

AUSTRALIAN NATIONAL UNIVERSITY

Behavioral and neuronal correlates of sensory prioritization in the rat whisker system

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requirements for the degree of Doctor of Philosophy

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Student Declaration

I hereby declare that this thesis contains no material that has been submitted, whether in part or full, for the award of another degree at this university or any other institution. To the best of my knowledge, this thesis contains no material previously published or written by another person except where due reference is made.

Conrad Lee

02/03/2017

Preface

All experiments in this thesis were performed at the Australian National University. Procedures conformed to the Australian National Health and Medical Research Council (NHMRC) and Australian Research Council (ARC) codes of practice for the use and care of animals, and institutional animal care and ethics committees at the Australian National University.

I was the first author of one publication during my PhD candidature:

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Abstract

Animals need to assess when to initiate actions based on uncertain sensory evidence. To formulate a response, decision making systems must prioritize extraction of neuronal signals that represent ecologically relevant events from signals that are behaviorally less relevant. This is commonly known as selective attention. The current thesis aims to investigate two simple forms of attention in rodents: sensory prioritization to a specific modality and temporal cueing. The rat whisker system is functionally efficient, and anatomically well characterized. We therefore utilize the whisker touch as a model sensory system to investigate the neuronal and behavioral correlates of attention in rats.

We begin this thesis by designing a novel simple detection task that investigated whether rats dedicate attentional resources to the sensory modality in which a near-threshold event is more likely to occur. Detection of low-amplitude events is critical to survival, and to formulate a response, animals must extract minute neuronal signals from the sensory modality that is more likely to provide key information. We manipulated attention by controlling the likelihood with which a stimulus was presented from one of two modalities. In a whisker session, 80% of trials contained a brief vibration stimulus applied to whiskers and the remaining 20% of trials contained a brief change of luminance. These likelihoods were reversed in a visual session. When a stimulus was presented in the high-likelihood context, detection performance increased and was faster compared with the same stimulus presented in the low-likelihood context. Sensory prioritization was also reflected in neuronal activity in the vibrissal area of primary somatosensory cortex: single units responded differentially to a whisker vibration stimulus when presented with higher probability compared to the same stimulus when presented with lower

probability. Neuronal activity in the vibrissal cortex displayed signatures of multiplicative gain control and enhanced response to vibration stimuli during the whisker session. In Chapter 3, we replicated these findings in a forced choice paradigm and extended the investigation from somatosensory/visual to the somatosensory/auditory. Attention was similarly manipulated by controlling likelihoods of stimulus presentation. Again, we observed improvements in detection performance and reaction time, as well as improvements in discrimination performance for stimuli presented in a high-likelihood context. The behavioral consequences of a forced choice compared to simple detection task are discussed.

Finally, we developed a novel task that investigated whether rats were able to dedicate attentional resources in time. Operating with some finite quantity of attentional resources, by direct these resources at the expected time, animals would benefit from prioritizing processing based on temporal cues. We manipulated temporal cueing by presenting an auditory cue that preceded a target vibration stimulus in a subset of trials. On another subset, no auditory cue was presented. Presentations of these trials were of equal probability. Critically in this paradigm, the auditory cue provided temporal information but did not provide any spatial information about the location of the vibration stimulus. The auditory cue increased detection and discrimination performances and resulted in faster responses compared to trials in which the cue was absent. We observed neuronal signatures of temporal cuing in the vibrissal area of the primary somatosensory cortex. Single units showed enhanced response to the vibration stimulus during trials in which the stimulus was temporally expected. However, we did not observe signatures of multiplicative gain control in this paradigm. Instead, a decrease in baseline activity was observed that was phase locked to the onset of the auditory cue.

In summary, this thesis presents two novel paradigms to study selective attention in rats in the form of sensory prioritization and temporal cueing. In addition, we investigate the neuronal correlates of selective attention in the vibrissal area of the primary somatosensory cortex. These series of experiments establish the rat as an alternative model organism to primates for studying attention.

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List of Abbreviations

BTC	Brainstem trigeminal complex
dlPFC	Dorsal lateral prefrontal cortex
ERP	Event related potential
FEF	Frontal eye field
fMRI	Functional magnetic imaging
FOF	Frontal orienting field
IT	Inferior temporal cortex
LFP	Local field potential
LGN	Lateral geniculate nucleus
LIP	Lateral intraparietal area
M1	Primary motor cortex
NMDA	N-methyl-D-aspartate
PET	Positron emission tomography
PFC	Prefrontal cortex
PMBSF	Posteromedial barrel subfield
PoM	Posteromedial complex
PrV	Rostral principal nucleus
ROC	Receiver operating characteristic

SC	Superior colliculus
SD	Standard deviation
SpV	Spinal tract
TRN	Thalamic reticular nucleus
V1	Visual area 1
V2	Visual area 2
V4	Visual area 4
VPM	Ventral posteromedial nucleus
VPMdm	Dorsal medial ventral posteromedial nucleus
VPMvl	Ventral lateral ventral posteromedial nucleus
vS1	Primary somatosensory area
vS2	Secondary somatosensory area

1. General Introduction

1.1. Motivation

We do not experience the world directly. Our representation of the world is formed from patterns of neuronal activity in the brain, which arise after a sequence of physical, chemical, and neuronal transformations of features of the outside world. For example, what we feel as a texture are spike trains generated in the nervous system as a result of mechanical stimulation of mechanoreceptors in the skin. However, our perception of the external world does not always correspond to these physical transformations. Our perception is also influenced by several factors such as expectations based on our past experience and our motivational demands. For example, the sight of an audience at the finish line would stimulate photoreceptors in the retina of a cyclist, but the cyclist may not perceive the audience during the sprint to the finish line. How do neuronal representations of sensory stimuli transform into the percept, which guides an animal's decisions and interactions with the world? And how do the sensory context and the behavioral relevance of the stimuli, in turn affect these neuronal representations?

The ability to acquire information about the external world and to respond appropriately is critical for an animal's survival. The environment contains a vast array of signals about prey or predator, as well as signals of less behavioral relevance. Selective attention is required because the brain has limited resources to process information and cannot process all possible information from the outside world. It must therefore selectively process those events that are likely to be of behavioral relevance. The visual system of humans and non-human primates is currently the major model system for studying selective attention. To acquire an understanding

of the neuronal mechanisms underlying attention, it is useful to develop rodent models to exploit the advantages of ease of behavioral experimentation, the simpler and more tractable neural circuitry and the availability of genetic tools (Deisseroth, 2011; Grienberger & Konnerth, 2012; Mayrhofer et al., 2015; Peterka, Takahashi, & Yuste, 2011; Yizhar, Fenno, Davidson, Mogri, & Deisseroth, 2011). Like primates, the rodent brain needs to distribute its limited processing capacity and prioritize its resources to achieve optimal interaction with the environment. This thesis investigates the neuronal and behavioral correlates of a simple form of attention defined in terms of sensory prioritization in rats. However, rodents are nocturnal animals and frequent in dark burrows. Thus, whilst they can use their visual system to interact with their surroundings, the whisker system represents the major channel to navigate and collect information from the environment. As such, we focus on the sensory processing in the whisker system.

To summarize the structure of this thesis, Chapter 1 provides an overview of the psychological and neurological work on attention across humans, non-human primates, and rodents with a particular focus on two of the four major domains of attention in the literature: (i) attention to sensory modality and (ii) temporal cueing. Additionally, Chapter 1 provides an overview of the circuitry and behavioral characteristics of the rodent whisker system. In Chapter 2 and 3, two novel behavioral paradigms are designed to investigate attention to modality in a simple detection (Chapter 2) and a two-alternative forced choice (Chapter 3) paradigm. The results in Chapter 2 have been published in Lee, Diamond, & Arabzadeh, 2016. Chapter 4 studies the neuronal and behavioral correlates of temporal cueing. Finally, Chapter 5 summarizes future directions of research, as well as open questions in the scope of whisker-mediated attention in rodents.

1.2. Selective Attention

The interruption of the attention network underlies a number of neurological and psychological disorders such as attention-deficit hyperactivity disorder, autism spectrum disorder, obsessive compulsive disorder and confusional states (Robbins and Arnsten, 2009; Mesulam, 2010). It is therefore imperative to understand the mechanisms of attention from both a behavioral and neurological perspective. For the layperson, the meaning and perhaps even the definition of 'attention' is self-evident as best captured by William James (1890)

"Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seems several simultaneous possible objects or trains of thought. Focalizations, concentration of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with other"

However, like all theories that are constructed using terms borrowed from ordinary language, when empirically investigating the phenomena of attention, a coherent understanding becomes difficult. For example, the lay concept of heaviness is ambiguous: it may refer to differences in mass (e.g. 5kg of iron is heavier than 2kg of iron) or density (e.g. a brick is heavier than a feather). To study a 'theory of heaviness', one would need to distinguish among these two processes. In the same light, except for the early 20th century at the rise of behaviorism in psychology, philosophers, writers and cognitive scientists slowly but systematically refined the definition of attention. In this thesis, we define attention as the prioritization of sensory processing for behaviorally relevant stimuli at the expense of behaviorally irrelevant stimuli.

Prioritization is a process of selection and filtering (Broadbent, 1966), and the consequence of this process is the more efficient processing of the behaviorally relevant sensory information.

Why does attention exist? Using Shannon's theory of mutual information (Shannon, 1948), Broadbent extended the view of information processing to the phenomenon of attention, characterizing it as information processing that is *capacity limited* (Broadbent, 1966): a process that can only deal with a limited amount of information at a time. For example, Itti & Koch (2001) suggest that information can flow at 10^7 - 10^8 bits per second along the optic nerve when transmitting information from the eye. How can sensory processing keep up with this vast input? Ultimately, for a limited capacity to deal with an overabundance of information, an animal needs to select information that is relevant for current goals to avoid information overload. That is, a capacity-limited system needs selection. Alternatively, with the addition of neuronal noise at every stage of processing, information inevitably decays and cannot be recaptured by any amount of further processing. Attention reduces this unavoidable decay for behaviorally relevant information at the expenses of the decay of behaviorally irrelevant information through a number of neuronal mechanisms (reviewed below). It is important to distinguish attention from other temporary changes in the efficiency of information processing such as arousal and alertness (Lindsley, 1988; Steriade, 1991). Whilst they share some neuronal mechanisms, these processes differ from attention by its non-selectivity (e.g. arousal influences the processing of all incoming stimuli).

1.2.1 Types of Attention

Aside from systematically defining and operationalizing attention, different modes and domains of attention exist and should be distinguished to conceptualize this phenomenon. Building upon the "network of attention" taxonomy as described by Posner & Petersen (1990), a framework of attention adopted from Posner (2012), is shown in Table 1. The framework describes four domains in which attention can be allocated (space, time, modality and task) and two different origins where attention can be deployed (exogenous and endogenous).

Table 1. Framework of attention, *Adapted from Posner(2012)*

		Mode of allocation	
		Exogenous	Endogenous
Domain of allocation	Space		
	Time		X
	Modality		X
	Task		

First described by Posner & Snyder (1975) and Posner (1980), attention is dichotomized into exogenous and endogenous attention. This is sometimes referred to as "bottom-up/involuntary" and "top-down/voluntary" attention. The former is determined exclusively by the physical characteristics of the environment, such as salience (e.g.: the sudden onset of an alarm). In classic experiments, bottom-up attention is described and investigated by the pop-out

phenomenon. In such experiments, subjects are presented with several items on a display and are asked to find a target item, such as a bar with a particular orientation, color or combination of the two. Pop-out occurs when the target item is distinctly different from surrounding items, such as a red bar amongst green bars. This salient difference automatically attracts bottom-up attention and allows rapid processing and detection independently of the number of distractors. In contrast, endogenous attention is determined by the immediate goals of the observer (Berger, Henik, & Rafal, 2005; Corbetta & Shulman, 2002; Jack, Shulman, Snyder, McAvoy, & Corbetta, 2006). For example, a cyclist applies top-down attention at the start of a race in anticipation of the starting gun. Endogenous attention is slower to deploy and requires effort to engage. A classic example of top-down attention is demonstrated by the Posner Paradigm (1980), whereby participants respond to targets that are located peripherally from fixation. The targets are preceded by cues present at the fixation point, which predict the location of the upcoming target with a set validity probability. The cue is argued to direct attention to the specified location with participants showing faster reaction times and higher performance when the cue correctly predicted the upcoming location of the target. This dissertation will focus on the top-down/endogenous process of attention. Within the four domains in which attention can be allocated, we will study time (temporal cueing) and modality.

1.2.2. Attention to modality

Attention research has traditionally considered selection among competing inputs within just a single sensory modality. However, recent decades have shown a growing interest in the existence and nature of cross-modal constraints on the ability to selectively attend across sensory modalities. This is particularly relevant in understanding the effectiveness of multitasking and the potential dangers associated with it: for example, the use of mobile phones whilst driving

(Gherri & Eimer, 2011). Cross-modal interactions in attention have now been demonstrated between most combinations of visual, auditory, tactile and olfactory stimuli (Calvert, Spence, & Stein, 2004).

The primary interest in cross-modal attention is to determine whether directing attention to one specific sensory modality occurs at the expense of others. That is, are attentional processes modality specific faculties or are they cross-modal? Large bodies of work have provided evidence for attentional interdependence across modalities (cross-modal). Firstly, neuronal-imaging studies in humans indicate that attention demanding processing in one modality leads to a reduction in neural activity in other modalities. For example, experiments using Positron Emission Tomography (PET) have shown that subjects carrying out tactile discriminations exhibit a reduction in activation in primary visual areas (Kawashima, O'Sullivan, & Roland, 1995; Merabet, Amedi, & Pascual-Leone, 2009; Sadato et al., 1996). Additionally, visual attention task results in a reduction in the amplitude of auditory evoked responses (Hillyard & Anllo-Vento, 1998; Luck, Chelazzi, Hillyard, & Desimone, 1997; Oatman, 1976) and reduced baseline activity in the primary auditory and somatosensory areas (Courtney, Ungerleider, Keil, & Haxby, 1996; Haxby et al., 1994). When attention is drawn away from an auditory event by the presence of a visual stimulus or by attending to vision, secondary auditory cortical areas have been shown to decrease in activity in response to auditory stimuli (Johnson & Zatorre, 2006; Laurienti et al., 2002; Shomstein, S. Yantis, 2004). In the same light, these cross-modal inhibition has been shown in non-human primates and rodents as well (Han et al., 2009; Iurilli et al., 2012; Shu, Hasenstaub, & McCormick, 2003).

Behaviorally, attentional interdependence has also been demonstrated whereby attention to a stimulus in one modality interferes with directing attention to a stimulus in another modality (Buchtel & Butter, 1988; Driver, 1996; Jolicoeur, 1999; Massaro & Warner, 1977; Charles Spence, 2001; Charles Spence, Nicholls, & Driver, 2001; Charles Spence & Parise, 2010). For example, one popular type of experiments used to investigate cross-modal attention is the temporal order judgement task (Spence and Parise, 2010; Spence, Shore and Klein, 2001). In this task, participants are presented with two stimuli from different sensory modalities with varying stimulus onset asynchronies and are asked to report which stimulus was presented first. In an experiment using visual and touch, Spence et al., (2001) found that the perception of signals presented to the attended modality was accelerated and the unattended modality was delayed.

In contrast, evidence for modality independence of attention can be implied by the fact that neurological damage can result in attentional deficits in one modality by not others (Umiltà, 1995). In the same light, rehabilitation of attention on one modality does not affect the rehabilitation of other modalities in individuals with attentional deficits in multiple modality (Làdavas, Menghini, & Umiltà, 1994). Experimentally, some experiments have shown that multiple stimuli presented in different modalities can be processed more easily than multiple stimuli presented within the same modality (Duncan, Martens, & Ward, 1997; Martens, Kandula, & Duncan, 2010).

Collectively, these findings do not point to a question of whether attention is cross-modal or modality specific. Rather, both modality specific and cross-modal attentional mechanism co-exist in a 'separate-but-linked' organization as proposed by Spence & Driver (1996). This

hypothesis proposes that separate auditory, visual, and tactile attentional systems exist at the earliest levels of information processing. However, these attentional systems are subsequently linked resulting in competition for attentional resources. This idea has also been proposed by Posner (1990) in a similar hybrid attentional system which involved interconnected modality-specific, and independent attentional systems. What determines the shift between cross-modal and independent attention may be a representation's competitiveness. That is, attention-based competition is governed by processing load (difficulty) and is often referred to as the "attentional load hypothesis". The more attention demanding a stimulus representation is, the more it will dominate the competition. Since attention is viewed as a limited resource, the more attention demanding a stimulus is in one modality, the fewer the resources is available for other stimuli in another modality (Hairston et al., 2008; Lavie, 1995; Rees, Frith, & Lavie, 2001). Finally, it has also been proposed that tasks requiring speeded responses are more likely to show effects of competing attention than un-speeded responding tasks (Spence, 2001; Spence et al., 2001; Spence, Shore, & Driver, 2001).

1.2.3. Temporal Cueing

The study of temporal cueing began with Wundt (1887) demonstrating that human reaction time to a target stimulus is facilitated by the prior presentation of a signal that predicts the time when the target will be presented. This was later refined in Kingstone's (1992) experiments which adapted Posner (1980) spatial cueing paradigm to the temporal domain. In studies of temporal cueing, typically a target stimulus is preceded by a cue, which indicates the timing of the forthcoming target stimulus. This cue may be explicit or implicit in indicating the timing of the target stimulus. The time period between the cue and the target is termed "foreperiod" or

sometimes called "*preparatory interval*", as it provides the temporal frame of reference in which subject can *prepare* to respond to the target stimulus.

In the simplest arrangement, the foreperiod duration is constant throughout a session. A common observation in constant foreperiod paradigms is the inverse relationship between foreperiod duration with reaction time and performance (Klemmer, 1956; Näätänen, Muranen, & Merisalo, 1974; Teichner, 1954; Woodrow, 1914). This is attributed to subjects' imperfect time-estimation capability. With relatively short foreperiods, subjects are able to better predict and estimate time, resulting in higher performances and decreased reaction time. Using a choice reaction task, Bertelson (1967) found the fastest reaction times at foreperiods of 100- 50 msec. However, there is also a ceiling effect with this inverse relationship between foreperiod and reaction speed. Bevan, Hardesty, & Avant (1965) showed that reaction time does not increase when the foreperiod is prolonged above 80 seconds in humans.

The effect of temporal cueing also depends on the modality and psychophysical intensity of the cue. Studies addressing the cue modality found that for visual target stimulus, auditory cues are more effective than visual ones (Paul Bertelson & Tisseyre, 1969; Davis & Green, 1969).

Additionally, loud auditory cues have been shown to be less affected by time uncertainty compared to soft auditory cues or visual cues (Niemi & Näätänen, 1981; Sanders, 1975; Sanders & Wertheim, 1973). On the other hand, experiments with variable foreperiod have been shown to result in poorer performances and slower reaction times due to the inability to effectively predict stimulus onset time (Bertelson, 1967; Bertelson & Tisseyre, 1968, 1969; Correa,

Lupiáñez, Milliken, & Tudela, 2004; Coull & Nobre, 1998; Karlin, 1959; Kingstone, 1992; Klemmer, 1956).

1.2.4. Neuronal signatures of selective attention

It is apparent that regardless of the domain in which attention is allocated, attention provides behavioral benefits, often characterized by the increase in performances and decrease in reaction time. At the neuronal level, the objective of attention can be viewed as increasing the signal-to-noise ratio of the readout from populations of neurons encoding the selected representation. This can be accomplished in a number of ways as outlined below.

1.2.4.1. Increase in firing rate

The first and most replicated neuronal signature of selective attention is the increase in firing rate of neurons that encode the attended stimulus. A large collection of studies have demonstrated this signature at multiple stages of processing throughout the visual cortex and across species, as well as in other sensory pathways in different animal models. In the visual pathway, increased stimulus-evoked firing rate has been shown in various visual areas including the lateral geniculate nucleus (LGN)(McAlonan, Cavanaugh, & Wurtz, 2008), thalamic reticular nucleus (TRN)(McAlonan et al., 2008), superior colliculus (SC) (Ignashchenkova, Dicke, Haarmeier, & Thier, 2004) and a number of visual cortical areas: V1 (Herrero et al., 2008; McAdams & Maunsell, 1999; Herrero et al., 2008; Buffalo et al., 2009), V2 (Buffalo, Fries, Landman, Liang, & Desimone, 2010), V4 (McAdams & Maunsell, 1999; Moran & Desimone, 1985; Buffalo et al., 2009), MT (Busse, Katzner, & Treue, 2008; Niebergall, Khayat, Treue, & Martinez-Trujillo, 2011; Treue & Trujillo, 1999), IT (Chelazzi, Duncan, Miller, & Desimone, 1998; Chelazzi, Miller, Duncan, & Desimone, 1993; Moran & Desimone, 1985), lateral intraparietal cortex

(LIP)(Bisley & Goldberg, 2003; Buschman & Miller, 2007a; Fitzgerald et al., 2013; Ibos & Freedman, 2014), frontal eye field (FEF)(Armstrong, Chang, & Moore, 2009; Buschman & Miller, 2007c; Crapse & Sommer, 2009; Gregoriou, Gotts, Zhou, & Desimone, 2009a; Monosov, Trageser, & Thompson, 2008; Thompson, Biscoe, & Sato, 2005a; Zhou & Thompson, 2009) and prefrontal cortex (PFC)(Everling, Tinsley, Gaffan, & Duncan, 2002; Lebedev, Messinger, Kralik, & Wise, 2004). In rodents, attention modulations by means of increase in firing have also been observed in a number of experiments across various sensory cortices (visual: Carli et al., 1983; Marote and Xavier, 2011; Wang et al., 2014; Wimmer et al., 2015; auditory: Jaramillo and Zador, 2010; Rodgers and DeWeese, 2014).

However, there are several questions regarding the increase in firing rate as a mechanism for increasing signal-to-noise ratio. Under certain circumstances, attention can increase the baseline firing of neurons. This has been reported in neurons with visual receptive fields that are at the attended visual location, or neurons that were responsive to the attended visual feature (Luck et al., 1997; Moran & Desimone, 1985; Reynolds & Chelazzi, 2004). Critically, this modulation in baseline firing has been observed even in the absence of the stimulus (Colby et al., 1996; Luck et al., 1997). The increase in baseline firing rate of neurons during an attended condition raises questions as to the mechanism by which neurons are modulated. One possibility is via a multiplicative increase in responsiveness, in which firing rate improves the signal to noise ratio by increasing the stimulus-evoked responses separately from the neurons' spontaneous activity via a gain modulation that multiplies neuronal response by a constant gain factor (Boynton, 2009; Connor, Gallant, Preddie, & Van Essen, 1996; McAdams & Maunsell, 1999b; Saproo & Serences, 2010; Scolari & Serences, 2010; Treue & Trujillo, 1999). However, a constant gain

modulation mechanism would predict an increase in sensitivity even for highly salient stimuli that are already at response saturation. Alternatively, a contrast-gain function has been proposed in which gain modulation is highest at the neuron's peak dynamic range. This mechanism allows for increased sensitivity except for highly salient stimuli that are already at response saturation (Reynolds, Pasternak, & Desimone, 2000).

1.2.4.2. Synchrony within and between areas

In addition to increases in firing rate, attention can enhance signal efficiency via increasing the synchrony among neurons encoding the attended stimulus. Synchronized spiking across a neuronal population would result in greater impact on downstream neurons (Fries, 2005; Emilio Salinas et al., 2001; Salinas & Sejnowski, 2000). The local synchrony can be determined by measuring changes in overall power in a particular frequency band of the Local Field Potential (LFP) or the temporal correlation among spikes, and between spikes and the LFP. Studies of selective attention have found increases in local gamma-band (Bichot, Rossi, & Desimone, 2005; Fries, 2015; Fries, Womelsdorf, Oostenveld, & Desimone, 2008; Gregoriou et al., 2009a; Lee, Simpson, Logothetis, & Rainer, 2005; Saalmann, Pigarev, & Vidyasagar, 2007; Taylor, Mandon, Freiwald, & Kreiter, 2005; Womelsdorf et al., 2007) and beta-band (Buschman & Miller, 2007b, 2009) synchrony across a range of areas in the visual pathway. For example, the effect of attention on local synchrony in the form of increased gamma-band LFP and spike-field synchrony has been demonstrated in area V4 (Fries et al., 2008; Gregoriou et al., 2009a; Taylor et al., 2005; Womelsdorf et al., 2006). However, this effect is varied and inconsistent in earlier stages of processing, with some studies reporting gamma power and coherence in area V1 to decrease (Chalk et al., 2010) whilst others report increases (Bosman et al., 2012; Buffalo, Fries, Landman, Buschman, & Desimone, 2011; Lutzenberger, Ripper, Busse, Birbaumer, & Kaiser,

2002). Nevertheless, these changes in synchrony have also been shown to correspond to improved behavioral outcomes (Taylor et al., 2005; Womelsdorf et al., 2006) or to predict shifts in attention (Buschman & Miller, 2009).

Just as synchrony within an area can enhance the impact of that area on downstream neurons, synchrony between areas can also enhance the influence of one area on another (Fries, 2005; Knoblich, Siegle, Pritchett, & Moore, 2010; Salinas et al., 2001; Salinas & Sejnowski, 2000). It is proposed that neuronal synchrony can link distant functional areas by providing a common temporal reference frame for communication (Buschman & Miller, 2007b; Pascal Fries, 2015; Gregoriou et al., 2009a; Saalmann et al., 2007). In this scheme, incoming spikes achieve maximal impact when they arrive at an optimal phase of the local oscillations. For example, the timing of sensory input relative to the gamma cycle has been shown to alter the magnitude of evoked responses in mouse primary somatosensory cortex (Cardin et al., 2009). Whilst gain modulation of firing rate can allow a selected representation to dominate over others, synchrony presents another potential way to resolve competition during attentional selection by setting a narrower window in time to gate information flow.

1.2.4.3. Decreased variability

Attention has also been found to decrease the trial-to-trial response variability of neurons, as quantified by the changes in mean-normalized variance (Fano factor) of simultaneously recorded pairs of neurons across trials (Cohen & Kohn, 2011; Cohen & Maunsell, 2009; Mitchell, Sundberg, & Reynolds, 2007). Response variability can arise from independent sources of noise within each neuron and/or correlated fluctuations shared across neurons. While independent

variability can be averaged out by pooling across the population response, averaging over shared variability would magnify noise variability. Attention has been shown to reduce the correlated variability of neurons in V4 (Cohen & Maunsell, 2009; Fries et al., 2008; Mitchell, Sundberg, & Reynolds, 2009) and has been suggested to arise mainly from a suppression of low frequency (<5 Hz) fluctuations shared across the population.

1.2.5. Neuronal origins of attention

The physiological phenomena of attention have traditionally been focused on the visual system in human and non-human primates. In the visual system, the most obvious candidates for the source of attention are areas in the prefrontal cortex (PFC). Historically, the PFC has been considered the area of 'executive control' as it is responsible for a variety of high-level cognitive functions (Kane & Engle, 2002; Miller & Wallis, 2010; Miller & Cohen, 2001). A number of studies have shown the involvement of the PFC in attention across a range of species (Asplund, Todd, Snyder, & Marois, 2010; Everling et al., 2002; Fuster, 1985; Grossmann & Johnson, 2010; Knudsen, 2007; Miller & Cohen, 2001) with a particular focus on the dorsal lateral prefrontal cortex (dlPFC) and the frontal eye fields (FEF). In particular, FEF was first identified as critical for the control of eye movements and gave rise to the "pre-motor theory of attention". This theory posits that attention is merely a side effect of preparing an eye movement that is not executed (Rizzolatti, Riggio, Dascola, & Umiltà, 1987). Evidence for this idea comes from experiments in which stimulation of neurons in FEF that is too weak to evoke an eye movement can nevertheless enhance detectability of stimuli in the location to which that FEF neuron would have driven an eye movement towards. Stimulation of FEF neurons has also been found to potentiate the response of sensory neurons in V4 with receptive fields that correspond to that of

the FEF neurons (Moore & Armstrong, 2003). More recent experiments have rejected this “pre-motor theory of attention” by dissociating eye preparation from the deployment of attention (Zhou & Thompson, 2009). Nevertheless, several studies have shown the role of FEF in regulating attention in downstream cortical areas (Armstrong et al., 2009; Buschman & Miller, 2007b; Gregoriou et al., 2009a; Monosov & Thompson, 2009; Monosov et al., 2008; Noudoost, Clark, & Moore, 2014; Thompson, Biscoe, & Sato, 2005b; Wardak, Ibos, Duhamel, & Olivier, 2006). For example, paired recordings in FEF and V4 reveal that FEF neurons exhibit attentional modulation before V4 neurons in the form of increased gamma-band coherence. Crucially, this coupling appeared to be initiated by FEF and as it was time-shifted by 8-13 ms across a range of frequencies (Gregoriou, Gotts, Zhou, & Desimone, 2009b). Critically for the scope of this thesis, an analogous area known as the frontal orienting field (FOF) (often referred to as the pre-motor cortex or M2)(Erlich, Bialek, & Brody, 2011; Leonard, 1969a) may play a similar role in rodents. Specifically, FOF has direct connections to the somatosensory cortex (Condé, Maire-Lepoivre, Audinat, & Crépel, 1995; Leonard, 1969a) and micro-stimulation of FOF evokes whisker movements (Brecht et al., 2004; Kleinfeld, Ahissar, & Diamond, 2006; Neafsey et al., 1986; Sinnamoni & Galer, 1984). Similar to primate FEF, the FOF projects to the superior colliculus (SC – discuss below) (Reep, Corwin, Hashimoto, & Watson, 1987) and has strong reciprocal projections to prefrontal cortex (Condé et al., 1995) and brainstem areas involving orienting behaviors (Stuesse & Newman, 1990). Finally, unilateral inactivation of FOF have been found to produce contralateral neglect in rats (Erlich et al., 2011). However, currently there is no direct evidence for the involvement of FOF in whisker-mediated attention (partly due to the lack of any studies investigating whisker-mediated attention).

A number of subcortical areas have been implicated in the neuronal circuitry of attention. For example, the superior colliculus (SC) have long been implicated as one of the main sources of attention. The activity of visually responsive neurons in the SC reflects the location of covert attention (Goldberg & Wurtz, 1972; Ignashchenkova et al., 2004). Whilst electric stimulation of SC evoke saccadic eye movements (Robinson, 1972), subthreshold micro-stimulation of the SC improves performance on attentional tasks (similar to FEF as discussed above). For example, spatially specific enhancements in performance that corresponds to the receptive field of the stimulated SC site have been demonstrated in a detection task (Cavanaugh, Alvarez, & Wurtz, 2006) and for a motion-discrimination task (Müller, Philiastides, & Newsome, 2005). Several other experiments have also demonstrated the role of SC in attention (Ignashchenkova et al., 2004; Lovejoy & Krauzlis, 2010; Zénon & Krauzlis, 2012)

Finally, several sub-nuclei of the thalamus have been proposed to play a role in modulating attention as they are well positioned to gate incoming sensory signals. For example, the thalamic reticular nucleus (TRN), which sends inhibitory inputs to the LGN and the pulvinar, receives signals from other areas implicated in attention such as the PFC and SC (Guillery & Harting, 2003; Zikopoulos & Barbas, 2006). TRN is thus anatomically positioned to regulate sensory processing by gating the flow of information to the cortex through the LGN. Consistent with this idea, attention has been shown to decrease the activity of TRN neurons (McAlonan et al., 2008) and thus reducing inhibitory input to the LGN and pulvinar, potentially contributing to the attention-driven increases in activity in those nuclei. However, only initial responses in TRN are affected by attention, whereas in LGN neurons, attentional modulations are present in the initial response but also re-emerge as a sustained response, suggesting the possible involvement of the

pulvinar nucleus. The pulvinar receives input from, and projects to, numerous cortical areas and has been proposed as a way of synchronizing activity between cortical areas (Shipp, 2003).

Visual responses of pulvinar neurons have also been shown to be modulated by attention (Bender & Youakim, 2001; Petersen, Robinson, & Keys, 1985), and pharmacological inactivation has been found to impair performance in an attentional task (Petersen, Robinson, & Morris, 1987).

1.3. Whisker-mediated Touch System

Rodents are nocturnal animals that tend to inhabit confined spaces underground where visual information is limited. As such, to navigate their environment, rodents have evolved a sensitive array of facial whiskers, or vibrissae, on each side of their snout. The vibrissal system is an example of an "expert" processing system (Diamond & Arabzadeh, 2013) which encodes the sensory environment in a fast and reliable manner.

The rodents' dependence on the sense of touch via whiskers was demonstrated as early as 1912, where rats were found to rely on their whiskers to navigate through a raised labyrinth (Vincent, 1912). Today, a wealth of studies demonstrate that the whisker system represents the major channel in which rodents collect information (Diamond, von Heimendahl, Knutsen, Kleinfeld, & Ahissar, 2008) for texture discrimination (Arabzadeh, Zorzin, & Diamond, 2005; Carvell & Simons, 1990; Guić-Robles, Valdivieso, & Guajardo, 1989; Hipp et al., 2006; Morita, Kang, Wolfe, Jadhav, & Feldman, 2011; von Heimendahl, Itskov, Arabzadeh, & Diamond, 2007; Zuo, Perkon, & Diamond, 2011), identification of shape and size of objects (Brecht, Preilowski, & Merzenich, 1997; Harvey, Bermejo, & Zeigler, 2001; Polley, Rickert, & Frostig, 2005), detection of distance, gap and aperture width (Guić-Robles et al., 1989; Harris, Petersen, & Diamond, 1999; Hutson & Masterton, 1986b; Jenkinson & Glickstein, 2000) and object localization (Ahissar & Knutsen, 2008; Hires, Gutnisky, Yu, O'Connor, & Svoboda, 2015; Knutsen, Pietr, & Ahissar, 2006; Kwon, Yang, Minamisawa, & O'Connor, 2016; Mehta, Whitmer, Figueroa, Williams, & Kleinfeld, 2007; O'Connor et al., 2010; O'Connor, Peron, Huber, & Svoboda, 2010; O'Connor et al., 2013; Yang, Kwon, Severson, & O'Connor, 2016). The whisker system serves as an exquisitely sensitive tactile sensory modality that approaches the acuity of primate

fingertips for fine texture discrimination tasks (Brecht, Preilowski, & Merzenich, 1997; Carvell & Simons, 1990). In fact, sensory information from the whiskers is disproportionately well represented in the cortex with 20% of the primary somatosensory cortex encoding whisker-mediated touch information.

One of the key advantages of using the whisker system as a sensory model to explore the neural and behavioral correlates of attention is its well-defined topographic map, in which each of the orderly arranged whiskers on the snout of the animal is processed largely in a corresponding functional column in the primary somatosensory cortex (Figure 1A). The next section provides a brief overview of the major areas of the whisker pathway (Figure 1B).

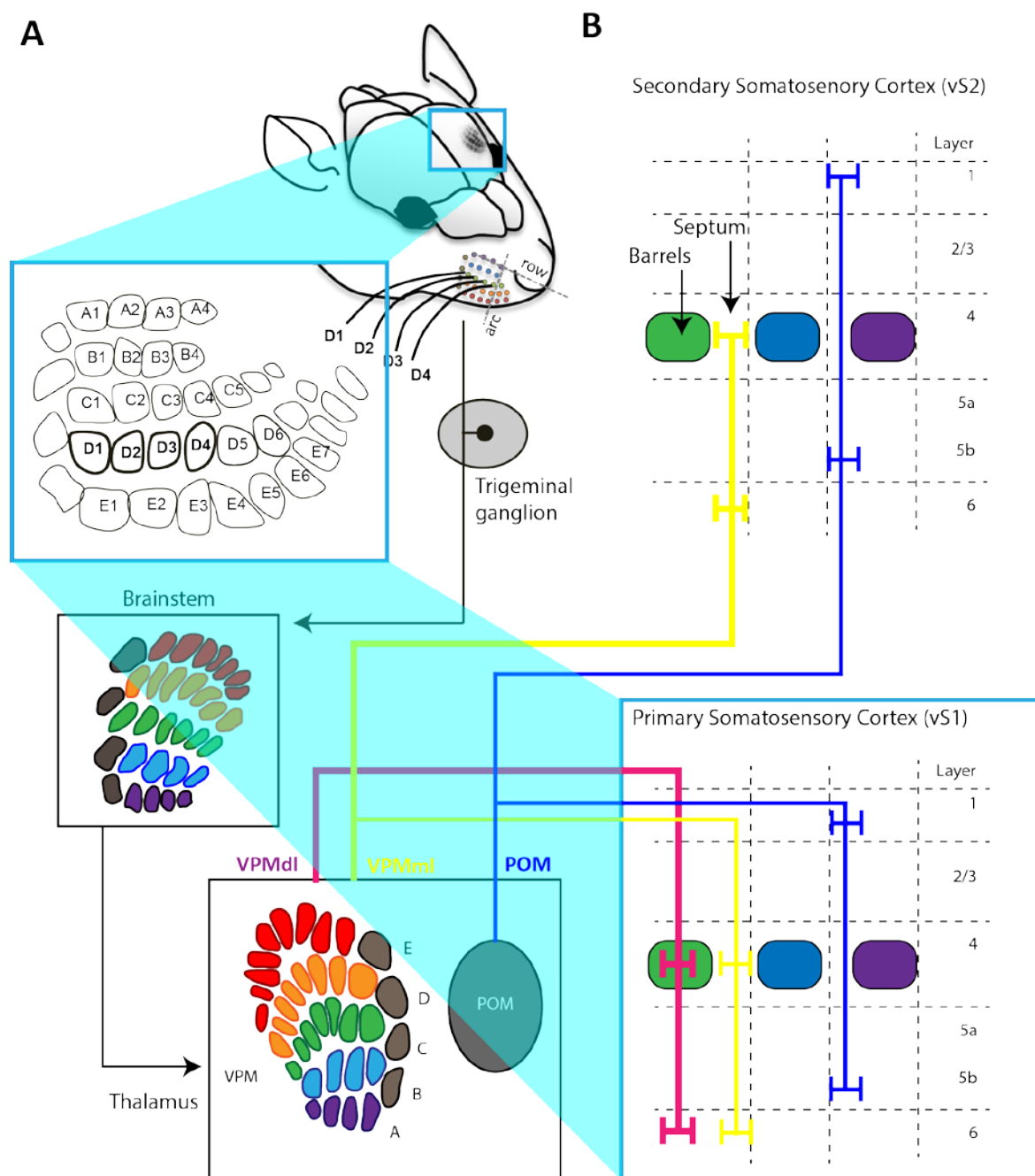


Figure 1. Schematic representation of the trigeminal-thalamo cortical whisker pathway. **A.** The preserved organization of the whisker system from the snout to the primary somatosensory – ‘barrel’ – cortex. **B.** The organization of the primary (vS1) and secondary (vS2) somatosensory area. Colored lines indicate the pathway and termination areas of axons. The line thickness indicates the relative strength of the pathway. Colored bubble rectangles represent barrel clusters of neurons in layer 4. The lemniscal pathway contains projections from VPMdm to layer 4 and sparsely to layer 6 (pink). The extralemniscal pathway contains projections from VPMvl to layer 4 and 6 in vS1 and vS2 (yellow). The paralemniscal pathway containing the projections from PoM to layers 1 and 6a in vS1 and vS2 (blue).

1.3.1. Whisker and follicle

Inspection of the rat's snout reveals a grid-like layout of 30 or so vibrissae on each side of the snout. This organization is highly preserved across individual animals. The vibrissae are categorized into two classes: 1) micro-vibrissae - which are short and thin hair near the nose, and ii) macro-vibrissae - which are long stiff mystical hairs caudal to micro-vibrissae on the whisker pad (Brecht et al., 1997). Macro-vibrissae are organized in five horizontal rows (A to E), and up to 7 arcs (1 to 7). As such, each whisker can be identified by a unique letter-number combination corresponding to its row and arc (e.g. row D, arc 2, or D2).

Vibrissae, like ordinary hair, are hollowed, tapered shafts, with cuticles made up of overlapping flat scales (Voges et al., 2012; Williams & Kramer, 2010). However, vibrissae differentiate from ordinary hair by the presences of large follicles - densely populated with sensory receptors and nerve terminals (Diamond, 2010; Ebara, Kumamoto, Matsuura, Mazurkiewicz, & Rice, 2002). As mechanical transducers, the vibrissae mediate the transfer of touch signals into these receptors. A range of mechanoreceptors can be found around the vibrissae shaft, each of which have distinct tuning properties and sensitivity to a variety of tactile stimulus parameters such as amplitude, duration, velocity, acceleration and direction of motion (Arabzadeh, Panzeri, & Diamond, 2004; Dykes, 1975; Ebara et al., 2002; Kerr & Lysak, 1964; Rice, Mance, & Munger, 1986; Stüttgen, Kullmann, & Schwarz, 2008; Zucker & Welker, 1969). These mechanoreceptors and nerve endings convert mechanical energy into action potentials, which travel past the cell bodies in the trigeminal ganglion and form synapses in the trigeminal nuclei of the brainstem.

1.3.2. Trigeminal ganglion

Sensory information from the whisker follicle is transferred to the trigeminal ganglion, which innervates the ipsilateral brainstem trigeminal complex (BTC)(Ma & Woolsey, 1984; Vincent, 1913). Each ganglion cell innervates only one whisker follicle (Dykes, 1975; Rice et al., 1986; Zucker & Welker, 1969). Like on the whisker pad, the trigeminal ganglion is somatotopically organized (Lichtenstein, Carvell, & Simons, 1990; Zucker & Welker, 1969). These neurons, are highly sensitive to whisker deflection with over 50% of units responding to $<1^\circ$ of whisker deflection (Gibson & Welker, 1983) and with little to no spontaneous activity (Yang et al., 2016). It is known that many neurons in the trigeminal ganglion are sensitive to features of whisker motion, such as velocity and acceleration (Arabzadeh, Zorzin, & Diamond, 2005; Jones, Lee, Trageser, Simons, & Keller, 2004; Shoykhet, Doherty, & Simons, 2000).

1.3.3. Brainstem trigeminal complex (BTC)

At the brainstem trigeminal complex, whisker mediated signals are subdivided into the principal sensory nucleus (PrV) and the spinal nucleus (SpV)(Arvidsson, 1982; Ma & Woolsey, 1984). Neurons in the trigeminal nuclei receive inputs from trigeminal ganglion cells and form discrete neuronal clusters called "barrelettes" (Durham & Woolsey, 1984; Jacquin, Renehan, Rhoades, & Panneton, 1993; Ma, 1993). Each barrelette correspond to an individual whisker on the whisker pad. Brainstem barrelettes therefore preserve the somatotopic organization of whiskers on the whisker pad (Belford & Killackey, 1979; Hayashi, 1980) with each barrelette being 55 μm in diameter, 1.2 mm in length and containing 160-200 neurons (Timofeeva, Merette, Emond, Lavallee, & Deschenes, 2003). This somatotopic organization is due to the barrelette-bounded dendritic trees found in PrV (Jacquin et al., 1993). However, a subset of neurons in PrV have large multipolar somata and expansive dendritic branches that spread over multiple barrelettes

and hence correspond to the representation of multiple whiskers (Jacquin, Golden, & Panneton, 1988; Jacquin & Rhoades, 1990). Like neurons with expansive dendritic branches in the PrV, neurons in the SpV spread their dendritic arbors across multiple barrelettes and hence respond primarily to multiple whiskers (Jacquin, Mooney, & Rhoades, 1986; Woolston, La Londe, & Gibson, 1982). Both PrV and SpV sub-nuclei represent the majority of whisker related projections to the thalamus.

1.3.4. Thalamus

The touch signals travel to the contralateral thalamus via parallel pathways and continue to the somatosensory cortex. The whisker area of thalamus is central to this network as it regulates passage to the primary somatosensory cortex, receiving sensory, cortical, inhibitory and modulatory afferents from multiple areas. There are two distinct nuclei in the whisker area of the thalamus: the ventro-posterior medial thalamus (VPM) and the medial sector of the posterior complex (POm), which receive direct synaptic afferents from the principal (PrV) and/or spinal (SpV) trigeminal nuclei complex (Veinante & Deschênes, 1999; Williams, Zahm, & Jacquin, 1994). Neurons in the whisker thalamus generally project to the vibrissae area of the primary (vS1) and/or secondary somatosensory cortex (vS2). Consequently, these neurons are often referred to as thalamocortical relay cells. However, this naming can be misleading - whilst the whisker area of the thalamus relays sensory information from the whiskers to the cortex, it does not just faithfully transmit sensory signals due to an array of inhibitory and excitatory connections from multiple areas. Instead, it should be view as an area that can play a modulatory role to the incoming signal.

1.3.4.1 Ventro Posterior Medial Thalamus (VPM)

Similar to the barrelettes in BTC, the vibrissal representation area in VPM is somatotopically organized into discrete clusters, called "barreloids" (Van Der Loos, 1976). Barreloids are 500~900 μm in size and contain 250 to 300 neurons each (Land, Buffer, & Yaskosky, 1995; Oberlaender et al., 2012; Van Der Loos, 1976; Wimmer, Bruno, De Kock, Kuner, & Sakmann, 2010). The size of the barreloids is positively correlated with the length of whiskers (Haidarliu & Ahissar, 2001). Cells within a barreloid have receptive fields composed of one principal and several surrounding whiskers (Friedberg, Lee, & Ebner, 1999).

Barreloids in VPM receive afferents from PrV cells and convey ascending sensory signals to cortex. Additionally, barreloid neurons are modulated by input from layer 6 of the primary somatosensory cortex (vS1) and the thalamic reticular nucleus (TRN). As such, it has been shown that the sensory signal relayed is dependent on cortical and behavioral state (Sherman & Guillery, 2006; Temereanca, Brown, & Simons, 2008). Interestingly, across these three main inputs, the projections are confined to the barreloid representing the corresponding whisker (Deschênes, Timofeeva, Lavallée, & Dufresne, 2005; Desîlets-Roy, Varga, Lavallée, & Deschênes, 2002; Jones, 2002; Varga, Sík, Lavallée, & Deschênes, 2002; Pierre Veinante, Jacquin, & Deschênes, 2000). In addition, VPM can be subdivided into the dorsal medial area (VPMdm) and the ventral lateral area (VPMvl). Afferents of VPMdm arborize in the corresponding neuronal aggregates – barrels – in layer 4 of vS1 and form a one-to-one connection between barreloids and cortical barrels (Chmielowska, Carvell, & Simons, 1989; Herkenham, 1980; Lu & Lin, 1993). Multi-barrel projections of VPMdm neurons have never been observed. On the other hand, VPMvl neurons sparsely project to the barrels and

predominantly branch their axons in the secondary somatosensory cortex (S2) as well as septal and dysgranular zone in S1 (Bokor, Acsady, & Deschenes, 2008; Pierret, Lavallée, & Deschênes, 2000).

1.3.4.2. Medial Posterior Complex (POm)

In contrast, the medial posterior complex (POm) is more homogeneous than VPM, with no barreloid-like structures. Although, there is evidence that POm is organized topographically (Alloway, Hoffer, & Hoover, 2003; Diamond, Armstrong-James, Budway, & Ebner, 1992), compared to VPM, the receptive field of POm neurons are larger (6-8 whiskers)(Diamond et al., 1992) exhibiting a weaker response to single whisker deflections. Additionally POm neurons show less preference to a particular principal whisker (Diamond et al., 1992) and are instead strongly driven by stimulation of multiple whiskers. POm projects to almost all sensory-motor areas of the neocortex, including the primary somatosensory (vS1), secondary somatosensory (vS2), peri-rhinal, insular and motor cortices, and to a lesser extent to thalamic reticular nucleus (Deschênes, Veinante, & Zhang, 1998).

POm may play a specific role in attention due to its projection to Layer 1 and Layer 5A in the primary somatosensory cortex; this projection is absent from VPM. These projections are of particular interest in the scope of attention as Layer 1 is known to modify sensory evoked responses through control of intra-cortical excitability (Shlosberg, Amitai, & Azouz, 2006). This suggests that through Layer 1, POm could modulate the mode of operation of the cortex and affect the firing of neurons in response to whisker stimulation. Recent experiments have demonstrated the role of POm in the precise control of the magnitude and duration of supra- and infra-granular layers of vS1 responses (Castejon, Barros-Zulaica, & Nunez, 2016). Additionally,

POm has also been demonstrated to adjust somatosensory cortical processing by controlling the processing in vS2 and through the regulation of the interaction between vS1 and vS2. In this light, POm may play a major role as a thalamic-cortical gain regulator and a mechanism with which attention may operate.

1.3.4.3. Thalamic Reticular Nucleus (TRN)

The thalamic reticular nucleus (TRN) plays interesting modulatory roles on the ascending signal. The TRN is a thin shell of neurons surrounding the thalamus and exclusively projects inhibitory connections to other thalamic nuclei. TRN forms an inhibitory feedback loop which is thought to play a role in sleep-related thalamocortical oscillations (Pinault, 2004; Steriade, McCormick, & Sejnowski, 1993), thalamic spindling (Steriade, Deschênes, Domich, & Mulle, 1985) and arousal (Steriade et al., 1993; Steriade, Domich, & Oakson, 1986). Importantly, the TRN has been shown to play a vital role in modulating visual attention in primates (Crick, 1984; Kerry McAlonan, Cavanaugh, & Wurtz, 2006) and more recently in rodents (Wimmer et al., 2015). First suggested by Francis Crick (1984) for its role in selective attention, TRN has been implicated in modulating attention in a number of experiments. Modulation of visual TRN neurons have been demonstrated in monkeys during shifts in attention between visual and auditory stimuli (McAlonan et al., 2008). In rats, lesions of visual TRN abolished priming effects associated with cues to visual targets in an attentional orienting task (Weese, Phillips, & Brown, 1999). Additionally, visual TRN has been further demonstrated to dynamically control visual thalamic gain through feed forward inhibition in a cross-modal divided-attention task in mice (Wimmer et al., 2015). In this experiment, neurons in visual TRN exhibit changes in firing rate predictive of attention and were causally linked to performance as confirmed by bidirectional

optogenetic manipulations. Other studies focused on the interactions between the modality-specific areas of TRN, showing a selective increase in Fos-positive neurons in the area of TRN associated with the modality of the attended stimulus (McAlonan, Brown, & Bowman, 2000; Montero, 1999; Vicente M. Montero, 2000).

Whisker TRN neurons receive vibrissae-related input from cortical Layer 6 neurons in S1 (Bourassa, Pinault, & Deschênes, 1995) and collateral input from thalamocortical neurons in VPM and POm (Harris, 1987). In turn, they send their GABAergic inhibitory projections back to ventrobasal nucleus and POm (Lam & Sherman, 2007; Pinault, Bourassa, & Deschênes, 1995). Whisker TRN neurons are arranged topographically, and project to VPM somatotopically (Pinault et al., 1995). Overall, given the modulatory role of TRN on the output of the thalamus, the TRN is a prime candidate to study the potential modulation of neuronal activity during selective attention.

1.3.5. Primary somatosensory cortex

Finally, whisker afferent signals travel from the thalamus to the primary somatosensory cortex. The cortical vibrissae representation in rodents is formally referred to as the posterior-medial barrel subfield (PMBSF) (Welker, 1971; Zucker & Welker, 1969). However, throughout this thesis, we will simply refer to this area as the vibrissae area of the primary somatosensory cortex (vS1). Whisker afferents from the thalamus mainly project to Layer 4 of vS1, where anatomically distinguishable clusters of neurons called "barrels" can be found (Woolsey & Van der Loos, 1970). Each barrel is approximately 300-500µm in diameter (Hodge, Stevens, Newman, Merola, & Chu, 1997) and contains an average of 2500 neurons (Bruno & Sakmann,

2006; Lee & Woolsey, 1975; Woolsey & Van der Loos, 1970). Each barrel represents it corresponding “principal” whisker and to a lesser degree, responds to one or more "surrounding" whiskers. Barrels are somatotopically arranged in a similar order as whiskers on the snout, much in the same way described earlier for barrelettes and barreloids. Between barrels, there are sparse-celled regions called septa where neurons encode multiple whiskers (Welker & Woolsey, 1974; Woolsey & Van der Loos, 1970). Almost all layers of the vS1 cortex receive synaptic input from either the VPM or POf of the thalamus. Axons from VPM neurons target mainly lower Layer 3, 4, 5B and 6A. Conversely, thalamic inputs from POf target mainly Layers 1 and 5A, and sparsely Layers 2, 5B/6A and the septa between the barrels in Layer 4.

The vS1 projects to a number of areas, to the vibrasae area of the secondary somatosensory cortex (vS2), the primary motor cortex (M1), thalamus sensory nuclei, superior colliculus and dorsolateral neostriatum (Carvell & Simons, 1987; Chakrabarti & Alloway, 2006; Deschênes et al., 1998; Hattox & Nelson, 2007; Larsen, Wickersham, & Callaway, 2007; White & DeAmicis, 1977). Additionally, vS1 across the two hemispheres are linked by a callosal connection (White & Czeiger, 1991). In turn, primary somatosensory cortex (vS1) receives inputs from the secondary somatosensory cortex (vS2) and motor cortex (Carvell & Simons, 1987; Kim & Ebner, 1999). Unlike in primates (Hsiao, O’Shaughnessy, & Johnson, 1993; Karhu & Tesche, 1999; Luna, Hernandez, Brody, & Romo, 2005; Mazzola, Isnard, & Mauguière, 2006; Mima, Nagamine, Nakamura, & Shibasaki, 1998; Romo, Hernández, Zainos, Lemus, & Brody, 2002; Ruben et al., 2001; Salinas, Hernandez, Zainos, & Romo, 2000), little is known about the functional properties of vS2 neurons in rodents, and understanding of this area are mostly limited to anaesthetised preparations (Carvell & Simons, 1986; Kwegyir-Afful & Keller, 2004).

1.3.6. Behavioral capabilities - modes of whisker-mediated sensation

The whisker system is an example of an active sense, entailing the control of vibrissae in a way that allows the brain to optimize the collection of task-relevant information. Whilst other sensory systems such as the visual system share similar dynamics (e.g. controlled saccadic eye movements to extract relevant visual information), the active control of the sensors is perhaps most evident in the modality of touch. This is clearly demonstrated in the two modes of operation by which rodents use their whiskers to navigate their environment (Diamond & Arabzadeh, 2013).

The first mode of operation is known as the generative mode. In much the same way we move our fingers back and forth on a surface to determine its texture, in the generative mode, rats rhythmically move their whiskers back (retraction) and forth (protraction), a motion known as 'whisking', to actively seek contact with objects and palpate them. In this mode, the animal generates a percept of the environment by its own motion (Grant, Mitchinson, Fox, & Prescott, 2009) and thereby is able to orientate itself in space and identify objects within its surroundings. Whisking is often synchronous to head, respiratory and nose movements, suggesting coordination of activity among many muscle groups (Cao, Roy, Sachdev, & Heck, 2012; Mitchinson & Prescott, 2013; Welker, 1964). Two different patterns of whisking has been observed by Berg & Kleinfeld (2003); the first pattern, referred to as the *exploratory whisking*, consisted of wide-angle sweeps with a frequency range of 1 to 5 Hz in bouts of 1 to 10 seconds. The second pattern of whisking consisted of small-amplitude high-frequency (ranging from 15 to 25 Hz) sweeps for a period of 0.5 to 1 second while whiskers are thrust forward in a dense

pattern (Berg & Kleinfeld, 2003; Carvell & Simons, 1995; Carvell & Simons, 1990). This pattern resembles the dense focalized arrangement of photoreceptors in the retina fovea, and hence was referred to as *foveal whisking*. A large body of works has focused on quantifying the behavioral capability of rats in this mode of operation. In the generative mode, rats are able to complete a variety of tasks such as texture discrimination (Arabzadeh et al., 2005; Carvell & Simons, 1990; Diamond, Von Heimendahl, & Arabzadeh, 2008; Hipp et al., 2006; Morita, Kang, Wolfe, Jadhav, & Feldman, 2011; von Heimendahl, Itskov, Arabzadeh, & Diamond, 2007; Zuo, Perkon, & Diamond, 2011), identification of shape and size of objects (Brecht et al., 1997; Harvey et al., 2001; Pammer et al., 2013; Polley et al., 2005), detection of distance, gap and aperture width (Guić-Robles et al., 1989; Harris et al., 1999; Hutson & Masterton, 1986b; Jenkinson & Glickstein, 2000; Krupa, Matell, Brisben, Oliveira, & Nicolelis, 2001) and object localization (Ahissar & Knutsen, 2008; Hires, Gutnisky, Yu, O'Connor, & Svoboda, 2015; Knutsen, Pietr, & Ahissar, 2006; Kwon, Yang, Minamisawa, & O'Connor, 2016; Mehta, Whitmer, Figueroa, Williams, & Kleinfeld, 2007; O'Connor et al., 2010; O'Connor, Peron, Huber, & Svoboda, 2010; O'Connor et al., 2013; Yang, Kwon, Severson, & O'Connor, 2016).

The second, but less investigated mode of operation is known as the receptive mode. In the same way that we keep our fingers still to determine our pulse, rats can immobilize their whiskers to actively "listen" for vibrations in their environment. Tasks involving whiskers in the receptive mode have the advantage that they enable the efficient study of sensory coding with precisely controlled stimulus presentation in the absence of whisking movement (Adibi, Diamond, & Arabzadeh, 2012; Lee et al., 2016; Miyashita & Feldman, 2012; Stuttgen & Schwarz, 2010; Stuttgen & Schwarz, 2008). Behavioral evidence indicates that self-generated whisker motions

reduce the rats' performance when detecting vibrations (Ollerenshaw et al., 2012). Studies involving the receptive mode typically include detection and discrimination of vibrations applied to whiskers (Adibi, Diamond, & Arabzadeh, 2012; Gerdjikov, Bergner, Stüttgen, Waiblinger, & Schwarz, 2010; Hutson & Masterton, 1986; Lee et al., 2016; McDonald et al., 2014; Stüttgen & Schwarz, 2010; Stüttgen & Schwarz, 2008) or discrimination of the width of an aperture (Krupa et al., 2001). The receptive mode of whisker-mediated perception forms the main focus in the present dissertation.

1.4. Scope of the dissertation

The rodent whisker system is an excellent model to understand sensory perception. This thesis focuses on top-down, endogenous attention in two domains of allocation: modality and time. Behavioral paradigms were developed in order to study whether rodents are capable of selectively attending to different modalities and across time with neural correlates of attention in the primary somatosensory cortex also investigated.

In Chapter 2, we first focus on selective attention across modalities. Here, a novel attention paradigm is developed in which rodents are trained to prioritize processing in two different modalities (somatosensory and visual). Centered on a simple detection paradigm, behavioral metrics of attention are analyzed. We introduce a novel method of calculating the first behaviorally significant reaction times. Additionally, recording of single-unit activity from the primary somatosensory cortex during the sensory prioritization task allows us to investigate the neuronal mechanism underlying the enhanced behavioral efficiency observed in this paradigm.

In Chapter 3, we replicate the above paradigm in a two-alternative forced choice variant with different sensory modalities (somatosensory and auditory). In Chapter 4, we change our focus onto selective attention via temporal cueing. A novel temporal cueing paradigm is developed in which rodents are trained to prioritize processing in time. An auditory stimulus temporally cued the onset of a target vibration stimulus without providing spatial information. Similar to sensory prioritization across modalities, recording of single-units activity allows investigation of the neuronal mechanisms underlying temporal attention. Finally, Chapter 5 summarizes a number of ongoing and future directions of research within the scope of whisker-mediated attention in rodents.

2. Sensory prioritization in the whisker modality– a detection paradigm

2.1. Introduction

In a natural environment, animals need to assess when to initiate actions based on uncertain or weak sensory inputs, such as small changes in luminance, or vibrations induced by predators. In such scenarios, animals benefit from prioritizing sensitivity in the modality that is more likely to provide the key information. Contemporary models of attention largely focus on the primate visual system. Although this system is highly efficient (Bisley, 2011; Carrasco, 2011; Thorpe, Fize, & Marlot, 1996), the mechanisms are difficult to unravel due to the complexity of the neuronal pathways and the large number of dimensions in the stimulus space. Rodent whisker touch represents an expert sensory system with the ability to encode the environment in a fast and reliable manner (Diamond & Arabzadeh, 2013). Besides its efficiency, this system is tractable and offers the chance to investigate the neuronal basis of object detection and identification. Here, we establish a detection paradigm to study the neuronal correlates of attention by controlling the likelihood with which sensory stimuli are presented in one of two modalities, vision and whisker touch. Our behavioral evidence shows that the stimulus in the more likely modality is better detected, an indication that the paradigm leads to sensory prioritization.

Rats and mice are frequently active in darkness, using their array of mobile whiskers to acquire sensory information. The system is structurally well-characterized; the vibrissal area of the primary somatosensory cortex (vS1) contains a magnified topographic map of the whiskers in

the form of distinct clusters of neurons, known as barrels, in layer IV (Welker, 1971; Woolsey & Van der Loos, 1970). Using its whiskers, a rat can quickly obtain sufficient information to complete complex behavioral tasks, such as discriminating between textures (Mathew E Diamond et al., 2008; Kuruppath, Gugig, & Azouz, 2014; Morita et al., 2011; von Heimendahl et al., 2007; Zuo et al., 2015), detecting and discriminating vibrations (Mehdi Adibi & Arabzadeh, 2011; Fassihi, Akrami, Esmaeili, & Diamond, 2014; McDonald et al., 2014; Miyashita & Feldman, 2012), and localizing objects (Ahissar & Knutsen, 2008; Hires, Gutnisky, Yu, O'Connor, & Svoboda, 2015; Knutsen, Pietr, & Ahissar, 2006; Mehta, Whitmer, Figueroa, Williams, & Kleinfeld, 2007; O'Connor et al., 2010; O'Connor, Peron, Huber, & Svoboda, 2010; O'Connor et al., 2013). The functional efficiency of the whisker pathway and its structural organization make it an ideal system in which to investigate how attention affects sensory processing.

At the behavioral level, attention has been shown to improve perceptual accuracy and shorten reaction times in primates (Carrasco, 2011; Cohen & Maunsell, 2009; Posner, 1980) with near-threshold stimuli gaining the strongest improvements (Herrmann, Montaser-Kouhsari, Carrasco, & Heeger, 2010; Reynolds, Pasternak, & Desimone, 2000). At the neuronal level, a number of signatures of attention have been identified in primates: an increase in stimulus-evoked firing rate in various visual areas [LGN (McAlonan et al., 2008), V1 (Buffalo et al., 2010; Herrero et al., 2008), V2 (Buffalo et al., 2010) and V4 (McAdams & Maunsell, 1999a; Moran & Desimone, 1985)]; an increase in baseline activity [V1, V2 (Luck et al., 1997), V4 (Luck et al., 1997; Reynolds et al., 2000)]; and anticipatory responses to stimuli (Chen & Seidemann, 2012;

Rodgers & DeWeese, 2014). Are any of these neuronal correlates of attention applicable to other species and sensory areas such as the rodent somatosensory cortex?

Here, we manipulated attention by controlling the likelihood with which a stimulus was presented from one of two modalities. In a *whisker session*, 80% of trials contained a brief vibration applied to whiskers and the remaining 20% of trials contained a brief change of luminance (flicker trials). During such a session, given the limited capacity of the attentional system (Posner, 1980), rats would be expected to prioritize processing in the whisker pathway. The opposite prioritization would be expected for a *visual session* (80% flicker trials and 20% vibration trials). We establish how alternating between whisker and visual sessions affect the sensitivity and reaction time in detecting stimuli from each modality and how the likelihood of receiving stimuli in the whisker modality affects single-unit activity in the vS1 cortex.

2.2. Materials and Method

2.2.1. Subjects

Subjects were 7 adult, male Hooded Long Evans rats with initial weights of 170-210g. All procedures were approved by the Animal Care and Ethics Committee at the Australian National University. Rats were housed in independently ventilated and air filtered transparent plastic boxes in a climate controlled colony room on a 12/12 hour light/dark cycle, where lights were turned off at 7pm. A combination of food and water restriction was used to motivate the rats to perform the detection task. Rats had abundant access to water except 2-3hrs before sessions. 25-30g of rat chow was provided after the session. All rats gained weight at a normal rate throughout the entire duration of the experiment.

2.2.2. Apparatus

Rats were trained in a chamber measuring 24x32x11cm. The front panel had an aperture with a diameter of 4cm, elevated 10cm from the floor. A stepping platform was placed below the aperture, 6cm from the floor. Outside the aperture was a nose-poke and reward spout, both of which had infra-red sensors to detect the animal's presence. On the right side, an aluminum mesh (5x5cm) was attached to a ceramic piezoelectric wafer (Morgan Matroc, Bedford, OH) to transmit a vibration stimulus. The mesh was placed at 45° from the center of the nose-poke sensor. To display the flicker stimulus, an LCD monitor (Dell – Model No. U2312HM, 60Hz refresh rate, 510cm x 290cm) was placed at a distance of 35cm behind the wafer, 45° from the center of the nose-poke sensor. The vibration stimulus was a sequence of discrete Gaussian deflections generated from MATLAB (MathWorks, Natick, MA) and presented through the analog output of a data acquisition card (National Instruments, Austin, TX) at a sampling rate of 44.1kHz. Each Gaussian deflection, with sigma 5ms, lasted for 15ms and was followed by a 10ms pause before the next deflection, yielding a frequency of 40Hz. Though the rats' trajectory was highly stereotyped (Movie 1) distance between the mesh and the follicle could vary from trial-to-trial due to head position and the curved surface of the snout; by examination of video records our estimate of median distance is about 4mm. The amplitude of the vibration was modulated depending on the stage of learning (*See Procedure*). The flicker stimulus was a change in luminance from baseline at 0.68cd/m² (black screen). This was generated and displayed using MATLAB Psychophysics Toolbox extensions (Brainard, 1996; Pelli, 1997). The percentage of change in luminance also was modulated depending on the stage of learning (*See Procedure*). The nose-poke behavior was monitored by a high-speed camera (Balser A3800) with a resolution of 22.68 pixels/mm through a Nikon Lens (Nikkor AF 50mm f/1.8) at 150

frames/s. The video provided a top view of the whiskers with illumination from below the nose-poke aperture using a 940nm LED. For all video sequences, we obtain 1s movies capturing the period from the nose-poke onset (see Movie 1). The example videos capture the stereotyped nose-poking and withdrawal behavior in the course of correct trials with 800ms delay in all 4 combinations of stimulus and modality-likelihood conditions (vibration/flicker stimulus; whisker/visual session) at 20x reduced speed.

2.2.3. Electrophysiology

After animals were trained in the behavioral task, microelectrodes supported by microdrives were surgically implanted into vS1. Two types of microdrives and microelectrodes were used. Rats were implanted with either a custom built micro-drive that supported a 16-channel array (Tucker-Davis Technology, FL), or an Axona Versa-Drive (Axona Systems, London) that supported independent movement of 4 custom-made tetrodes. The array was arranged in a 2 by 8 configuration with 250 μ m spacing between shanks, and 375 μ m spacing between the 2 rows. Tetrodes were made from four 7 μ m platinum iridium micro-wires that were twisted together and plated with platinum black plating solution (Neuralynx, MT) and gold plating solution (SIFCO ASC, OH). Spacing between tetrodes was 200 μ m center to center.

Animals were given ab-lib food and water at least 24h before surgery and for at least 5d after surgery. Anesthesia was induced with 3% isoflurane in O₂ and maintained with 2-3% isoflurane provided through a breathing mask throughout surgery. Depth of anesthesia was monitored by tail and hind-paw pinch responses. Body temperature was maintained at 37°C using a heating pad (Physitemp Instruments, NJ). Craniotomies were made through which electrodes were lowered at coordinates of 2.5mm anterior to bregma and 4.3mm from midline. In 2 out of 5 brains,

recording sites were histologically verified by comparing Nissl-stained 60 μ m coronal brain sections with reference anatomical planes (Paxinos & Watson, 2007). The array positions indicated that recordings were made in the supragranular layers of the vibrissal area of the primary somatosensory cortex (Fig. 7B). A multi-neuronal acquisition processor (16 channels, Axona Systems) was used to amplify and record signals. Single-units were filtered at 300-7000Hz (Butterworth) and extrapolated by using Offline Sorter 3.2.4 (Plexon, TX) according to the following criteria: (1) <0.1% of inter-spike intervals smaller than 1.0ms (2) spike waveform shapes as determined by a waveform template algorithm and principal component analysis.

2.2.4. Task

Figure 2A and 2B show the behavioral setup and the training paradigm. Rats initiated a trial by performing a nose-poke. As they maintained the nose-poke, either a flicker or a vibration stimulus was presented at one of two delays (300 or 800ms). The delays were pseudo-randomized independently from the presentation order of stimulus modality. The randomization was such that on every session, 50% of trials would contain each of the two delays. The stimulus had a maximum duration of 400ms and was terminated if the rat left the nose-poke earlier. Upon detecting the presence of the stimulus, rats were required to respond by leaving the nose-poke and entering the reward spout within 500ms after the onset of the stimulus; correct actions were rewarded with 0.08mL of 7% sucrose. We discouraged the rats from leaving nose-poke prematurely – that is, before detecting the stimulus – by setting the length of each trial to a fixed duration of 2.5 seconds. This was done by adjusting the inter-trial interval on a trial-by-trial basis: when rats left the nose-poke prior to the stimulus onset, the inter-trial interval was proportionately longer, hence acting as a time-out punishment.

Sessions were categorized as either whisker or visual. In a whisker session, 80% of trials consisted of a vibration stimulus whilst 20% of trials consisted of a flicker stimulus. These frequencies were reversed for a visual session. Each session contained 180 trials, with 2 low-likelihood trials inserted in random order within every 10 trial block. In one group of rats ($n=4$), two sessions were conducted each day (3h break between each session, no food or water was provided during this break) and the order of session type was counterbalanced daily. In order to facilitate tracking neurons across the two session types (visual and whisker), in a second group of rats ($n=3$) the break between the two sessions was removed and the number of trials in each session was reduced to 100, effectively forming a single session with a continuous series of 200 trials and a modality likelihood switch at the midpoint. The order of the switch was counterbalanced and no cues were provided to the animal as to the occurrence of the switch in likelihoods. This protocol allowed us to quantify the temporal profile of prioritization after the switch in likelihoods on trial 101 (Fig. 6B).

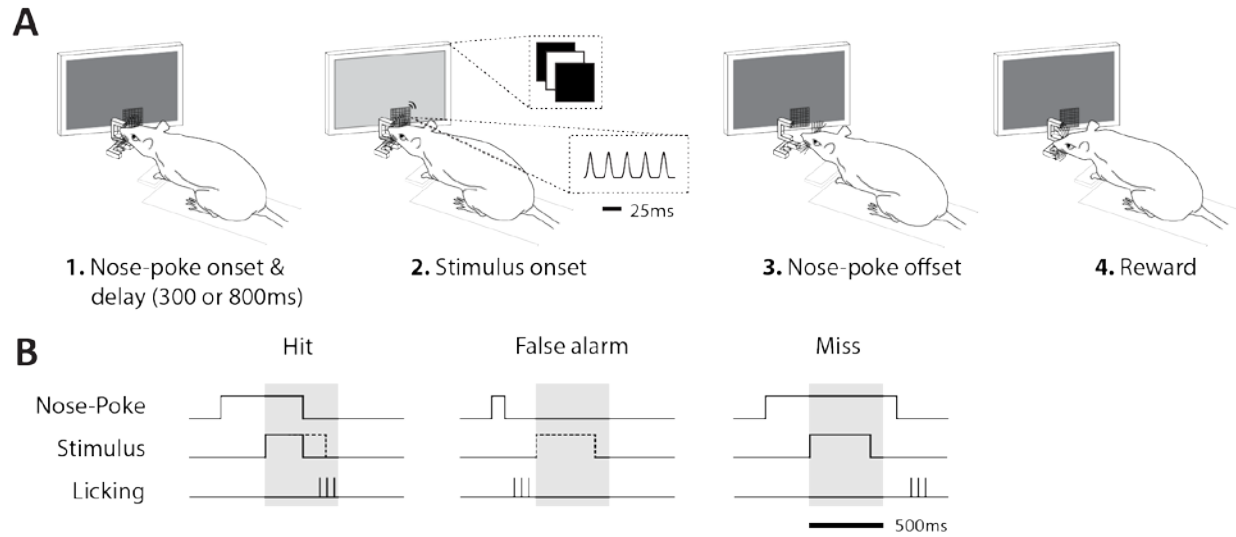


Figure 2 Schematic representation of the detection task. **A.** The rat initiated a trial by nose poking into the aperture while touching the mesh plate with its whiskers (1). After a delay of either 300 or 800ms, during which nose poke was continually maintained, the rat received either a vibration (a sequence of Gaussian wavelet pulses) or visual stimulus (a change in luminance from a black display) (2). The rat expressed detection of the stimulus by leaving the nose-poke (3) and entering the reward spout (4). Correct detection was rewarded by 7% sucrose water. **B.** Schematic representation of the three trial types that arose from the animal's behavior. Shaded gray area defines the 500ms window of opportunity. Nose-poke steps represent entrance and exit from nose-poke. Stimulus steps represent onset and offset of stimulus presentation. Licking bars represent the first few licks at the reward spout. Trial types were defined as the following: hit, which was leaving the nose-poke within the window of opportunity and entering the reward spout; false alarm, leaving the nose-poke before the onset of the stimulus and entering the reward spout; or miss, leaving the nose-poke after the window of opportunity. The stimulus was aborted upon exit from the nose-poke (see "hit"), and was not presented at all in the case of "false alarm." The dashed line represents the stimulus profile if it was not aborted or cancelled.

2.2.5. Procedure

Shaping to go to spout. Rats were placed in the experimental chamber and reward was freely available from the reward spout for 100 trials. The nose-poke sensor was blocked at this stage.

When rats arrived at the reward spout to receive sucrose, both the visual stimulus (100% change in luminance) and the whisker stimulus (a series of deflections at 50 μ m amplitude) were presented simultaneously.

Shaping to perform nose-poking. Rats were rewarded only after performing a nose-poke. Two delays were imposed from the first nose-poke shaping day, with 80% of trials with a short delay (starting at 100ms) and 20% with the longer delay (starting with 200ms). The required duration of nose-poke gradually increased to reach the final delays of 300 and 800ms and the proportion of short- and long-delay was gradually shifted to 50%. At this stage, the two session types were also introduced.

Adjustment of the stimulus intensity. When animals reached a performance above 75% and a false alarm rate below 15%, 4 separate levels of stimulus intensity were presented in an intermixed fashion on each session. Vibration intensity was manipulated by adjusting the amplitude of the Gaussian wavelets. Note that a change in amplitude causes a linearly related change in speed of the two phases (rise and fall) of the wavelet; previous work (Arabzadeh et al., 2004; Arabzadeh, Petersen, & Diamond, 2003) indicates that whisker deflection speed is encoded by cortical neurons. The starting deflection amplitude was 25 μ m and was reduced with steps of 3 μ m to generate lower intensities. Flicker intensity was adjusted by the percentage change from baseline (0.68cd/m²). The starting change in luminance was 47% and was reduced with steps of 7.8% to generate flickers of progressively lower intensity. At each level of difficulty, detection performance was indexed by the proportion of misses, defined as the number of miss trials divided by the sum of miss and hit trials. The stimulus difficulty increased until

miss proportions grew to 30%. At the final stage, the stimulus difficulty was 3-8 μ m for the vibration stimulus across rats, and 4-12% change in contrast for the visual stimulus.

2.2.6. Data Analysis

As shown in Figure 2B, trials were categorized as: Hit – rat successfully waited in the nose-poke for the stimulus, then left the nose-poke and licked the reward spout within 500ms of the onset of the stimulus. False Alarm – rat left the nose-poke before stimulus presentation. Miss – rat successfully waited in the nose-poke for the stimulus but failed to leave in response to stimulus presentation (i.e. it left the nose-poke more than 500ms after stimulus onset).

To quantify ‘onset’ reaction times, we applied signal detection theory (Green & Swets, 1966) to determine perceptual accuracy, d' , for each stimulus modality and session type (visual or whisker). For this analysis, we compared nose-poke leaving times (nose-poke offset minus nose-poke onset) between short- and long-delay trials. Perceptual accuracy was calculated as:

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$$

where Z is the inverse of the cumulative Gaussian distribution function. The hit rate distribution was derived from the nose-poke leaving times of short-delay trials (300ms), whilst false alarm rates were derived from the nose-poke leaving times of long-delay trials (800ms). The d' values were calculated as a function of time at a resolution of 5ms. This was compared against a shuffled distribution where 1,000 d' traces were calculated by sampling from a randomized

distribution of hits and false alarms. The first point of deviation of the observed d' from the shuffled distribution was taken as the 'onset' reaction time.

Stimulus detectability was computed from distributions of spike counts occurring 200ms before and after each stimulus onset. A criterion shifted in steps of 1 spike across the 2 distributions was used to determine the hit and false alarms of the neuron, and thus forming a receiver operating characteristic (ROC) curve. Detectability is expressed as the area under the ROC, and significance testing was performed by bootstrapping spike counts across the two distributions.

For neuronal data recorded from vS1, the sequence of spikes corresponding to the same trial types (4 types - vibration or flicker stimulus in whisker or visual session) were separated and aligned with respect to their corresponding stimulus onsets to generate raster and PSTH plots. To obtain an index of stimulus detectability, a receiver operating characteristic (ROC) analysis was performed in the framework of signal detection theory (Green & Swets, 1966). ROC curves were calculated by counting the average spike rate for each trial in a 200ms window pre-stimulus onset as the false alarm rate; 200ms window post stimulus onset as the hit rate. This analysis was performed for each neuron. The area under each ROC curve was calculated and averaged. Area under ROC value can vary from 0 to 1 with 0.5 indicating chance level. A value of 1 indicates perfect decoding. In sum, this provided an index of detection sensitivity of the population between the 4 conditions. A similar analysis was performed for hit and miss trials to determine whether activity in vS1 predicted behavioral performance.

2.3 Results

2.3.1 Learning of the detection task

Rats were trained to report the presence of either a vibration applied to their whiskers or a luminance flicker on the display monitor (Fig.2A). They initiated a trial by performing a nose-poke, registered by an optic sensor. On each trial, the stimulus was presented at one of two fixed delays after nose-poke: half of trials had an early stimulus onset (300ms) and half had a late stimulus onset (800ms). The stimulus had a maximum duration of 400ms and was terminated when the rat left the nose-poke, for both vibration and flicker trials. Every trial was classified as either: hit – leaving the nose-poke within the 500-ms window of opportunity and entering the reward spout; false alarm – leaving the nose-poke before the onset of the stimulus and entering the reward spout; or miss – not leaving the nose-poke for that trial or leaving the nose-poke after the window of opportunity (Fig.2B). Since every trial, except those aborted by false alarm, contained a stimulus presentation, the usual class of “correct rejection” did not apply. Rats learnt to perform the task for both modalities over several sessions (Fig. 3A). Once performance was stable, we modulated stimulus difficulty to yield similar performance across rats and for both modalities (see Materials and Methods). To characterize the overall detection performances for the vibration and flicker stimuli, we first combined the trials of a given modality across both high- and low-likelihood sessions (Fig. 3B). False alarm rates were low and consistent across all rats (vibration: $5.72 \pm 2.78\%$, mean $\pm$ SD; flicker: $5.30 \pm 3.76\%$ across rats). Vibration and flicker stimuli showed similar hit rates (student t-test, Rat 1: $p=0.07$, Rat 2: $p=0.53$, Rat 3: $p=0.86$, Rat 4: $p=0.13$) and miss rates (student t-test, Rat 1: $p=0.19$, Rat 2: $p=0.94$, Rat 3: $p=0.98$, Rat 4: $p=0.17$). To establish that rats’ behavior was based on stimulus detection rather than a non-specific strategy such as timing, we quantified performance by comparing nose-poke durations between short (300ms) and long (800ms) delay trials. If rats left the nose-poke

consequent to stimulus detection, the time spent in the nose-poke would depend on the duration of the delay preceding stimulus presentation. During vibration trials, rats showed significantly longer nose-poke durations for the long-delay trials ($967 \pm 11\text{ms}$, mean $\pm$ SD) than for the short-delay trials ($539 \pm 8\text{ms}$) (Wilcoxon rank-sum test, $p < 0.01$), and this stimulus onset dependence was consistent across rats (Fig. 3C). In flicker trials, just as in vibration trials, the time spent in the nose-poke depended on stimulus timing (Fig. 3C: long-delay: $976 \pm 27\text{ms}$; short-delay: $593 \pm 25\text{ms}$; Wilcoxon rank-sum test, $p < 0.01$). In sum, early and late stimulus onset trials led to distinct response timing profiles.

Given that a trial was equally likely to have an early or late stimulus, at the onset of nose-poke, the probability of stimulus presentation at 300ms was 0.5. However, if the rat detected no stimulus at 300ms, the probability of stimulus presentation at 800ms was approximately 83% (calculated as 1 divided by 1 plus the probability of having failed to detect a true stimulus presentation at 300ms, the average miss probability across all rats and modality being $20 \pm 5.4\%$). We examined whether the expectation of a late stimulus (based on not sensing the early stimulus) resulted in faster reaction times and found it to be the case for both modalities: the distribution of reaction times – time interval between stimulus onset and nose-poke exit – showed a faster rise and a lower median for the long-delay trials compared to the short-delay trials (Fig. 3D; vibration, $p < 0.01$; flicker, $p < 0.01$, Wilcoxon rank-sum test).

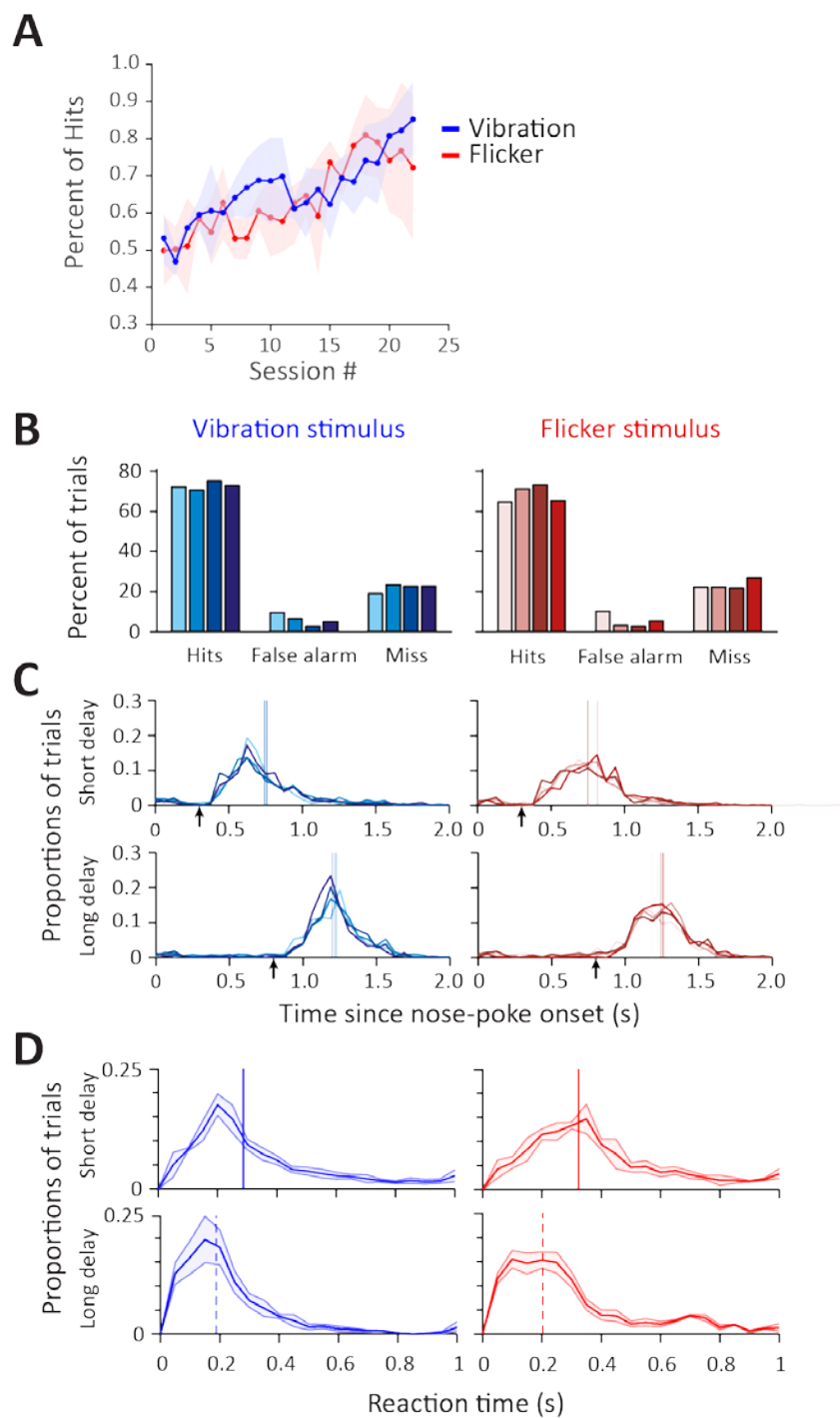


Figure 3 Rats showed high levels of behavioral detection performance. **A.** Learning profile for vibration and flicker stimulus across 4 rats. Performance was calculated as the proportion of hits. **B.** Detection performance when a vibration stimulus was presented (blue) and when a visual stimulus was presented (red). Each shade represents the performance of a single rat. **C.** Distribution of nose-poke durations (nose-poke offset - nose-poke onset). Top, Short-delay trials

(300ms). Bottom, Long-delay trials (800ms). Arrows represent stimulus onset. Vertical lines represent median nose-poke duration for each rat. Miss trials in which the rat did not leave the nose-poke were excluded. Each shade and color represents a single rat and stimulus as in A. **D.** Distribution of reaction times (nose-poke offset minus stimulus onset) between short- and long-delay trials averaged across all four rats. Shaded area represents 1 SD. Top, Short-delay trials (300ms). Bottom, Long-delay trials (800ms). Vertical line represents median reaction time. Miss trials in which the rat did not leave the nose-poke were excluded. Color notations are the same as previous panels.

2.3.2 Reaction times to vibration and flicker stimuli

For the interval between 300 and 800ms post nose-poke, all trials can be divided into two categories: stimulus-present and stimulus-absent, with equal number of trials in each category (stimulus-absent trials in this first interval correspond to late stimulus trials). This design allowed us to calculate hit rate and false alarm rate and combine them to estimate sensitivity (d') at each time point during the 300-800ms interval (Fig. 4). The first point in time where d' values deviated from chance (chance estimated by bootstrapping; see Materials and Methods) revealed remarkably fast reaction times. These “onset” reaction times capture the earliest reliable behavioral manifestation of stimulus detection and were consistent across rats. Averaged across all sessions in all rats, vibration and flicker trials gave a first reaction of 48ms and 56ms respectively (Table 2).

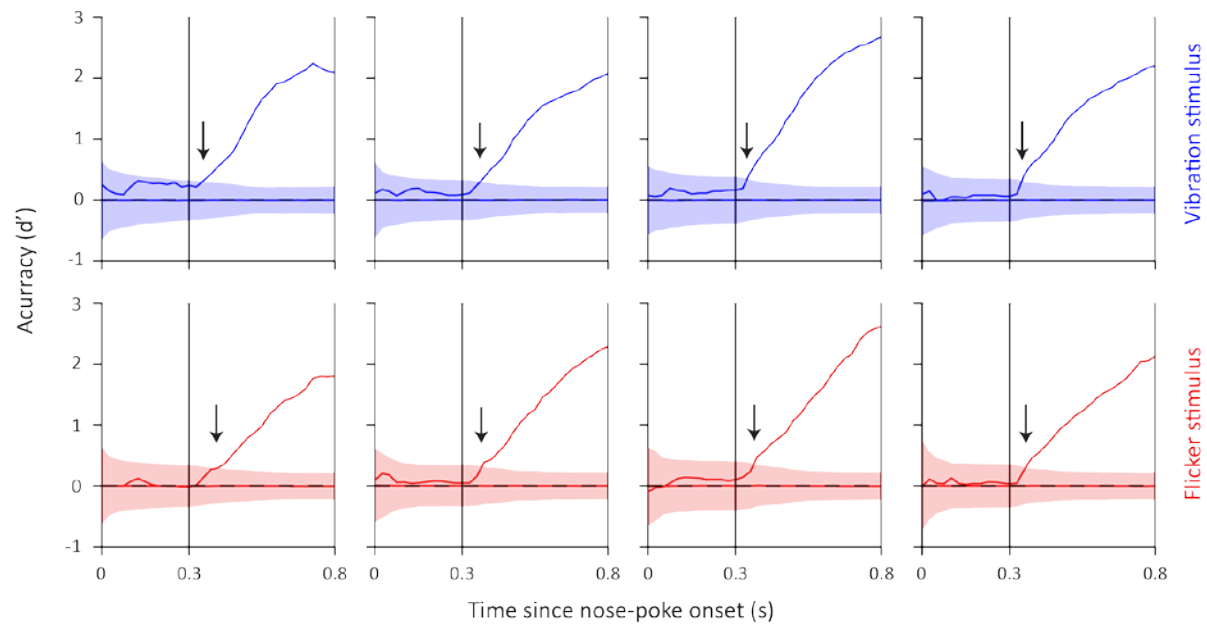


Figure 4 Rats showed fast onset reaction times as revealed by a change in detection accuracy (d') as a function of trial time course. Each rat's detection accuracy is shown across panels. Shaded areas represent d' chance level as calculated from bootstrapping. Dashed horizontal line represents the mean value of shaded area. Arrows indicate the first point in time d' reached above chance level. Red represents detection accuracy for flicker stimulus. Blue represents detection accuracy for vibration stimulus.

Table 2. Onset reaction times (ms)

	Rat 1	Rat 2	Rat 3	Rat 4
Vibration	61	50	40	39
Flicker	55	60	58	51

2.3.3. Effects of attention on performance and reaction time

Does attention modulate the speed and accuracy of stimulus detection? To address this question, we manipulated the likelihood with which a stimulus was presented within each modality. In a *whisker session*, 80% of trials required detection of a vibration and the remaining 20% of trials required detection of a flicker. These likelihoods were reversed in the *visual session*. In the preceding sections, we pooled the two session types, but we now consider the sessions separately to determine whether manipulation of stimulus likelihood resulted in systematic differences in behavioral performance. Trials in which the presented stimulus was in the modality corresponding to the session type were denoted as *high-likelihood* trials (i.e. vibration trials in whisker sessions and flicker trials in visual sessions), whilst trials where the stimulus modality did not correspond to the session type were denoted *low-likelihood* trials (i.e. vibration trials in visual sessions and flicker trials in whisker sessions). When a vibration stimulus was presented in a whisker session (high-likelihood), all 4 rats were less likely to miss the stimulus compared to when it was presented in a visual session (low-likelihood) (Fig.5A; Rat 1, $p < 0.05$; Rat 2, $p < 0.01$; Rat 3, $p < 0.05$; Rat 4, $p < 0.01$). This change in sensitivity was consistent across rats: on average, miss rates for vibration were 0.18 ± 0.01 and 0.34 ± 0.03 in whisker and visual sessions, respectively. Similar improvements in detection were observed for flicker stimuli when presented in a visual session (Fig. 5A; Rats 1-4, all $p < 0.01$; miss rates for flicker stimuli were 0.19 ± 0.02 and 0.32 ± 0.29 in visual and whisker sessions, respectively).

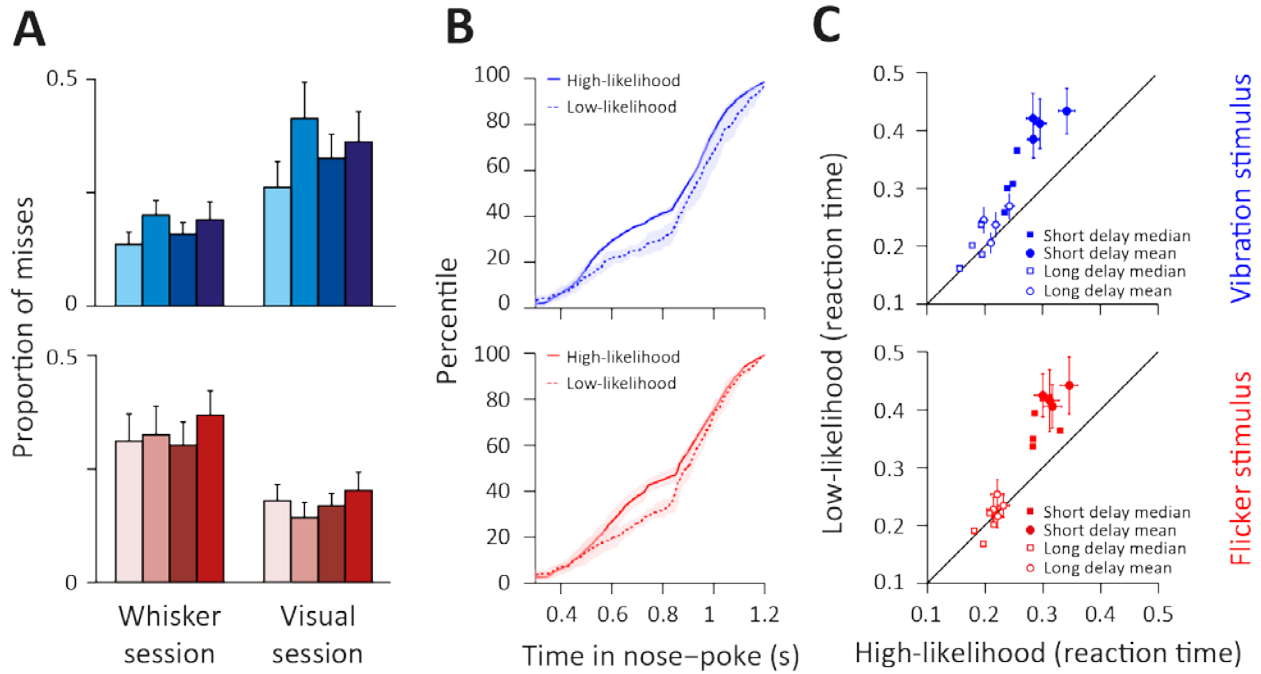


Figure 5 Increased detection performance and speed when stimulus was presented in a high-likelihood versus low-likelihood session. **A.** Proportion of misses calculated as the number of miss trials divided by the sum of miss and hit trials. Top (blue), Miss proportion when vibration stimulus was presented in a whisker (high-likelihood trials) and visual session (low-likelihood trials). Bottom (red), Miss proportion when flicker stimulus was presented in a visual (high-likelihood trials) and whisker session (low-likelihood trials). Error bars indicate SDs for each rat. Color notations are the same as in Figure 3. **B.** Cumulative distribution frequency of nose-poke duration of hit and miss trials. Top (blue), Cumulative distribution frequency of vibration trials presented in high- (solid line) and low-likelihood session (dashed line). Bottom (red), Cumulative distribution frequency of flicker trials presented in high-likelihood session (solid line) and low-likelihood session (dashed line). Shaded area represents SD across rats. **C.** Scatter plot comparing reaction time between stimuli presented in high- and low-likelihood sessions for each rat. Trials were separated by short-delay stimulus (filled markers) and long-delay stimulus (open markers). Circles represent mean values. Squares represent median values. Error bars indicate SEMs.

We next asked if stimulus likelihood affected the speed of detection. Figure 5B plots the cumulative distribution of nose-poke duration for high-likelihood (solid line) and low-likelihood

(dashed line) stimuli. Across rats, the high-likelihood stimulus resulted in significantly shorter nose-poke duration compared to the low-likelihood stimulus, for both vibration and flicker trials (vibration and flicker, Rats 1-4: $p < 0.01$, Wilcoxon rank-sum). Though reaction times were on the whole (Fig. 3C) longer on short-delay trials (300ms stimulus onset) compared to long-delay trials (800ms stimulus onset), the short-delay trials showed a more prominent benefit in detection speed on high-likelihood versus low-likelihood trials (filled symbols in Fig. 5C) than did the long-delay trials (open symbols in Fig. 5C). On short-delay trials, rats reacted significantly faster to the vibration stimulus when presented in a whisker session (filled circles, 301 ± 27 ms, mean $\pm$ SD across rats) compared to a visual session (430 ± 17 ms, Mean $\pm$ SD, Wilcoxon rank-sum, $p < 0.01$). The context-dependent improvement in reaction time was also the case for flicker stimulus (in visual session: 318 ± 19 ms; in whisker session: 438 ± 48 ms, $p < 0.01$). To examine whether the improvement in the overall reaction time was due to miss trials with long reaction times, we measured the median reaction times to minimize the effect of outliers. For short-delay trials, the median values also replicated the enhanced reaction time (filled squares in Fig. 5C; high-likelihood vibration trials: 244ms; low-likelihood vibration trials: 308ms; high-likelihood flicker: 295ms; low-likelihood flicker: 360ms; all values averaged across rats). Unlike short-delay trials, the long-delay trials did not exhibit a robust difference in reaction times: the difference between high- and low-likelihood trials was significant for vibration trials (218 ± 18 ms versus 239 ± 26 ms, $p = 0.04$) but not for flicker trials (221 ± 7 ms versus 232 ± 16 ms, $p = 0.95$).

To investigate how rapidly the enhanced sensitivity for the high-likelihood stimulus emerged, we divided each 180-trial session into four 45-trial quartiles (Fig. 6A, left panel) and found that the differential performance was present from the first quartile. During the first quartile, the

vibration stimulus gave a miss rate of 0.15 when presented in a whisker session (solid line) and 0.28 when presented in a visual session (dashed line); the difference in miss rate was significant across rats ($p < 0.01$). Enhanced sensitivity was also observed for the flicker stimulus when its likelihood was elevated, giving a miss rate of 0.17 (first quartile of visual session) versus 0.34 (first quartile of whisker session), a significant difference ($p < 0.01$). As the session progressed, the performances in the high- versus low-likelihood conditions appear to converge (Fig. 6A, left panel) however this trend was not statistically significant (difference in miss performance over time, $r(30) = -0.02$, $p = 0.91$; Pearson correlation test). Figure 6A, right panel, demonstrates in more detail how prioritization developed at the beginning of the session by plotting the proportion of misses for high- and low-likelihood trials in non-overlapping windows of 10 trials (trial 1-10, 11-20, and 21-30). The trend of increased performance for the high-likelihood stimulus was present in the first 10 trials, and reached statistical significance at 20-30 trials (vibration: $p < 0.05$; flicker: $p < 0.05$; Fig. 5A).

To further quantify the temporal profile of prioritization, 3 rats were trained in a modified version of the paradigm: a 200-trial session that contained an uncued switch in likelihoods after 100 trials. Rats detected the switch in likelihood and shifted their performance accordingly (Fig. 6B, left panel). Again we investigated in more detail how prioritization developed after the switch by plotting the proportion of misses for high- and low-likelihood trials in non-overlapping windows of 10 trials (Fig. 6B, right panel). By 20 trials after the switch in likelihoods, the previous prioritization was no longer expressed (miss rates were approximately equivalent for the high- and low-likelihood trials) and within 20-30 additional trials the rats expressed

prioritization in relation to the new likelihoods (Fig. 6B). The first change in performance appears to be a decrease in miss rate for the high-likelihood stimuli.

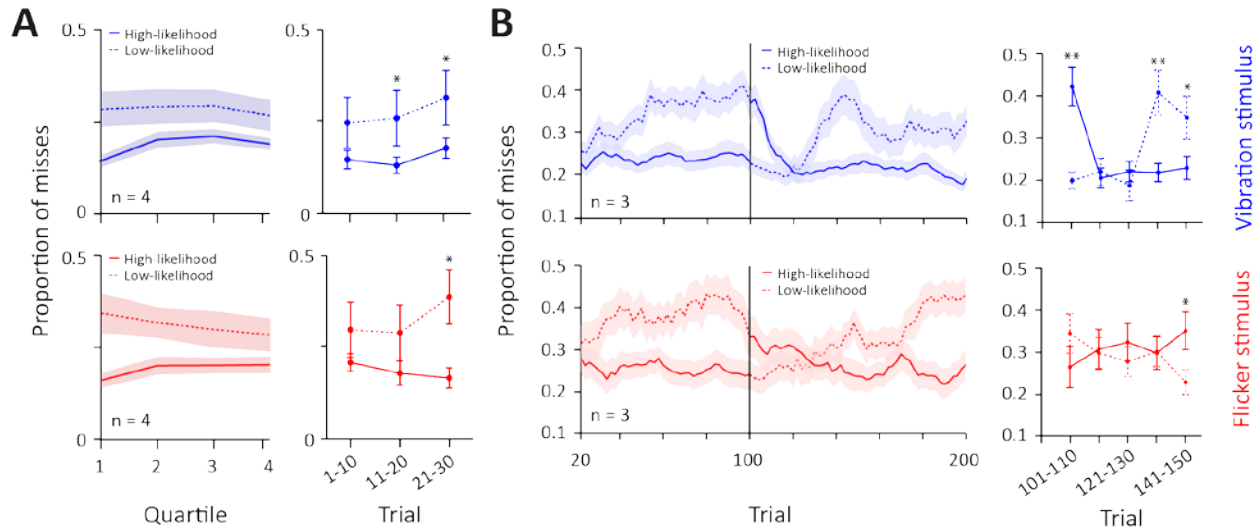


Figure 6 Time course of sensory prioritization. **A.** Left, Proportion of misses as a function of trial quartiles, pooled across rats ($n=4$) and sessions. Top (blue), Proportion of misses of vibration trials presented in high-likelihood condition (solid line) and low-likelihood condition (dashed line). Same notations are retained for bottom panel (red) representing flicker trials. Shaded areas indicate SEM. Right, Proportion of misses for the first 30 trials divided into non-overlapping windows of 10 trials. Asterisks indicate statistically significant differences, $p<0.05$, Student's t test. **B.** Left, Proportion of misses as a function of trials, pooled across rats ($n=3$) in the within-session likelihood switching paradigm. Proportion of misses was calculated in windows of 20 trials at steps of two trials. The vertical line represents the switch in likelihood after trial 100. Top (blue), Proportion of misses when vibration stimulus was presented in a high-likelihood condition (solid) and low-likelihood condition (dashed). Note the line changes in notation as likelihood proportions are switched. The same notation is retained for bottom panel (red) representing flicker trials. Shaded areas indicate SEM. Right, Proportion of misses for the first 50 trials after the onset of the switch in likelihood. Each data point represents non-overlapping windows of 10 trials. Asterisks indicate statistically significant differences, $*p<0.05$, $**p<0.01$, Student's t test.

2.3.4. Effects of sensory prioritization on neuronal activity in vS1

In 5 rats, we implanted electrodes into vS1 cortex contralateral to the side of whisker stimulation and recorded single-unit activity whilst the animals performed the detection task. One of the signatures of activity in vS1 is the response to whisker movement (Peron, Freeman, Iyer, Guo, & Svoboda, 2015) typically found during exploration (Diamond & Arabzadeh, 2013). We identified three key time points: nose-poke entry, stimulus presentation, and nose-poke exit as depicted in Fig. 7A. The recording site was verified functionally based on the activity during each behavioral time point and was histologically confirmed for two rats (Fig. 7B). Overall, vS1 units ($n=41$) showed low firing rates (< 5 spikes per second), typical of supragranular neurons. As expected, neurons showed changes in firing rate during entry into (NP+) and exit from (NP-) the nose-poke. Firing rate increased after nose-poke as the whiskers came in contact with the mesh (Wilcoxon rank-sum, 200ms pre and post nose-poke onset: $p<0.01$; Fig. 6C – left). The presentation of the vibration stimulus produced a significant increase in firing rate (Wilcoxon rank-sum, 200ms pre and post stimulus onset: $p<0.01$; Fig. 7C - middle). Finally, withdrawal from the nose-poke was accompanied by a significant decrease in firing rate (Wilcoxon rank-sum, 200ms pre and post nose-poke offset: $p<0.01$; Fig. 7C - right).

We then asked how sensory prioritization affected neuronal activity in vS1. Figure 7D, raster plots and upper PSTHs show the activity of an example neuron aligned to the 3 behavioral time points during a visual (red) and whisker (blue) session. During the whisker session, the neuron's firing rate increased at nose-poke entry, after stimulus presentation, and prior to nose-poke exit. The neuron's firing rate was reduced during the visual session, and the modulations of activity when aligned to the three behavioral events were either absent or reduced. These findings were

replicated averaging across 31 single-units that were maintained in both a visual and a whisker session (Fig. 7D, lower PSTHs). For every trial we measured the average firing rate from 0.5s before nose-poke entry to 0.5s after nose poke exit. Across neurons and trials, the average firing rate was 24.6% lower during the visual sessions compared to the whisker sessions and this difference was statistically significant (Wilcoxon rank-sum test, $p < 0.05$). To better quantify the differences between the two sessions, we characterized spike rates across these behavioral time windows. Figure 7E separates trials into four discrete categories based on their stimulus type (vibration or flicker) and likelihood (high or low): a whisker session is composed of vibration high-likelihood and flicker low-likelihood trials (dark blue and orange bars). A visual session is composed of flicker high-likelihood and vibration low-likelihood trials (light blue and red bars). Across neurons, vS1 firing rates were generally enhanced during whisker sessions compared to visual sessions (dark blue larger than light blue and orange larger than red) and this gain modulation was statistically significant (pooled across all behavioral windows, p values < 0.01 , Wilcoxon rank-sum). We also applied the Wilcoxon rank-sum test to separately examine the gain modulation at each behavioral time window: before nose-poke entry, $p = 0.19$; after nose-poke entry, $p = 0.45$; before stimulus onset, $p = 0.09$; after vibration onset, $p = 0.03$; after flicker onset, $p = 0.15$; before nose-poke exit, $p = 0.06$; after nose-poke exit, $p = 0.04$.

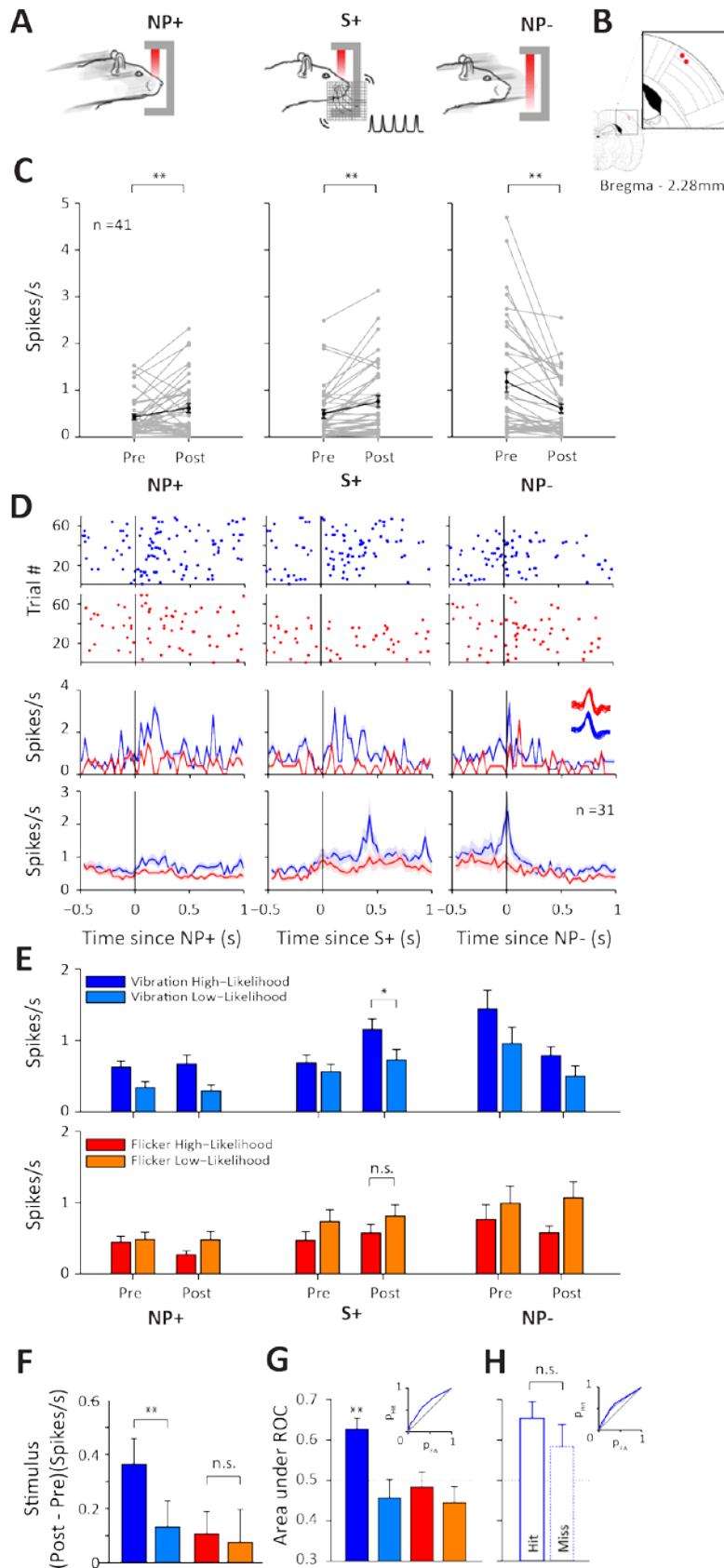


Figure 7. Single-unit activity in vS1. **A.** Schematic representation of behavioral time points of interest: NP+, nose-poke onset; S+, stimulus onset; NP-, nose-poke offset. **B.** Location of final recording sites in two rats on the rat brain atlas (Paxinos and Watson, 2007). **C.** Single-unit ($n=41$) activity at each behavioral time period. Pre and Post represent average spike rate in a 200ms window before and after each discrete behavioral event, respectively. Each gray line represents a neuron. Black line represents the average across all neurons. Error bar indicates SEM. **D.** Top, Raster plots showing spiking activity of the example neuron aligned to each behavioral event. Red dots represent spikes during visual session; blue dots represent spikes during whisker session. Middle, Perievent time histogram of the example neuron binned at 30ms. Shaded areas represent SEM across trials. Insert, 50 subsampled raw neuronal traces of example neuron during a whisker and visual session. Bottom, Averaged perievent time histogram of all recorded neurons ($n=31$) isolated in both a whisker and visual session. Shaded areas represent SEM across neurons. **E.** Average spike rate before and after each event (nose-poke onset, stimulus onset, nose-poke offset – 200ms window). Trials are separated based on the type of stimulus (vibration or flicker) and the session type (whisker or visual) in which it was presented. Dark blue represents vibration trials in a whisker session; light blue represents vibration trials in a

visual session; red represents flicker trials in a visual session; orange represents flicker trials in a whisker session. Error bars represent the SEM across neurons ($n = 31$). **F.** Analysis of stimulus response. Color notations are the same as in E. Each bar represents the mean difference in spike rate across neurons, calculated as the difference of post-stimulus spike rate from pre-stimulus spike rate. **G.** Analysis of stimulus detectability. Color notations are the same as in E. Each bar represents the mean area under ROC across neurons. Inset shows the ROC curve for detection of vibration high-likelihood stimulus. **H.** Area under ROC from G plotted separately for the hit versus miss trials of vibration high-likelihood stimulus. Inset shows the ROC curves for hit trials (solid blue line) and for miss trials (dotted blue line).

What is the effect of prioritization on stimulus detectability? We quantified the change in neuronal activity with stimulus presentation in a whisker and visual session. The evoked response was quantified as the difference in firing rate around stimulus onset (the firing rate 200-ms post-stimulus onset minus the firing rate 200-ms pre-stimulus onset). Vibration stimuli produced an evoked response that was statistically higher during the whisker session compared to the visual session ($p < 0.01$, student t-test; Fig. 7F). The modulation in firing rate around flicker presentation was not affected by session type ($p = 0.901$; Fig. 7F). An ROC analysis (see Materials and Methods) revealed that an ideal observer of neuronal activity in vS1 could reliably detect the vibration stimulus only when it was presented in the whisker session ($p < 0.01$, Fig. 7G). Z-score normalization during the stimulus period (firing rate 200-ms pre-stimulus and post-stimulus onset) revealed the same relationship, with neuronal activity in vS1 being significantly higher than chance only during vibration presentation in whisker sessions ($p < 0.01$, student t-test), which was also significantly higher compared to vibration presentation in visual sessions ($p < 0.01$, student t-test).

In the preceding section we reported that sensory prioritization increased the overall firing of vS1 neurons and, specifically, boosted the neuronal response to vibration stimuli. Next, we asked whether the neuronal encoding of the vibration stimulus correlated with the rat's behavioral performance (hit versus miss). To address this question, we compared the vibration-evoked activity (the firing rate 200-ms post-stimulus onset minus the firing rate 200-ms pre-stimulus onset) between the hit and miss trials but found no significant difference ($p = 0.318$; student t-test). In fact on miss trials, an ideal observer of neuronal activity in vS1 could still detect the

vibration stimulus better than chance (area under ROC of 0.58; $p < 0.05$; Fig. 7H; see Materials and Methods).

2.4. Discussion

Animals need to assess when to initiate actions based on uncertain sensory evidence. This is most evident when dealing with weak sensory inputs, such as small changes in luminance or vibrations induced by an approaching predator. Operating with some finite quantity of attentional resources, an animal would benefit from prioritizing the modality expected to provide key information. For instance, in a dark burrow the signal is likely to come from the tactile domain; upon leaving the burrow at daybreak, visual events would be more relevant.

To better understand how animals delegate attentional resources, we devised a paradigm that encouraged rats to prioritize processing in one sensory modality. Prioritization led to a drop in miss rates (Fig. 5A) and faster reaction times (Fig. 5B, C), in line with previous findings where attention improved performance (Carrasco, 2011; Cohen & Maunsell, 2009; Posner, 1980) and reduced reaction time (Eriksen & Hoffman, 1972; Henderson & Macquistan, 1993). In every 10-trial block, 2 trials presented the low-likelihood stimulus. Therefore, an ideal observer would be able to identify the session type after as few as 3 trials of the same stimulus modality. The first group of rats was tested with just one likelihood condition per session and required a small number of trials to identify the session type: they improved detection for the high-likelihood stimulus as early as 10 trials into the session, reaching statistical significance after 20-30 trials (Fig. 6A). A second group of rats was tested in a modified version of the paradigm that contained an uncued switch in likelihoods in the middle of the recording session. Within 20 trials after the

switch, rats no longer expressed the previous prioritization and within 20-30 more trials they prioritized modalities in accordance with the new likelihoods (Fig. 6B).

Detection paradigms involving whiskers typically use a variable delay with uniform distribution to increase uncertainty (go-no-go tasks: Sachidhanandam et al. 2013; Stüttgen & Schwarz 2010; Guo et al. 2014; two-alternative forced-choice tasks: Adibi et al. 2012; Miyashita & Feldman 2012; McDonald et al. 2014). The current study used only two discrete delays, providing the temporal precision and statistical power to quantify the earliest withdrawal from nose-poke. The d' analysis revealed that rats reacted to vibrations as early as 39ms (Fig 4; Table 2).

Electrophysiological and imaging studies uncover touch-evoked signals in vS1 as early as 4-6ms after whisker deflection (Matyas et al., 2010; R. S. Petersen & Diamond, 2000), whilst signals arrive in the V1 as early as 42-44ms after presentation of 100% contrast flash (Wang et al., 2014). The fast reaction times in our task suggest that the perceptual/motor system operates close to threshold: small differences in sensory cortex are amplified in a cascade that recruits motor outputs already primed for action execution (de Lafuente & Romo, 2006). The use of only two discrete delays would allow rats to prepare the motor response prior to the expected stimulus onset times. Motor preparation is likely to have contributed to the fast reaction times observed in our study. Consistent with this hypothesis, during 800ms-delay trials, in video records a brief head bob is visible around 300ms, which may correspond to a preparatory action which would be transformed to a complete nose-poke withdrawal in the event that a flicker or vibration stimulus were sensed (see Movie 1).

The use of two discrete delays also creates non-stationary demands on attention. If rats detected no stimulus at 300ms, the probability of stimulus presentation at 800ms was approximately 83% (see Results). This reduction in temporal uncertainty of stimulus onset timing in long-delay trials resulted in significantly faster reaction times (Fig. 3C). Temporal uncertainty interacted with modality uncertainty – as shown in Fig 5C, improvements in reaction time to the high-likelihood stimulus with respect to the low-likelihood stimulus were strongest for short-delay trials. We speculate that, on 800ms presentations, the temporal certainty masked the advantage of being able to predict modality (with about 80% certainty), leading to a diminished reaction time difference between high- and low-likelihood trials.

Neuronal recordings revealed changes in firing rate during nose-poke entry and exit (Fig 6C). This can reflect the two modes in which rats use their whiskers to interact with the environment (Mathew E. Diamond & Arabzadeh, 2013a). In the generative mode, rats ‘whisk’ to actively seek and palpate objects (Bagdasarian et al., 2013; Berg & Kleinfeld, 2003; Kuruppath et al., 2014; Mehta et al., 2007; Morita et al., 2011). In the receptive mode, when self-generated movement would produce noise and reduce detectability of external events, rats immobilize whiskers to capture mechanical energy from their environment (Miyashita and Feldman, 2012; Fassihi et al., 2014). The self-generated whisker movements would allow rats to enter and exit the nose-poke with precision, meanwhile evoking activity in vS1 neurons. As they remain in the nose-poke, the switch to receptive mode would enhance the encoding of the vibration stimulus.

Responses of neurons recorded during whisker sessions were consistently greater than during visual sessions (Fig 7E). Sensory prioritization may act via sensory amplification or

‘multiplicative gain control’ (McAdams & Maunsell, 2000; Olsen, Bortone, Adesnik, & Scanziani, 2012; Zhang et al., 2014) in the cortex. Specifically, prioritization of the whisker pathway is achieved by increasing overall excitability in the vS1 cortex, whereby evoked activity is amplified disproportionately more than is spontaneous activity. This increase in gain would allow deflections to be more reliably detected by subsequent stages in processing. As such, unit-recordings showed enhanced response to vibration stimuli during whisker sessions compared to visual sessions (Fig. 7F). A consequence of the gain modulation was improved signal detectability: in our sample of neurons, an ideal observer of neuronal activity in vS1 could decode the presence of vibration only in whisker sessions (Fig. 7G). This increased stimulus-evoked response accompanying prioritization is consistent with attention studies in the visual pathway (Herrero et al., 2008; McAdams & Maunsell, 1999a; Kerry McAlonan et al., 2008).

Whilst multiple studies have demonstrated multiplicative gain modulation under attention across different areas of the cortex, the underlying biophysical mechanisms have been rarely studied. In general, synaptic input synchrony is largely thought to play a role in attention modulation. Initially proposed by Niebur & Koch (1994), input synchrony has been demonstrated to have multiplicative effect on firing rate (Salinas & Sejnowski, 2000; Tiesinga, Fellous, Salinas, José, & Sejnowski, 2004) as well as balanced synaptic inputs (Chance, Abbott, & Reyes, 2002). Simulations using biophysical neuronal models support this idea with balanced synaptic input having a modulatory effect on overall gain and variability (Burkitt, Meffin, & Grayden, 2003). Specifically, attention may act through changes in the synchrony of inhibitory networks enhancing the coherence of neurons (Tiesinga et al., 2004)..

An alternative explanation of the increased detectability and enhanced firing may be bottom-up differences, such as alterations in head position or whisking behavior across the conditions. Yet, inspection of high-speed videos (e.g. Movie 1) revealed stereotyped behavior across trials with no evident systematic differences between session types in head and whisker motion or position. However, our data do not exclude the possibility of minute differences outside our resolution.

Recently, decision making experiments with mice trained in a tactile detection task have demonstrated that neurons in vS1 show robust choice-related activity (Yang et al., 2016) – correlation between single-trial activity and the animal's decision on that trial - with top-down axons projections from vS2 to vS1 signaling choice. Similarly, vS2 has been shown to correlate strongly to choice-related activity - more so than in vS1 (Kwon et al., 2016), with vS1 neurons projecting to vS2 feeding forward activity that predicted choice and with touch and choice information propagating in a feedforward and feedback loop between vS1 and vS2. In our experiment, we did not observe such choice-related activity in vS1. On vibration miss trials, an ideal observer of neuronal activity in vS1 could still detect the stimulus better than chance. This may be due to the comparatively lower number of recorded neurons in our experiment and/or that our population was primarily comprised of supragranular neurons. Nevertheless, the absence of significant choice probability is consistent with observations of sensory cortex in monkeys (de Lafuente & Romo, 2005, 2006). Single-unit firing in the monkey primary somatosensory cortex

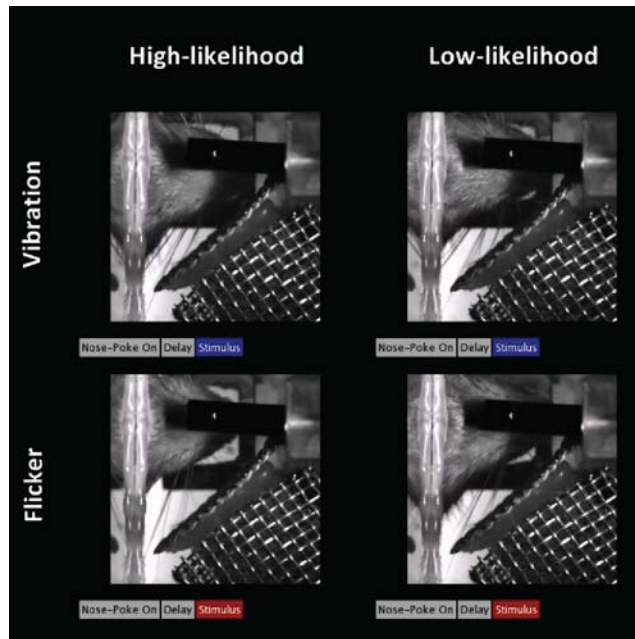


Figure 8 Movie screenshot of example hit trials of a well-trained rat performing the detection prioritization task. Four example trial types with stimulus presentation at 800 ms are shown: vibration high likelihood, vibration low-likelihood, flicker high-likelihood, and flicker low-likelihood. The rat places its snout in the nose-poke to initiate the trial. After the prestimulus delay, the stimulus (vibration or flicker) is presented. The rat then leaves the nose-poke and enters the reward spout (below the nose-poke) to receive reward. Infrared lighting is used to illuminate the video sequence, which was not visible to the animal. The video playback is at 20x reduced speed.

did not covary with the monkeys' perceptual reports to near threshold vibration stimuli. Our results suggests that differences between hits and misses may be due to fluctuation in the state of the networks in higher-order brain areas that "read out" vS1 activity, e.g. variation in their receptivity to inputs from sensory cortex.

Attention is thought to arise through two possible routes (Corbetta & Shulman, 2002). The bottom-up route is activated by salient or unexpected stimuli (Kayser, Petkov, Lippert, & Logothetis, 2005). A second route is activated by expectation, a top-down process of selection. In our experiment, as the stimuli in all sessions were of equivalent intensity, attention cannot be due to a bottom-up saliency effect. In the same light, investigations of adaptation indicate that repeated whisker stimulation decreases vS1 activity, but produces a net effect of increased total information (Mehdi Adibi, Clifford, & Arabzadeh, 2013; Mehdi Adibi, McDonald, Clifford, & Arabzadeh, 2013). However, our results indicate that in whisker sessions, where whisker stimuli were more frequent, neuronal signals in vS1 were amplified, arguing against adaptation as a detection enhancement mechanism. More likely is a top-down process of expectation, which in humans involves intraparietal cortex and superior frontal cortex and might involve analogous regions in rat cortex. The vibrissal motor cortex, also known as the premotor cortex, is a candidate area (Leonard, 1969b). This area is considered analogous to the primate Frontal Eye Fields (FEF), critical in the voluntary control of visual attention. Similar to FEF, the premotor area in rat has strong reciprocal projections to prefrontal cortex (Condé et al., 1995), and direct brainstem projections to areas involving orienting response (Stuesse & Newman, 1990). Unilateral lesions in this area produce contralateral neglect in both primates and rats (Erlich et al., 2011). A recent study found that prefrontal cortex exerts its top-down modulation through a

circuit involving the thalamic reticular nucleus (TRN) rather than directly on sensory cortex (Wimmer et al., 2015). The dynamic control of sensory gain through feedforward inhibition from the TRN could underlie the observed gain modulations of cortical activity in our study.

Recently, a number of studies have used rodents to investigate aspects of visual (Carli et al., 1983; Marote & Xavier, 2011; Wang et al., 2014; R. D. Wimmer et al., 2015) and auditory (Jaramillo & Zador, 2010; Rodgers & DeWeese, 2014) attention. Our results provide evidence for sensory selection in rodents and a potential neuronal correlate in the primary somatosensory cortex.

3. Sensory prioritization in the whisker modality– a two-alternative forced-choice paradigm

3.1. Introduction

Simple detection paradigms such as the one employed in the previous chapter have been used as a standard method in psychophysics. However, a two-alternative forced-choice (2AFC) paradigm presents some advantages over simple detection paradigms such as Go/No-Go (GNG) tasks when probing the mechanism underlying sensory decision-making problems. Typically, 2AFC involves a forced choice between two responses based on two discrete target stimuli, with measures of accuracy (calculated as the percentage of correct choices) and reaction times as proxies for the cognitive and neuronal processes underlying behavior. Past research has suggested that solving the two tasks requires divergent cognitive structures and/or strategies (Frederick, Rojas-Libano, Scott, & Kay, 2011; Shenoy & Yu, 2012). The fundamental difference between the two tasks arises from the stimulus-response pairing. In GNG, a response is associated with one stimulus, whereas in a 2AFC, two distinct responses are associated with two distinct stimuli. This difference results in an extra ‘response selection stage; which require additional cognitive and processing load that is absent in GNG tasks (Donders, 1969; Gordon & Caramazza, 1982). The consequence of this extra ‘response selection stage’ provides three main advantages in utilizing a two-alternative forced-choice design over simple detection tasks.

Firstly, simple detection paradigms like Go/No-Go task tend to have a go response bias. The aim of the animal is to distinguish stimulus present (S+) from stimulus absent (S-). However, the animal may generalize its response from S+ to S- resulting in a go response bias. The degree of

such generalization depends on the animal's decision criterion, but also a mirage of other factors that an experimenter does not have direct access to such as motivation, the value of the reward and satiety, to name a few. On the other hand, a two-alternative forced-choice paradigm does not require animals to judge whether a single stimulus is S+ or S-. Instead, the animal's aim is to identify which of the two stimuli is S+. Secondly, two-alternative forced-choice paradigms are more likely to involve sensory decisions in the context of a goal-directed action. As there are two distinct responses associated with two distinct stimuli, reflexive behavior such as habitual licking responses are avoided and therefore less prone to impulsivity. Finally, previous research have demonstrated that even after decortication of barrel cortex, rats are capable of performing Go/No-Go tasks but are unable to be trained to jump onto a reward-platform in which they use their whiskers to localize (Hutson & Masterton, 1986b). It is hypothesized that rats are able to perform simple detection task in the absence of the cortex by utilizing the direct transfer of information from subcortical areas to motor networks. Two-alternative forced choice paradigms forces animals to interact with the environment when cued by the stimulus – a behavioral that is more likely to involve the contribution of the cortex.

Aside from the need for processing in sensory areas, two alternative forced choice tasks rely on several areas of the brain. Of particular interest is the posterior parietal cortex (PPC), which receives input from auditory, visual and somatosensory areas (Kolb & Walkey, 1987; Reep, Chandler, King, & Corwin, 1994). This places PPC central to the decision making network as it allows integration across the sensory cortices. Importantly, PPC neurons have been shown to gradually increase their firing during accumulation of sensory information in a decision making task (Erlich, Brunton, Duan, Hanks, & Brody, 2015). Another area of interest is the orbital

frontal cortex (OFC). The activity of OFC neurons have been shown to correlate with outcome prediction and decision confidence (Kepecs, Uchida, Zariwala, & Mainen, 2008; Sinnamon & Galer, 1984).

Previously in Chapter 2, we demonstrated the capacity of rats in modulating sensory attention across the somatosensory and visual domains. In addition, we demonstrated neuronal signatures of sensory prioritization in the primary somatosensory cortex in the form of multiplicative gain control and increased signal-to-noise ratio in single-unit activity. Here, we test the behavioral correlates of sensory prioritization in a 2AFC paradigm. One of the unexpected findings in our experiment was the fast ‘onset reaction’ times. We hypothesized that in the GNG detection paradigm, the perceptual/motor systems were operating close to threshold. As a result, small differences in sensory cortex were amplified in a cascade that recruited motor outputs already primed for action execution. In the current 2AFC experiment, the requirement for ‘response selection’ due to the availability of two distinct actions would prevent upstream decision-making and motor areas to be primed for action execution. We predict a consequence for the need for action selection to be slower ‘onset reaction’ times. In addition to examining our paradigm with the added cognitive load, we take this opportunity to extend our investigation of attention across modality to the auditory domain.

Similar to Chapter 2, we manipulated sensory prioritization by controlling the likelihood with which a stimulus was presented from one of two modalities of whisker touch and audition. Each session was divided into four blocks, alternating between two block types: whisker and auditory block. In a whisker block, 80% of trials contained a brief vibration applied to the whiskers

(vibration trials) and the remaining 20% of trials contained a brief auditory signal (tone trials). During such a block, the limited capacity of the attentional system (Posner, 1980) would predict rats to prioritize processing the whisker pathway. The opposite prioritization would be expected during auditory blocks (80% tone trials and 20% vibration trials). We establish how alternating between whisker and auditory blocks affect the sensitivity and reaction time in detecting stimuli from each modality.

3.2. Method

3.2.1. Subjects

Subjects were 4 adult male Hooded Long Evans rats with initial weights of 170-200g. All procedures were approved by the Animal Care and Ethics Committee at the Australian National University. Rats were housed in independent ventilated and air filtered transparent plastic boxes in a climate controlled colony room on a 12/12/ hour light/dark cycle, where lights were turned off at 7pm. A combination of food and water restriction was used to motivate the rats to perform the detection task. Rats had abundant access to water except 2-3 hours before training session. 15-25g of rat chow was provided after the session. All rats gain weight at a normal rate throughout the entire duration of the experiment.

3.2.2 Apparatus

Rats were train in a chamber measuring 31cm (length) x 31cm (width) x 36cm (height). The floor of the chamber comprised of plastic bars spaced at 1 cm intervals. The front panel had three infrared optical sensors (Sharp, GP1A57HRJ00F) to detect the animal's presences. The middle sensor was denoted as the nose-poke sensor, whilst the other two were denoted as reward sensors. All optical sensors were elevated 4cm from the floor. Adjacent to the nose-poke sensor,

two aluminum mesh (2.5 x 2.5cm) was attached to a ceramic piezoelectric wafer (Morgan Matroc, Bedford, OH) that transmit vertical movements to the whiskers. Each mesh was slanted at 45° angle towards the nose-poke sensor. Behind the aluminum mesh, out of the rat's whiskers' reach, a second pair of piezoelectric wafer, one behind the right mesh which vibrated with the left mesh, and another behind the left mesh which vibrated with the right mesh. This rendered any potential sound cues from the vibrating mesh non-informative. Two speakers (Creative Labs Inspire 245 2.0) were placed on the left and right side of the wall to provide the auditory stimulus. Drinking spouts were placed at the reward sensors which delivered 0.11ml of 7% sucrose reward which were operated by two separate gravity fed solenoid pumps. Three light emitting diodes were placed in the roof of the chamber, which flashed when the rat made an error (incorrect choice or false alarm trial – *see task*).

The vibration stimulus was a sequence of discrete Gaussian deflections generated from MATLAB and presented through the analogue output of a Data Acquisition Card (National Instruments, Austin, TX) at a sampling rate of 44.1kHz. Each deflection lasted for 15ms and was followed by a 10ms pause before the next deflection, yielding a frequency of 40Hz. The auditory stimulus was comprised of the same shape and frequency and was presented through the sound card of the computer. The amplitude of both the auditory and vibration stimulus was modulated depending on the stage of learning (see procedure).

3.2.3. Task

Figure 9 shows the behavioral setup and the 2AFC paradigm. At their own volition, rats initiated a trial by performing a nose-poke. As they maintained the nose-poke, either a whisker vibration

or an auditory tone was presented on the left or right side. The side of stimulus presentation was adaptively selected based on the inverse proportion of the response that was made towards either side in the last 20 trials. For example, on the last 20 trials, if 70% of responses were made on the left side, the probability of a stimulus presentation on the right on the 21st trial would be 70%. This adaptive strategy prevented the rats from forming a response bias by ensuring that roughly equal number of choices was made towards either spout. The stimulus was presented at one of two delays (300ms or 800ms). This delay was pseudo-randomized with equal probability, in such a way that one delay would not consecutively repeat more than twice. Rats indicated detection of the stimulus by leaving the nose-poke and selecting the reward spout of the side at which the stimulus was presented to receive a reward. For example, if the left mesh vibrated, then the reward was only available on the left. The first lick at either drinking spout was considered as the behavioral choice. Selecting the spout on the opposite side of the stimulation resulted in no reward. A 500ms response window was imposed: from the onset of the stimulus, rats had 500ms to leave the nose-poke. Failure to leave the nose-poke resulted in no reward and these trials were denoted as miss trials. Leaving the nose-poke before the onset of the stimulus and making a behavioral choice also resulted in no reward and these trials were denoted as false-alarm trials. In sum, each trial was differentiated as one of four possible trial outcomes: correct, incorrect, miss, and false alarm. We discouraged the rats from leaving the nose-poke prematurely – that is, before detecting the stimulus – by setting the length of each trial to a fixed duration of 2.5s. To achieve this we adjusted the inter-trial interval on a trial-by-trial basis: when rats left the nose-poke before the stimulus onset, the inter-trial interval was proportionately longer, thus acting as a time-out punishment. Additionally, LEDs positioned on the roof of the chamber flashed for 1s when the rat made an incorrect choice or in false alarm responses.

Sensory prioritization was manipulated by changing the probability of presentation between the two modalities. Each session (of 280 trials) was made up of four blocks of two block types: whisker and auditory blocks. In a whisker block, 80% of trials consisted of a vibration stimulus and 20% of trials consisted of a tone stimulus. These frequencies were reversed for an auditory block. Each block contained 70 trials, with two low-likelihood trials inserted in random order within every 10 trials. The switch between blocks was counterbalanced across sessions: i.e. if one session was auditory-whisker-auditory-whisker, the subsequent session would be whisker-auditory-whisker-auditory. No cues were provided to the animal as to the occurrence of the switch in block types. Rats were trained progressively towards the behavioral task via a series of simpler tasks as described below.

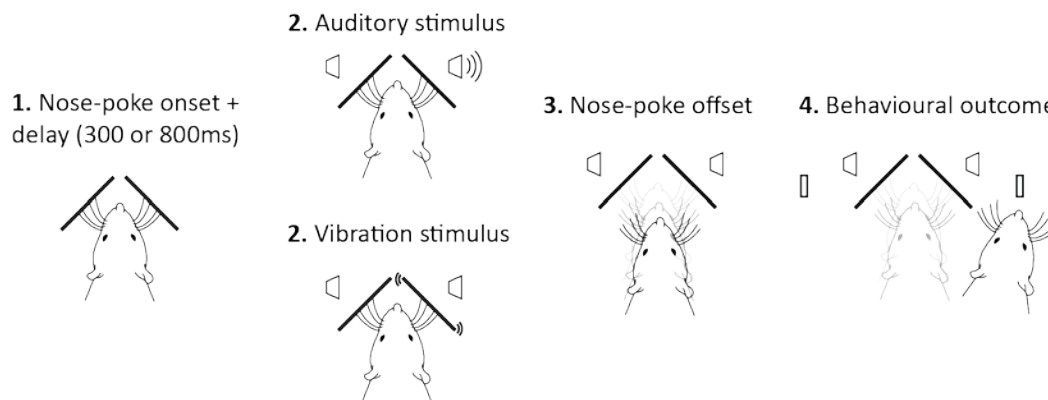


Figure 9. Schematic representation of the forced choice discrimination task. The rat initiated a trial by nose poking into the aperture (1). Rats maintained nose-poke for a delay of either 300 or 800ms, after which an auditory tone or a whisker vibration stimulus was presented on either the left or right side (2). The rats expressed detection of the stimulus by leaving the nose-poke (3) and expressed their discrimination by moving to the corresponding reward spout to receive a sucrose reward (4).

3.2.4. Procedure

Spout Shaping. Rats were placed in the experimental chamber and reward was available from both reward spouts for 100 trials. The availability of reward from each spout was based on the rat's response history. Rats could receive reward from one spout only for up to 20 consecutive attempts at that spout; the nose-poke area was blocked at this stage. This arrangement prevented a spout preference being formed. When rats arrive at the reward spout to receive sucrose, both the auditory and vibration stimuli were presented simultaneously.

Nose-poke and discrimination shaping. Rats were rewarded only after performing a nose poke. Two delays were imposed from the first nose-poke shaping day, with 80% of trials with a short delay (starting at 100ms) and 20% with longer delay (starting at 200ms). After stimulus presentation on either left or the right side, rats had to orientate towards the corresponding spout to receive a reward. Performance was monitored for both delays. If rats performed above 75%, the delay was incremented by 50ms until it reached the final delays of 300 and 800ms. After which, the proportion of short and long delay was gradually shifted to 50%. The stimulus intensity did not change during this stage and remained at 50 μ m for the vibration stimulus and 90dB-SPL for the auditory stimulus.

Adjusting stimulus intensity. Once the final delays of 300 and 800ms was reached with performance above 75%, the amplitude of the Gaussian wavelets for the vibration and auditory stimulus was incrementally decreased until miss proportions grew to 10%. At the final stage, the stimulus amplitude was 20-25 μ m for the vibration stimulus across rats, and 65-75 dB for the auditory stimulus.

3.2.5. Data analysis

Nose-poke duration was defined as the interval between nose-poke onset and nose-poke offset.

Reaction time was defined as the interval between stimulus onset and nose-poke offset.

Performance was defined as the number of correct trials divided by the sum of correct and incorrect trials. Trials were categorized as follows: (1) Hit – the rat successfully waited in the nose-poke for the stimulus and then left the nose-poke to lick one of the two reward spouts within 500ms of stimulus onset. These trials were further categorized as correct choice – in which the rat licked the correct spout and was rewarded; and incorrect choice – in which the rat licked the incorrect spout and was not rewarded. (2) False alarm – the rat left the nose-poke before the stimulus presentation. (3) Miss – the rat successfully waited in the nose-poke for the stimulus but failed to leave in response to the stimulus presentation (i.e., the rat left the nose-poke >500ms after stimulus onset). To calculate behavioural performance with respect to time, trials were separated into the 4 conditions: vibration and tone trials for sessions that started with an auditory block; vibration and tone trials for sessions that started with a whisker block. The proportion of correct trials within a 20 trial window was calculated for each condition at steps of 1 trial.

‘Onset’ reaction time was calculated as before by applying signal detection theory (Green & Swets, 1966) to determine perceptual accuracy, d' , for each stimulus modality and session type (auditory or whisker). For this analysis, we compared nose-poke leaving times (nose-poke offset minus nose-poke onset) between short- and long-delay trials. For the interval between 300 and 800ms after nose poke, all trials can be divided into two categories: stimulus-present and stimulus-absent, with equal number of trials in each category (stimulus-absent trials in this first

interval correspond to late stimulus trials). From this, hit and false alarm rate can be calculated and combine to estimate sensitivity (d') at each time point during the 300–800ms interval.

Therefore, perceptual accuracy was calculated as:

$$d' = Z(\text{hit rate}) - Z(\text{false alarm rate})$$

where Z is the inverse of the cumulative Gaussian distribution function. The hit rate distribution was derived from the nose-poke leaving times of short-delay trials (300ms), whilst false alarm rates were derived from the nose-poke leaving times of long-delay trials (800ms). The d' values were calculated as a function of time at a resolution of 5ms. This was compared against a shuffled distribution where 1,000 d' traces were calculated by sampling from a randomized distribution of hits and false alarms. The standard deviation was calculated and multiplied by 2 to obtain the 95% confidence interval. The first point of deviation of the observed d' from the shuffled distribution was taken as the 'onset' reaction time

3.3. Results

3.3.1 Learning of the detection task

Four rats were trained in the discrimination paradigm to report the location of either a vibration or an auditory tone (Fig. 9). Each session (consisting of 280 trials) comprised of four blocks (70 trials); alternating between whisker high-likelihood and auditory high-likelihood blocks. In a whisker high-likelihood block, 80% of trials consisted of a vibration stimulus and 20% of trials consistent of a tone stimulus; vice versa for an auditory block. Each trial was initiated by performing a nose-poke as registered by an optic sensor. Rats were required to maintain nose-poke for one of two delays (300ms or 800ms) to trigger the stimulus. To receive a sucrose reward, rats had to identify the side of the stimulation and turn to the corresponding reward

spout. Rats had a 500ms window of opportunity to initiate a response from the onset of the stimulus resulting in 4 possible outcomes: 1) Hit, where the rat made a behavioral choice within this window of opportunity. This can be further divided into two outcomes: correct choice (where the rat licked the corresponding reward spout and was rewarded) and incorrect choice (where the rat licked the non-corresponding reward spout and was not rewarded); 2) False alarm, where the rat made a behavioral choice before the onset of the stimulus; 3) Miss, where the rat did not make a behavioral choice and remained in the nose-poke, or a behavioral choice was made after the window of opportunity.

Rats learnt to perform the task for both modalities over several sessions (Fig. 10A). To characterize the overall performances, we analyzed trials across the likelihood type for vibration and tone trials. As shown in Figure 10B, stimulus difficulty was adequately adjusted between the two stimulus types. Both false alarm and miss trials were low and consistent across all rats (false alarm rates - vibration: $8.1 \pm 1.2\%$, tone: $8.8 \pm 1.4\%$; miss rates: vibration: $6.1 \pm 3.2\%$, tone: $11.4 \pm 5.0\%$, mean $\pm$ SD). Hit rates were high and consistent across rats (vibration: $85.6 \pm 3.1\%$, tone: $79.8 \pm 4.5\%$, mean $\pm$ SD).

To establish that the rats' behavior was based on stimulus detection rather than a non-specific strategy such as timing, we quantified performance by comparing nose-poke durations between short (300ms – filled circles) and long (800ms – open circles) delay trials (Figure 10C). For both stimulus types, rats showed significantly longer nose-poke durations for long-delay trials (vibration median: 686 ± 94 ms, tone median: 788 ± 89 ms, mean $\pm$ SD) than for the short-delay trials (vibration median: 1030 ± 46 ms, tone median: 1052 ± 36 ms, mean $\pm$ SD) (Wilcoxon rank-

sum test, $p < 0.01$). In short, the time spent in the nose-poke depended on stimulus timing - early and late stimulus onset trials led to distinct response timing profiles. As in the previous paradigm, we also observed rats were sensitive to elapsed time and tracked the likelihood of stimulus presentation. As shown in Figure 10D, for the vibration stimulus, reaction time was significantly faster for the late stimulus (800ms) (239 ± 52 ms, mean $\pm$ SD) compared to the early stimulus (300ms) (334 ± 87 ms, mean $\pm$ SD) (Wilcoxon rank-sum, $p < 0.01$). This was also true for the tone stimulus, in which reaction times for the late stimulus (257 ± 36 ms, mean $\pm$ SD) were significantly faster than for the early stimulus (398 ± 90 ms, mean $\pm$ SD) (Wilcoxon rank-sum, $p < 0.01$).

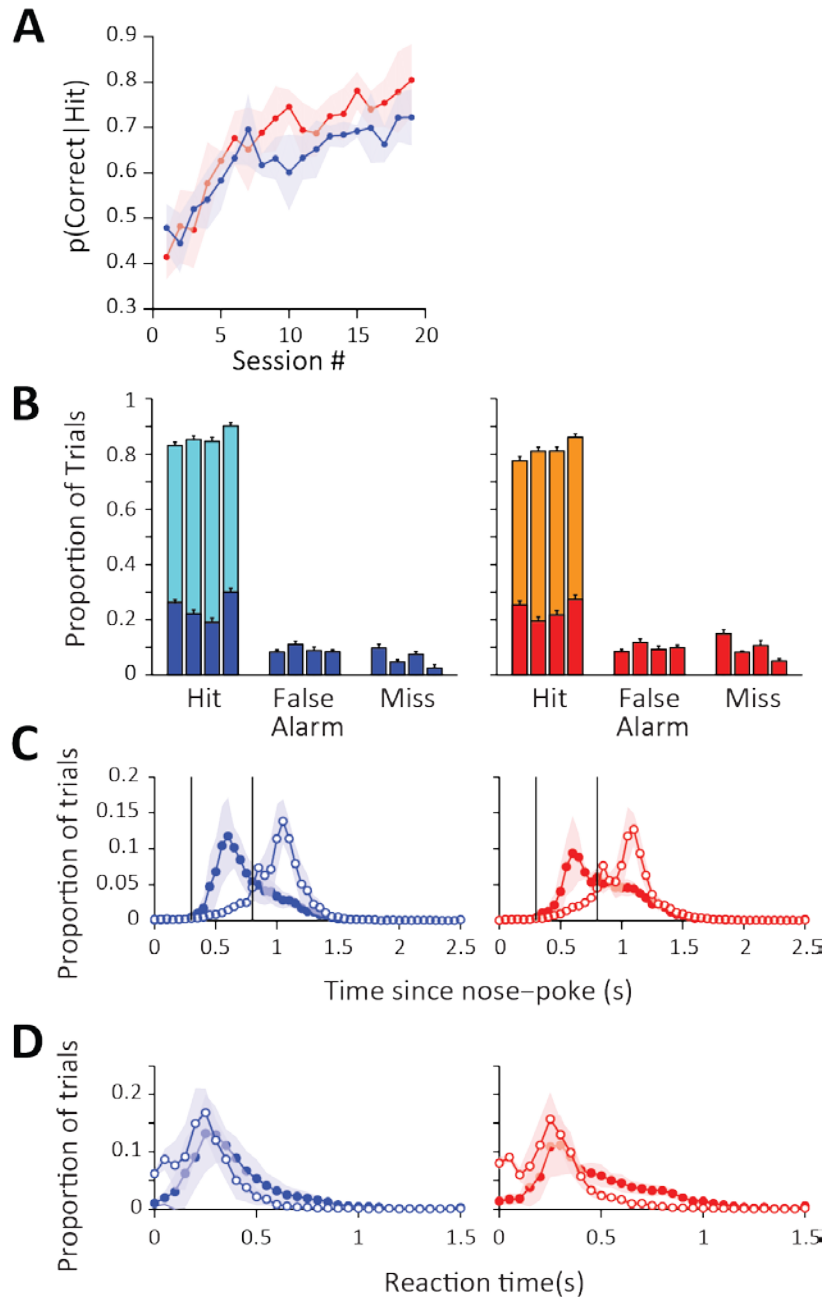


Figure 10 Rats demonstrated high levels of discrimination performance **A**. Learning profile for vibration and tone stimulus across 4 rats. Performance was calculated as the proportion of hits **B**. Behavioral performance when a vibration stimulus was present (blue) and when a tone stimulus was presented (red). Trials are categorized by Hit, False Alarm and Miss (defined in Methods). Rewarded trials (correct) are denoted by lighter colors, whilst unrewarded trials (Incorrect hits, false alarm and miss) are denoted by darker colors. **C**. Distribution of nose-poke durations (nose-poke offset – nose-poke onset). Filled circles represent short delay trials (300ms). Open circles represent long delay trials (800ms). Vertical lines represent stimulus onset. Shaded areas represent 1 SD across 4 rats. **D**. Distribution of reaction times (nose-poke offset minus stimulus onset) between short (300ms – filled circles) and long (800ms – open circles) trials. Shaded areas represent 1 SD across 4 rats.

3.3.2. Effects of attention on performance and reaction time

In the preceding sections, we pooled the two block types for initial analysis, but we now consider the block types separately to determine whether manipulation of stimulus likelihood resulted in systematic differences in behavioral performance. Trials in which the presented stimulus was in the modality corresponding to the session type are denoted as *high-likelihood* trials (i.e. vibration trials in whisker block and flicker trials in visual block), whilst trials where the stimulus modality did not correspond to the session type are denoted *low-likelihood* trials (i.e. vibration trials in visual block and flicker trials in whisker block). Crucially, we alternated between the two block types throughout a session without explicitly cueing the transition. Each session was counterbalanced with the order of block type presentation (i.e. whisker/tone/whisker/tone vs. tone/whisker/tone/whisker). We therefore first examined the performance of the rats in time to determine whether rats were capable of switching which stimulus to prioritize processing to. As shown in Figure 11A and B, rats demonstrated a systematic shift in their discrimination performance depending on the block type. The shifts occurred regardless of whether the session began with a whisker or auditory high-likelihood block.

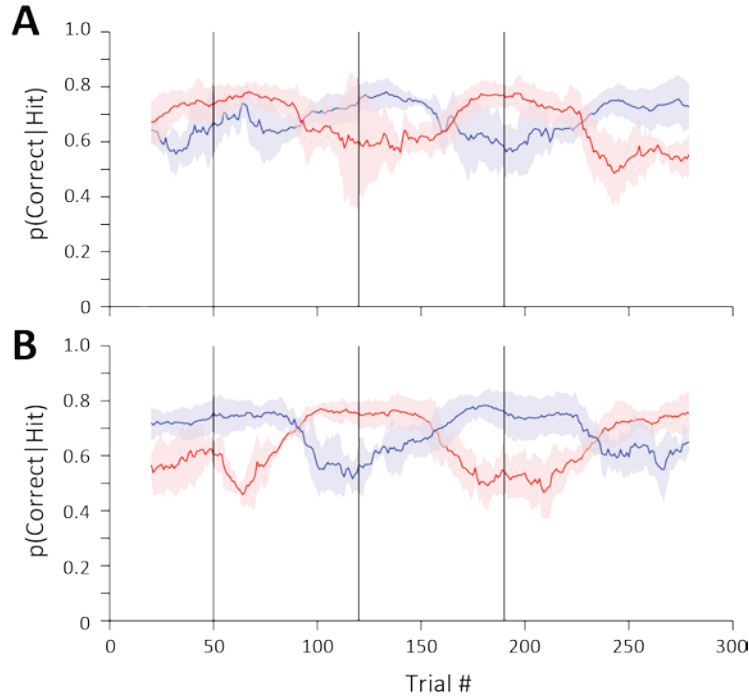


Figure 11. Behavioral performance with respect to time. **A.** Average performance across all 4 rats for vibration (blue) and tone (red) trials for sessions starting with auditory block. Shaded area represents 1 SD. Performance was calculated in 20 trial bins at steps of 1 trial. Vertical lines indicate transition between blocks types. **B.** Average performance for sessions starting with whisker block.

We next quantified how attention modulated the speed and accuracy of stimulus discrimination. For both modalities, presentation of a stimulus in a high-likelihood context led to improvements in several metrics of performance. Firstly, when a vibration stimulus was presented in a whisker block (high-likelihood), all 4 rats were less likely to miss the stimulus compared to when it was presented in an auditory block (low-likelihood) (Fig. 12A, $p < 0.01$ for all rats). On average, miss rates for the vibration stimulus were $5.1 \pm 5.8\%$ and $19.7 \pm 22.4\%$ (mean $\pm$ SD) in whisker and auditory blocks, respectively. Similar improvements in detection were observed for the tone stimulus when presented in an auditory block (high-likelihood) compared to when it was presented in a whisker block (low-likelihood) (Fig. 12A, $p < 0.05$ for all rats). On average, miss

rates for the tone stimulus were $10.2 \pm 9.7\%$ and $16.1 \pm 13.4\%$ (mean $\pm$ SD) in auditory and whisker blocks, respectively. Secondly, for hit trials, rats were more likely to make a correct choice in a high-likelihood context compared to a low-likelihood context (Fig 12B). Rats performed on average better for a vibration stimulus presented in a whisker block $72.9 \pm 8.9\%$, mean $\pm$ SD) compared to a vibration presented in an auditory block ($64.2 \pm 16.3\%$, mean $\pm$ SD). For most rats, this difference was statistically significant (Rat 1: $p=0.11$; Rat 2: $p<0.05$; Rat 3: $p<0.01$; Rat 4: $p<0.01$, student t-test). This difference in discriminability was also found for the tone stimulus, with rats performing on average better in a high-likelihood context ($72.5 \pm 14.7\%$, mean $\pm$ SD) compared to a low-likelihood context ($58.4 \pm 15.3\%$, mean $\pm$ SD). For all rats, this difference was statistically significant ($p<0.05$ for all rats).

Finally, averaging across both stimulus delays (300ms and 800ms), rats displayed faster reaction times when the stimulus was presented in a high-likelihood block compared to a low-likelihood block. Vibrations presented in a whisker block were significantly faster on average (305 ± 219 ms, mean $\pm$ SD) compared to auditory blocks (370 ± 313 ms, mean $\pm$ SD) (for all rats: $p<0.05$, Wilcoxon rank-sum) (Fig. 12C). This was also true for the tone when presented in the auditory block (361 ± 265 ms, mean $\pm$ SD) compared to the whisker block (416 ± 304 ms, mean $\pm$ SD) (for all rats: $p<0.05$, Wilcoxon rank-sum) (Fig. 12C)

In the previous paradigm, we found a delay dependent effect for improvements in reaction time. That is, sensory prioritization led to an improvement in reaction time only for the short delay where rats could not predict the onset of the stimulus. In the current paradigm, we did not find a delay dependent effect for improvements in reaction time for the vibration stimulus (Fig. 12D).

For short-delay trials (300ms), the mean values indicated enhanced reaction time for the vibration stimulus presented in whisker blocks (blue open circle in Figure 12D, high-likelihood vibration trials: 372 ± 238 ms; low-likelihood vibration trials: 450 ± 332 ms, mean $\pm$ SD across rats) (for all rats: $p < 0.01$, Wilcoxon rank-sum). The enhanced reaction time was also present for most rats in the long-delay trials (blue filled circle in Figure 12D, high-likelihood vibration trials: 241 ± 177 ms; low-likelihood vibration trials: 282 ± 265 ms, mean $\pm$ SD across rats) (Rat 1: $p = 0.24$; Rat 2: $p < 0.01$; Rat 3: $p < 0.01$; Rat 4: $p < 0.01$, Wilcoxon rank-sum). However, we did observe a delay dependent effect for improvements in reaction for the tone stimulus. Short-delay trials showed an improvement in reaction time, with an average time of 461 ± 288 ms for high-likelihood tone trials compared to 537 ± 306 ms (mean $\pm$ SD across rats) for low-likelihood tone trials (for all rats: $p < 0.01$, Wilcoxon rank-sum). On the other hand, long-delay trials on average did not show a statistically significant difference in reaction time, with an average time of 264 ± 196 ms for high-likelihood tone trials compared to 283 ± 238 ms (mean $\pm$ SD across rats) for low-likelihood tone trials (Rat 1: $p = 0.06$; Rat 2: $p = 0.13$; Rat 3: $p = 0.39$; Rat 4: $p < 0.05$, Wilcoxon rank-sum).

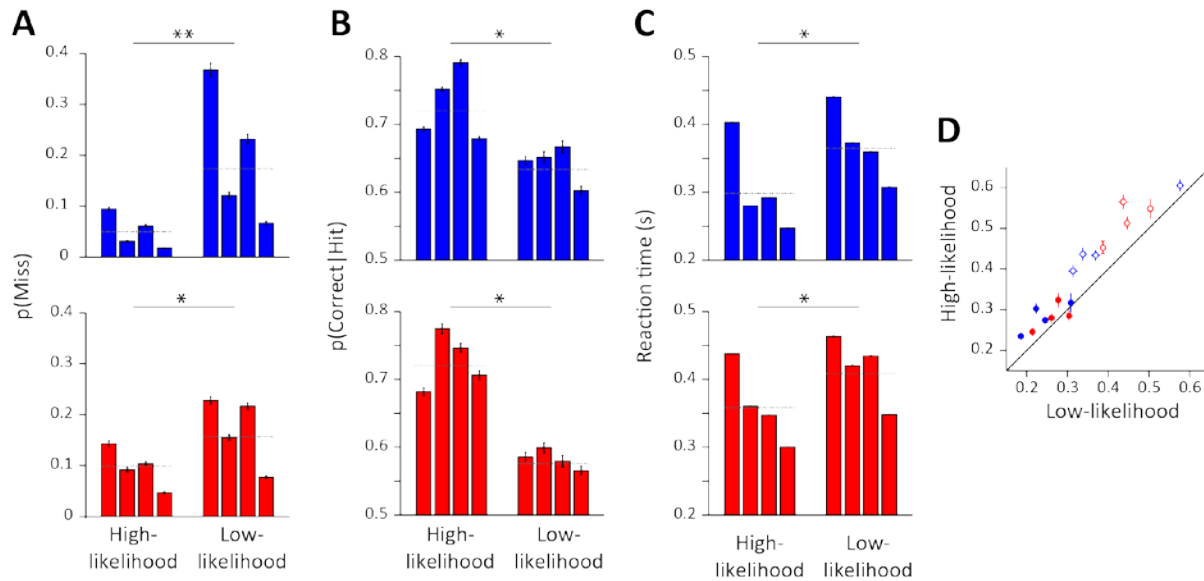


Figure 12. Enhanced behavioral performance and speed when stimulus was presented in a high-likelihood versus low-likelihood context. **A.** Detection performance as calculated by the proportion of misses. Lower numbers indicate better detection performance. Top (blue), proportion of misses for vibration trials presented in a high-likelihood block (whisker block) versus low like-likelihood block (auditory block). Each bar represents an individual rat. Bottom (red), proportion of misses for tone trials presented in a high-likelihood block (auditory block) versus low like-likelihood block (whisker block). Horizontal dashed line represents the average value. **B.** Discrimination performance, as defined by the number of correct trials divided by total hit trials. **C.** Reaction time averaged across short and long delay trials for high-likelihood and low-likelihood blocks. **D.** Scatter plot comparing reaction time between stimuli presented in high- and low-likelihood blocks for each rat. Trials are separated into short-delay (filled circles) and long-delay (open circles).

3.3.4 Segregation of true discrimination from guess responses

Detailed observation of the reaction time and nose-poke leaving profile reveal an interesting distribution for the long-delay stimuli - in both vibration and tone trials, two peak response times are observed: one at ~100ms post stimulus onset, and another at ~300ms post stimulus onset. We suspected that the first peak comprised of trials that were guess responses that were triggered by the stimulus but the behavioral choice was not informed by the stimulus. To access the

underlying process, we aimed to parse informed choices (discrimination) from uninformed choices (guess). From an experimenter's point of view, we have access to two observable outcomes on 'hit' trials: correct and incorrect choices. As shown in Figure 13A, the two-peaked profile is present for correct and incorrect trials in both stimulus types (left- example rat; right averaged across rats). This was more visible for high-likelihood trials (solid lines). Given the balanced distribution of left and right stimuli across trials, any random responses that the animal makes would be expected to be 50% incorrect and 50% correct. To estimate the frequency distribution of informed choices, we therefore subtracted the number of incorrect trials from correct trials. This analysis is presented in Fig. 13B (left – example rat; right – averaged across rats). When only observing the frequency of trials in which choices were informed by the stimulus, we observe minimal difference in the first ~100ms post stimulus but an increase hereafter. This indicates that the responses within the first ~100ms post stimulus were comprised of guess responses – responses in which the behavior was triggered by the stimulus but the choice was not.

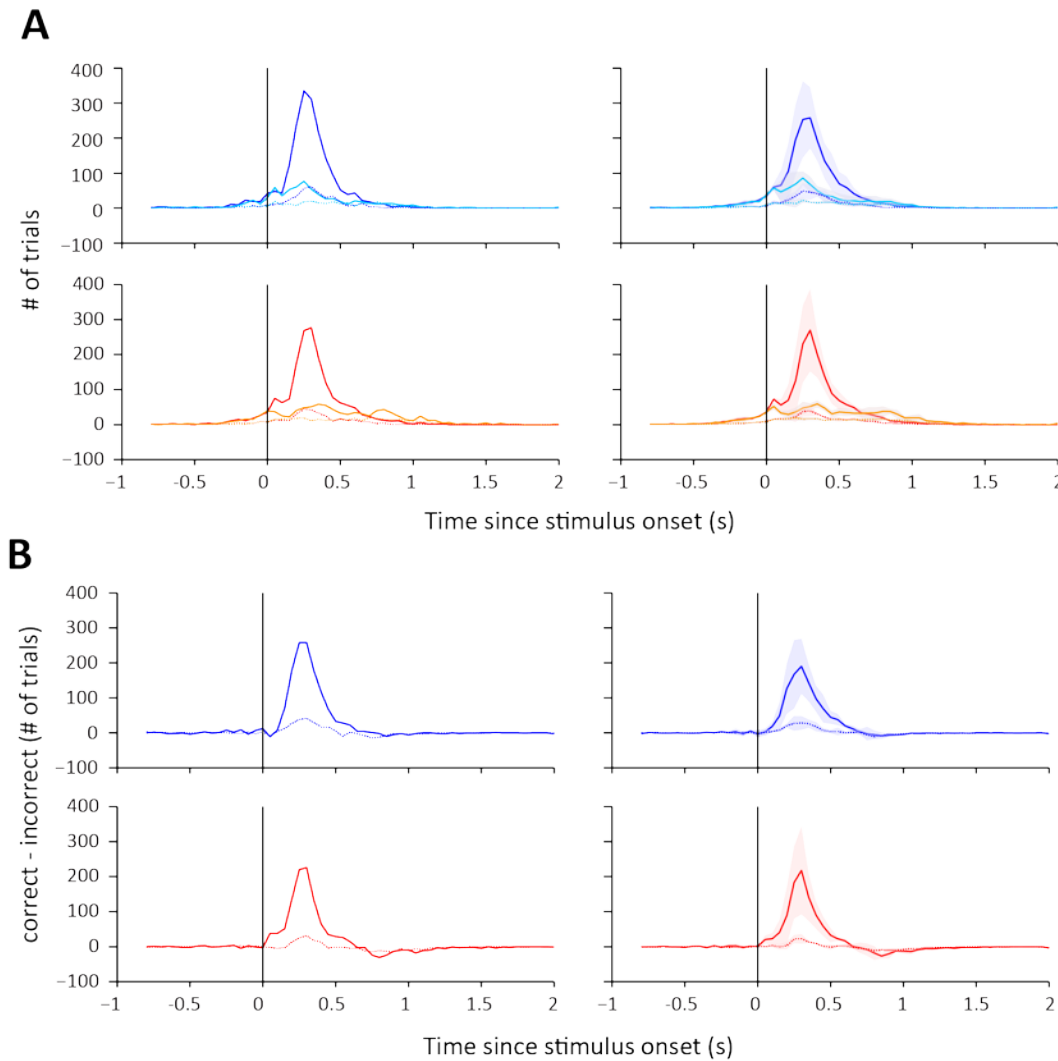


Figure 13. Characterization of true discrimination performance. For each panels, blue represents vibration stimulus trials, red represents tone stimulus trials. Solid lines represent high-likelihood trials, dashed lines represents low-likelihood trials. Lighter hue represents incorrect decisions, darker hue represents correct decisions. **A.** Number of trials in each condition. Left column represents an example rat; right column represents averages across all 4 rats. Shaded area represents 1 SD. **B.** Comparison of the number correct minus incorrect trials. This represents a distribution of true discrimination and guess decisions

3.3.3. ‘Onset’ reaction time and comparison to detection paradigm

As in the previous chapter, for the interval between 300 and 800ms after nose poke, all trials can be divided into two categories: stimulus-present and stimulus-absent, with equal number of trials in each category (stimulus-absent trials in this first interval correspond to late stimulus trials). From this, hit and false alarm rate can be calculated and combine to estimate sensitivity (d') at each time point during the 300–800ms interval (Fig. 14). The first point in time where d' values deviated from chance (chance estimated by bootstrapping; see Materials and Methods) revealed the onset reaction times. Averaged across all sessions and all rats, vibration and tone trials gave a first reaction of 174 and 206ms, respectively (Table 3). Next, we compared the vibration ‘onset’ reaction times obtained in the 2AFC paradigm to those obtained in the simple GNG detection paradigm reported in the previous chapter. As shown in Figure 15, ‘onset’ reaction times in the current 2AFC variant were on average significantly slower by 126ms.

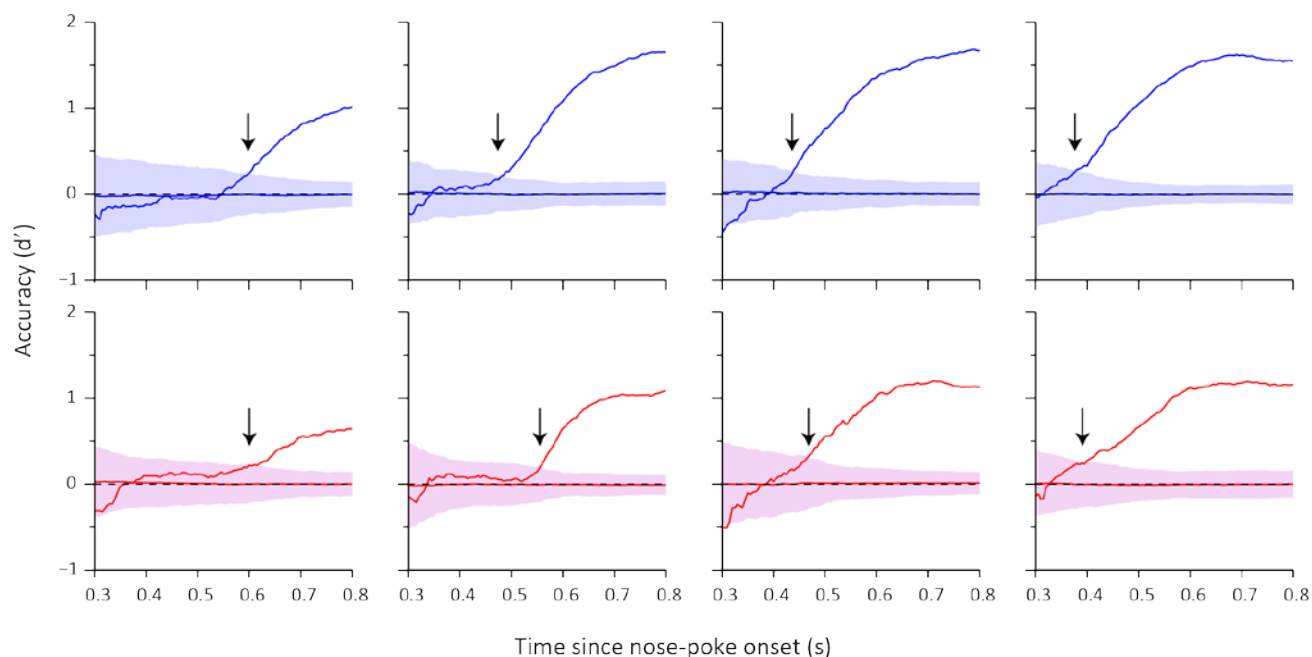


Figure 14. Onset reaction times as revealed by a change in detection accuracy (d') as a function of trial time course. Each rat's detection accuracy is shown across panels. Shaded areas represent d' chance level as calculated from bootstrapping. Dashed horizontal line represents the mean value of shaded area. Arrows indicate the first point in time d' reached above chance level. Top row (blue) represents d' values for vibration trials. Bottom row (red) represents d' values for tone trials.

Table 3. Onset reaction times (ms)

	Rat 1	Rat 2	Rat 3	Rat 4
Vibration	299	179	138	78
Tone	305	255	166	98

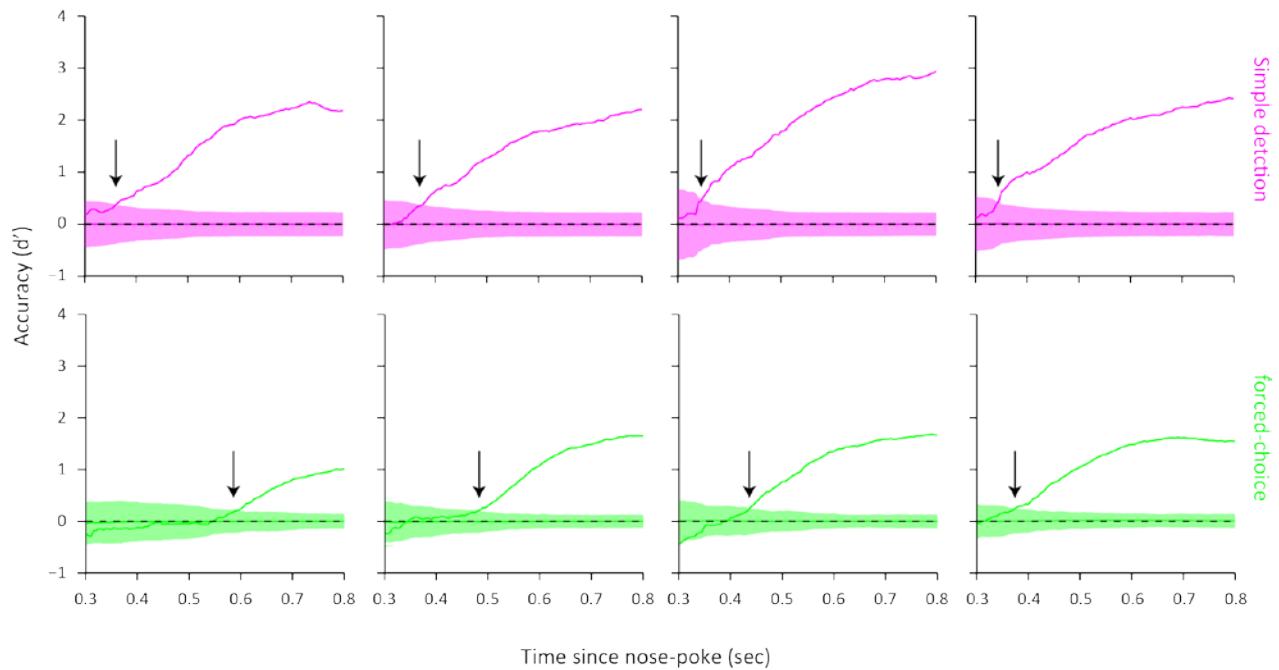


Figure 15. Comparison of detection accuracy (d') across 8 rats for vibration stimulus as a function of trial time course between simple detection (magenta; same as blue in Figure 4; Chapter 2) and force choice (green; same as blue in Figure 14; current Chapter) paradigms. Shaded area represents d' chance level as calculated from bootstrapping. Arrows indicate the first point in time that d' deviates from chance level.

3.4. Discussion

Operating with finite quantity of processing resources, animals benefit from prioritizing the modality expected to provide key information. To examine whether sensory prioritization as demonstrated in the previous chapter can be generalized to other sensory modalities, we extended our investigation to the auditory domain. A two-alternative forced choice task was used and attention was manipulated by controlling the likelihood with which a stimulus was presented from one of two modalities (tactile or auditory). Prioritization led to a decrease in detection miss rates (Fig. 12A), an increase in discrimination performance (Fig. 12B), and faster reaction times

(Fig. 12C). These results were consistent with the findings in our first experiments and other previous works where attention improved performance (Carrasco, 2011; Cohen & Maunsell, 2009; Posner, 1980) and reaction time (Eriksen & Hoffman, 1972; Henderson & Macquistan, 1993).

Often discussed in terms of ‘hazard functions’ (Luce, 1986) - the probability of an event occurring at a specific time given that it has not yet occurred, rats were sensitive to the likelihood of stimulus presentation by implicitly tracking the elapsed time. Since there are only two possible times in which the stimulus could be presented, for an ideal observer, if no stimulus was detected at 300ms, then the probability of stimulus presentation at 800ms would be 86.7% (calculated as $1 \text{ divided by } 1 \text{ plus the probability of having failed to detect a true stimulus presentation at } 300\text{ms}$). This ability to implicitly track the elapsed time was demonstrated by the faster reaction time found in long-delay trials (Fig. 10C) and replicates findings from the previous chapter as well as other studies (Coull & Nobre, 1998; Kingstone, 1992; Niemi & Näätänen, 1981; Oswal, Ogden, & Carpenter, 2007; Reuter-Lorenz, Oonk, Barnes, & Hughes, 1995; Sharma et al., 2015).

Additionally, for the tone stimulus, the reduction in temporal uncertainty for long-delay trials also interacted with modality uncertainty as shown in Figure 12D. For the tone stimulus, improvements in reaction time from changes in likelihood were strongest for short-delay trials as the removal of temporal uncertainty masked the effects of modality predictability. Interestingly, we also observed a bimodal distribution in nose-poke leaving (and reaction time) for the long-delay stimulus. Two peaks were observed: one at ~100ms and another at ~300ms post stimulus

onset. We hypothesized that the first peak represented behavior that were established from trials in which the rat had pre-determined/primed motor outputs for action execution. On these trials, the behavior would therefore be triggered by the stimulus but not informed by it. We therefore anticipate that these trials would result in chance performance with regards to discrimination performance. By estimating the proportion of trials in which behavior was triggered and informed by the stimulus from trials in which behavior was triggered but not informed by the stimulus, we found that the responses from the first peak were predominantly at chance level (Fig 13B). Finally, we further compared the ‘onset’ reaction time between the two paradigms. This analysis allowed us to estimate the first time point in which stimulus discrimination was above chance. As shown in Figure 14, the d' analysis revealed that on average, rats reacted to vibrations as early as 78ms and 98ms for the tone stimulus. This is in comparison to 39ms for the vibration stimulus in the simple detection task.

In the present study, the average reaction time across rats was 363ms. Reaction time distributions and median values were similar to previously reported two-alternative forced choice tasks within the whisker system (Adibi & Arabzadeh, 2011; Carpenter & Williams, 1995; Mayrhofer et al., 2013; McDonald, Adibi, Clifford, & Arabzadeh, 2014). Previous studies of two-alternative forced choice task within the whisker system report differences in reaction time for correct and incorrect trials (Mayrhofer et al., 2013; McDonald, Adibi, Clifford, & Arabzadeh, 2014), with performance improving with increase stimulus sampling duration. However, in our study, we did not detect any difference in reaction time between the two trial types.

Indeed, as suggested by past research, solving a two-alternative forced choice task requires divergent cognitive and/or strategies compared to a simple detection task (Frederick et al., 2011; Shenoy & Yu, 2012). The addition of an extra ‘response selection’ stage required additional cognitive and processing which was absent in the simple detection task. This resulted in slower reaction times in trials which were informed by the stimulus. These trials required the animal to process the stimulus and select an appropriate motor response, preventing motor outputs to be primed for action before stimulus processing. However, in our experiment, the forced-choice also led to an adoption of a unique strategy in which a subset of trials that were triggered but not informed by the stimulus. These trials increased the number of guess selections but also decreased miss rates. This may reflect a balance of cognitive effort and average reward rate that the animal aims to optimize.

4. Temporal cuing in the whisker modality– a two-alternative forced-choice paradigm

4.1. Introduction

In a natural environment, impending danger is often preceded by sensory signals such as auditory cues (e.g. rustling of leaves indicating the approach of a predator). In such scenarios, animals benefit from orienting their attention to the relevant sensory modality at the appropriate time. For example, at the sound of a cat as it approaches the burrow, a rat might prioritize processing in the somatosensory domain to determine the safest burrow exit. Here, we establish a paradigm to study the neuronal correlates of attention in time, by providing an auditory cue that signals the onset of a vibration stimulus. The paradigm is set such that the auditory cue reduces the temporal uncertainty about the vibration stimulus without providing information on its location, which in turn indicates the correct choice.

In one of the earliest studies investigating temporal orienting, Coull & Nobre (1998) developed a simple-reaction detection task in which a cue explicitly indicated whether a task-relevant stimulus would appear after a short (early) or long (late) interval. Although the results showed that the early cue produced faster reaction times compared to the late cue at the short interval, fMRI and ERP analysis attributed the behavioral enhancement to increased preparatory motor responses rather than perceptual enhancement (Coull, Frith, Bu, & Nobre, 2000; Coull & Nobre, 1998; Miniussi, Wilding, Coull, & Nobre, 1999). It was argued that the failure to observe perceptual enhancement by temporal orienting was because: 1) the visual system is rich in spatial rather than temporal information 2) the simple-reaction detection task emphasizes the execution

of a speeded response and does not require a detailed perceptual analysis of the stimulus. Subsequent experiments in audition, a temporally rich modality, found temporal orienting enhanced early perceptual processing of auditory information (Lange, Rösler, & Röder, 2003). Additionally, temporal cueing in visual discrimination tasks has been shown to enhance the perceptual processing of visual stimuli (Correa et al., 2004; Los & Heslenfeld, 2001; Milliken, Lupianez, Roberts, & Stevanovski, 2003).

Studies of temporal orienting of attention have mainly focused on humans and non-human primates (Bertelson, 1967; Paul Bertelson & Tisseyre, 1968; Correa et al., 2004; Coull et al., 2000; Coull, Vidal, Nazarian, & Macar, 2010; Kingstone, 1992; Klemmer, 1956; Miniussi et al., 1999; Näätänen et al., 1974; Teichner, 1954; Woodrow, 1914). Here, we establish a discrimination paradigm to study the behavioral correlates of cross-modal temporal cueing using the rat whisker system. We trained rats on a forced-choice task in which a vibration stimulus was presented at one of two spatial locations (left or right). The vibration was randomly presented at 1 of 10 delays after trial onset. We manipulated temporal expectation by providing an auditory stimulus that cued the onset of the vibration stimulus. This allows us to establish how the addition of an auditory cue affects the behavioral performance of the rat as measured by changes in discrimination sensitivity and reaction time. Furthermore, we explore the neuronal correlates of temporal expectation by recording single-unit activity in the vibrissal area of the primary somatosensory (vS1) cortex. Our behavioral results demonstrate that the presence of an auditory cue that provided temporal information improved the discriminability of the vibration stimulus. Neural data show modulation of activity at the onset of the auditory cue and enhanced detectability of the vibration stimulus.

4.2. Methods

4.2.1. Subjects

Subjects were 4 adult, male Hooded Long-Evans rats with initial weights of 170-200g. All procedures were approved by the Animal Care and Ethics Committee at the Australian National University. Rats were housed in independently ventilated and air filtered transparent plastic boxes in a climate controlled colony room on a 12/12 hour light/dark cycle, where lights were turned off at 7pm. A combination of food and water restriction was used to motivate the rats to perform the discrimination task. Rats had abundant access to water except 2-3hrs before training sessions. 15-25g of rat chow was provided after each session. All rats gained weight at a normal rate throughout the entire duration of the experiment.

4.2.2. Apparatus

Rats were trained in a chamber measuring 31cm (length) x 25cm (width) x 25cm (height). The floor of the chamber comprised of metal bars spaced at 1cm intervals with a metal tray containing saw dust beneath. The front panel had three infrared optical sensors to detect the animal's presence. All three optical sensors (Sharp, GP1A57HRJ00F) were elevated 4 cm from the floor. The middle sensor was denoted as the nose-poke, whilst the other two were denoted as reward sensors. Adjacent to the nose-poke sensor, two aluminum meshes (2.5 x 2.5cm) were attached to two ceramic piezoelectric wafers (Morgan Matroc, Bedford, OH) that transmitted vertical movements to the whiskers. Each mesh was slanted at a 45° angle towards the nose-poke sensor. Behind the aluminum mesh beyond the reach of the rat's whiskers was a second pair of piezoelectric bars; one behind the right mesh which vibrated with the left mesh, and another behind the left mesh which vibrated with the right mesh. The purpose of this was to render any potential piezo related sound cues non-informative. Drinking spouts were placed at the spout

sensors, which delivered 0.09mL of 7% sucrose reward and were operated by two gravity-fed solenoid pumps.

A micro-speaker was placed 3 cm above the nose-poke sensor to play a 3kHz pure tone at 75dB-SPL for 100ms. This was the auditory cue stimulus. The vibration stimulus was a sequence of discrete Gaussian deflections. Each deflection lasted for 15ms and was followed by a 10ms pause before the next deflection, yielding a frequency of 40Hz. The amplitude of the vibration was modulated depending on the stage of learning (see procedure). Stimuli were generated in MATLAB and presented through the analog output of a data acquisition card (National Instruments, Austin, TX) at a sampling rate of 44.1kHz.

4.2.3. Task

Figure 16 shows the behavioral setup and the discrimination paradigm. Rats initiated a trial by performing a nose poke (breaking the infra-red beam at the nose-poke sensor). As they maintained the nose-poke, a vibration stimulus was presented on either the left or right mesh after one of ten possible discrete delays (500ms to 1400ms at 100-ms steps) in a pseudorandom order to produce an equal number of trials per delay. Rats indicated their discrimination response by leaving the nose-poke and selecting the drinking spout of the side on which the mesh vibrated to receive a sucrose reward. For example, if the left mesh vibrated, the reward was on the left. The first lick at either drinking spout was considered as the behavioral choice. Interleaved across trials, 45.5% of trials (10 out of 22 trials) contained the 100ms auditory cue presented 150ms before the onset of the vibration stimulus. This cue provided temporal predictability to the onset of the vibration stimulus but did not provide any spatial information (i.e., which side the vibration stimulus would be presented). These trials are denoted as “cued” trials. Another 45.5%

of trials (10 out of 22 trials) did not contain the auditory cue. These trials are denoted as “uncued” trials. The remaining 9% of trials (2 out of 22 trials) contained the auditory cue but did not contain a vibration stimulus. These trials are denoted as “catch” trials.

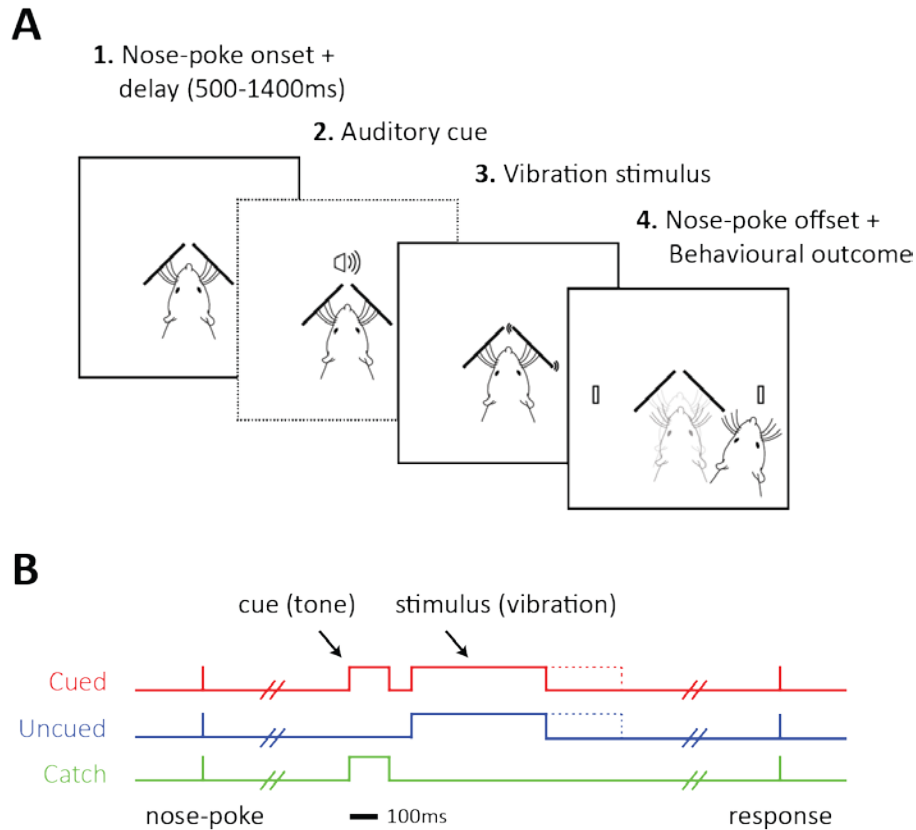


Figure 16. Schematic representation of the discrimination task. **A.** The rat initiated a trial by nose poking into the aperture while contacting both mesh plate with its whiskers. Rats had to maintain nose-poke for a delay ranging from 500-1400ms (at 100ms interval) before a vibration stimulus is presented (1). On subsets of trials, an auditory cue is presented (2). After 150ms from the onset of the auditory cue, a vibration is presented on one of the two mesh (3). Rats indicated discrimination of the stimulus by leaving the nose-poke and entering the corresponding reward spout (4). Correct decisions were reward by 7% sucrose water. **B.** Schematic representation of the relative timing of each stimulus. After initiation and maintenance of nose-poke, a vibration stimulus was presented with a maximum duration of 600ms. The vibration stimulus stopped if the rat left the nose-poke prior to end of the presentation. On cued trials, the auditory cue preceded the vibration stimulus by 150ms. The auditory cue had a duration of 100ms.

We discouraged the rats from leaving the nose-poke prematurely - that is before detecting the stimulus by setting the length of each trial to a fixed duration of 2.5 seconds. This was done by adjusting the inter-trial interval on a trial by trial basis: when rats left the nose-poke prior to the

stimulus onset, the inter-trial interval was proportionally longer, hence acting as a time out punishment. The proportion of stimulus presentations on each side was adaptively chosen based on the inverse proportion of the history of responses (previous 20 trials) that the rat made toward either side. This adaptive strategy prevented the rats from forming a response bias by ensuring that roughly equal numbers of choices were made toward either spout. Rats were trained progressively towards the behavioral task via a series of simpler tasks as described below.

4.2.4. Procedure

Spout Shaping. Rats were placed in the experimental chamber and were rewarded from either reward spout for 100 trials. The nose-poke sensor was blocked at this stage. The availability of reward was based on the rat's response history. Rats could only receive reward consecutively from one spout for 20 trials. This arrangement prevented a spout preference being formed.

Shaping to perform nose-poke. Rats were rewarded only after performing a nose-poke. No delay was imposed, and no stimulus was presented. Rewards were available from either spout as long as the rat nose poked. However, spout bias prevention was still imposed.

Shaping to wait and discriminate. Rats had to nose poke and maintain nose-poke until the presentation of the vibration stimulus. The onset of the stimulus was delayed from the onset of nose poke. Beginning at 40ms from the onset of nose poke, this delay systematically increased over trials by the following regime: the delay increased by 20ms after a correct choice, and did not change after an incorrect choice or early response (false alarm: leaving the nose-poke before the stimulus onset). The delay decreased by 20ms after 3 false alarm trials. Rats were trained until they reach a maximum delay of 1400ms. The stimulus was fixed at 1400ms until detection

performance reached above 80%. The 10 discrete stimulus delays were then introduced and the stimulus amplitude was adjusted for each rat until performance reached 75% for three consecutive sessions (final amplitude ranged from 20-25 μm across rats). After this, cued and catch trials were introduced on 45.5% and 9% of trials respectively.

4.2.5. Data analysis

Nose-poke duration was defined as the interval between nose-poke onset and nose-poke offset.

Reaction time was defined as the difference between stimulus onset and nose-poke offset.

Performance was defined as the number of correct trials divided by the sum of correct and incorrect trials. Trials were categorized as follows: (1) Hit – the rat successfully waited in the nose-poke for the stimulus and then left the nose-poke to lick one of the two reward spouts within 700ms of stimulus onset. These trials were further categorized as correct choice – in which the rat licked the corresponding spout and was rewarded; and incorrect choice – in which the rat licked the non-corresponding spout and was not rewarded. (2) False alarm – the rat left the nose-poke before the stimulus presentation. (3) Miss – the rat successfully waited in the nose-poke for the stimulus but failed to leave in response to the stimulus presentation (i.e., the rat left the nose-poke >700ms after stimulus onset).

For distribution analyses, we examined the instantaneous probability of leaving the nose-poke at each time point. Trials were divided into 3 categories: (1) Cued – trials that were assigned for presentation of the auditory cue and the vibration stimulus. This includes trials in which the rat may not have experienced the cue or stimulus (i.e.: trials when a cue was programmed but not executed due to a false alarm). (2) Uncued – trials that were assigned for presentation of the vibration stimulus only (including false alarm trials). (3) Catch – trials that were assigned for

presentation of the auditory cue only (including false alarm trials). The instantaneous probability of response was calculated as the number of trials on which the animal left the nose-poke within a specified time window as a proportion of the total number of trials available at the onset of that time window (Fig. 3A). The window was 50ms in size and the instantaneous probability was calculated every 1ms. The cumulative probability distribution (Fig. 3B) was derived from the instantaneous probability distributions and calculated as follows:

$$P_n = 1 - [(1-p_1)(1-p_2)\dots(1-p_{n-1})(1-p_n)]$$

Where P_n is the cumulative probability at time n , and p_n is the instantaneous probability at time n .

To quantify 'onset' discrimination reaction times, we applied signal detection theory (Green & Swets, 1966) to determine perceptual accuracy, d' , for cued and uncued conditions. For this analysis we compared nose-poke leaving times between stimulus present and stimulus absent trials. Perceptual discrimination performance was calculated as follows:

$$d' = Z(p(D_L | S_L)) - Z(p(D_L | S_R))$$

where Z is the inverse of the cumulative Gaussian distribution function. For discrimination onset reaction time, the hit rates were derived from the number of left responses when the stimulus was presented on the left (D_L) divided by the total number of trials when the stimulus was presented on the left (S_L). False alarm rates were derived from the number of left responses when the stimulus was presented on the right (D_L) divided by the total number of trials when the stimulus was presented on the right (S_L).

The d' values were compared against a shuffled distribution where 1000 d' traces were calculated after randomly reallocating the left and right stimuli across trials. The first point of deviation of the observed d' beyond the 95th percentile of the shuffled distribution was taken as the onset reaction time. Due to unequal numbers of trials between the cued and uncued conditions, we subsampled an equal number of trials from each to equate power across the two conditions.

4.2.6. Electrophysiology

After rats were trained in the behavioral task, they were implanted with a custom built microdrive that supported a 16-channel array (Tucker-Davis Technology). The array was arranged in a 2x8 configuration with 250 μ m spacing between shanks and 375 μ m spacing between the two rows. Animals were given food and water *ad libitum* a minimum of 24 hours before surgery and a minimum of 5 days after surgery. Anesthesia was induced with 3% isoflurane in O₂ and maintained with 2-3% isoflurane provided through a breathing mask throughout surgery. Depth of anesthesia was monitored by tail and hind-paw pinch responses. Body temperature was maintained at 37% using a heating pad (Physitemp Instruments). Craniotomies were made through which electrodes were lowered at coordinates of ~2.5mm anterior to Bregma and ~4.3mm from Midline. Recording sites were verified histologically by comparing Nissl-stained 60 μ m coronal brain sections with reference anatomical planes (Paxinos & Watson, 2007). Histological reconstruction of the array positions indicated that recordings were made in the vibrissal area of the primary somatosensory cortex. A multi-neuronal acquisition processor (16 channels, Axona Systems) was used to amplify and record signals. Single-units were filtered at 300-7000Hz (Butterworth) and extrapolated by using Offline Sorter 3.2.4 (Plexon) according to the following criteria: (1) 0.1% of interspike intervals smaller than

1.0ms and (2) spike waveform shapes as determined by a waveform template algorithm and principal component analysis.

4.3. Results

4.3.1. Rats learned the vibration discrimination task

Four rats were trained in the discrimination paradigm to report the location of a vibration applied to their whisker pad (Fig. 16A and 16B). Each trial was initiated by a nose poke where the whiskers came in contact with two independent meshes, to the left and right of the snout. The rat was required to maintain nose-poke for one of ten delays (500-1400ms, 100ms interval) in order to trigger the presentation of the vibration stimulus on one of the two meshes. The task of the rat was to identify the side of stimulation and turn to the corresponding reward spout to collect sucrose water. On ~45.5% of trials, the vibration stimulus was preceded by an auditory cue (cued trials); on ~45.5% of trials, this auditory cue was absent (uncued trials); on ~9% of trials, an auditory cue was presented but was not followed by the vibration stimulus (catch trials). Rats had a 700-ms window of opportunity to initiate a response from the onset of the vibration stimulus resulting in 4 possible outcomes (Fig17A): 1) Hit, where the rat made a behavioral choice within this window of opportunity. This can be further divided into two outcomes: correct choice (where the rat licked the corresponding reward spout and was rewarded; gray) and incorrect choice (where the rat licked the non-corresponding reward spout and was not rewarded; black); 2) False alarm, where the rat made a behavioral choice before the onset of the vibration stimulus; 3) Miss, where the rat did not make a behavioral choice and remained in the nose-poke, or a behavioral choice was made after the window of opportunity. To characterize the overall performances, we first analyzed trials across cued and uncued conditions (Fig 2A). Both false alarm and miss trials were low and consistent across all rats (false alarm rates: $10 \pm 1.5\%$, mean $\pm$

SD; miss rates: $3 \pm 0.1\%$ across rats). Hit rates were high and consistent across rats ($61 \pm 2.3\%$, mean $\pm$ SD).

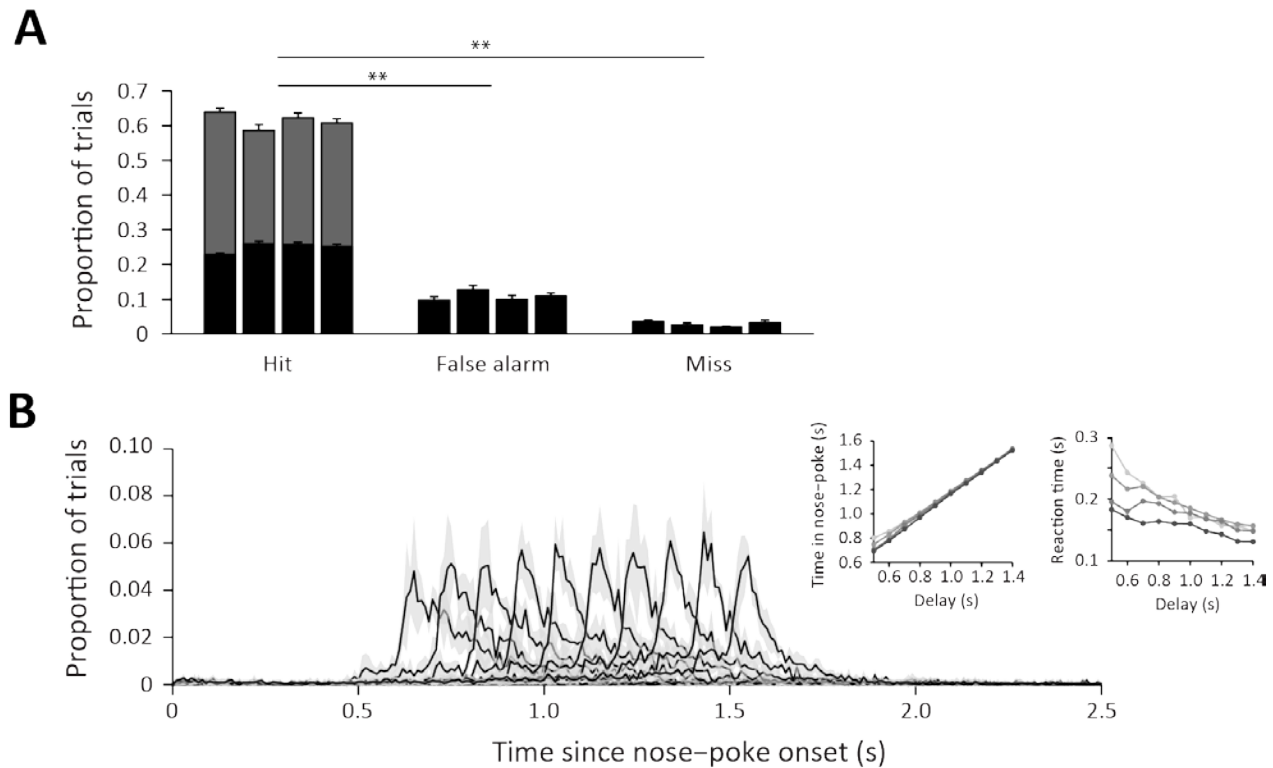


Figure 17 Rats showed high levels of behavioral performance. **A.** Mean proportion of total trials for each rat which were hit, false alarm or miss trials. Subplot: Mean proportion of total trials which were correct or incorrect trials. Error bars represent standard error of mean. Each column represents each rat. **B.** Distribution of nose-poke duration (nose-poke offset – nose-poke onset) across all 4 rats. Shaded error bars represent 1SD. Left Subplot: Median time in nose-poke for each stimulus delay. Different shaded lines represent each rat. Right Subplot: Median reaction time (nose-poke offset – stimulus onset) for each stimulus delay. Different shaded lines represent each rat.

To confirm that the rats' behavior was consistently based on stimulus detection, we examined the performance, defined as the proportion of correct choices. Across the 4 rats, average performance was $71 \pm 1.9\%$ (mean $\pm$ SD). To further establish if the rats' behavior was based on stimulus detection rather than a non-specific strategy such as timing, we quantified performance by comparing nose-poke durations across all 10 stimulus delays. If the rats left the nose-poke consequent to stimulus, the time spent in the nose-poke should depend on the duration of the delay preceding stimulus presentation. Figure 17B shows the profile of leaving for each stimulus delay averaged across all rats: 10 distinct leaving profiles can be observed time locked to the 10 stimulus onsets. This is quantified by the correlation between the median nose-poke duration and the stimulus delay ($r = 0.99$, $p < 0.01$, Spearman's test, Fig 17B left subplot). Across all rats, the median reaction times (time between stimulus onset and nose-poke offset) also showed a strong inverse correlation with trial duration ($r = 0.91$, $p < 0.01$, Spearman's test; Fig 17B right subplot). As time elapses, given the absence of stimulus, the probability of the stimulus occurring increases. The observed systematic decrease in reaction time with increasing trial duration indicates that rats were sensitive to elapsed time and implicitly tracked the likelihood of stimulus presentation. This may be a consequence of increased perceptual enhancement and/or increased motor preparation. Similar expectation related response changes have been shown previously in rodents (Lee et al., 2016), monkeys (Sharma et al., 2015) and human psychophysics (Coull & Nobre, 1998; Nobre, 2001; Oswal, Ogden, & Carpenter, 2007). In sum, initial characterization indicated that rats responded to the onset of the vibration stimulus and were capable of discriminating its spatial location.

4.3.2. The auditory cue changed the behavioral response

Next, we characterized the effect of temporal cueing on leaving behavior. Figure 18A and B examine the response profile in detail by plotting the instantaneous and cumulative probability of leaving for cued, uncued, catch and false alarm trials, relative to the stimulus onset across all delays (see methods for calculation for instantaneous and cumulative probabilities). The cued and uncued conditions elicit distinct response profiles: As expected, prior to the onset of the auditory cue, all 4 conditions showed similar leaving profiles. However, the response profile of the cued condition began to diverge from that of the uncued condition at the time of stimulus onset. The profile of the cued distribution (~0-100ms post stimulus onset) closely matched that of the catch condition (green). The cumulative probability distribution further revealed this similarity. This distinct and constant change in leaving rate can be attributed to the onset of the auditory cue as it was only observable in the cued (red) and catch (green) trials. In comparison, this distinct change in the leaving rate was not observed in the uncued (blue) and false alarm (black) trials. In short, the auditory cue set a new but higher false alarm rate. After ~100ms post stimulus, the leaving profile for cued and uncued trials (conditions where the stimulus was present) deviated from the catch and false alarm trials (stimulus absent) respectively. This second change in leaving profile reflects the change in behavior due to the perception of the vibration stimulus. Overall, the difference between the catch and false-alarm trials suggests that a subset of responses in the cued condition were triggered by the auditory cue alone.

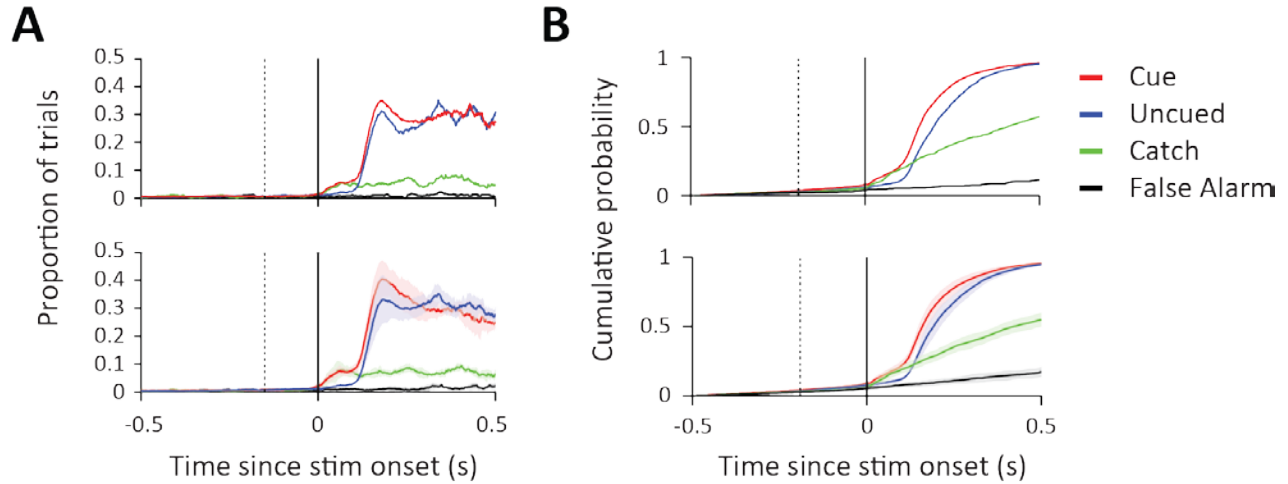


Figure 18 Profile of nose-poke leaving with respect to stimulus onset. For all panels, red represents cued trials, blue represents uncued trials, green represents catch trials, black represents false alarms. For each panel, an example rat is shown in the top, and the average data across all 4 rats are shown in the bottom. Shaded area represents 1 SD. **A.** Instantaneous probability of nose-poke leaving. Probabilities are calculated on non-overlapping windows of 10ms. **B.** Cumulative probability of nose-poke leaving. Cumulative probability is calculated as the probability of leaving the nose-poke given the animal had not left since a given time point. See methods and materials for details.

4.3.3. Temporal cueing improves discrimination performance

The distinct leaving profiles observed above have important implications on interpreting the effects of cueing on behavioral performances. We therefore first characterize the general effect of temporal cueing on behavior by quantifying performance in each condition. The presence of the auditory cue significantly reduced the number of miss trials (Fig. 19A, $p < 0.01$, student t-test) and significantly decreased reaction times across all stimulus delays (Fig. 19B, $p < 0.01$, student t-test). The difference in miss rate between cued and uncued trials did not vary significantly across stimulus delays. This lack of interaction was also true for reaction time differences (2-way ANOVA, miss: $F(1,9) = 0.78$, $p = 0.63$; reaction time: $F(1,9) = 0.41$, $p = 0.92$). Temporal cueing

produced a slight but non-significant increase in discrimination performance ($p = 0.06$, student t-test, Fig. 19C).

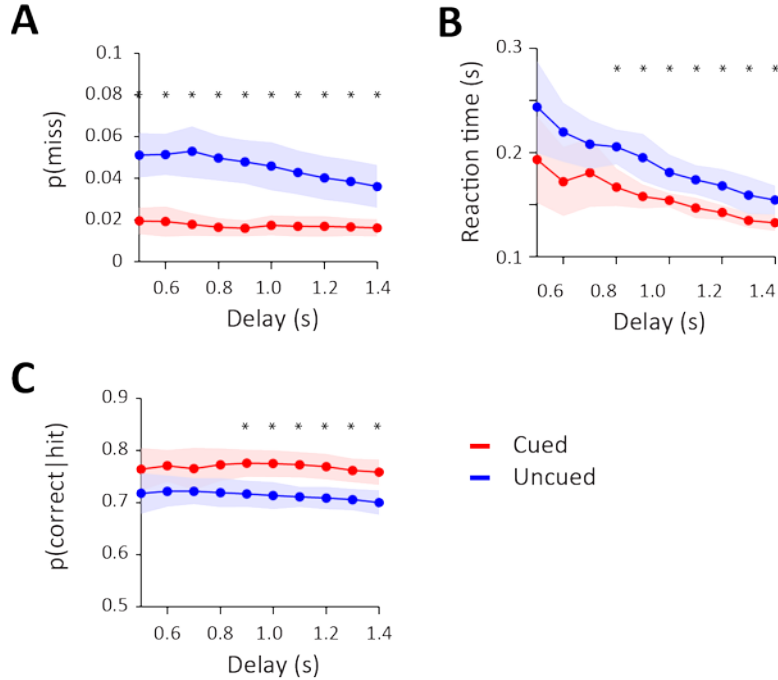


Figure 19. General characterization of behavior between cued and uncued trials. **A.** Proportion of miss trials across each stimulus delay. Shaded area represents 1SD across all rats. Cued trials are represented in red. Uncued trials are represented in blue. **B.** Median reaction time across each stimulus delay. Shaded area and color notation is retained from previous panel. **C.** Performance (correct trials divided by the sum of correct and incorrect trials) across each stimulus delay. Shaded area and color notation is retained from previous panel.

4.3.4. Estimation of true discrimination

Given the distinct leaving profile between cued and uncued conditions (Fig. 18), we examined in further detail whether temporal cueing had an effect on perceptual discrimination across different time points. First, we compared the number of correct and incorrect trials in the two conditions

(Fig. 20A). This analysis revealed small differences in the distribution of incorrect trials across the two conditions, but a large difference in the distribution of correct trials.

From an experimenter's point of view, we have access to two observable outcomes on 'hit' trials: correct and incorrect choices. However, we are interested in the two underlying decision types: informed discrimination of the stimulus and random responses. Given the balanced distribution of left and right stimuli across trials, any random responses that the animal makes would be expected to be 50% incorrect and 50% correct. We therefore estimated the frequency and temporal distribution of true discrimination by subtracting the number of incorrect trials from correct trials. This analysis is presented in Fig. 20B (left – example rat; right – averaged across rats). We observe minimal difference in the first ~100ms post stimulus but an increase hereafter in the number of true discriminations in the cued condition, as well as a leftward shift in time corresponding to faster responding in the cued condition. This suggests that the earliest responses in the cued condition were predominantly comprised of random choices; a feature that is absent from the uncued condition. In sum, the presence of an auditory cue affected behavioral performance in four ways: 1) cueing increased random responses in the first ~100ms; 2) cueing decreased miss rates (Fig. 19A)); 3) cueing enhanced the discrimination performance ; 4) informed discrimination responses were faster when cued compared to uncued condition.

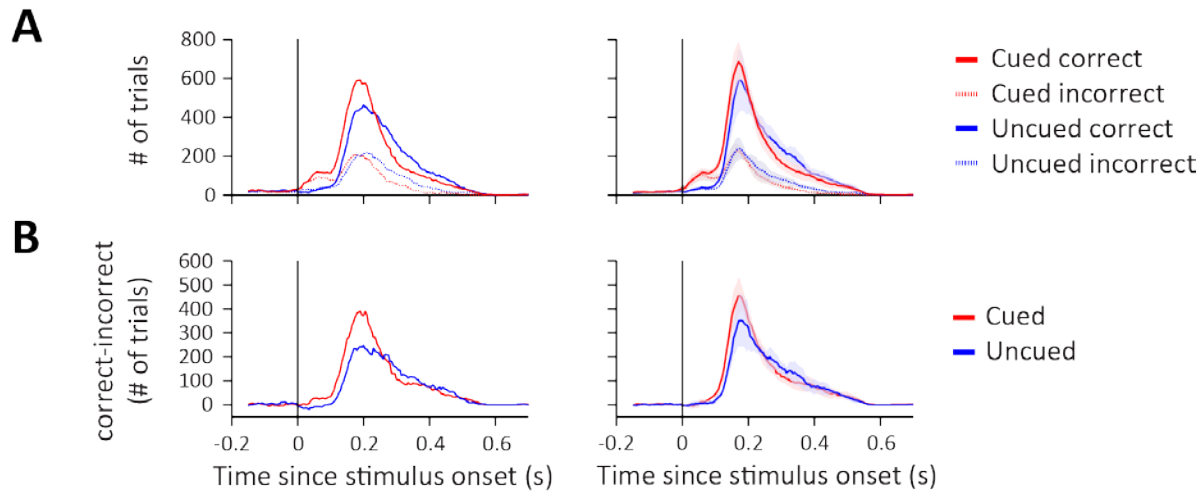


Figure 20. Characterization of true discrimination performance. For a panels, red represents cued condition, blue represents uncued condition. Solid lines represents correct decisions, dashed lines represents incorrect decisions. Left column represents an example rat; right column represents averages across all 4 rats. Shaded area represents 1 SD. **A.** Top panels show the number of trials in each condition. Bottom panel shows the difference between cued and uncued condition for correct and incorrect trials. **B.** Comparison of the number correct minus incorrect trials (solid minus dashed lines from A). This represents a distribution of true discrimination.

4.3.4. Temporal cueing decreased the reaction times for the discrimination

Next, we further quantify the observed changes in discriminability by performing a discrimination onset reaction time analysis. This allows us to estimate the first time point in which stimulus discrimination was above chance (Fig. 21A and 21B). Hit rates were calculated as the proportion of correct left responses when the stimulus was presented on the left; whilst false alarm rates were calculated as the proportion of incorrect left responses when the stimulus was presented on the right. The first point in time where d' values deviated from chance was consistent across rats with cued discrimination onset reaction time significantly faster than uncued discrimination onset reaction time (Table 4). These reaction times capture the earliest reliable behavioral manifestation of stimulus discrimination. Averaged across all sessions and all

rats, cued trials had an average early reaction time of $112 \pm 2.3\text{ms}$ (mean $\pm$ SD) for significant stimulus discrimination. The average early reaction time for the uncued trials was $133 \pm 7.4\text{ms}$ (mean $\pm$ SD). Additionally, the discrimination onset reaction times confirmed what we observed previously (Fig. 20B): up to $\sim 100\text{ms}$ post stimulus onset d' values did not differ between the two conditions or from chance performance. In the cued condition, discriminability was on average higher than in the uncued condition and deviated from chance earlier in time (Fig. 21B).

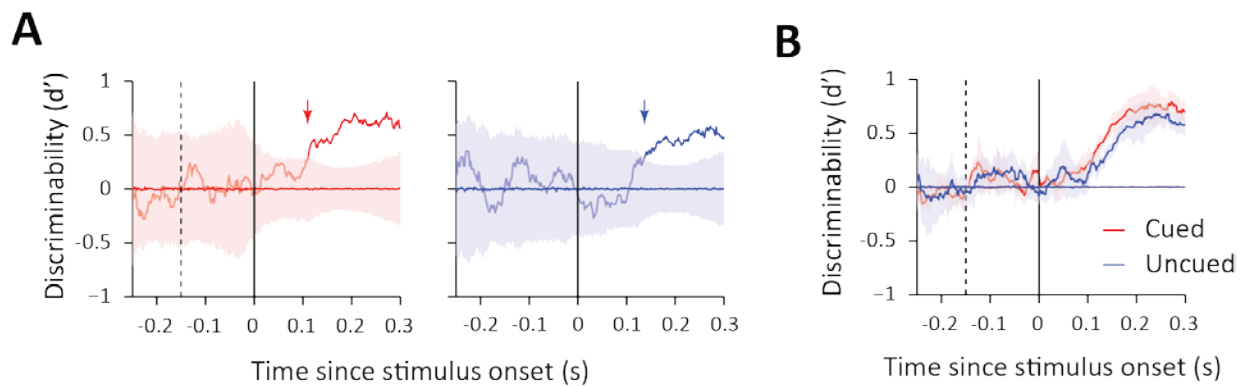


Figure 21. Rats show fast discrimination onset reaction time as revealed by a change in discrimination accuracy (d') as a function of trial time course. **A.** Instantaneous discrimination probability of leaving on cued (red), uncued (blue), catch (green) and false alarm (black) trials. Probability are calculated in every 50ms window at steps of 1ms. Dashed vertical line represents onset auditory cue. Solid line represents onset of vibration stimulus. Top panel shows example rat. Bottom panel shows average probability across 4 rats. Shaded error bar represents 1 SD. **B.** Discrimination onset reaction time. Red panels represent cued condition; blue panels represent uncued conditions. Shaded areas represent d' chance level as calculated from bootstrapping. Dash horizontal line represents the mean value of shaded area. Dash vertical line represent onset of auditory cue. Arrow indicates the first time point in which d' reach above chance level. See methods and material for calculation of discrimination accuracy.

Table 4. Onset reaction times (ms)

	Rat 1	Rat 2	Rat 3	Rat 4
Cued	115	110	110	112
Uncued	132	136	139	122

4.3.5. Neuronal correlates of temporal cueing

In three rats, we unilaterally implanted electrodes into vS1 cortex and recorded single-unit activity whilst the animal performed the discrimination task. As the electrodes were implanted only on one side of vS1 cortex, we confirmed our recording site by comparing responses to vibration stimuli presented on the contralateral side against the ipsilateral side (recalling that sensory information from the whisker pad arrive on the contralateral side in the cortex). As shown in Figure 22A, vibration stimuli presented on the ipsilateral side (grey) did not evoke a significant response from baseline ($p=0.22$, student t-test). Alternatively, vibration stimuli presented on the contralateral side (black) evoked a significant response from baseline ($p<0.01$, student t-test). Additionally, the location of the electrode was confirmed by histological recovery after data collection. A total of 24 neurons were selected to study how the auditory cue affected neuronal activity in vS1.

Figure 22B and C show the activity of an example neuron and across all recorded neurons during the stimulus period respectively. In this cued condition (red), we observe a sustain decrease in firing rate that was absent in uncued trials (blue). This systematic decrease in firing was specific to the auditory cue, as it was observed in catch (green) trials as well. This systematic decrease in firing rate is further quantified by the scatter plot in Figure 22D (x-axis). The auditory cue

evoked decrease in neuronal activity was present in trials in which the stimulus was present on the ipsilateral side of the recording area. What is the effect of temporal predictability on stimulus detectability? We quantified the changes in neuronal activity with respect to stimulus presentation during cued and uncued trials. The evoked response was quantified as the difference in firing rate around stimulus onset (firing rate 150ms post-stimulus onset minus the firing rate 150 pre-stimulus onset). The vibration stimulus produced an evoked response that was significantly higher during cued trials compared to uncued trials ($p < 0.01$, student t-test, Fig. 22D (solid red and blue)). We performed an ROC analysis on each single unit by comparing a 150ms pre-stimulus onset against post-stimulus onset in the cued and uncued condition. The ROC analysis reveal that an ideal observer of neuronal activity in vS1 could reliably detect the vibration stimulus in both cued and uncued conditions, however the stimulus was significantly better detected in the cued condition compared to the uncued condition ($p < 0.01$, student t-test, Fig. 22E)

In the preceding behavioral sections, we reported that the presence of an auditory cue improved discrimination performance. The presence of an auditory cue is marked by a decrease in firing rate in vS1 and subsequently improves the detectability of the vibration stimulus. We therefore investigated whether the neuronal encoding of the vibration stimulus correlated with the rat's behavioral performance (correct vs incorrect). To address this question, we compared the evoked response and detectability of the stimulus between correct and incorrect trials and found no significant differences ($p = 0.412$, student t-test).

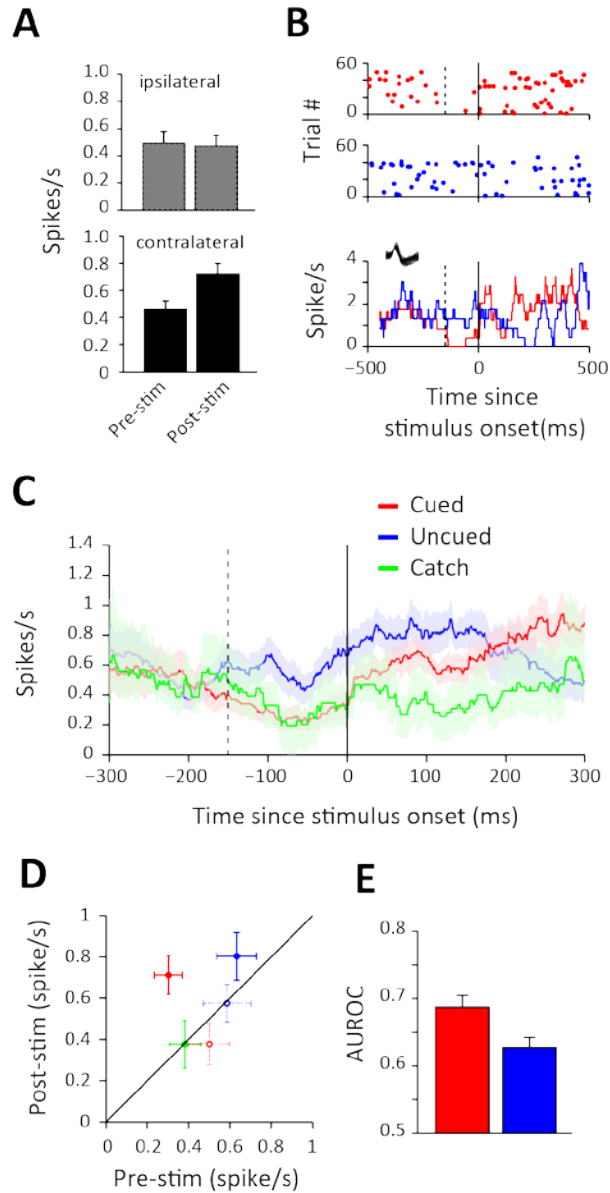


Figure 22. Single-unit activity in vS1 **A.** average firing rate within a 150ms window before and after stimulus presentation. Grey represents stimulus presentation on the ipsilateral side. Black represents stimulus presentation on the contralateral side. **B.** Top, raster plot showing spiking activity of an example aligned to the stimulus onset (contralateral). Red dots represent spikes in cued trials. Blue dots represent spikes in uncued trials. Bottom, perievent time histogram of example neurons in sliding window of 50ms at 1ms steps. Insert, 50 example traces of example neuron. Vertical dotted line represents onset of auditory cue. Vertical solid line represents onset of vibration stimulus. **C.** Perievent time histogram of all recorded neurons ($n=24$) aligned to stimulus onset. Red represents average activity during cued trials. Blue represents average

activity during uncued trials. Green represents average activity during catch trials. Shaded error bars represent SD across neurons. **D.** Scatter plot of average activity across neurons within a 150ms window before and after stimulus presentation for cued, uncued and catch trials (color notion retained from previous panels). Solid circles represent activity for stimulus presented on the contralateral side. Open circles represents activity for stimulus presented on the ipsilateral side. Error bars represent SD across neurons. **E.** Area under ROC for contralateral stimulus detection for cued and uncued trials. Error bars represent SD of ROC for each neuron.

4.4. Discussion

In the wild, animals need to access certain cues that may predict imminent danger or reward in order to optimize actions for survival. For example, the rustling of leaves from the presence of a predator may allow animals to allocate attention in time to efficiently assess upcoming sensory signals to initiate appropriate escape behavior. To better understand how animals delegate attentional resources in time, we devised a paradigm that encouraged rats to orientate attention to a specific time interval.

We trained rats in a forced-choice task in which a vibration stimulus was presented at one of two spatial locations (left or right) at a temporally uncertain time. On a subset of trials, an auditory cue preceded the vibration stimulus by 150ms and thus reduced the temporal uncertainty of the vibration stimulus. Critically, the auditory cue did not provide any spatial information about the correct behavioral choice. Behavioral metrics indicated that the addition of the auditory cue improved performance as measured by an overall decrease in miss probability (Fig. 19A), decrease in reaction time (Fig. 19B) and most importantly an increase in discrimination performance (Fig. 19C). This is in line with previous findings where temporal cueing yielded improvements in performance and reduction in reaction time across various simple detection and discrimination tasks (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Coull & Nobre, 1998; Griffin, Miniussi, & Nobre, 2001; Lange et al., 2003; Los & Heslenfeld, 2001; Miniussi et al., 1999; Nobre, 2001).

Closer inspection of the leaving profiles across conditions (cued, uncued, catch and false alarm) provided further insight as to the underlying mechanism (Fig. 18). The presence of the auditory cue led to a constant increase in base-line response rate as revealed by a change in nose-poke

cumulative leaving profiles (Fig. 18B). This increase in base-line response was akin to setting a new false alarm rate. Beyond the systematic increase in base-line false-alarm rate, the cue improved discrimination performance and decreased reaction times to the vibration stimulus (Fig. 19). To better quantify changes in discrimination performance, we identified the distribution of trials in which the behavior of the rat was triggered and informed by the stimulus (true discrimination trials) by separating trials in which the behavior was triggered but not informed by the stimulus (random responses)(Fig. 20). From an experimenter's point of view, we have access to only two behavioral outcomes on hit trials: correct and incorrect outcome. From the animal's perspective, these behavioral outcomes are the manifestation of two underlying choice types: informed choices (correct outcome) and random responses (50% - correct outcome; 50% incorrect outcome). By subtracting the number of incorrect outcomes from correct outcomes, we estimated the number and distribution of trials that were informed choices. As shown in Fig 20B, the number of informed choices was higher in the cued condition compared to the uncued condition, and the average speed at which these informed choices were made was faster in the cued compared to the uncued condition. Furthermore, this analysis revealed that the earliest responses in the cued condition were primarily random responses - responses that were triggered by the cue or stimulus, but were not informed by it. Finally, the discrimination onset reaction time analysis (Fig 21) revealed that, on average, rats discriminated the location of the vibration stimulus about 21ms faster in the cued condition.

Temporal predictability could be exploited to improve performance in at least two ways. Firstly, it may be used to prime motor outputs. Of course, since the animal cannot predict the spatial location of the vibration stimulus, priming the motor system for a particular choice would lead to

a decrease in reaction time but not to an improvement in response accuracy. Several studies have shown similar behavioral changes with improved reaction time speeds consistent with enhanced motor preparedness (Bausenhardt, Rolke, & Ulrich, 2008; Correa, Lupiáñez, & Tudela, 2005). This first type of exploitation of temporal predictability strongly resembles the behavioral changes we observed in the previous chapters. In the current study, this is revealed by the trials in which a response was made within the first ~100ms post stimulus in the cued conditions (Fig. 18A). These trials were primarily random choices with performance at chance levels, and were triggered by the cue/stimulus but not informed by the vibration (Fig. 20B).

Alternatively, temporal predictability could be exploited to enhance sensory processing at appropriate moments, improving the accuracy and the speed of responses. This has been typically observed in perceptually demanding tasks (Correa et al., 2005; Correa, Lupiáñez, & Tudela, 2006; Nobre, Correa, & Coull, 2007). In the current study, this was revealed by trials in which responses were made after ~100ms post stimulus. These trials were triggered and informed by the vibrations and these responses were made earlier and more frequently in the cued condition compared to the uncued condition (Fig. 20B). This was further illustrated by the faster discrimination onset reaction time and higher d' values (Fig. 21).

To optimize reward in the cued condition, the fast but uninformed trials (<~100ms trials) would be more optimal if reallocated to a later stage in time where the cue could augment the discriminability of the vibration stimulus (>~100ms trials). However, regardless of the location of the vibration stimulus or behavioral choice (left/right), the auditory cue reduces temporal uncertainty in stimulus onset. Reacting based on timing alone, trials that would have been missed

and receive no reward (i.e. uncued missed trials), now have a 50% probability of receiving a reward. This is demonstrated by the decrease in miss trials in the cued condition compared to the uncued condition (Fig. 19A). In this light, it may be the most optimal strategy for the animal to balance effort and reward outcome. Nevertheless, our analysis indicates that future behavioral metrics used in psychophysics experiments should aim to parse informed discriminations from uninformed discriminations.

Neuronal studies on temporal cueing typically find varied results: some report temporally predictable events lead to less neural activity than temporally unpredictable events (Alink, Schwiedrzik, Kohler, Singer, & Muckli, 2010; Bendixen, SanMiguel, & Schröger, 2012; Lange, 2009; Schwartze, Farrugia, & Kotz, 2013), whilst others find more neural activity for temporally predictable events (Correa, Lupiáñez, Madrid, & Tudela, 2006; Jaramillo & Zador, 2010; Schroeder & Lakatos, 2009). In our study, neuronal recordings from the primary somatosensory cortex (vS1) showed a clear enhancement of activity evoked by the vibration stimulus (Fig. 22). Critically, on trials in which the vibration stimulus was temporally predicted by the auditory cue, neuronal activity in vS1 showed a clear enhancement over trials in which the auditory cue was absent (Fig 22). ROC analysis indicated that for both conditions, an ideal observer of neuronal activity in the primary somatosensory cortex could reliably detect the vibration stimulus, with the cued condition being significantly better detected than in the uncued condition. These observation shows that temporal cueing not only influences late stages of processing such as in the inferior temporal cortex or lateral intraparietal cortex (Anderson & Sheinberg, 2008; Ghose & Maunsell, 2002; Janssen & Shadlen, 2005) but also can enhance representations as early as primary somatosensory cortex. However, this modulation of activity should not be interpreted as

evidence that the somatosensory cortex helps to keep the time of relevant events. Instead, our results should be interpreted as showing that the somatosensory cortex changes its representation of vibrations according to timing information it receives from other areas.

Possible cellular mechanisms that may contribute to such attention related neuronal enhancements are largely unknown. However, recent experiments indicate the role of NMDA receptor-dependent electrogenesis (NMDA spiking)(Larkum, Nevian, Sandler, Polsky, & Schiller, 2009; Schiller, Major, Koester, & Schiller, 2000) across different layers of the cortex in perception. For example, Layer 1 of the cortex has been shown to be critical in conveying feedback information during cognitive tasks (Self, van Kerkoerle, Supèr, & Roelfsema, 2013). Recent experiments have demonstrated the role of local NMDA spikes in tufts dendrites of Layer 2/3 pyramidal neurons in primary somatosensory cortex *in vivo* (Palmer et al., 2014). This was observed during spontaneous and crucially during sensory input - influencing on the number of output action potentials. Ultimately, this would enhance the effectiveness of Layer 1 inputs, and therefore could pose a possible synaptic mechanism supporting the enhanced representation during attention. Similarly, studies in awake rodents indicate that dendritic Ca^{2+} activity in Layer 5 pyramidal neurons are amplified during cognitive processes (Gambino et al., 2014; Murayama & Larkum, 2009; Xu et al., 2012). Recent experiments demonstrate Ca^{2+} activity in the apical dendrites of Layer 5 pyramidal neurons in vS1 is correlated with threshold for perceptual detection of whisker deflection - with manipulation of these dendritic activity shifting perceptual threshold (Takahashi, Oertner, Hegemann, & Larkum, 2016). This may also offer a potential cellular mechanism in which enhanced representation during attention could be modulated.

In Chapter 2, prioritization was captured by an overall increase of neuronal activity in the attended condition. Admittedly, the paradigm was characterized by long-durations of prioritizing to a specific modality (minutes). Nevertheless, we did not observe an increase in spontaneous firing rate during the cue-stimulus period in the current experiment. Instead, at the onset of the auditory cue, we observed a decrease in activity in the somatosensory cortex, followed by a strong increase at the onset of the vibration stimulus. Temporal cueing was captured only by changes in firing rate that were specific to stimulus driven activity. A possible interpretation is that suppression plays an important role in the neural mechanism underlying temporal attention in the sensory cortex. Suppressing neuronal activity during the cue period can prevent premature responding and effectively improves the signal to noise ratio to the stimulus. Alternatively, previous research in multisensory interaction has shown that focal cortical activation can inhibit neuronal activity of neighbouring cortical sensory networks (Han et al., 2009; Shu et al., 2003). For example, *in vivo*, focal photostimulation in monkey neocortex is immediately followed by firing suppression in neighbour units (Han et al., 2009). Specifically on the interaction of auditory and somatosensory cortex, past research has demonstrated acoustic stimulation can cause widespread and near synchronous hyperpolarization in non-auditory related cortical areas. For example, an acoustic noise burst stimulus can cause hyperpolarization in layer 2/3 pyramidal neurons in the somatosensory cortex (peak amplitude: $5.2 \pm 0.3\text{mV}$; onset latency: $31.3 \pm 2.2\text{ms}$)(Iurilli et al., 2012). However, this explanation does not account for the increase in discrimination performance observed in our study. Whilst stimulus driven or focally driven excitation in the auditory cortex may lead to a decrease in activity in the somatosensory cortex, no studies have shown that this would lead to increases in neuronal and behavioral performance. Alternatively, the decrease in neuronal activity during the cue period and the increases in

discrimination performance may be due to the changes in whisking behavior. From this perspective, the auditory stimulus may have cued the rats to better engage in the receptive mode and inhibit whisking activity to improve detection of the vibration stimulus. As a result of this inhibition of whisking, neuronal activity in vS1 would be suppressed during the cue period. However, visual inspection of the whisking activity by high-speed videos during the task did not reveal any evident differences in whisking after the presentation of the cue.

Finally, in our experiment, we did not observe choice-related activity. ROC analysis indicated that an ideal observer of neuronal activity in vS1 could not significantly differentiate stimulus evoked activities between hit and miss trials. This is in contrast to decision making experiments utilizing the whisker system in which vS1 show robust choice-related activity (Yang et al., 2016). Yang et al (2016) demonstrated an increase choice-related activity (hit vs. miss) along the ascending whisker pathway, with trigeminal ganglion cells showing no choice-related activity and vS1 displaying robust choice-related activity with top-down axons projections from vS2 to vS1 signaling choice. Similarly, in a study by Kwon et al., (2016), vS2 was shown to correlate strongly to choice-related activity - more so than in vS1. The authors demonstrate vS1 neurons projecting to vS2 fed forward activity that predicted choice, with touch and choice information propagating in a feedforward and feedback loop between vS1 and vS2. Of course, the lack of choice-related activity observed in our experiment does not dismiss the existence of choice-related activity in vS1. Rather, this discrepancy may be due to the comparatively lower number of recorded neurons in our experiment and/or that our population was primarily comprised of supragranular neurons.

Additionally, in our experiments, we did not observe choice-related activity between correct and incorrect trials - ROC analysis indicated no significant difference between the two trial types. Taking into account to the amalgamation of guess and informed decision within correct trials (Fig. 20), the power of observing a significant choice probability from correct and incorrect trials would be reduced. Nevertheless, the absence of significant choice probability is consistent with observations of sensory cortex in monkeys (de Lafuente & Romo, 2005, 2006) and to our observations in Chapter 2.

Very little is known about how the brain codes temporal intervals and the existence of a dedicated *timing* system in the brain. Some propose that temporal intervals are computed by a centralized neural system, possibly organized around thalamocortical-striatal motor circuits (Matell & Meck, 2000), the cerebellum (Ivry, 1996; Ivry & Schlerf, 2008; O'Reilly, Mesulam, & Nobre, 2008) or their combination (O'Reilly et al., 2008). Others propose that the computation of temporal parameters occurs in a distributed fashion, across many or all neural systems (Buonomano & Laje, 2010; Buonomano, Bramen, & Khodadadifar, 2009; Joaquín M. Fuster, 2001). It remains unclear which brain area may constitute a system for controlling the allocation for anticipatory temporal biases or indeed whether such a control system even exists.

5. Conclusion

An important question in neuroscience is how neuronal representations of sensory stimuli transform into the percepts which can guide an animal's behavior. The experiments presented in this thesis investigated how a rat interacts with its sensory environment in order to achieve efficient encoding of the sensory signals based on the context. Specifically, we aimed to explore how sensory context and the behavioral relevance of a stimulus affect neuronal coding in the cortex. In a series of experiments, we demonstrated that the rat whisker system is a viable alternative model in which to investigate simple forms of attention - a phenomenon that has previously been predominately studied in human and non-human primate subjects. These novel rodent paradigms allow a more mechanistic approach to questions in attention research due to the availability of an array of molecular and genetic tools such as optogenetic (Deisseroth, 2011; Yizhar et al., 2011), calcium (Grienberger & Konnerth, 2012) and voltage (Peterka et al., 2011) imaging techniques in rodents. These techniques allow the control and monitoring of vast populations of neurons in real time, enabling better understanding of the computational and coding mechanisms during attention, which would otherwise be difficult or impossible in non-human and human primates. Whilst some of these techniques are confined to head-fixed preparations, recent development in 2-photon imaging has enable the possibility for imaging freely moving animals at high optical performances (Mayrhofer et al., 2015). The experiments outline in the current thesis revealed the correlates of attention within the rodent whisker system. The use of optogenetics would allow future experiments to perturb areas across the whisker pathway on their role in modulating attention. As cell-type-specific neurophysiology and control of neuronal activity are more readily available in mice, future experiments could modify the

behavioral paradigms presented here to reproduce the findings in mice models in order to fully utilize these techniques. However, the use of transgenic rats are emerging (Do Carmo & Cuello, 2013; Filipiak & Saunders, 2006; Yamazaki et al., 2000) and the experiments outline in this thesis represent a starting point in attention research that would allow future experiments to examine possible cellular mechanisms of attention. For example, Layer 1 of the cortex has been demonstrated to convey feedback information crucial for cognitive performances (Self et al., 2013). These neurons synapse onto apical tuft dendrites of layer 2/3 and 5 pyramidal neurons and has been shown to influence action potential of these cells via NMDA receptor-dependent electrogenesis (NMDA spikes)(Larkum et al., 2009; Schiller et al., 2000) resulting in a nonlinear voltage response to localized synaptic inputs. Recently, sensory stimulation has been demonstrated to increase the probability of these NMDA spikes in tuft dendrites of layer 2/3 pyramidal neurons, influencing the number of output action potentials (Palmer et al., 2014). This may pose a possible synaptic mechanism underpinning the enhanced representation during attention and warrants further investigation. Alternatively, studies in awake rodents indicate that dendritic Ca^{2+} activity in Layer 5 pyramidal neurons are amplified during cognitive processes (Gambino et al., 2014; Murayama & Larkum, 2009; Xu et al., 2012). A recent experiment demonstrated Ca^{2+} activity in the apical dendrites of Layer 5 pyramidal neurons in primary somatosensory cortex was correlated with threshold for perceptual detection of whisker deflection - with manipulation of these dendritic activity shifting perceptual threshold (Takahashi et al., 2016). This may offer another potential cellular mechanism in which enhanced representation during attention could be modulated.

In Chapter 2, a novel simple detection task was developed to investigate sensory prioritization across the somatosensory and visual domain. This was manipulated by varying the probability at which a stimulus was presented in high or low likelihood context. Similar to human and non-human primates, behavioral signatures of attention were observed. Detection performance was higher for stimuli that were presented in a high-likelihood context and detection speed was faster for stimuli that were presented in a high-likelihood context. This is in line with previous findings where attention improved performance (Carrasco, 2011; Cohen & Maunsell, 2009; Posner, 1980) and reduced reaction time (Eriksen & Hoffman, 1972; Henderson & Macquistan, 1993). We also observed that rats tracked the elapsed trial time which resulted in the extraction of the conditional probability of stimulus presentation. This was demonstrated by the decrease in reaction time speed for presentation of stimulus with a longer delay. This observation has been found in humans and non-human primates (Coull & Nobre, 1998; Kingstone, 1992; Niemi & Näätänen, 1981; Oswal et al., 2007; Reuter-Lorenz et al., 1995; Sharma et al., 2015). Additionally, calculating ‘onset’ reaction times revealed remarkable decision speeds. We attributed these speeds to perceptual/motor system operating close to threshold whereby small differences in sensory cortex are amplified in a cascade that recruits motor outputs already primed for action execution. At the neuronal level, there were similarities between our results and the main observations in primate research. Activity in the primary somatosensory cortex showed increased multiplicative-gain when attention was directed to whiskers in the high-likelihood context. This form of sensory amplification is commonly termed as ‘multiplicative gain control’ in the scope of human and non-human primate research (McAdams & Maunsell, 2000; Olsen, Bortone, Adesnik, & Scanziani, 2012; Zhang et al., 2014). Importantly, the multiplicative gain modulation in our experiment resulted in increases in neuronal performance

in stimulus detectability. This increased stimulus-evoked response accompanying prioritization is consistent with attention studies in the visual pathway (Herrero et al., 2008; McAdams & Maunsell, 1999; McAlonan, Cavanaugh, & Wurtz, 2008)

The behavioral signatures of sensory prioritization between two modalities were replicated in Chapter 3. In this chapter, we used a two-alternative forced choice paradigm instead of a simple detection task, and extended our findings from the somatosensory and visual domain to the somatosensory and auditory domain. The results replicated the behavioral correlates of sensory prioritization found in Chapter 2. Detection and discrimination performance were improved in the prioritized context, as well as reaction times. The adaptation of a two-alternative forced choice paradigm from a simple detection paradigm imposed an extra ‘response selection’ stage, which imposed additional cognitive and processing load. This difference was manifested in our analysis of ‘onset’ reaction times.

In Chapter 4, we investigated whether rodents could orient attention in time by developing a two alternative forced choice task in which an auditory cue preceded the target vibration stimulus. The cue provided temporal information to the onset of the target vibration without providing spatial information to the location of the vibration. As hypothesized, cued trials were performed faster and resulted in higher discrimination performance. This is in line with previous findings where temporal cueing yielded improvements in performance and reduction in reaction time across various simple detection and discrimination tasks (Correa et al., 2004; Correa, Lupiáñez, & Tudela, 2006; Coull & Nobre, 1998; Griffin, Miniussi, & Nobre, 2001; Lange et al., 2003; Los & Heslenfeld, 2001; Miniussi et al., 1999; Nobre, 2001). However, we did not observe a

multiplicative increase in gain in the primary somatosensory cortex, as had been observed in the sensory prioritization paradigm (Chapter 2). Instead, at the onset of the cue, a decrease in activity in the cortex was observed. Nevertheless, this provided a mechanism to increase the signal-to-noise ratio for neurons in the primary somatosensory cortex encoding the vibration stimulus. This was showed as an increase in neuronal performance in stimulus detectability. As cross cortical multisensory inhibition in the cortex typically have a constant time course, it may be possible that the observed inhibition may have masked the underlying preparatory modulations induced by the auditory cue. Future approaches utilizing a variable cue-stimulus period (Bertelson, 1967; Bertelson & Tisseyre, 1968, 1969; Correa et al., 2004; Coull & Nobre, 1998; Karlin, 1959; Kingstone, 1992; Klemmer, 1956) or a longer cue-stimulus duration could be used to parse the inhibition caused by multisensory interaction from the inhibition induced by preparatory mechanisms. The experiments outlined in this thesis demonstrate that the rat whisker system is a viable model to investigate simple forms of attention. Can this system be extended to other domains such as spatial and feature based attention? Future experiments should aim to investigate the viability of using the whisker system to capture these remaining types of attention.

Akin to the primate visual system where numerous studies have shown similar modulations in early visual areas (Herrero et al., 2008; McAdams & Maunsell, 1999; Herrero et al., 2008; Buffalo et al., 2009; Buffalo et al., 2010), in this thesis, we have shown modulating of attention in the primary somatosensory area. The next step is to investigate the circuitry underlying these two forms of attention: is the primary somatosensory cortex the first area to display such neuronal correlates of attention or are these signatures inherited from other processing areas?

Studies in humans and non-human primates have shown attention dependent modulations at the level of the lateral genicular nucleus (LGN) of the thalamus (Kerry McAlonan et al., 2008). We therefore posit that future experiments using the whisker system as a model of attention in rodent should investigate the role of the thalamus – specifically the VPM, PoM, and TRN subnuclei. These areas would be prime candidates for further investigation due to their anatomical connections and position in the ascending whisker pathway. Whisker TRN neurons receive vibrissae-related input from vS1 (Bourassa et al., 1995) and in turn send their inhibitory projections back to VPM and POr (Scheibel and Scheibel, 1966; Pinault et al., 1995; Lam and Sherman, 2007). This feedback loop makes it a likely area for relaying attention related modulations into the cortex.

Upstream from the vS1 cortex, the frontal orienting field (FOF)(Erlich et al., 2011; Leonard, 1969a) (often referred to as the pre-motor cortex or M2) would be another candidate for further investigation due to its direct connections to the somatosensory cortex (Condé et al., 1995; Leonard, 1969a), superior colliculus (Reep et al., 1987) and prefrontal cortex (Condé et al., 1995), as well as its similar functional role as the primate FEF. Rooted by the "pre-motor theory of attention", this area is especially interesting. Similar to FEF, which has been shown to play a major role in modulating attention in the visual system (Armstrong et al., 2009; Buschman & Miller, 2007c; Crapse & Sommer, 2009; Gregoriou et al., 2009a; Monosov et al., 2008; Thompson et al., 2005a; Zhou & Thompson, 2009), micro-stimulation of FOF evokes whisker movements (Brecht et al., 2004; Kleinfeld et al., 2006; Neafsey et al., 1986; Sinnamon & Galer, 1984) and has been shown to be important for orienting behaviors (Erlich et al., 2011; S L Stuesse & Newman, 1990).

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