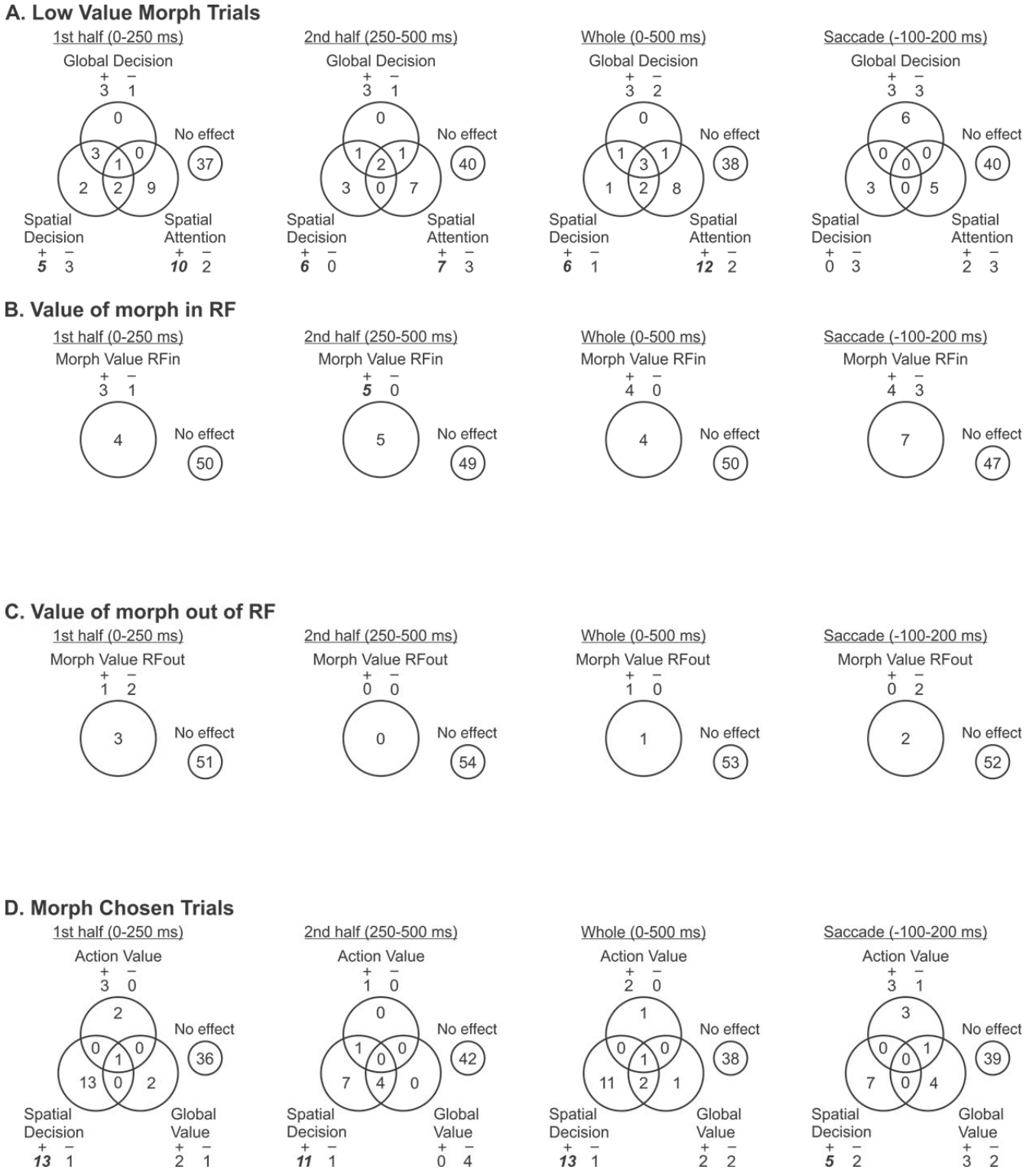


Figure 68. M2: Single Neuron Effects (n = 54)

Same conventions as Figure 35.

3.4 LIP & AMYGDALA EFFECTS COMPARISONS

To compare the magnitude of effects between LIP and amygdala, we created firing rate indices for each neuron, for each of the four analyses epochs, and for each of the eight effects (Figures 25-26). How we calculated the index for each effect is described in "Indices for Eight Effects" (Section 3.2.1.6bii). Simply put, each effect is the raw firing rate difference (not normalized) between the appropriate conditions (blue minus green) for that effect (Figures 25-26). For each epoch, for each effect, we created histograms to plot a distribution of the counts of neurons by the size and sign of their effect index grouped in 1 Hz bins, so that the x-axis would be spikes/second. Finally, we tested for differences in the means of the effect-indices distributions from LIP and amygdala using two-tailed unpaired t-tests separately for each epoch, for each effect.

We used three pairs of *LIP-amygdala* data for these comparisons.

Both-Both. We used the data combined across monkeys within each brain area. For LIP, this is M1 (Ju) and M2 (Eg). For amygdala, this is M1 (Ju) and M2 (Je). This comparison has two caveats. First, the identity of M2 differed between brain areas. Second, the task timing for monkey Je was different than that for Ju and Eg. Monkey Je had a short, fixed delay (500 ms), but monkeys Ju and Eg had a longer variable delay (1000-1200).

Ju-Ju. This is simply a comparison between LIP and amygdala data collected from the same monkey. There are no caveats.

Je-Je. This is a comparison between LIP and amygdala data collected from the same monkey. However, there is one caveat. The LIP data for Je is multi-unit, but the amygdala data for Je is single-unit.

Nevertheless, we tested for differences in effects strength between the above three pairs of LIP and amygdala data using two-tailed unpaired t-tests ($\alpha = 0.05$).

3.4.1 RESULTS

3.4.1.1 DATA COMBINED ACROSS MONKEYS

(a) Primary Effects

Here we present results from the *Both-Both* comparison defined above for Primary Effects.

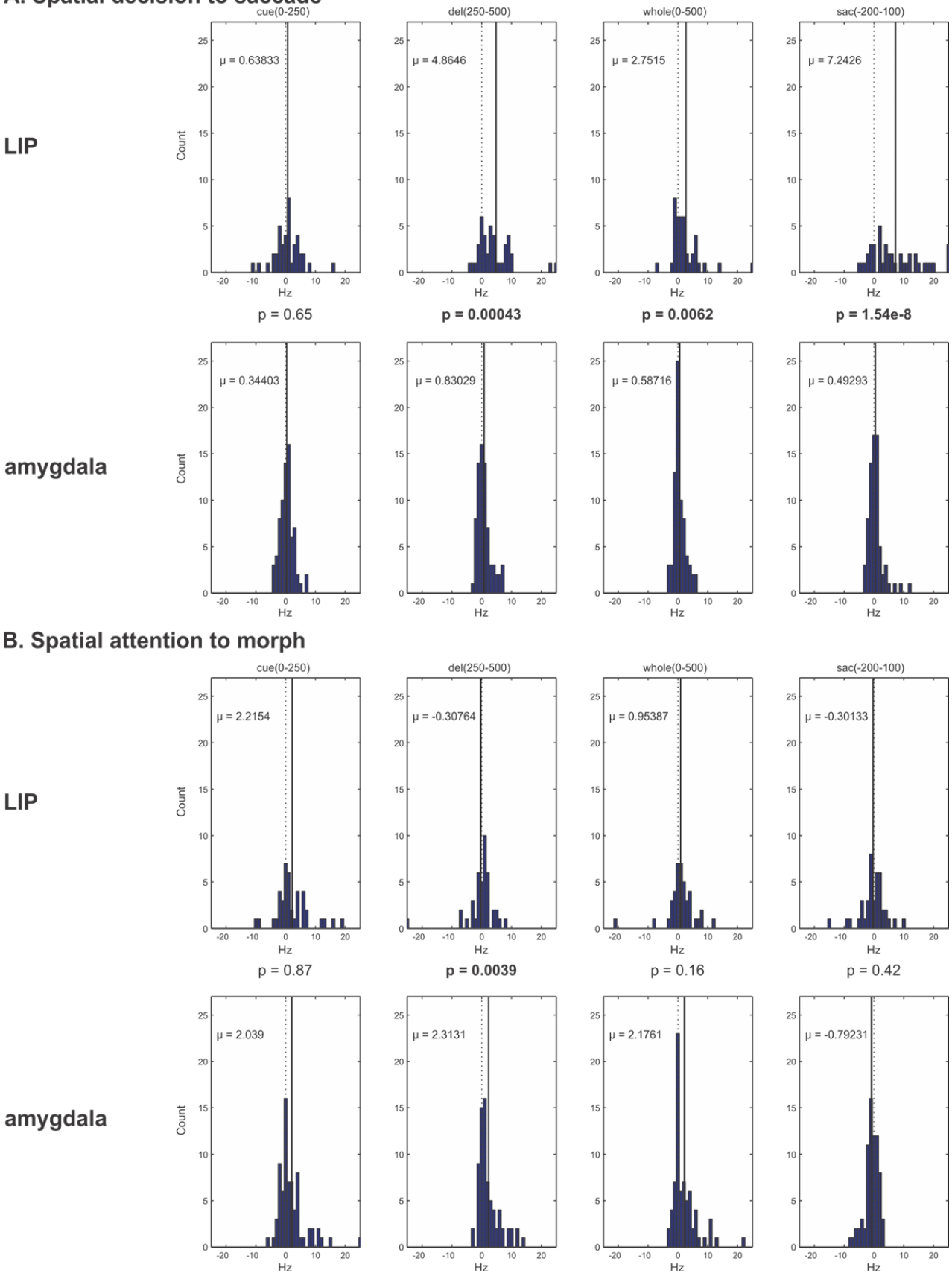
Spatial Decision to Saccade. The mean of the distribution of firing rate indices was significantly greater in LIP than amygdala for the second, full, and saccade epochs (Figure 69A).

Spatial Attention to Morph. The mean of the distribution of firing rate indices was significantly greater in amygdala than LIP during the second epoch (Figure 69B).

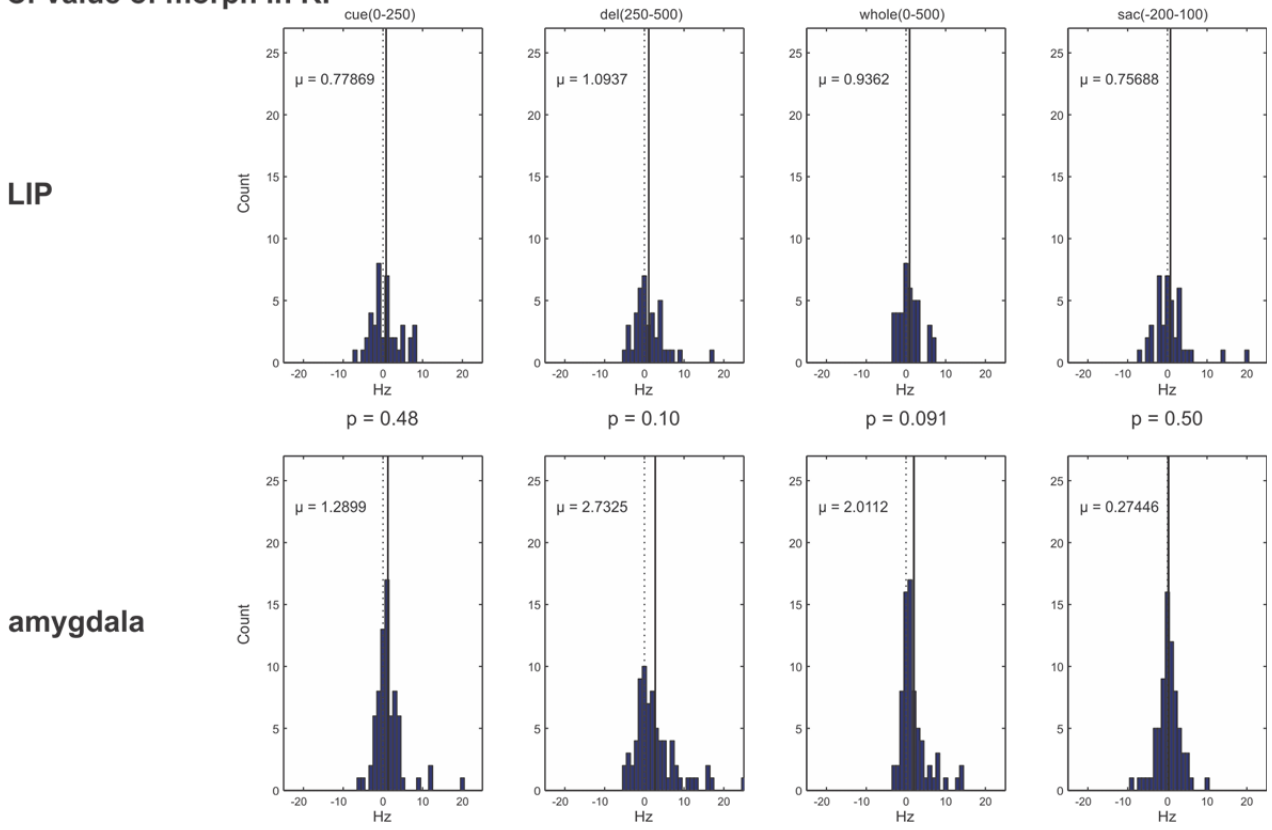
Value of Morph in RF. The mean of the distribution of firing rate indices were greater in amygdala than LIP during the second ($p = 0.10$) and full ($p = 0.09$) epochs (Figure 69C), but these trends did not reach the threshold for statistical significance.

Value of Morph out RF. No significant differences were observed between LIP and amygdala (Figure 69D)

Therefore, in terms of raw firing rate, the reward-effects in amygdala trend toward being stronger than those in LIP. The saccadic decision signal is significantly stronger in LIP than amygdala. The spatial attention signal is significantly stronger in amygdala than in LIP.


A. Spatial decision to saccade
LIP
amygdala
cue(0-250)
del(250-500)
whole(0-500)
sac(-200-100)
μ = 0.63833
μ = 4.8646
μ = 2.7515
μ = 7.2426
p = 0.65
p = 0.00043
p = 0.0062
p = 1.54e-8
μ = 0.34403
μ = 0.83029
μ = 0.58716
μ = 0.49293
B. Spatial attention to morph
LIP
amygdala
μ = 2.2154
μ = -0.30764
μ = 0.95387
μ = -0.30133
p = 0.87
p = 0.0039
p = 0.16
p = 0.42
μ = 2.039
μ = 2.3131
μ = 2.1761
μ = -0.79231
Count
Hz

C. Value of morph in RF



D. Value of morph out of RF

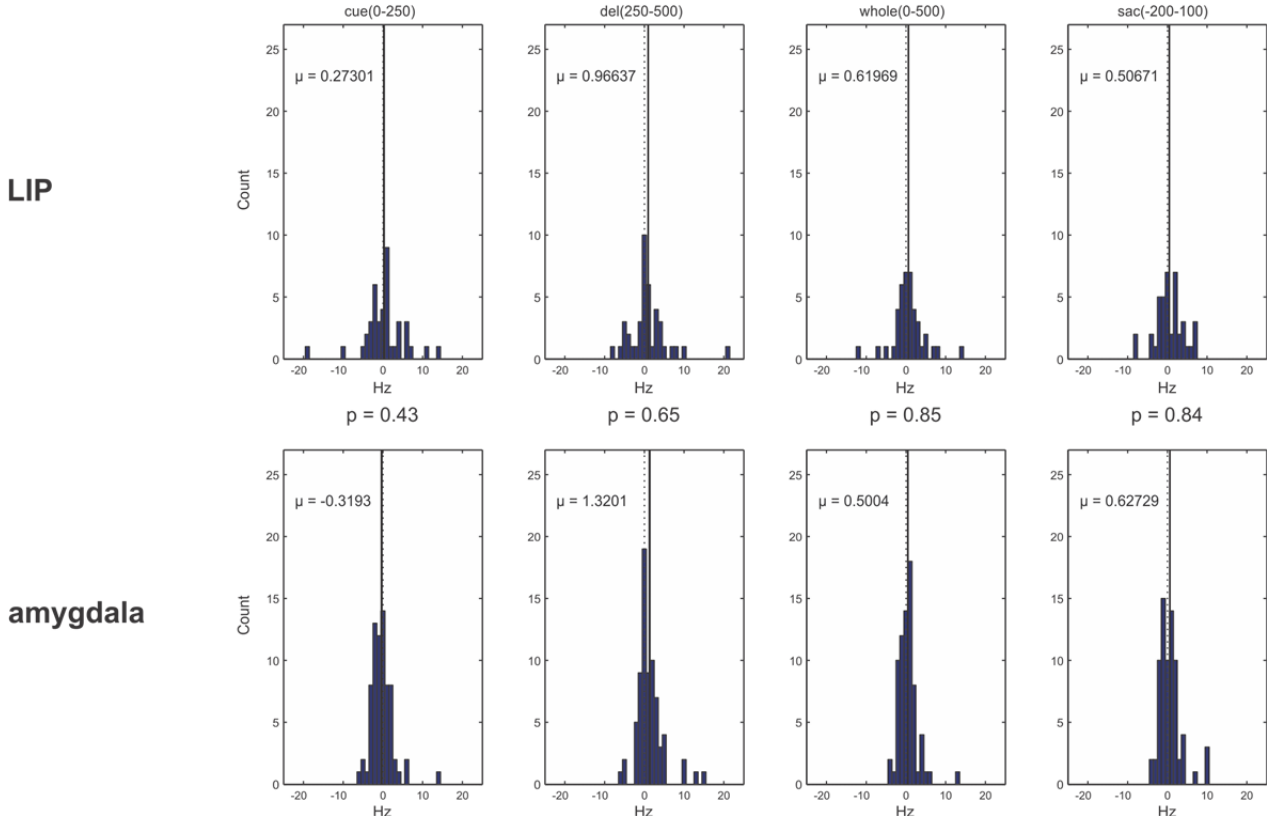


Figure 69. Primary Effects: Distributions of Neuronal Indices by Epoch
LIP and amygdala comparisons of the four primary effects. Data is from both monkeys (LIP: n = 41, amygdala: n = 73). **(A)** Spatial decision to saccade. **(B)** Spatial attention to morph. **(C)** Value of morph in RF. **(D)** Value of morph out of RF. Raw firing rate effect distributions (blue – green from previous plots). Bin width = 1 Hz. Top: LIP. Bottom: amygdala. P values in bold reached statistical significance (two-tailed, unpaired t-test, $\alpha = 0.05$).

(b) Secondary Effects

Here we present results from the *Both-Both* comparison defined above for Secondary Effects.

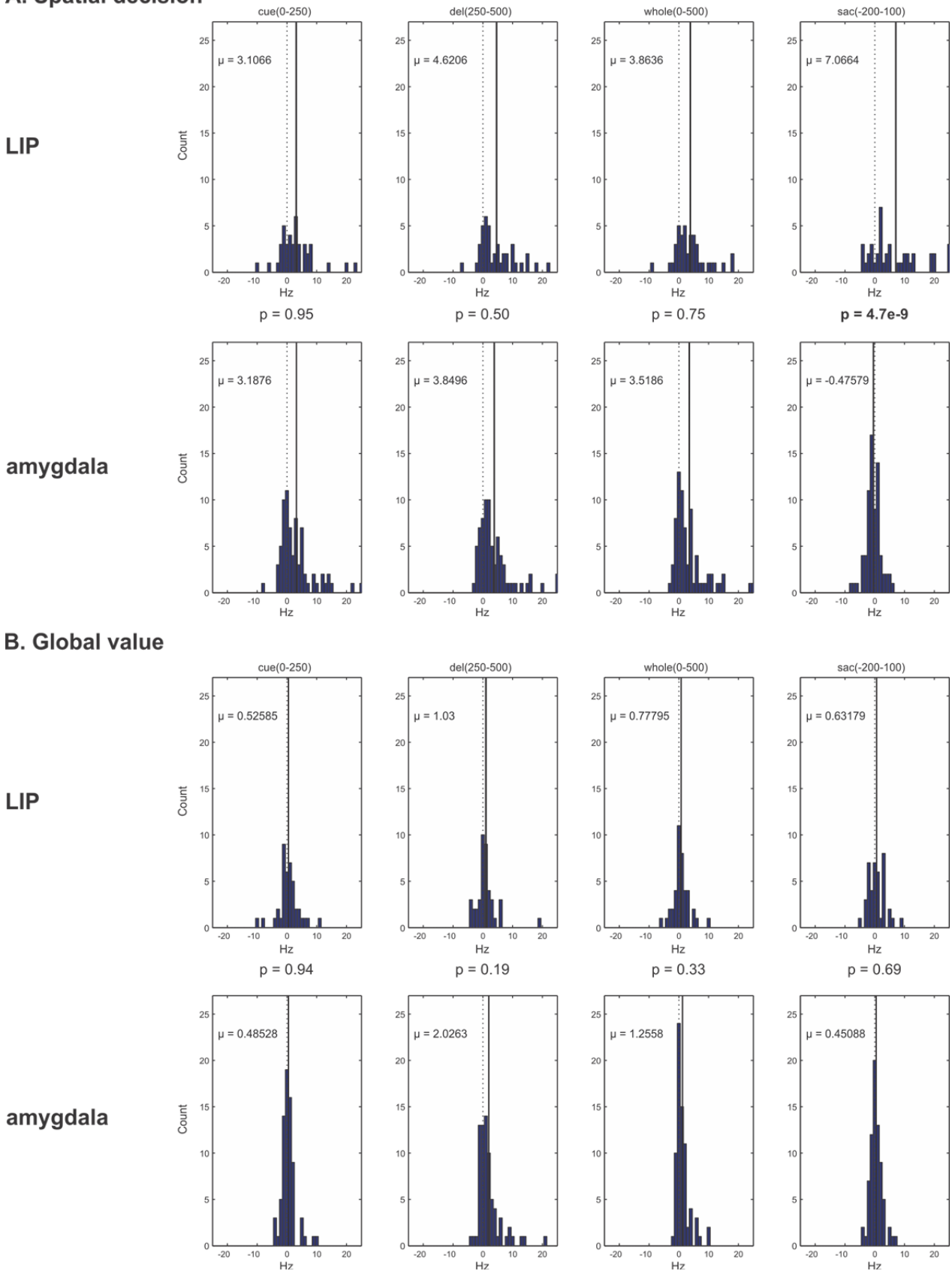
Spatial Decision. The mean of the distribution of firing rate indices was not significantly greater in LIP than amygdala until the saccade epoch (Figure 70A).

Global Value. No significant differences were observed between LIP and amygdala (Figure 70B).

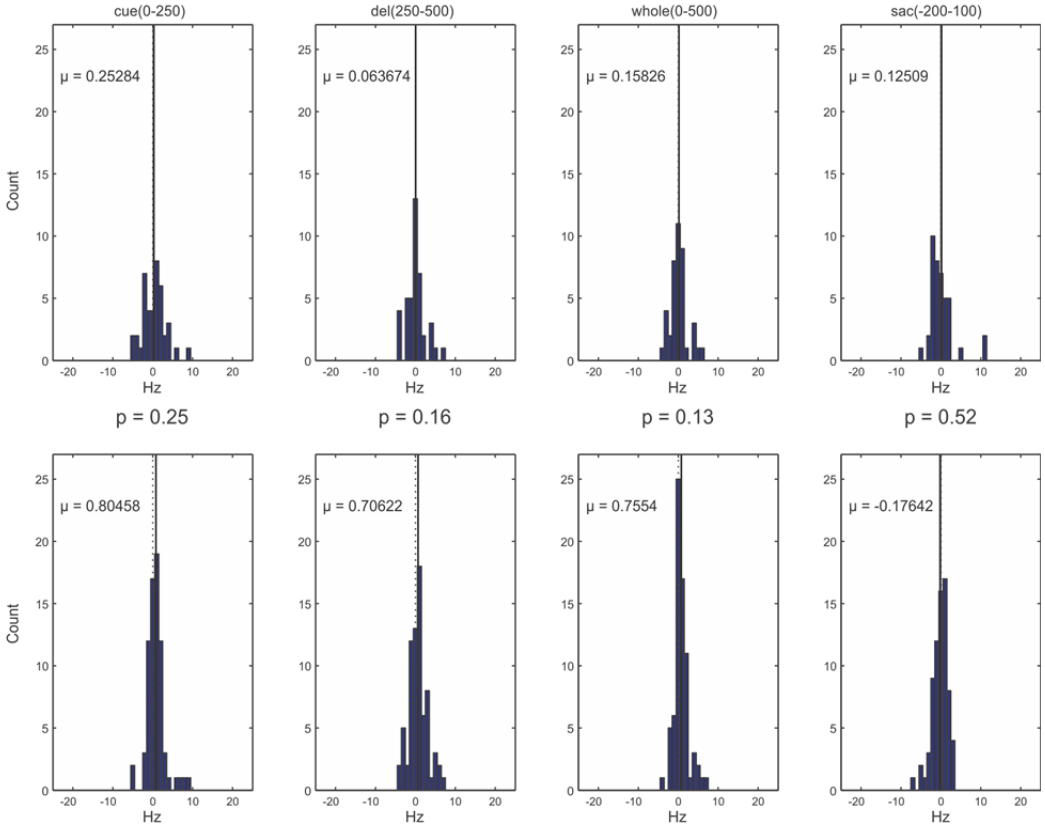
Action Value. No significant differences were observed between LIP and amygdala (Figure 70C).

Global Decision. The distribution of firing rate indices showed a trend ($p = 0.06$) for being greater in amygdala than in LIP (70D).

Therefore, in terms of raw firing rate, the spatial decision signal is of similar strength in amygdala and LIP except around the time of the saccade where it becomes significantly stronger in LIP than amygdala. The global decision signal (choose morph vs. reject morph) is trending toward being significantly stronger in amygdala than in LIP during the second epoch.


A. Spatial decision
LIP
amygdala
B. Global value
LIP
amygdala
cue(0-250)
del(250-500)
whole(0-500)
sac(-200-100)
μ = 3.1066
μ = 4.6206
μ = 3.8636
μ = 7.0664
p = 0.95
p = 0.50
p = 0.75
p = 4.7e-9
μ = 3.1876
μ = 3.8496
μ = 3.5186
μ = -0.47579
μ = 0.52585
μ = 1.03
μ = 0.77795
μ = 0.63179
p = 0.94
p = 0.19
p = 0.33
p = 0.69
μ = 0.48528
μ = 2.0263
μ = 1.2558
μ = 0.45088
Count
Hz

C. Action value



D. Global decision

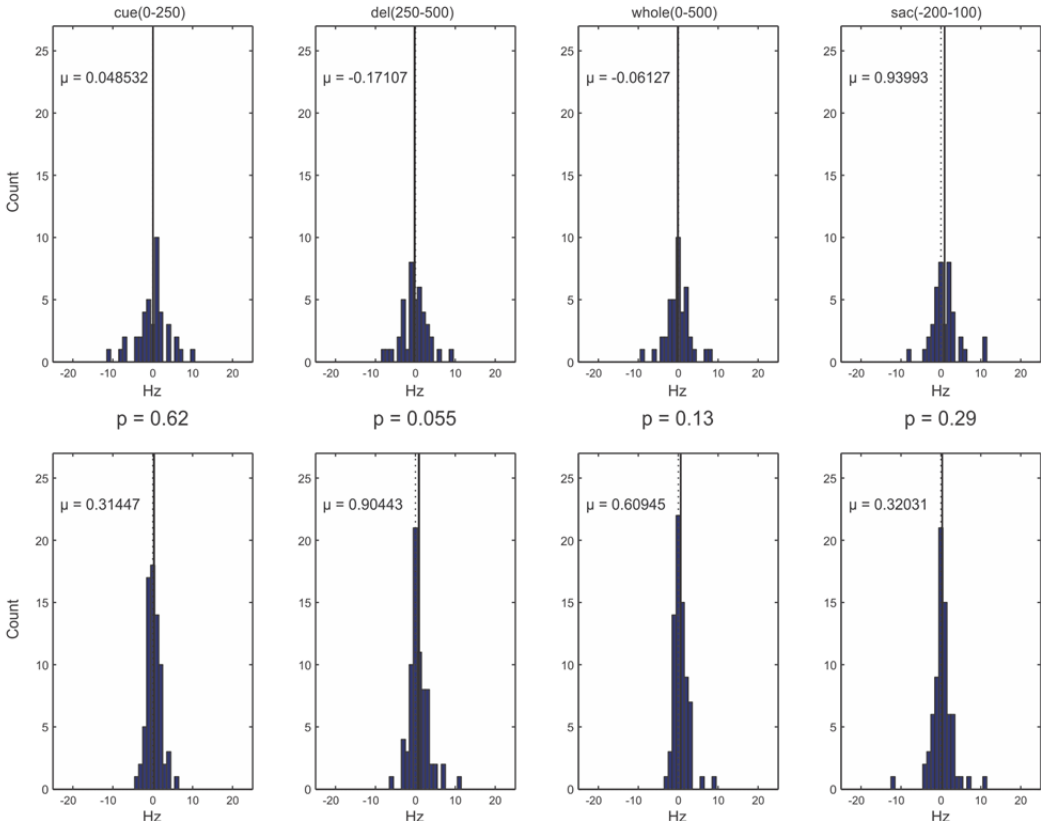


Figure 70. Secondary Effects: Distributions of Neuronal Indices by Epoch
LIP and amygdala comparisons of the four secondary effects. Data is from both monkeys (LIP: n = 41, amygdala: n = 73). **(A)** Spatial decision. **(B)** Global Value. **(C)** Action Value. **(D)** Global Decision. Same conventions as Figure 68.

3.4.1.2 INDIVIDUAL MONKEY DATA

(a) Primary Effects

(i) Ju-Ju

Here we present results from the *Ju-Ju* comparison defined above for Primary Effects.

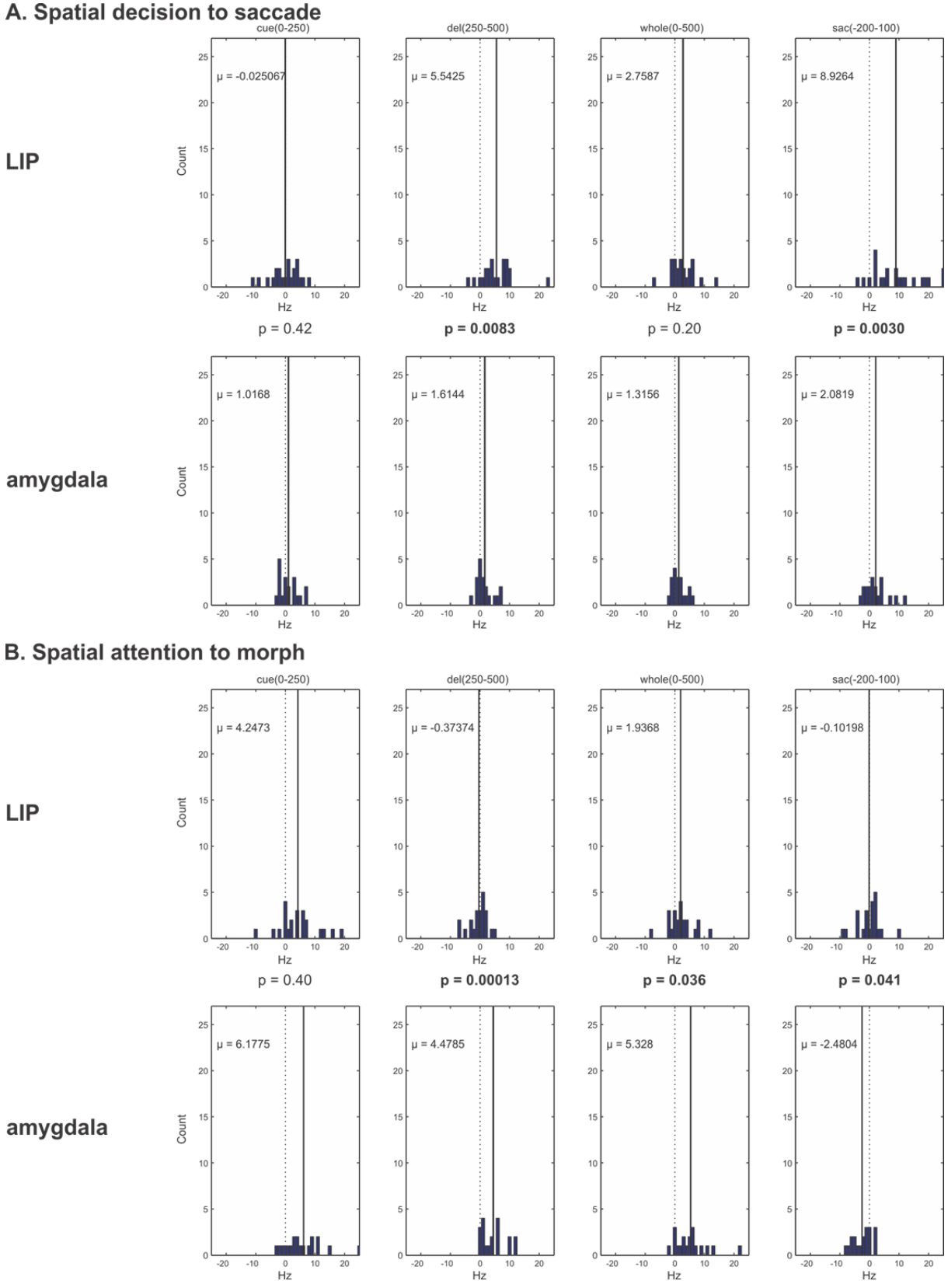
Spatial Decision to Saccade. The mean of the distribution of firing rate indices was significantly greater in LIP than amygdala for the second and saccade epochs (Figure 71A).

Spatial Attention to Morph. The mean of the distribution of firing rate indices was significantly greater in amygdala than LIP during the second and full epochs, but the reverse was true for the saccade epoch (Figure 71B).

Value of Morph in RF. The mean of the distribution of firing rate indices were significantly greater in amygdala than LIP during the second and full epochs (Figure 71C).

Value of Morph out RF. No significant differences were observed between LIP and amygdala (Figure 71D)

Therefore, in terms of raw firing rate, the reward-effects in amygdala are significantly stronger than those in LIP. The saccadic decision signal is significantly stronger in LIP than amygdala. The spatial attention signal is significantly stronger in amygdala than in LIP before the saccade epoch.


A. Spatial decision to saccade
LIP
amygdala
cue(0-250)
del(250-500)
whole(0-500)
sac(-200-100)
μ = -0.025067
μ = 5.5425
μ = 2.7587
μ = 8.9264
p = 0.42
p = 0.0083
p = 0.20
p = 0.0030
μ = 1.0168
μ = 1.6144
μ = 1.3156
μ = 2.0819
B. Spatial attention to morph
LIP
amygdala
μ = 4.2473
μ = -0.37374
μ = 1.9368
μ = -0.10198
p = 0.40
p = 0.00013
p = 0.036
p = 0.041
μ = 6.1775
μ = 4.4785
μ = 5.328
μ = -2.4804
Count
Hz

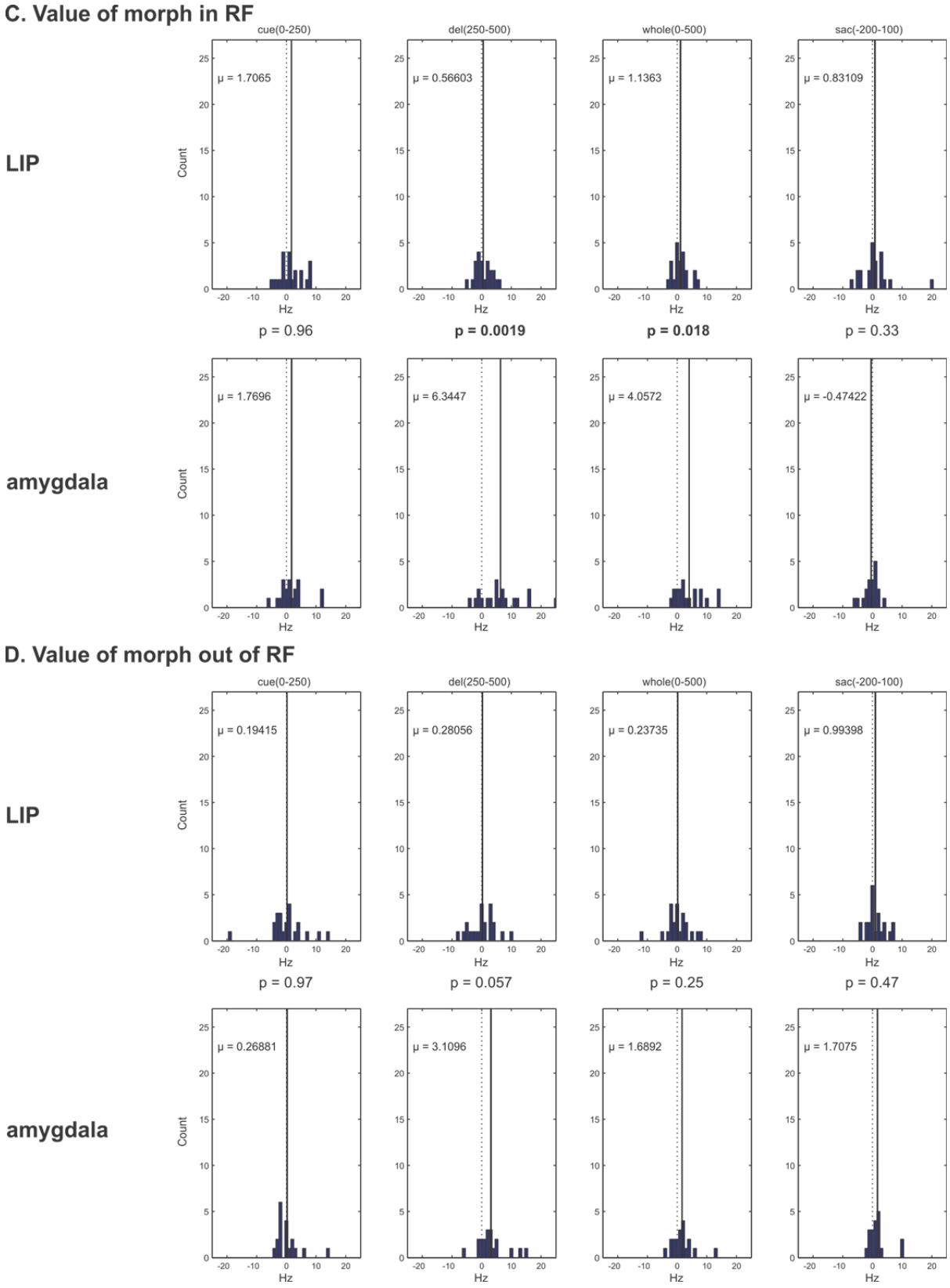


Figure 71. Monkey Ju: Primary Effects Comparisons
Same conventions as Figure 69. LIP: n = 22 neurons, amygdala: n = 19 neurons.

(ii) Je-Je

Here we present results from the *Je-Je* comparison defined above for Primary Effects.

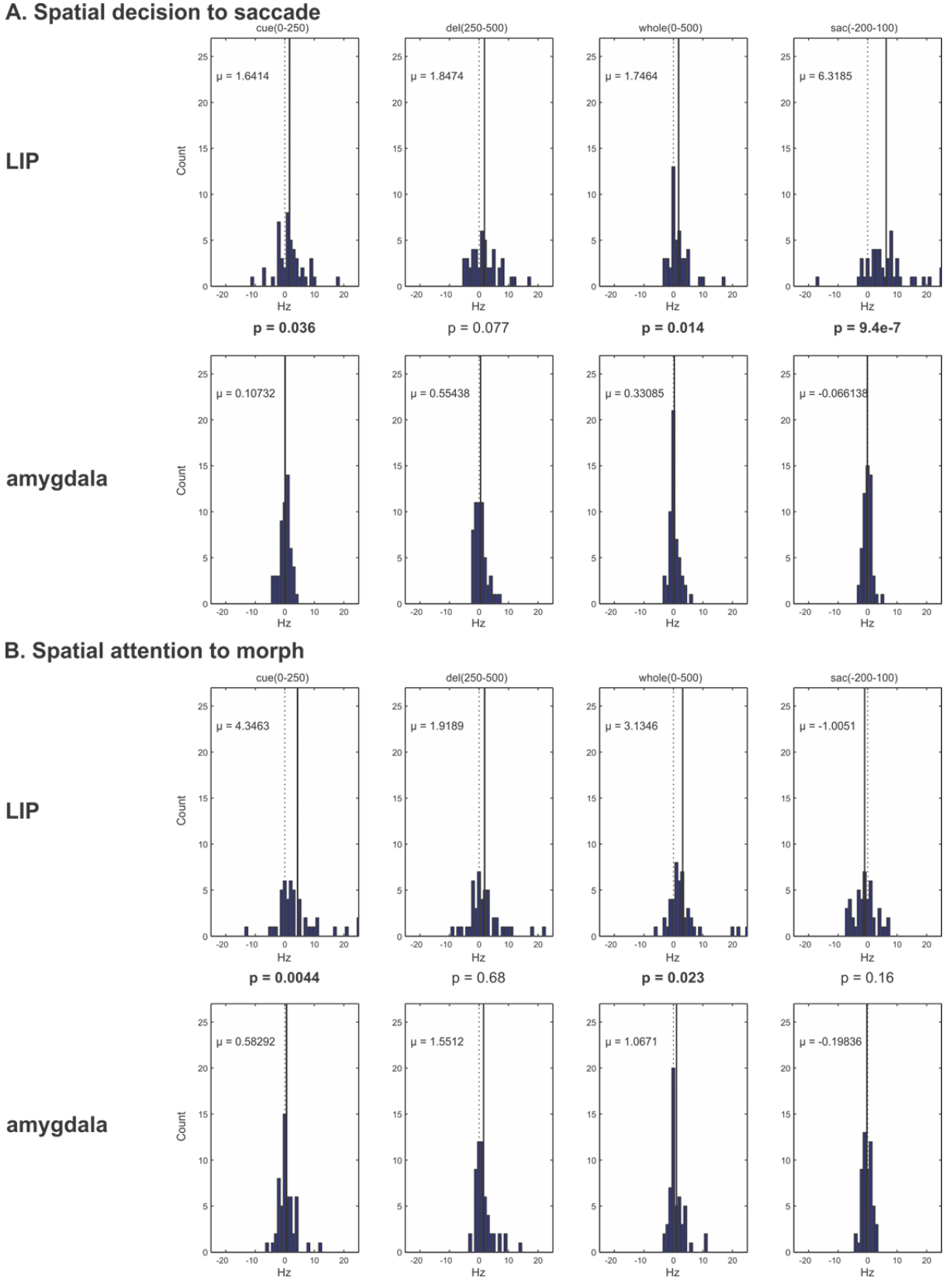
Spatial Decision to Saccade. The mean of the distribution of firing rate indices was significantly greater in LIP than amygdala for the first, full, and saccade epochs (Figure 72A).

Spatial Attention to Morph. The mean of the distribution of firing rate indices was significantly greater in LIP than amygdala during the first and full epochs (Figure 72B).

Value of Morph in RF. The mean of the distribution of firing rate indices was significantly greater in amygdala than LIP during the cue epoch (Figure 72C).

Value of Morph out RF. No significant differences were observed between LIP and amygdala (Figure 72D)

Therefore, in terms of raw firing rate, the reward-effects in amygdala are significantly stronger than those in LIP early during decision-making. The saccadic decision signal is significantly stronger in LIP than amygdala. The spatial attention signal is significantly stronger in LIP than amygdala for monkey Je, which is the opposite pattern for monkey Ju.


A. Spatial decision to saccade
LIP
amygdala
cue(0-250)
del(250-500)
whole(0-500)
sac(-200-100)
μ = 1.6414
μ = 1.8474
μ = 1.7464
μ = 6.3185
p = 0.036
p = 0.077
p = 0.014
p = 9.4e-7
μ = 0.10732
μ = 0.55438
μ = 0.33085
μ = -0.066138
B. Spatial attention to morph
LIP
amygdala
μ = 4.3463
μ = 1.9189
μ = 3.1346
μ = -1.0051
p = 0.0044
p = 0.68
p = 0.023
p = 0.16
μ = 0.58292
μ = 1.5512
μ = 1.0671
μ = -0.19836
Count
Hz

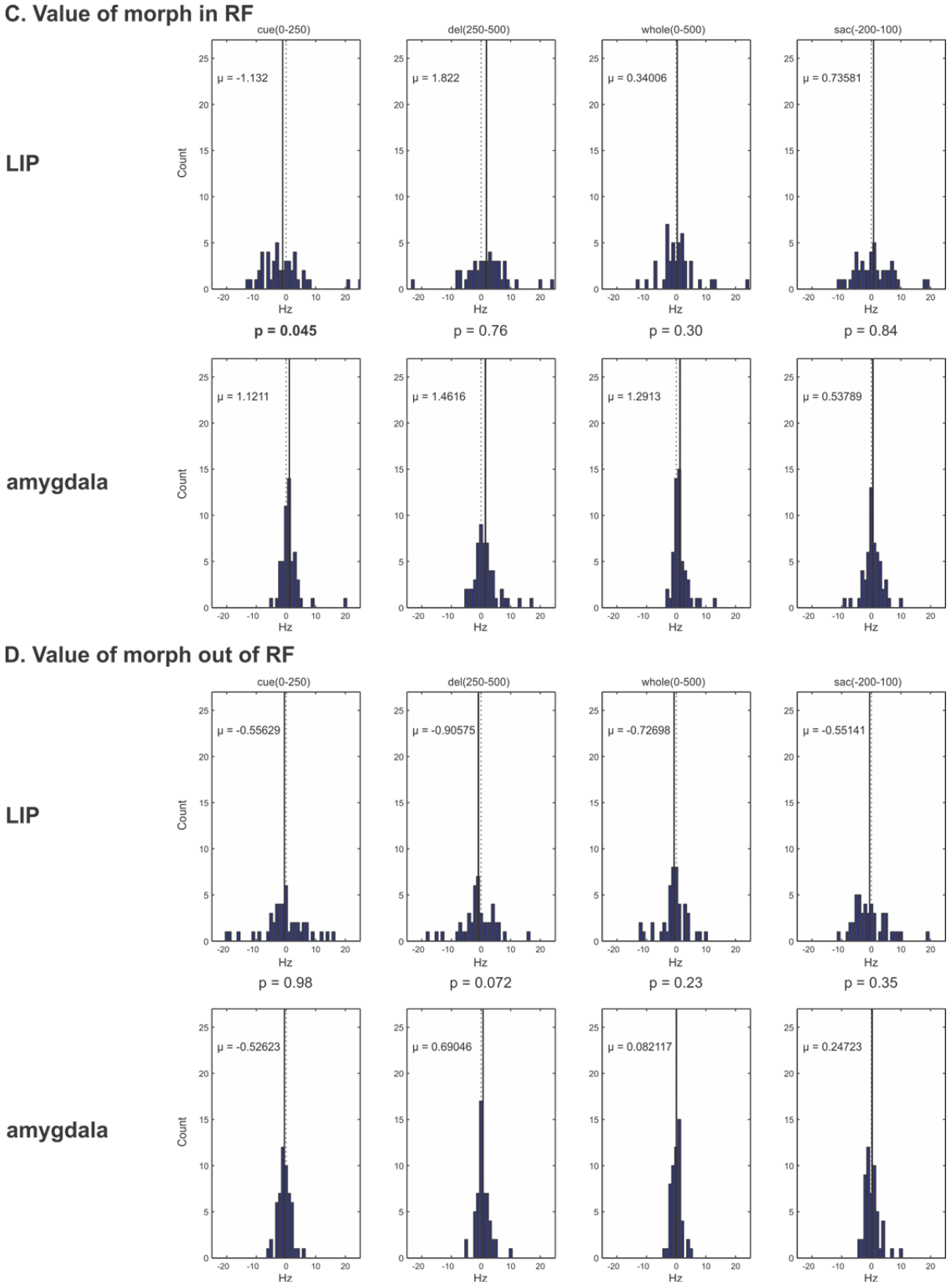


Figure 72. Monkey Je: Primary Effects Comparisons
Same conventions as Figure 69. LIP: n = 45 multi-units, amygdala: n = 54 neurons.

(b) Secondary Effects

(i) Ju-Ju

Here we present results from the *Ju-Ju* comparison defined above for Secondary Effects.

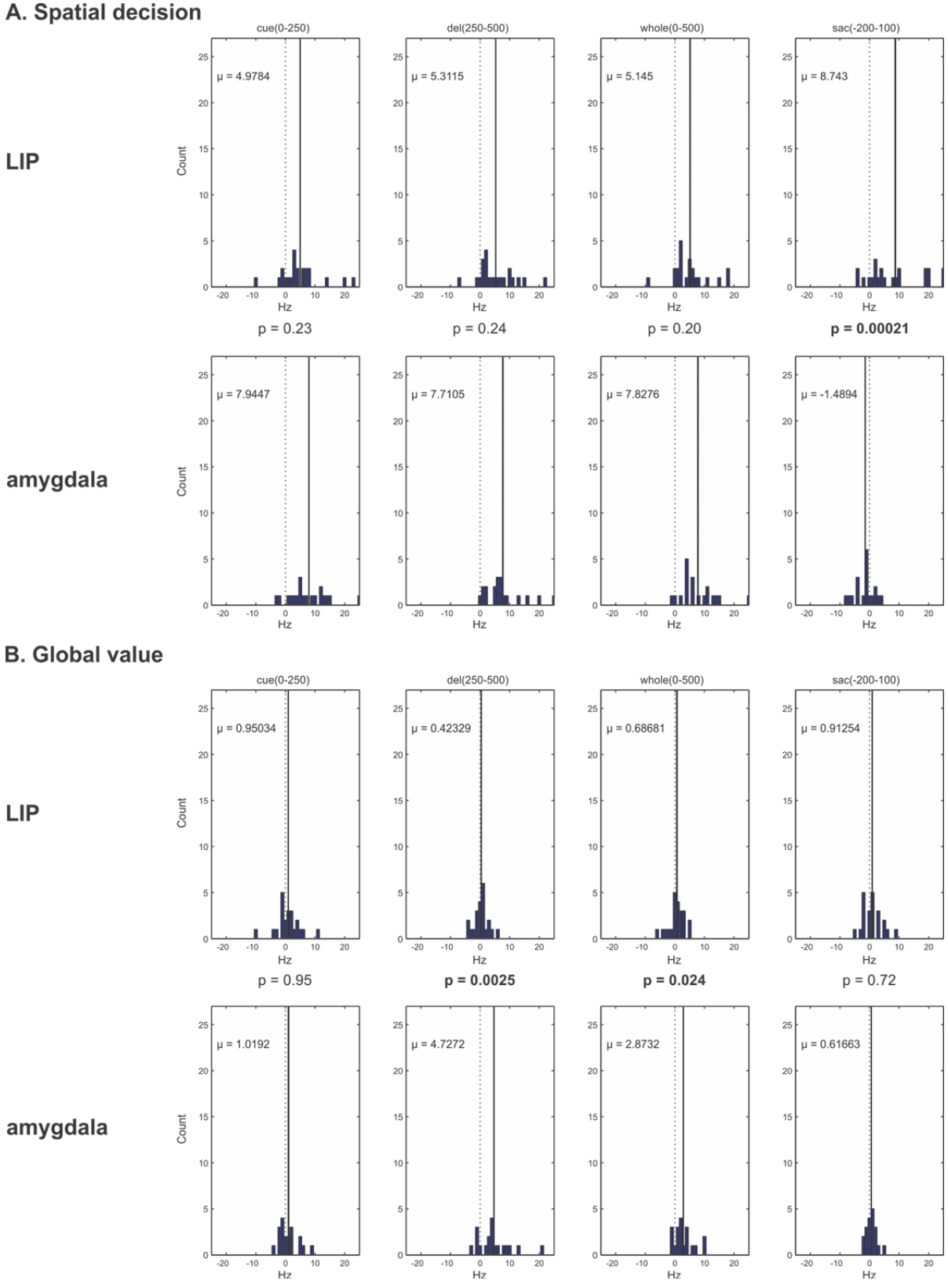
Spatial Decision. The mean of the distribution of firing rate indices was not significantly greater in LIP than amygdala until the saccade epoch (Figure 73A).

Global Value. The mean of the distribution of firing rate indices was significantly greater for amygdala than LIP during the second and full epochs (Figure 73B).

Action Value. No significant differences were observed between LIP and amygdala (Figure 73C).

Global Decision. No significant differences were observed between LIP and amygdala (Figure 73D).

Therefore, in terms of raw firing rate, the spatial decision signal is of similar strength in amygdala and LIP except around the time of the saccade when it becomes significantly stronger in LIP than amygdala. The global decision signal (choose morph vs. reject morph) is significantly stronger in amygdala than in LIP during the second and full epochs.


A. Spatial decision
LIP
amygdala
B. Global value
LIP
amygdala
cue(0-250)
del(250-500)
whole(0-500)
sac(-200-100)
μ = 4.9784
μ = 5.3115
μ = 5.145
μ = 8.743
p = 0.23
p = 0.24
p = 0.20
p = 0.00021
μ = 7.9447
μ = 7.7105
μ = 7.8276
μ = -1.4894
μ = 0.95034
μ = 0.42329
μ = 0.68681
μ = 0.91254
p = 0.95
p = 0.0025
p = 0.024
p = 0.72
μ = 1.0192
μ = 4.7272
μ = 2.8732
μ = 0.61663
Count
Hz

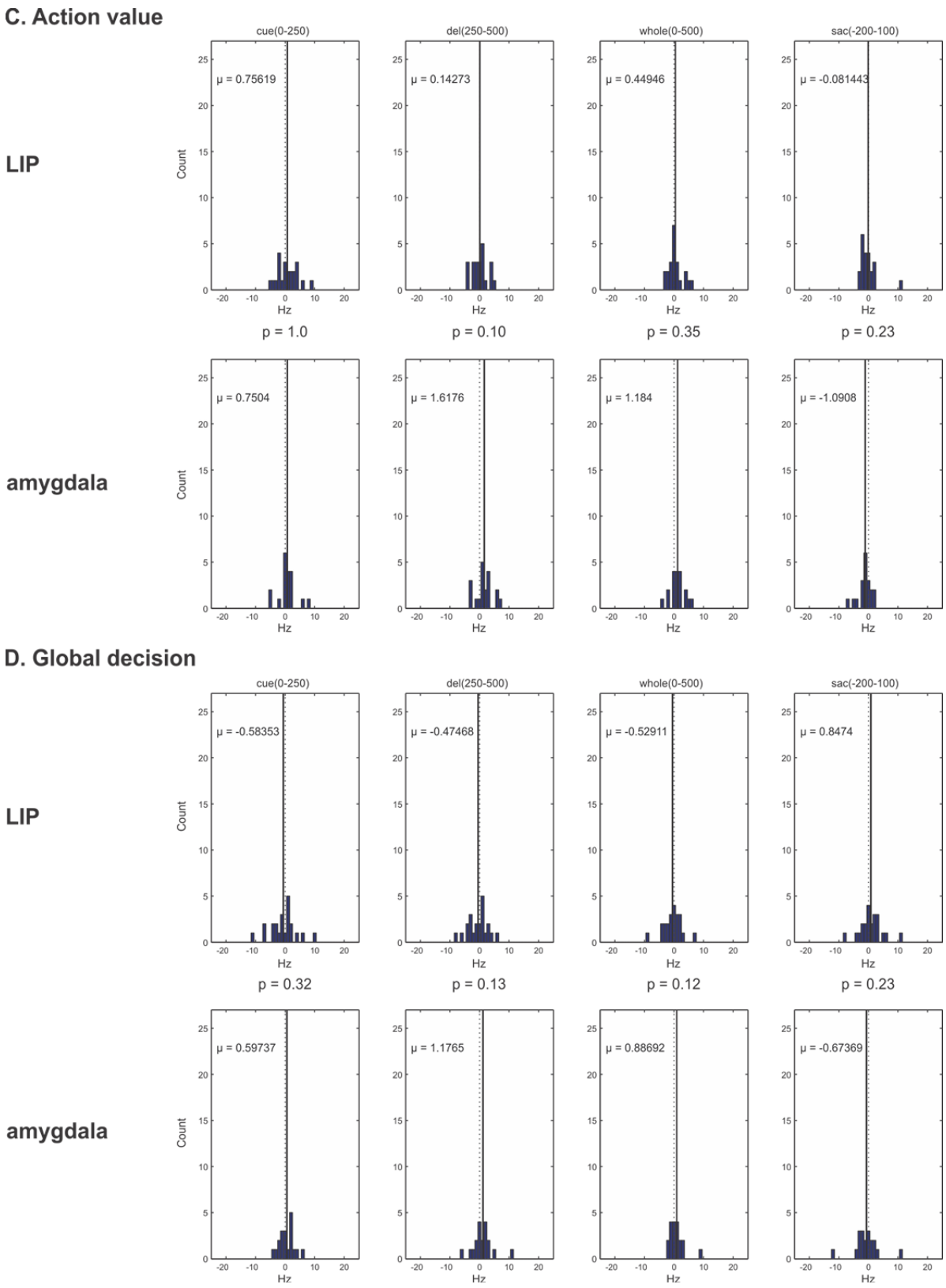


Figure 73. Monkey Ju: Secondary Effects Comparisons
Same conventions as Figure 70. LIP: n = 22 neurons, amygdala: n = 19 neurons.

(ii) Je-Je

Here we present results from the *Je-Je* comparison defined above for Secondary Effects.

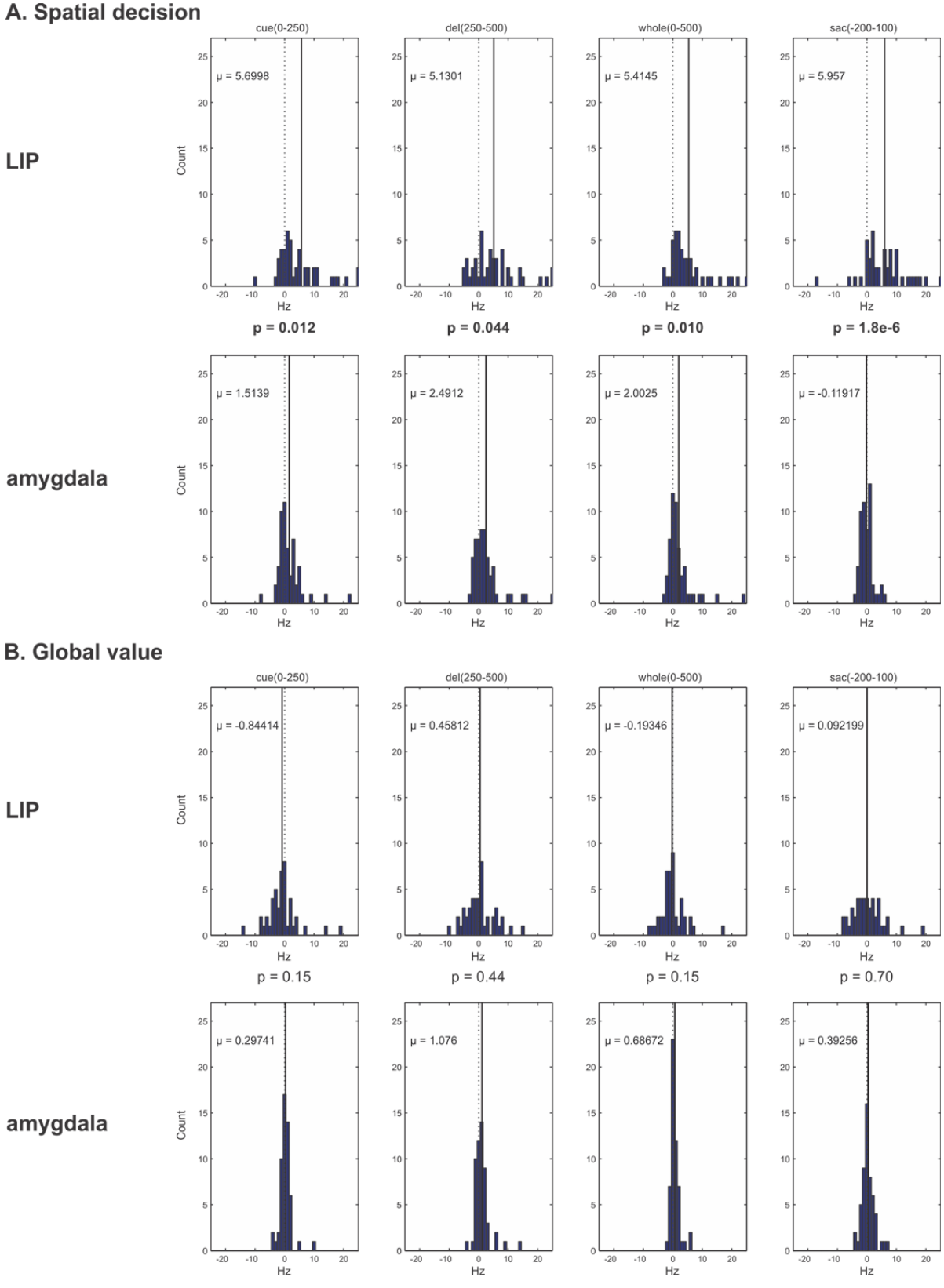
Spatial Decision. The mean of the distribution of firing rate indices was significantly greater in LIP than amygdala across all epochs (Figure 74A).

Global Value. No significant differences were observed between LIP and amygdala (Figure 74B).

Action Value. No significant differences were observed between LIP and amygdala (Figure 74C).

Global Decision. The mean of the distribution of firing rate indices was significantly greater in amygdala than LIP in the saccade epoch (Figure 74D).

Therefore, in terms of raw firing rate, the spatial decision signal is stronger in LIP than in amygdala across all epochs. The global decision signal (choose morph vs. reject morph) is only significantly stronger in amygdala than in LIP during the saccade epoch.


A. Spatial decision
LIP
amygdala
B. Global value
LIP
amygdala
cue(0-250)
del(250-500)
whole(0-500)
sac(-200-100)
μ = 5.6998
μ = 5.1301
μ = 5.4145
μ = 5.957
p = 0.012
p = 0.044
p = 0.010
p = 1.8e-6
μ = 1.5139
μ = 2.4912
μ = 2.0025
μ = -0.11917
μ = -0.84414
μ = 0.45812
μ = -0.19346
μ = 0.092199
p = 0.15
p = 0.44
p = 0.15
p = 0.70
μ = 0.29741
μ = 1.076
μ = 0.68672
μ = 0.39256
Count
Hz

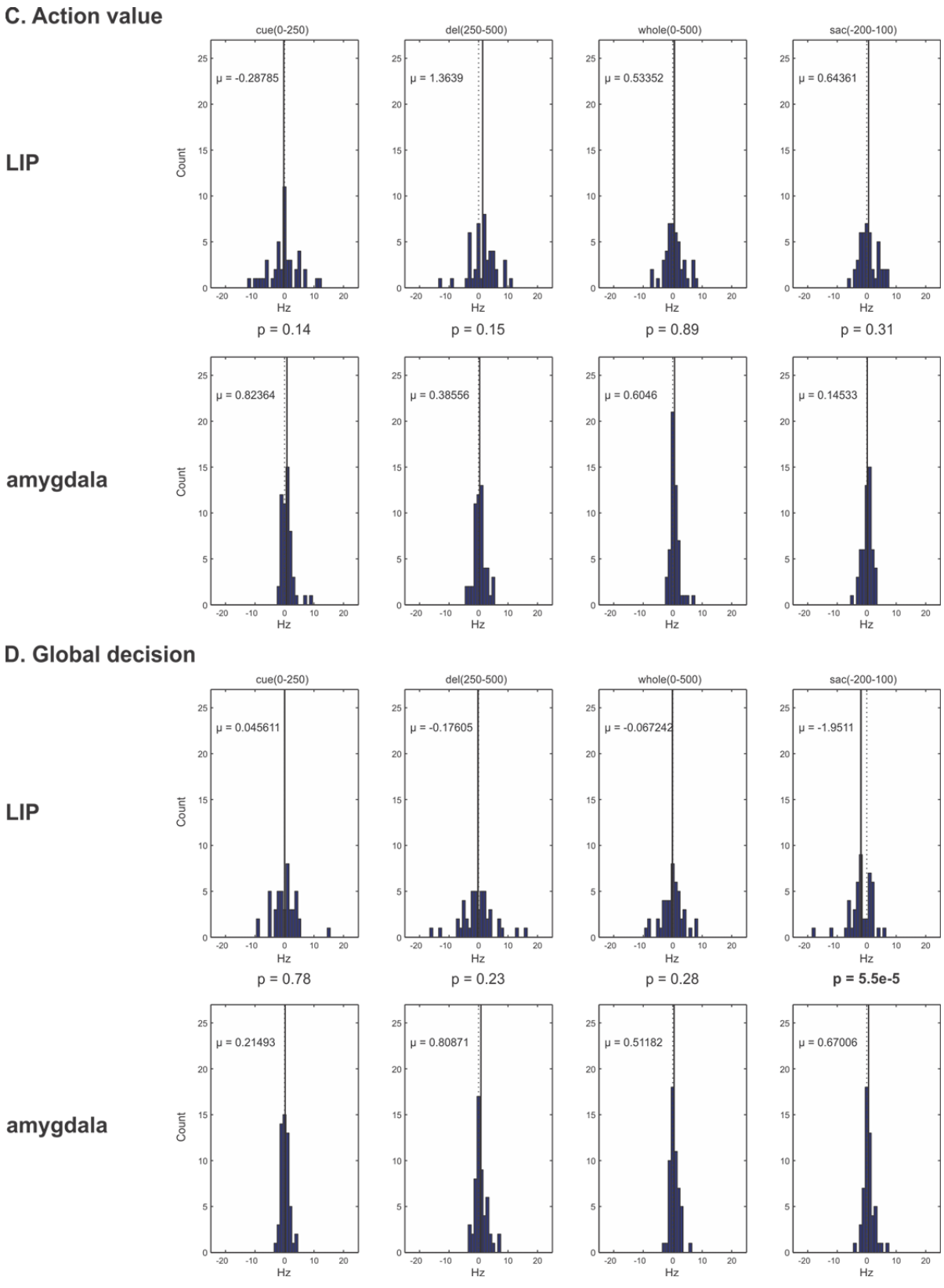


Figure 74. Monkey Je: Secondary Effects Comparisons
Same conventions as Figure 70. LIP: n = 45 multi-units, amygdala: n = 54 neurons.

3.5 DISCUSSION

In this experiment, we recorded LIP and amygdala neurons in monkeys making-value based decisions involving cues that were differentially rewarding but whose ability to acquire differential salience was controlled for by a morphing manipulation that gave the cues near-identical visual features. During both LIP and amygdala recording sessions, monkeys chose the ambiguous cue more often when it was the morph associated with a large reward than if it was the morph associated with no-reward. Our main analysis was to test for reward-effects on trials when the monkeys chose the ambiguous option in the RF. In LIP, effects of morph-value were weakened and delayed. The population of LIP neurons did not show a significant reward-effect within the first 250 ms after cue onset. The number of single LIP neurons with significant reward-effects was no greater than expected by chance. In amygdala, effects of morph-value were stronger and earlier than in LIP. The number of single amygdala neurons with significant reward-effects was greater than expected by chance. Therefore, the main result of Experiment 2 (Chapter 3.0) showed that early reward-effects depend upon cue-salience in LIP but not in the amygdala.

4.0 GENERAL DISCUSSION

The overall goal of this dissertation was to study representation of value and salience in the primate brain. To do this, we recorded neuronal activity in two brain areas, LIP and the amygdala, while monkeys made value-based decisions. We focused on neuronal activity that appeared early after the onset of the two choice-options at which time the monkeys were putatively weighing the values of each option and deciding between them. We posed two experimental questions. (1) Do neurons in LIP and amygdala encode the worth (value) or importance (salience) of choice-options early during value-based decision-making? (2) Do early reward-effects in neurons in LIP and amygdala depend on stronger automatic capture of visual attention by the option promising larger reward?

To dissociate value from salience, we designed a value-based decision-making task with options associated with differential reward-sizes as well as options associated with differential penalty-sizes. *Value* increases with the promise of reward but decreases with the threat of penalty. *Salience* increases with the intensity of promises as well as threats. In LIP, neurons encoded salience. The population of LIP neurons fired more for options promising more reward and also fired more for options threatening more penalty. In the amygdala, we observed value-coding in the form of a negative correlation. The population of amygdala neurons fired more for options promising more reward but fired less for options threatening more penalty. Therefore,

the main result of Experiment 1 (Chapter 2.0) was that neurons in LIP encoded cue-salience but neurons in the amygdala encoded cue-value early during value-based decision-making.

To determine whether early reward-effects depended on cue-salience, we designed a value-based decision-making task in which one visually distinct "safe" option promised small but certain reward and the other visually ambiguous option was either a morph associated with a large reward or a near-identical looking morph associated with no reward. Making the physical properties of the largest reward-option virtually identical to the no-reward option precluded greater early automatic capture of attention by the morph associated with greater reward. The monkeys chose the large-reward morph over the safety almost every time but chose the no-reward morph about as often as they chose the safety. Our main analysis compared trials when the monkeys chose the ambiguous option in the RF. On the one hand, neurons involved in encoding value for value-based decision making might show early-reward effects that do not depend on option-salience. On the other hand, neurons whose early reward-effects reflect an option's associative-salience might not differentiate the two differentially valuable but visually similar morph-options. In LIP, effects of morph-value were weakened and delayed. The population of LIP neurons did not show a significant reward-effect within the first 250 ms after cue onset. The numbers of single LIP neurons with significant reward-effects was no greater than expected by chance. In amygdala, effects of morph-value were stronger and earlier than in LIP. The numbers of single amygdala neurons with significant reward-effects was greater than expected by chance. Therefore, the main result of Experiment 2 (Chapter 3.0) was that early reward-effects depend upon cue-salience in LIP but not in the amygdala.

4.1 CHALLENGES TO REWARD-PENALTY RESULTS IN LIP

This dissertation presents a result from LIP (Chapter 2.1) that was challenged by those who consider LIP to encode action-value for mediating value-based decision-making (Leathers & Olson, 2013; Newsome et al., 2013). However, Newsome et al. (2013) question neither our key result – that large-penalty cues elicited stronger responses than small-penalty cues – nor our key conclusion – that neurons early in the trial signaled cue salience and not action value. Instead, they focus on subsequent neuronal activity. The patterns of delay-period activity which they note can be explained by reference to experimental methodology.

The stated goal of our study (Chapter 2.1) was to test a specific hypothesis: that LIP neurons mediate value-based decisions by signaling early in the trial, prior to the decision, the values of the outcomes associated with the possible actions. This hypothesis has been put forward explicitly by some of the commentators (Louie & Glimcher, 2010; Sugrue et al., 2005) and is concordant with the description by others of early reward-related activity (Klein et al., 2008; Platt & Glimcher, 1999; Rorie et al., 2010; Seo et al., 2009; Sugrue et al., 2004). Our demonstration that LIP neurons did not carry value signals early in the trial, despite the fact that monkeys were making value-based decisions, constitutes an existence disproof of the hypothesis. Having shown it to be false in the context of one task, we argue that it cannot have general truth. This conclusion is appropriately broad without being unduly sweeping.

Which neurons should we have studied? Newsome et al. suggest that the neurons we selected for study were not an appropriate population on which to test the action-value hypothesis. We argue, on the contrary, that these neurons were exactly the appropriate population because they displayed the key functional trait on the basis of which the action-value hypothesis was propounded. Early in the trial, at the time of the value-based decision, they fired

more strongly when a saccade into the response field would elicit a large reward than when it would elicit a small reward.

What is normal delay-period activity? Newsome et al. focus in their comments on a period of the trial later than the period on which our analysis was based. They suggest that activity during the delay period deviated from the norm for LIP. We respond that the norm depends on the experimental conditions. Among authors studying value-related signals in LIP, some recorded only from neurons with strong delay-period activity (Rorie et al., 2010; Sugrue et al., 2004) while others including us sampled neurons broadly (Klein et al., 2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Seo et al., 2009). Some placed targets in and opposite the center of each neuron's response field (Klein et al., 2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Rorie et al., 2010; Sugrue et al., 2004) while others including us positioned them to the right and left of fixation (Seo et al., 2009). Others allowed targets to remain visible on the screen during the delay period (Klein et al., 2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Rorie et al., 2010; Seo et al., 2009; Sugrue et al., 2004) whereas we did not. Each of our design decisions reduced delay-period activity – not our ability to test the hypothesis that neurons signaled action value early in the trial. We expand on this point below in connection with three issues.

1. Memory delay activity. This is commonly defined as firing that rises above baseline during the delay period preceding a saccade to the center of the response field. The rate of incidence of memory delay activity in LIP is around 25% according to a recent report based on unbiased sampling (Premereur, Vanduffel, & Janssen, 2011). We cannot estimate the percentage of neurons in our sample that exhibited memory delay activity because we placed targets to the right and left of fixation rather than at the center of and opposite the response field. However, we

do note that memory delay activity is a poor predictor of decision-related activity among LIP neurons (Meister, Hennig, & Huk, 2013).

2. Saccade-direction activity. Neurons in our study unquestionably signaled the direction of the impending saccade during the delay period. They fired more strongly for a saccade into than for a saccade out of the response field as shown in Figure 1D-E of the original paper. Neurons whose response fields were not precisely centered on a target may, however, have carried comparatively weak signals. To be sure that the critical observations of the experiment were not specific to neurons weakly selective for saccade direction, we analyzed the correlation between the strength of the delay-period saccade-direction signal and the cue-period reward and penalty signals. The tendency for a large-reward cue to elicit stronger firing than a small-reward cue was actually positively correlated with the strength of the delay-period saccade-direction signal. So was the tendency for a large-penalty cue to elicit stronger firing than a small-penalty cue.

3. Late bias activity. In prior studies, reward-related activity persisted to the end of the trial as if reflecting an enduring post-decisional motoric or attentional bias in favor of the target associated with greater reward (Klein et al., 2008; Louie & Glimcher, 2010; Platt & Glimcher, 1999; Rorie et al., 2010; Seo et al., 2009; Sugrue et al., 2004). This effect might have occurred because the targets remained visible during the delay period and thus could attract attention or incite a bias in proportion to their associated value. The absence of a late bias signal in our study may be attributable to the absence of visible targets during the delay period or to other unique features of task design such as the use of cues with absolutely fixed significance.

We conclude by noting that all three neurons displaying the entire triad of effects discussed above – (1) memory delay activity, (2) saccade direction activity and (3) late bias

activity – also exhibited the two cue-period effects at the heart of our study: they responded more strongly to large-reward than to small-reward cues and they responded more strongly to large-penalty than to small-penalty cues. Even among these neurons, in other words, firing early in the trial depended on the salience of the cues and not on their value. We present data from these neurons in Figure 75.

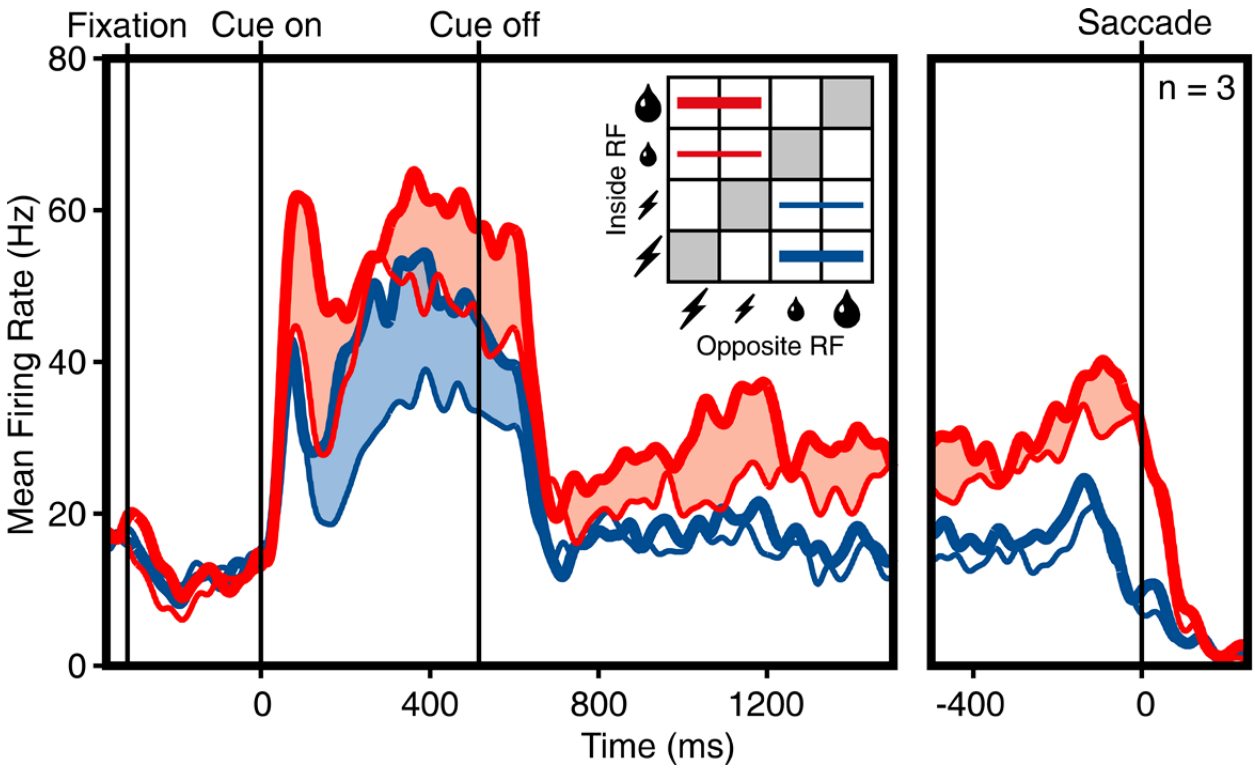


Figure 75. Mean Firing Rate
Mean firing rate of three LIP neurons under conditions indicated in the inset. The freely chosen saccade was directed into the response field under red conditions and away from it under blue conditions. The neurons responded more strongly to large-reward than to small-reward cues (red fill) and to large-penalty than to small penalty cues (blue fill).

As shown in Chapter 2, we not only recorded from LIP neurons (Chapter 2.1) but also from amygdala neurons while monkeys performed the same reward-penalty task (Chapter 2.2). During the same task, LIP neurons encoded cue-salience but amygdala neurons encoded cue-value—early during decision-making. Added to Roesch and Olson's (2004) use of an earlier reward-penalty task to dissociate value in orbitofrontal cortex from salience in premotor cortex,

the reward-penalty paradigm has dissociated value from salience in four areas of the primate brain. This further validates the reward-penalty task as a useful tool for disentangling representations of value and salience in the primate brain.

4.2 CHALLENGES FROM THE MORPH RESULTS IN LIP

Many studies of decision-making at the single neuron level have recorded neurons from parietal area LIP in monkeys making perceptual decisions by indicating their choice via saccade for reward (Gold & Shadlen, 2007; Shadlen & Kiani, 2013). We recorded from LIP neurons during a perceptual decision-making task in which monkeys indicated their choice via saccade for reward (Chapter 3.2). There is a form of salience acquired by different looking and differentially rewarding visual features (Anderson, 2013). Perceptual decision tasks do not control for the associative salience acquired by their stimulus. In fact, differences in feature intensity are the key variable in perceptual decision tasks. Unlike previous perceptual decision tasks, we prevented our stimuli from acquiring differential salience by morphing them to control for the strength of their visual signal. We held difficulty constant throughout our task at about 75% correct or near psychophysical threshold. We found that, under these conditions, LIP neurons do not show early reward-effects decision-making. This result shows that early reward-effects in LIP neurons depend upon differential, automatic capture of visual attention. Our result casts doubt on the view that LIP neurons mediate value-based decisions by encoding action-value early during decision-making. Do our results from the morph experiment also challenge previous studies claiming that LIP mediates perceptual decisions?

As has been pointed out in the literature, physically distinct and differentially rewarding cues can lead to increased neuronal activity that could masquerade as value but instead be related to other processes such as motivational modulation of motor plans in premotor cortex (Roesch & Olson, 2004, 2007) or of salience in LIP (Leathers & Olson, 2012). Further, proponents of the view that LIP neurons encode action-value have claimed specifically that the decision-variables in LIP observed during perceptual decision tasks are in fact representations of action-value (P. W. Glimcher, 2010). During perceptual decision-making, the probability of the RF saccade earning reward is a function of the probability of the perceptual decision being correct which is a function of the intensity of the sensory stimulus. These confounds are real. This dissertation has demonstrated that early reward-effects are LIP are present for visually distinct stimuli (Chapter 2.1) but absent for ambiguous stimuli that cannot acquire differential associative-salience (Chapter 3.2). Therefore, the decision-variable in LIP observed during perceptual decision tasks could reflect differential cue-salience by virtue of differential visual stimulus strengths being repeatedly associated with differential reward. Could the claims that LIP neurons instantiate the conversion of sensory evidence to commitment/confidence/certainty in that the RF saccade plan is the correct one and will be rewarded (Shadlen & Newsome, 1996); (Kiani & Shadlen, 2009) be explained by the results in this dissertation that early activity in LIP neurons during perceptual decision making depends on cue-salience, instead of reflecting an economic or perceptual decision-process taking place in LIP (P. Glimcher, 2014; Shadlen & Kiani, 2013)?

The fundamental claim supported by results from perceptual decision tasks is that LIP neurons encode a decision-variable, quantified as the log-likelihood ratio of evidence in favor of making a saccade into the RF over making a saccade out of the RF (Gold & Shadlen, 2001; Shadlen & Kiani, 2013). This weight of evidence is defined as a type of "common currency" for

saccadic decision-making based on visual cues: “common” because the currency is said to incorporate not only sensory signals that a stimulus provides in favor of the RF saccade-target location but also non-sensory evidence like the expected value of reward associated with that RF saccade (Gold & Shadlen, 2001). Sensory signals and associated value are hypothesized to combine additively into this decision-variable in LIP firing rates (Gold & Shadlen, 2001). In short, the greater the sensory evidence and expected value, the greater the LIP response, and the greater the likelihood that the monkey decides to make an RF saccade. That is an indisputable scientific fact based on observation. The interpretation of it is what is in question. Are LIP neurons biologically instantiating the sum of value- and sensory-based evidence in a common currency of firing rate or simply reflecting the uncontrolled for cue-salience that exists in all previous perceptual-decision recording-studies besides the morph task?

The possibility exists. Value is discounted (subtracted from) by the effort, difficulty, or uncertainty associated with a particular choice. In the morph task, the monkeys nearly always choose the good morph over safety but are approximately indifferent to the bad morph and safety. Expected value, as sometimes defined by neuroeconomists, is the amount of reward multiplied by the probability of receiving it (P. Glimcher, 2013, 2014). Thus, the choices made to the good morph should possess higher expected value than choices to the bad morph. The question is not whether the morph is more valuable than the safety. We infer, no matter which morph is chosen, that the monkey deemed that morph more valuable than safety on that trial. Instead, the question is whether LIP differentiates the higher expected value for good-morph choices than bad-morph choices. Our main result in LIP in the morph task is that there is no statistically significant difference, early during decision-making, between LIP firing rates for the high-value morph choices versus the low-value morph choices. Sensory evidence is nearly

constant between the good and bad morph. However, expected value is different. If sensory evidence and value sum into a decision variable that LIP represents to mediate saccadic choices (Gold & Shadlen, 2001; Shadlen & Kiani, 2013), then why is this decision-variable reflected in the amygdala but apparently not in LIP?

There are two models of perceptual decision-making that could result from the model presented by Gold and Shadlen (2001). No one knows the answer to which is correct at this point in time. If sensory-evidence and expected value determine what is perceived and, therefore, chosen then it appears that LIP is not discounting the bad morph by the lower likelihood that it will result in reward (Chapter 3.2). However, the amygdala is (Chapter 3.3). If perception happens first and then value expectation follows, then it is possible that LIP neurons, by not differentiating between good-morph and bad-morph choices, are in fact encoding the perceived value of those options and could be mediating the decision-process using a common neuronal currency of firing rate in LIP. Also, amygdala neurons could simply be reflecting the value, not of what is perceived, but of what is actually there. That the monkeys' choose the good-morph when amygdala firing rates are high and still choose the bad-morph when amygdala firing rates are low could mean that the amygdala is not involved in process of associating value with percepts but with objects that are objectively present. However, until these questions are answered, I think the most parsimonious interpretation of the morph results are as follows. Amygdala neurons encode the expected value of the morph that is actually present but do not carry out the decision-making process. LIP neurons, unlike amygdala neurons, do not differentiate the expected values of the two morphs because LIP neurons encode cue-salience, which is controlled for in this experiment to not be differential between the two morphs. In other words, to challenge the hypothesis that LIP neurons encode value discounted by the level of

uncertainty about committing to or being confident in the decision (Gold & Shadlen, 2001; Shadlen & Kiani, 2013; Shadlen & Newsome, 1996, 2001), LIP neurons instead show early reward-effects during value-based and perceptual decision-making tasks in which cue-salience is an uncontrolled variable.

Collectively, the results from the two experiments in this dissertation cast doubt upon the idea that LIP mediates value-based decisions (Chapter 2.1) and perceptual decisions (Chapter 3.2) in accordance with the action-value (P. Glimcher, 2014; Sugrue et al., 2004) or intentional framework (Shadlen, Kiani, Hanks, & Churchland, 2008). Instead, our experiments show that the amygdala encodes cue-value for contralateral choice-options early during both types of decision-making (Chapters 2.2 and 3.3). This supports the idea that value-based decisions are mediated in limbic circuits involving amygdala and orbitofrontal cortex (Roesch & Olson, 2004), perhaps in a goods-based framework (Padoa-Schioppa & Cai, 2011) that does not depend upon the visual properties of the choice-options having acquired differential salience via associative learning.

BIBLIOGRAPHY

Aggleton, J. P., & Passingham, R. E. (1981). Syndrome produced by lesions of the amygdala in monkeys (Macaca mulatta). *J Comp Physiol Psychol, 95*(6), 961-977.

Amaral, D. G., & Price, J. L. (1984). Amygdalo-cortical projections in the monkey (Macaca fascicularis). *J Comp Neurol, 230*(4), 465-496. doi: 10.1002/cne.902300402

Andersen, R. A., Asanuma, C., Essick, G., & Siegel, R. M. (1990). Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. *J Comp Neurol, 296*(1), 65-113. doi: 10.1002/cne.902960106

Andersen, R. A., Essick, G. K., & Siegel, R. M. (1985). Encoding of spatial location by posterior parietal neurons. *Science, 230*(4724), 456-458.

Anderson, B. A. (2013). A value-driven mechanism of attentional selection. *J Vis, 13*(3). doi: 10.1167/13.3.7

Anderson, B. A., Laurent, P. A., & Yantis, S. (2011). Learned value magnifies salience-based attentional capture. *PLoS One, 6*(11), e27926. doi: 10.1371/journal.pone.0027926

Arcizet, F., Mirpour, K., & Bisley, J. W. (2011). A pure salience response in posterior parietal cortex. *Cereb Cortex, 21*(11), 2498-2506. doi: 10.1093/cercor/bhr035

Baizer, J. S., Desimone, R., & Ungerleider, L. G. (1993). Comparison of subcortical connections of inferior temporal and posterior parietal cortex in monkeys. *Vis Neurosci, 10*(1), 59-72.

Balan, P. F., & Gottlieb, J. (2009). Functional significance of nonspatial information in monkey lateral intraparietal area. *J Neurosci, 29*(25), 8166-8176. doi: 10.1523/jneurosci.0243-09.2009

Barbas, H., & De Olmos, J. (1990). Projections from the amygdala to basoventral and mediodorsal prefrontal regions in the rhesus monkey. *J Comp Neurol, 300*(4), 549-571. doi: 10.1002/cne.903000409

Bartolomeo, P. (2006). A parietofrontal network for spatial awareness in the right hemisphere of the human brain. *Arch Neurol, 63*(9), 1238-1241. doi: 10.1001/archneur.63.9.1238

Bartolomeo, P. (2007). Visual neglect. *Curr Opin Neurol, 20*(4), 381-386. doi: 10.1097/WCO.0b013e32816aa3a3

Belova, M. A., Paton, J. J., & Salzman, C. D. (2008). Moment-to-moment tracking of state value in the amygdala. *J Neurosci, 28*(40), 10023-10030. doi: 10.1523/jneurosci.1400-08.2008

Ben Hamed, S., Duhamel, J. R., Bremmer, F., & Graf, W. (2001). Representation of the visual field in the lateral intraparietal area of macaque monkeys: a quantitative receptive field analysis. *Exp Brain Res, 140*(2), 127-144.

Bendiksby, M. S., & Platt, M. L. (2006). Neural correlates of reward and attention in macaque area LIP. *Neuropsychologia, 44*(12), 2411-2420. doi: 10.1016/j.neuropsychologia.2006.04.011

Berridge, K. C. (2003). *Well-Being: Foundations of Hedonic Psychology*. New York: Russell Sage Foundation.

Bisley, J. W., & Goldberg, M. E. (2010). Attention, intention, and priority in the parietal lobe. *Annu Rev Neurosci, 33*, 1-21. doi: 10.1146/annurev-neuro-060909-152823

Braesicke, K., Parkinson, J. A., Reekie, Y., Man, M. S., Hopewell, L., Pears, A., . . . Roberts, A. C. (2005). Autonomic arousal in an appetitive context in primates: a behavioural and neural analysis. *Eur J Neurosci, 21*(6), 1733-1740. doi: 10.1111/j.1460-9568.2005.03987.x

Brosch, T., Pourtois, G., Sander, D., & Vuilleumier, P. (2011). Additive effects of emotional, endogenous, and exogenous attention: behavioral and electrophysiological evidence. *Neuropsychologia, 49*(7), 1779-1787. doi: 10.1016/j.neuropsychologia.2011.02.056

Buschman, T. J., & Miller, E. K. (2007). Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science, 315*(5820), 1860-1862. doi: 10.1126/science.1138071

Coe, B., Tomihara, K., Matsuzawa, M., & Hikosaka, O. (2002). Visual and anticipatory bias in three cortical eye fields of the monkey during an adaptive decision-making task. *J Neurosci, 22*(12), 5081-5090.

Colby, C. L., & Duhamel, J. R. (1996). Spatial representations for action in parietal cortex. *Brain Res Cogn Brain Res, 5*(1-2), 105-115.

Colby, C. L., & Goldberg, M. E. (1999). Space and attention in parietal cortex. *Annu Rev Neurosci, 22*, 319-349. doi: 10.1146/annurev.neuro.22.1.319

Dorris, M. C., & Glimcher, P. W. (2004). Activity in posterior parietal cortex is correlated with the relative subjective desirability of action. *Neuron, 44*(2), 365-378. doi: 10.1016/j.neuron.2004.09.009

Freese, J. L., & Amaral, D. G. (2005). The organization of projections from the amygdala to visual cortical areas TE and V1 in the macaque monkey. *J Comp Neurol, 486*(4), 295-317. doi: 10.1002/cne.20520

Glimcher, P. (2013). Value-Based Desicion Making. In P. Glimcher & E. Fehr (Eds.), *Neuroeconomics: Decision Making in the Brain* (2nd ed.). St. Louis, MO: Academic Press.

Glimcher, P. (2014). Understanding the Hows and Whys of Decision-Making: From Expected Utility to Divisive Normalization. *Cold Spring Harb Symp Quant Biol, 79*, 169-176. doi: 10.1101/sqb.2014.79.024778

Glimcher, P. W. (2010). *Foundations of Neuroeconomic Analysis*: Oxford University Press.

Gold, J. I., & Shadlen, M. N. (2001). Neural computations that underlie decisions about sensory stimuli. *Trends Cogn Sci, 5*(1), 10-16.

Gold, J. I., & Shadlen, M. N. (2007). The neural basis of decision making. *Annu Rev Neurosci, 30*, 535-574. doi: 10.1146/annurev.neuro.29.051605.113038

Goldberg, M. E., Bisley, J. W., Powell, K. D., & Gottlieb, J. (2006). Saccades, salience and attention: the role of the lateral intraparietal area in visual behavior. *Prog Brain Res, 155*, 157-175. doi: 10.1016/s0079-6123(06)55010-1

Gottlieb, J. (2007). From thought to action: the parietal cortex as a bridge between perception, action, and cognition. *Neuron, 53*(1), 9-16. doi: 10.1016/j.neuron.2006.12.009

Gottlieb, J., Balan, P., Oristaglio, J., & Suzuki, M. (2009). Parietal control of attentional guidance: the significance of sensory, motivational and motor factors. *Neurobiol Learn Mem, 91*(2), 121-128. doi: 10.1016/j.nlm.2008.09.013

Gottlieb, J. P., Kusunoki, M., & Goldberg, M. E. (1998). The representation of visual salience in monkey parietal cortex. *Nature, 391*(6666), 481-484. doi: 10.1038/35135

Grabenhorst, F., Hernadi, I., & Schultz, W. (2012). Prediction of economic choice by primate amygdala neurons. *Proc Natl Acad Sci U S A, 109*(46), 18950-18955. doi: 10.1073/pnas.1212706109

Gupta, R., Koscik, T. R., Bechara, A., & Tranel, D. (2011). The amygdala and decision-making. *Neuropsychologia, 49*(4), 760-766. doi: 10.1016/j.neuropsychologia.2010.09.029

Hernadi, I., Grabenhorst, F., & Schultz, W. (2015). Planning activity for internally generated reward goals in monkey amygdala neurons. *Nat Neurosci, 18*(3), 461-469. doi: 10.1038/nn.3925

Itti, L., & Koch, C. (2001). Computational modelling of visual attention. *Nat Rev Neurosci, 2*(3), 194-203. doi: 10.1038/35058500

Izquierdo, A., Suda, R. K., & Murray, E. A. (2005). Comparison of the effects of bilateral orbital prefrontal cortex lesions and amygdala lesions on emotional responses in rhesus monkeys. *J Neurosci, 25*(37), 8534-8542. doi: 10.1523/jneurosci.1232-05.2005

Kable, J. W., & Glimcher, P. W. (2009). The neurobiology of decision: consensus and controversy. *Neuron, 63*(6), 733-745. doi: 10.1016/j.neuron.2009.09.003

Kiani, R., & Shadlen, M. N. (2009). Representation of confidence associated with a decision by neurons in the parietal cortex. *Science, 324*(5928), 759-764. doi: 10.1126/science.1169405

Klein, J. T., Deaner, R. O., & Platt, M. L. (2008). Neural correlates of social target value in macaque parietal cortex. *Curr Biol, 18*(6), 419-424. doi: 10.1016/j.cub.2008.02.047

KlÜVer, H., & Bucy, P. C. (1939). PReliminary analysis of functions of the temporal lobes in monkeys. *Archives of Neurology & Psychiatry, 42*(6), 979-1000. doi: 10.1001/archneurpsyc.1939.02270240017001

Leathers, M. L., & Olson, C. R. (2012). In monkeys making value-based decisions, LIP neurons encode cue salience and not action value. *Science, 338*(6103), 132-135. doi: 10.1126/science.1226405

Leathers, M. L., & Olson, C. R. (2013). Response to comment on "In monkeys making value-based decisions, LIP neurons encode cue salience and not action value". *Science, 340*(6131), 430. doi: 10.1126/science.1233367

Lewis, J. W., & Van Essen, D. C. (2000a). Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *J Comp Neurol, 428*(1), 112-137.

Lewis, J. W., & Van Essen, D. C. (2000b). Mapping of architectonic subdivisions in the macaque monkey, with emphasis on parieto-occipital cortex. *J Comp Neurol, 428*(1), 79-111.

Lim, S. L., Padmala, S., & Pessoa, L. (2009). Segregating the significant from the mundane on a moment-to-moment basis via direct and indirect amygdala contributions. *Proc Natl Acad Sci U S A, 106*(39), 16841-16846. doi: 10.1073/pnas.0904551106

Louie, K., & Glimcher, P. W. (2010). Separating value from choice: delay discounting activity in the lateral intraparietal area. *J Neurosci, 30*(16), 5498-5507. doi: 10.1523/jneurosci.5742-09.2010

Louie, K., Grattan, L. E., & Glimcher, P. W. (2011). Reward value-based gain control: divisive normalization in parietal cortex. *J Neurosci, 31*(29), 10627-10639. doi: 10.1523/jneurosci.1237-11.2011

Lynch, J. C., Graybiel, A. M., & Lobeck, L. J. (1985). The differential projection of two cytoarchitectonic subregions of the inferior parietal lobule of macaque upon the deep layers of the superior colliculus. *J Comp Neurol, 235*(2), 241-254. doi: 10.1002/cne.902350207

Maunsell, J. H. (2004). Neuronal representations of cognitive state: reward or attention? *Trends Cogn Sci, 8*(6), 261-265. doi: 10.1016/j.tics.2004.04.003

McDonald, A. J. (1998). Cortical pathways to the mammalian amygdala. *Prog Neurobiol, 55*(3), 257-332.

Medalla, M., & Barbas, H. (2006). Diversity of laminar connections linking periarcuate and lateral intraparietal areas depends on cortical structure. *Eur J Neurosci, 23*(1), 161-179. doi: 10.1111/j.1460-9568.2005.04522.x

Meister, M. L., Hennig, J. A., & Huk, A. C. (2013). Signal multiplexing and single-neuron computations in lateral intraparietal area during decision-making. *J Neurosci, 33*(6), 2254-2267. doi: 10.1523/jneurosci.2984-12.2013

Mesulam, M. M. (1999). Spatial attention and neglect: parietal, frontal and cingulate contributions to the mental representation and attentional targeting of salient extrapersonal events. *Philos Trans R Soc Lond B Biol Sci, 354*(1387), 1325-1346. doi: 10.1098/rstb.1999.0482

Mirpour, K., & Bisley, J. W. (2012). Dissociating activity in the lateral intraparietal area from value using a visual foraging task. *Proceedings of the National Academy of Sciences*. doi: 10.1073/pnas.1120763109

Morrison, S. E., & Salzman, C. D. (2010). Re-valuing the amygdala. *Curr Opin Neurobiol, 20*(2), 221-230. doi: 10.1016/j.conb.2010.02.007

Moscarello, J. M., & LeDoux, J. (2014). Diverse Effects of Conditioned Threat Stimuli on Behavior. *Cold Spring Harb Symp Quant Biol, 79*, 11-19. doi: 10.1101/sqb.2014.79.024968

Murray, E. A. (2007). The amygdala, reward and emotion. *Trends Cogn Sci, 11*(11), 489-497. doi: 10.1016/j.tics.2007.08.013

Murray, E. A., & Rudebeck, P. H. (2013). The drive to strive: goal generation based on current needs. *Front Neurosci, 7*, 112. doi: 10.3389/fnins.2013.00112

Newsome, W. T., Glimcher, P. W., Gottlieb, J., Lee, D., & Platt, M. L. (2013). Comment on "In monkeys making value-based decisions, LIP neurons encode cue salience and not action value". *Science, 340*(6131), 430. doi: 10.1126/science.1233214

O'Brien, J. L., & Raymond, J. E. (2012). Learned predictiveness speeds visual processing. *Psychol Sci, 23*(4), 359-363. doi: 10.1177/0956797611429800

Padoa-Schioppa, C. (2011). Neurobiology of economic choice: a good-based model. *Annu Rev Neurosci, 34*, 333-359. doi: 10.1146/annurev-neuro-061010-113648

Padoa-Schioppa, C., & Assad, J. A. (2006). Neurons in the orbitofrontal cortex encode economic value. *Nature, 441*(7090), 223-226. doi: 10.1038/nature04676

Padoa-Schioppa, C., & Cai, X. (2011). The orbitofrontal cortex and the computation of subjective value: consolidated concepts and new perspectives. *Ann N Y Acad Sci, 1239*, 130-137. doi: 10.1111/j.1749-6632.2011.06262.x

Padoa-Schioppa, C., & Cai, X. (2014). Contributions of orbitofrontal and lateral prefrontal cortices to economic choice and the good-to-action transformation. *Neuron*(81).

Paton, J. J., Belova, M. A., Morrison, S. E., & Salzman, C. D. (2006). The primate amygdala represents the positive and negative value of visual stimuli during learning. *Nature, 439*(7078), 865-870. doi: 10.1038/nature04490

Peck, C. J., Jangraw, D. C., Suzuki, M., Efem, R., & Gottlieb, J. (2009). Reward modulates attention independently of action value in posterior parietal cortex. *J Neurosci, 29*(36), 11182-11191. doi: 10.1523/jneurosci.1929-09.2009

Peck, C. J., Lau, B., & Salzman, C. D. (2013). The primate amygdala combines information about space and value. *Nat Neurosci, 16*(3), 340-348. doi: 10.1038/nn.3328

Peck, C. J., & Salzman, C. D. (2014a). The amygdala and basal forebrain as a pathway for motivationally guided attention. *34*(41), 13757-13767. doi: 10.1523/jneurosci.2106-14.2014

Peck, C. J., & Salzman, C. D. (2014b). Amygdala neural activity reflects spatial attention towards stimuli promising reward or threatening punishment. *Elife, 3*. doi: 10.7554/eLife.04478

Pessoa, L. (2010). Emotion and cognition and the amygdala: from "what is it?" to "what's to be done?". *Neuropsychologia, 48*(12), 3416-3429. doi: 10.1016/j.neuropsychologia.2010.06.038

Platt, M. L. (2002). Neural correlates of decisions. *Curr Opin Neurobiol, 12*(2), 141-148.

Platt, M. L., & Glimcher, P. W. (1999). Neural correlates of decision variables in parietal cortex. *Nature, 400*(6741), 233-238. doi: 10.1038/22268

Premereur, E., Vanduffel, W., & Janssen, P. (2011). Functional heterogeneity of macaque lateral intraparietal neurons. *J Neurosci, 31*(34), 12307-12317. doi: 10.1523/jneurosci.2241-11.2011

Rangel, A., & Hare, T. (2010). Neural computations associated with goal-directed choice. *Curr Opin Neurobiol, 20*(2), 262-270. doi: 10.1016/j.conb.2010.03.001

Roesch, M. R., & Olson, C. R. (2003). Impact of expected reward on neuronal activity in prefrontal cortex, frontal and supplementary eye fields and premotor cortex. *J Neurophysiol, 90*(3), 1766-1789. doi: 10.1152/jn.00019.2003

Roesch, M. R., & Olson, C. R. (2004). Neuronal activity related to reward value and motivation in primate frontal cortex. *Science, 304*(5668), 307-310. doi: 10.1126/science.1093223

Roesch, M. R., & Olson, C. R. (2007). Neuronal activity related to anticipated reward in frontal cortex: does it represent value or reflect motivation? *Ann N Y Acad Sci, 1121*, 431-446. doi: 10.1196/annals.1401.004

Roitman, J. D., & Shadlen, M. N. (2002). Response of neurons in the lateral intraparietal area during a combined visual discrimination reaction time task. *J Neurosci, 22*(21), 9475-9489.

Rorie, A. E., Gao, J., McClelland, J. L., & Newsome, W. T. (2010). Integration of sensory and reward information during perceptual decision-making in lateral intraparietal cortex (LIP) of the macaque monkey. *PLoS One, 5*(2), e9308. doi: 10.1371/journal.pone.0009308

Rudebeck, P. H., Mitz, A. R., Chacko, R. V., & Murray, E. A. (2013). Effects of amygdala lesions on reward-value coding in orbital and medial prefrontal cortex. *Neuron, 80*(6), 1519-1531. doi: 10.1016/j.neuron.2013.09.036

Samuelson, P. A. (1938). A Note on the Pure Theory of Consumer's Behaviour. *Economica, 5*(17), 61-71. doi: 10.2307/2548836

Seo, H., Barraclough, D. J., & Lee, D. (2009). Lateral intraparietal cortex and reinforcement learning during a mixed-strategy game. *J Neurosci, 29*(22), 7278-7289. doi: 10.1523/jneurosci.1479-09.2009

Shadlen, M. N., & Kiani, R. (2013). Decision making as a window on cognition. *Neuron, 80*(3), 791-806. doi: 10.1016/j.neuron.2013.10.047

Shadlen, M. N., Kiani, R., Hanks, T. D., & Churchland, A. K. (2008). Neurobiology of Decision Making: An Intentional Framework. In C. Engel & W. Singer (Eds.), *Better Than Conscious? Decision Making, The Human Mind, and Implication for Institutions*. Cambridge, MA: The MIT Press.

Shadlen, M. N., & Newsome, W. T. (1996). Motion perception: seeing and deciding. *Proc Natl Acad Sci U S A, 93*(2), 628-633.

Shadlen, M. N., & Newsome, W. T. (2001). Neural basis of a perceptual decision in the parietal cortex (area LIP) of the rhesus monkey. *J Neurophysiol, 86*(4), 1916-1936.

Snyder, L. H., Batista, A. P., & Andersen, R. A. (2000). Intention-related activity in the posterior parietal cortex: a review. *Vision Res, 40*(10-12), 1433-1441.

Stefanacci, L., & Amaral, D. G. (2002). Some observations on cortical inputs to the macaque monkey amygdala: an anterograde tracing study. *J Comp Neurol, 451*(4), 301-323. doi: 10.1002/cne.10339

Sugrue, L. P., Corrado, G. S., & Newsome, W. T. (2004). Matching behavior and the representation of value in the parietal cortex. *Science, 304*(5678), 1782-1787. doi: 10.1126/science.1094765

Sugrue, L. P., Corrado, G. S., & Newsome, W. T. (2005). Choosing the greater of two goods: neural currencies for valuation and decision making. *Nat Rev Neurosci, 6*(5), 363-375. doi: 10.1038/nrn1666

Swanson, L. W., & Petrovich, G. D. (1998). What is the amygdala? *Trends Neurosci, 21*(8), 323-331.

Tanaka, K. (1996). Inferotemporal cortex and object vision. *Annu Rev Neurosci, 19*, 109-139. doi: 10.1146/annurev.ne.19.030196.000545

Thier, P., & Andersen, R. A. (1998). Electrical microstimulation distinguishes distinct saccade-related areas in the posterior parietal cortex. *J Neurophysiol, 80*(4), 1713-1735.

Wallis, J. D., & Rich, E. L. (2011). Challenges of Interpreting Frontal Neurons during Value-Based Decision-Making. *Front Neurosci, 5*, 124. doi: 10.3389/fnins.2011.00124

Wardak, C., Olivier, E., & Duhamel, J. R. (2002). Saccadic target selection deficits after lateral intraparietal area inactivation in monkeys. *J Neurosci, 22*(22), 9877-9884.

Wardak, C., Olivier, E., & Duhamel, J. R. (2004). A deficit in covert attention after parietal cortex inactivation in the monkey. *Neuron, 42*(3), 501-508.

Wellman, L. L., Gale, K., & Malkova, L. (2005). GABAA-mediated inhibition of basolateral amygdala blocks reward devaluation in macaques. *J Neurosci, 25*(18), 4577-4586. doi: 10.1523/jneurosci.2257-04.2005

Wunderlich, K., Rangel, A., & O'Doherty, J. P. (2010). Economic choices can be made using only stimulus values. *Proc Natl Acad Sci U S A, 107*(34), 15005-15010. doi: 10.1073/pnas.1002258107

Yang, T., & Shadlen, M. N. (2007). Probabilistic reasoning by neurons. *Nature, 447*(7148), 1075-1080. doi: 10.1038/nature05852

Zhang, W., Schneider, D. M., Belova, M. A., Morrison, S. E., Paton, J. J., & Salzman, C. D. (2013). Functional circuits and anatomical distribution of response properties in the primate amygdala. *J Neurosci, 33*(2), 722-733. doi: 10.1523/jneurosci.2970-12.2013