ABSTRACT

Title of Thesis:	NEURAL REPRESENTATION OF AUDITORY STIMULI IN DIFFERENT BEHAVIORAL PARADIGMS IN FERRET FRONTAL CORTEX
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The frontal cortex (FC) plays a key role in higher-order cognitive functions and goal-directed behaviors. It is also crucial for the top-down modulation of sensory processing. In auditory tasks, FC interacts with the auditory cortex (AC) dynamically, which modulates the activity of AC to adaptively process and represent task-relevant signals. Task paradigm is an essential factor that influences frontal responses and top-down modulation. The attentional effect on sensory processing varies with different behavioral requirements and reward structures. Therefore, the neural mechanisms of top-down control may vary in different behavioral task paradigms. This study investigates how the neural representation of auditory stimuli in dorsolateral FC of the ferret is shaped by task and reward structure during different behavioral tasks. The results show that frontal neurons have differential responses and selectivity during the two behavioral tasks, and diverse temporal dynamics associated with task variables.

NEURAL REPRESENTATION OF AUDITORY STIMULI IN DIFFERENT
BEHAVIORAL PARADIGMS IN FERRET FRONTAL CORTEX

by

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Chapter 1: Introduction

1.1 The functional role of the prefrontal cortex

The prefrontal cortex (PFC) is the brain area that plays a crucial role in executive functions. It is central to higher-order cognitive functions and goal-directed behaviors (Fuster, 2015; Miller & Cohen, 2001). Numerous studies have shown that prefrontal cortex is involved in many fundamental and complex cognitive activities, including the allocation of attention, inhibitory control, working memory, planning, decision-making, goal-directed actions, and categorization (Aron et al., 2007; Freedman et al., 2001; Gold & Shadlen, 2007; Fuster, 2015; Miller & Cohen, 2001; Narayanan & Laubach, 2006; Wiecki & Frank, 2013).

Traditionally, early animal studies on the function of the prefrontal cortex relied on lesion approaches and the influence on behavior. Frontal lesion would lead to deficits in inhibitory and cognitive task performance, as well as disorders in emotion and social behavior. One type of the commonly used tasks to evaluate task performance and cognitive functions is the delay task. Impaired performance in delay tasks indicated that frontal lesion would cause a deficit in working memory and inhibitory control. Early studies showed that monkeys with frontal lesions usually failed in delayed matching-to-sample tasks (Glick et al., 1969; Spaet & Harlow, 1943). More recent neuropsychological studies also showed that PFC lesion or inactivation may cause deficits in inhibitory control and impair behavioral performance (Funahashi et

al., 1993; Johnston et al., 2013; Plakke et al., 2015). In an oculomotor delayed-response study, lesions in monkey prefrontal cortex caused impairment in behavioral performance especially when the delay period was longer (Funahashi et al., 1993). Inactivation of prefrontal cortex with cortical cooling impaired monkeys' performance in auditory or audiovisual task that requires memorizing faces and vocalization stimuli (Plakke et al., 2015). In general, these lesion studies indicated the functional role of prefrontal cortex in cognitive tasks. In human neuropsychological studies, patients with prefrontal damage commonly experience emotional and cognitive disorders (Fuster, 2015).

In addition to anatomical evidence and neuropsychological studies, electrophysiological studies in animals have provided insights into the properties of neuronal activity of the prefrontal cortex. One of the most remarkable findings is the single-cell response during delayed tasks, which indicated the role of prefrontal neurons in working memory. In delayed tasks, prefrontal neurons showed sustained elevated firing rate change during the delay period (Funahashi et al., 1989; Fuster & Alexander, 1971; Miller et al., 1996; Niki, 1974; Romo et al., 1999). In a variety of different studies, the involvement of PFC in cognitive control and executive functions indicates that PFC may have a comprehensive role in integrating and processing sensory inputs, controlling goal-directed behaviors, and completing complex behavioral tasks. PFC activity during complex tasks has been reported from many behavioral studies. PFC neurons can encode the task-relevant information to solve cognitive problems. In a series of visual categorization tasks, monkeys were trained

on a visual delayed-match-to category tasks that requires judging whether a test image match matched to the category of a previously presented sample image by holding or releasing a bar (Cromer, Roy, & Miller, 2010; Cromer, Roy, Buschman, & Miller, 2011; Freedman et al., 2001). The categorization task requires many fundamental cognitive processes, including discriminating and grouping sensory features, and generating responses to fulfill the task requirements. In addition, the delayed task paradigm requires holding information for a short period of time (i.e., working memory). Prefrontal neuron activity was correlated with the boundary of categorical discrimination, or the category membership of stimuli. These results support PFC neurons' ability to combine and integrate perceptual features of visual stimuli.

Other studies showed that PFC activity could reflect the actual choices in behavioral tasks. In an auditory same-different task, monkeys were required to make a leftward or rightward saccade to report if the reference and test stimuli were the same or different. Neural activity recorded from ventrolateral PFC was correlated with the monkeys' choices (Russ, Orr, & Cohen, 2008). Although it has been reported that premotor cortex (PMC), instead of prefrontal cortex, represents the decision variable (Cromer et al., 2011; Muhammad, Wallis, & Miller, 2006), the interaction and connectivity between these two areas indicate that they may be dynamically involved in processing sensory information and generating task-relevant behavior.

The processing of auditory information also involves several areas of the frontal cortex. In humans, the frontal cortex plays an important role in speech and language processing (Fuster, 2015). Traditionally, most neurophysiology studies of the frontal cortex were in the visual domain. Visual working memory paradigms were widely used to study the mechanisms of visual information processing. Therefore, much less is known about the frontal processing of auditory information. Recent studies in non-human primates have provided an understanding of the auditory cortical system as well as the neural mechanisms of auditory attention and auditory cognition.

Anatomical and lesion studies showed the existence of temporal prefrontal connectivity, which indicated that the auditory cortex sends projections to the prefrontal cortex (Barbas, 1992; Pandya & Kuypers, 1969; Petrides & Pandya, 1988). Reciprocal connections were found between the superior temporal gyrus (STG) and different areas of the frontal cortex. More recent studies characterized the organizations of the auditory cortex and the connectivity between auditory areas and the PFC (Gerbella et al., 2010; Rauschecker et al., 1995; Saleem et al., 2008). Those anatomical studies demonstrated the afferents from the auditory areas to the PFC, thus suggesting the role of the PFC in receiving auditory information. More direct evident was obtained from studies that combined anatomical and physiological approaches (Romanski et al., 1999; Romanski & Goldman-Rakic, 2002), indicating

that the projections are carrying auditory information and predicting an auditory-responsive region in the ventrolateral prefrontal cortex (vlPFC).

Early physiology studies reported neuronal responses to auditory stimuli in the frontal regions of monkeys (Ito, 1982; Newman & Lindsley, 1976; Vaadia et al., 1986; Watanabe, 1992). More recent physiological studies, based on the findings of temporal frontal connectivity, investigated the neuronal activity in the auditory responsive region in ventrolateral PFC. Romanski and Goldman-Rakic (2002) described an auditory responsive region in monkey prefrontal cortex. They recorded the neuronal activity from the ventrolateral PFC of awake monkeys in response to auditory cues, and found neurons in the ventrolateral PFC showed responses to complex auditory stimuli. In further studies, they showed that prefrontal neurons typically responded to stimuli that had similar acoustic features (Romanski et al., 2005).

Distinct pathways have been reported in the processing of "what" and "where" information respectively. In addition to the ventrolateral PFC which receives input from rostral auditory areas and responds to acoustic features, the dorsolateral PFC (dlPFC), on the other hand, has been shown to receive inputs from caudal auditory areas and process the location information (Rauschecker & Tian, 2000). Neurons in the dorsolateral PFC were spatially selective during spatial working memory tasks that required the processing of auditory and visual locations (Artchakov et al., 2007; Kikuchi-Yorioka & Sawaguchi, 2000). Other studies indicated that neurons in the

dorsolateral PFC also responded in non-spatial auditory tasks (Bodner et al., 1996; Watanabe, 1992). In an auditory delayed match-to-sample task, Plakke et al. (2013) demonstrated that neurons in both dorsal and ventral portion showed task-relevant activity, suggesting a role of the dorsolateral PFC in representing task rules and cognitive requirements.

The functional role in auditory attention and cognitive control has also been demonstrated in studies using animal models other than non-human primates. PFC neurons responded to the changing rules of behavioral tasks and encoded auditory signals that had changing behavioral meanings. Rodger and DeWeese (2014) trained rats on an auditory task with switching rules. In each behavioral session, rats were required to either pay attention to the location or the frequency of the auditory stimuli and make a corresponding selection. This task requires require selectively attending to different features of auditory stimuli and switching attention dynamically across behavioral sessions with changing task rules. The prestimulus activity in PFC was associated with the selection rule of which features to select. In addition, disruption of PFC through microstimulation would impair task performance. Francis et al. (2018) recorded in ferret dorsolateral frontal cortex during an auditory reversal task in which the behavioral meanings of stimuli change with task switching. Ferrets were trained to detect high or low frequency pure tones in a conditioned avoidance go/no-go paradigm. During the initial task, the low tones were assigned to be targets, whereas high tones became the target in a subsequent reverse task. Therefore, the behavioral meanings of high and low tones changed after task switching. Results indicate that

prefrontal activity was correlated with the behavioral meaning of auditory stimuli. Target responses were strongly enhanced, while non-target noises were strongly suppressed. However, the response to a previous target tone (the tone that was the target in a previous behavioral session) was weakly enhanced. Moreover, PFC activity was correlated with the interference observed in behavior: target responses decreased after reversal, most significantly during incorrect behavioral responses. These findings suggest that PFC activity could reflect the task rules and behavioral interference.

1.3 Top-down modulation of sensory processing

One important aspect of the PFC functions is the top-down modulation of sensory processing (Baluch & Itti, 2011; Squire et al., 2013). Previous studies have found that during sensory and perceptual behavioral tasks, prefrontal neurons selectively responded to behavior-relevant sensory information, providing top-down control signals by allocating the concentration of attention (Funahashi et al., 1993; Tomita et al.,1999; Zanto et al., 2011).

The top-down influence of sensory processing has been most intensively studied in the visual domain. The processing of sensory signals is subject to top-down influences, which involves the interaction of feedforward and feedback brain circuits (Baluch & Itti, 2011; Squire et al., 2013). The attentional effect on top-down modulation increases the firing rate of visual neurons that respond to the attended

stimulus at different stages of visual processing (for reviews, see Noudoost et al., 2010; Reynolds & Chelazzi, 2004). For example, to assess whether attentive selection for a visual feature would affect the visual processing in V4, monkeys were trained on a discrimination task to select a bar stimuli based on the color or luminance, then discriminate the angular tilt of the selected stimulus. Results showed that most of V4 neurons were selectively activated when the color or luminance feature was in the neuron's receptive field (Motter, 1994). In a visual searching task, simultaneous recordings in monkey frontal eye fields (FEF) and V4 found increased firing rate in both areas (Gregoriou et al., 2009). Increased spike rate by top-down attention has also been observed in different visual areas (V1, V2, V4), thalamus (lateral geniculate nucleus), midbrain (superior colliculus), lateral intraparietal (LIP) area and inferotemporal cortex (Noudoost et al., 2010).

Attention does not only increases the firing rate of neurons in the visual cortex, but also enhances signaling efficacy and increases the signal to noise ratio for the attended stimuli in various manners, thereby increasing the sensitivity and discriminability of the attended visual features or locations (for reviews, see Noudoost et al., 2010; Paneri & Gregoriou, 2017; Reynolds & Chelazzi, 2004; Sapountzis & Gregoriou, 2018). For example, attention can also change the size and position of visual receptive fields (RFs) and feature tuning of neurons (Clark et al., 2015). In a visual task, monkeys were required to discriminate a target stimulus while ignoring non-targets. The stimuli had different luminance contrasts. Recordings from V4 neurons showed increased firing rate and an increase in effective contrast of the

attended stimuli, especially when the luminance contrast was low. This result indicate that attention can cause an increase in V4 neuron's sensitivity for discriminating sensory stimuli (Reynolds et al., 2000).

In addition, attention also leads to changes in the activity of neuron populations and interaction between brain regions. Attention decreases the variability of responses across trials (Mitchell et al., 2007) and the correlated variability among neurons (Cohen & Maunsell, 2009). Attentional modulations in the synchrony of oscillatory activity have also been reported at multiple levels of visual processing (for a review, see Gregoriou et al., 2015; Noudoost et al., 2010). For example, simultaneous recordings in monkey FEF and V4 in a visual task found enhanced the coherence in gamma frequency oscillation between these two areas (Gregoriou et al., 2009). Similarly, gamma oscillatory coupling between prefrontal and visual areas has been observed in human MEG studies (Baldauf & Desimone, 2014).

The prefrontal cortex has long been considered as a source of the top-down modulation of attention on visual cortex (for reviews, see Baluch & Itti, 2011; Paneri & Gregoriou, 2017). PFC activity has been observed in a variety of behavioral tasks that require top-down attention. When monkeys were performing a visual detection task that requires attentively searching for a target stimulus, activity of prefrontal neurons reflected the target location during the top-down attention process (Buschman & Miller, 2007). Simultaneous recordings in monkey FEF and V4 found increased firing rate in both area and enhanced coherence in gamma frequency

oscillation between these two areas during a visual search task (Gregoriou, et al., 2009). These results indicated that prefrontal cortex may be a source of top-down signals.

Studies have been using lesion and stimulation approaches to investigate the causal role of PFC in the attentional modulation of visual processing (for reviews, see Baluch & Itti, 2011; Paneri & Gregoriou, 2017). Microstimulation of monkey frontal eye field has been shown to influence monkeys' behavioral performance and responses of visual neurons. Moore & Fallah (2001; 2004) examined whether manipulating neural activity of FEF could change the allocation of attention. They stimulated FEF sites while monkeys monitored a target stimulus among distractors for a small change in luminance. Monkeys were able to detect smaller luminance changes on trials with microstimulation than on control trials. FEF microstimulation can also alter the responses of neurons in the posterior visual cortex, specifically area V4. Moore & Armstrong (2003) found that subthreshold microstimulation of the FEF enhanced the visual responses in V4 neurons at retinotopically corresponding locations, whereas responses at other locations were suppressed. In addition, this enhancement was larger for V4 neuron's preferred stimulus than for a non-preferred stimulus, resulting in an increase in the V4 neurons discriminability between preferred and non-preferred stimuli (Armstrong & Moore, 2007).

Furthermore, studies in cellular mechanisms found corresponding evidence for this attentional effect. Noudoost and Moore (2011) reported that changes in dopaminergic

activity in the FEF can modulate V4 activity. They injected an antagonist of the dopaminergic D1 receptor in FEF while recording V4 activity. They found that this manipulation increased neuronal activity and orientation selectivity in V4, which were comparable to the effects of top-down attention. This result provided additional insights into the cellular mechanisms of top-down attentional effect.

Similar attentional effect has been observed in the auditory system, although relatively fewer studies have focused on the top-down modulation of auditory attention. Auditory attention may selectively modulate the neural activity in primary auditory cortex (A1) during behavioral tasks (Fritz et al., 2007). In auditory tasks, the receptive field and selectivity of A1 neurons were modulated by the engagement of behavioral tasks, increasing the discriminability of task-relevant auditory features. Long-term effects have also been reported in studies with perceptual training and learning. Perceptual training could change the topographic map of rat primary auditory cortex. In a perceptual learning study (Polley et al., 2006), different groups of rats were trained to attend to independent features of the same set of auditory stimuli, either frequency or intensity. Rats trained to attend to frequency exhibited an expanded area to represent target frequency in their tonotopic map, whereas rats trained to attend to intensity cue exhibited an increased proportion of neurons tuned to the target intensity range but no change in tonotopic map organization. In another study, rats were trained in a series of operant conditioning tasks (Rutkowski & Weinberger, 2005). Their motivation to do the task was manipulated by different levels of water deprivation. Tonotopic map of A1 showed expanded relative

representation of the conditioned stimulus. The magnitude of this expansion was correlated with behavioral performance. These results provided support for the attentional modulation of behavior-related stimuli on auditory cortex.

The top-down effect varies across different behavioral paradigms and contexts. Neurons in the primary auditory cortex respond differently to the same auditory stimuli when they are associated with different behavioral contexts or task reward structures (Fritz et al., 2005). Task reward structures would also change the top-down modulation of receptive field properties of A1 neurons (David et al., 2012; Fritz et al., 2003). These findings suggest that the top-down influences on sensory processing may be modulated different task strategies and behavioral demands. In addition, similar task-related plasticity has been observed in the auditory midbrain, higher-order auditory areas, and prefrontal cortex (Atiani et al., 2014; Fritz et al., 2010; Slee & David, 2015). These findings suggest a hierarchical brain network in which the processing of auditory information in auditory cortex and the top-down control in prefrontal cortex would interact dynamically.

1.4 Task reward structure and its influence on cognitive control

One major concern when designing a behavioral experiment for animals is the task reward structure. In general, animals are trained in certain ways to respond to task-relevant stimuli according to the task demands. The demand of the task and the way to respond would affect the goal-directed behavior.

A classic behavioral paradigm to study perceptual decision making is the go/no-go paradigm. In a typical go/no-go task, one stimulus requires responding with an action (go response), and the other stimulus requires withholding an action (no-go response). Another experiment design, typically called "forced choice" or "two-alternative forced choice (2AFC)", involves a forced choice between two responses based on the presentation of a stimulus. Although the two paradigms both measure decision-making processes, their different requirements in behavioral responses lead to the critical differences in cognitive demands and decision processes. The key requirement in go/no-go tasks is the inhibition of a single response or withholding an action to the no-no stimuli (Braver et al., 2001). Therefore, an issue with go/no-go tasks is that they are vulnerable to the response tendency and criterion. Many studies have reported a consistent tendency for subjects to make more go responses. In animal behavioral studies, the animal's motivation may affect its response criterion and overall task performance (Carandini & Churchland, 2013). For instance, in a single behavioral session, an animal may respond less frequently because of decreased motivation for rewards. This could lead to the false conclusion that the ability to detect the stimulus has decreased. One advantage of the 2AFC tasks is that it is immune to the changing of decision criterion when comparing to the go/no-go tasks. In 2AFC tasks, the critical requirement is the selection process between two responses. This design eliminates changes in the motivation to perform the task and the tendency to respond (Carandini & Churchland, 2013). Therefore, although both paradigms require the selection and inhibitory control functions of the frontal cortex,

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they highlighted different features: the 2AFC task emphasizes the selection and decision-making processes, whereas the go/no-go task especially requires inhibitory control. Thus, the neural correlates of these two processes may be different in the frontal cortex.

Therefore, it is important to evaluate the influence of task structure on behavioral response and the underlying neural mechanisms. Different perspectives have been proposed on how task structure would influence the perceptual decision-making processes (Gomez et al., 2007). First, different procedures might lead to different strategies during the decision process, while the sensory processing components are not affected. The other explanation proposes that different task procedures would influence the sensory processing as well as the decision process. An approach to understand the processing across task paradigms is to investigate the interaction between the frontal and sensory areas during different tasks. If the influence of top-down modulation on sensory processing differs across tasks, then it supports the perspective that task procedures not only affect the decision process, but also modulates the sensory discrimination process.

1.5 The localization and function of ferret frontal cortex

Ferrets (*Mustela putoris furo*) have become an important animal model for studies in neuroscience. Despite the numerous studies in ferret visual cortex (Chapman, & Stryker, 1993; White, Coppola, & Fitzpatrick, 2001) and auditory cortex (Bizley et

al., 2005; Depireux et al., 2001), there are relatively few studies focusing on the frontal cortex of ferrets (Francis et al., 2018; Fritz et al., 2010; Seller et al., 2016; Zhou et al., 2016).

Traditionally, the dorsolateral frontal cortex has been defined as the part of the cerebral cortex that has dopaminergic projections and reciprocal connectivity with the mediodorsal nucleus of the thalamus (MD). This definition can be traced back to Rose and Woolsey (1948). They proposed the use of projection field of the MD to define the frontal cortex in primates and other mammals. The granulation of layer IV in the frontal cortex was only found in primates. This definition has been applied to other species and in other studies (Divac et al., 1978; Krettek & Price, 1977; Markowitsch et al., 1978; Tobias, 1975).

The anatomical localization of ferret frontal cortex still remains debatable. In an anatomical study, Duque and McCormick (2010) examined the extent of the ferret prefrontal cortex and its reciprocal connections with the MD nucleus of the thalamus by anterograde and retrograde labeling in ferrets. They located the ferret prefrontal cortex at the rostrodorsal anterior sigmoid gyrus (ASG) and the orbital gyrus (OBG) based on the heavy reciprocal connections with the MD nucleus of the thalamus. This definition has been used in a few in vivo studies of ferrets.

In vivo electrophysiological studies primarily localized the ferret prefrontal cortex on the ASG and OBG (Francis et al., 2018; Fritz et al., 2010; Zhou et al., 2016). Using a

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conditioned avoidance go/no-go task, Fritz et al. (2010) found that neurons in the

dorsolateral frontal cortex (dlFC) of ferrets responded selectively to behavior-relevant

auditory and visual signals. Moreover, simultaneous recordings in the frontal cortex

and primary auditory cortex indicated the frontal cortex could contribute to the top-

down modulation of sensory areas. Zhou et al. (2016) examined the role of

dorsolateral frontal cortex of freely moving ferrets with a two-alternative forced

choice visual discrimination task. They found that the neurons in the dlFC could

dynamically encode task variables, including task difficulty and target location. In

addition, they used optogenetic stimulation to demonstrate the causal role of dlFC in

behavioral tasks. In the study of Francis et al. (2018), they found that neurons in ferret

dorsolateral frontal cortex could dynamically encode the behavioral meaning of

sounds and reflect the changing task rules in an auditory reversal task. These studies

provided an insight into the functional role of ferret frontal cortex. However,

comparing to the studies using monkeys or rodents, the behavioral tasks that were

used to study ferret were simple and the understanding of the ferret frontal function is

still primitive. More complex tasks, large scale recording techniques, and

simultaneous recording from different brain regions could provide a more intensive

understanding of ferret frontal cortex.

1.6 Rational for the current study

The attentional effect on sensory processing and the role of frontal cortex in the top-

down modulation are important topics in the study of sensory and cognitive

processes. Although this top-down influence has been studied in the visual domain (for reviews, see Noudoost et al., 2010; Paneri & Gregoriou, 2017; Sapountzis & Gregoriou, 2018), the underlying neural mechanisms still remain debatable. Compared to the numerous studies in vision, relatively fewer studies have focused on the neural mechanisms of auditory attention and the top-down influence on auditory areas. Although auditory processing shares many common characteristics with visual processing, the top-down influence may be different for auditory and visual systems. The auditory connectivity and function of frontal cortex was different from those in the visual domain (for a review, see Plakke & Romanski, 2014). The role of frontal cortex in auditory discrimination tasks, especially tasks with different behavioral paradigms, has never been extensively studied. Measuring the neural correlates of auditory signals in behavioral tasks would help understand the mechanisms for auditory attention.

The task structure and behavioral demands would influence the top-down modulation of sensory processing. Different task paradigms may be associated with different core functions of PFC. Therefore, it is important to evaluate the influence of task paradigms when measuring the top-down influence on sensory processing. Previous studies have found that task structures would change behavioral strategies and therefore different modulate the auditory processing in primary auditory cortex. Although distinctive patterns of receptive field changes have been reported in A1 neurons, these studies did not directly measure the neural correlates of task paradigms directly. Previous studies also did not directly compare the two different task

paradigms: the go/no-go paradigm and 2AFC paradigm. The two paradigms would feature different aspects of frontal functions and therefore posting different demands on cognitive control. Measuring the neural responses in the frontal cortex could provide an understanding of the encoding of task rules and behavioral meanings of auditory information as well as the neural correlates of task-relevant variables.

Ferrets have become an increasingly used model for behavioral studies in neuroscience. However, compared to non-human primates and rodents, the anatomy and functions of ferret prefrontal cortex has not been well studied (Fritz et al., 2010; Zhou et al., 2016). Understanding the structure and function of ferret frontal cortex would be important for further developing the ferret modal for behavioral neuroscience studies. Previous studies have not trained head-fixed ferrets on a 2AFC task that requires to make decisions with different licking patterns. Compared to freely moving animals, recordings from head-fixed ferrets would provide more stability and reduce the influence of spatial information and motor action during task performance.

This study aims to investigate how the neural representation of sensory stimuli in dorsolateral frontal of the ferret is shaped by task and reward structure during different behavioral tasks. In this study, ferrets were trained on a simple category discrimination task in two different behavior paradigms: the 2AFC paradigm and the go/no-go paradigm. Both task positive used positive reinforcement: a liquid reward was given after the ferret gave a correct behavioral response. Both tasks required

discriminating between two types of auditory stimuli: pure tones and temporally orthogonal ripple combination (TORC) stimuli. The tasks require the same sensory discrimination as in the previous conditioned avoidance study (Fritz et al.,2010) but required different motor responses and had different reward structures. Single unit activity in the frontal cortex was measured when ferrets were performing behavioral tasks with different paradigms. The neuronal activity was compared between the two task paradigms to investigate how different task reward structure would influence the neural correlates of task-relevant auditory signals and other task variables.

Chapter 2: Methods

All experimental procedures were approved by the Institutional Animal Care and Use Committee of the University of Maryland and were performed in compliance with the National Institute of Health guide for the care and use of laboratory animals.

2.1 Behavioral tasks

Spayed adult female ferrets (*Mustela putoris furo*) were trained to perform a simple auditory discrimination tasks with different behavior paradigms. Ferrets were trained on either a two alternative forced choice (2AFC) task or a go/no-go task paradigm. Both tasks required discriminating between two types of auditory stimuli: (1) pure tones and (2) a series of temporally orthogonal ripple combination (TORC) stimuli. Ferrets were primarily trained on a head-restrained setting.

In the positive reinforcement go/no-go task, the pure tone was used as the target stimulus and the TORCs were used as the non-target stimulus. In each trial, a random number of TORC stimuli were presented before the pure tone stimuli. The number of TORCs varied randomly from 1 to 4. Both TORC and tone stimuli had the same duration and separation (1 s duration, 0.5 s ISI). Ferret learned to lick a water spout placed in front of their nose when they heard the pure tone stimuli, and restrain licking when they hear the TORC stimuli. Correct responses were rewarded with

water, while incorrect responses (either licking before the target or no licking response) were punished with a timeout.

In the 2AFC task, the same stimuli were used as in the go/no-go task. Two separate water spouts were placed in front of the ferrets. In each trial, either a pure tone or a TORC stimulus was presented. The duration of stimuli was the same as in the go/no-go task. The total numbers of TORC and tone stimuli were the same in each behavioral session. TORC and tone trials were randomly intermixed. Ferrets were trained to lick up to one water spout when they heard the pure tone stimulus and lick down to another water spout when they heard the TORC stimulus, or vice versa. The pairing of stimuli and water spouts was counterbalanced among ferrets. Correct responses were rewarded with water, while incorrect responses (licking to a non-target water spout, or licking before the target stimulus, or no licking response) were punished with a timeout.
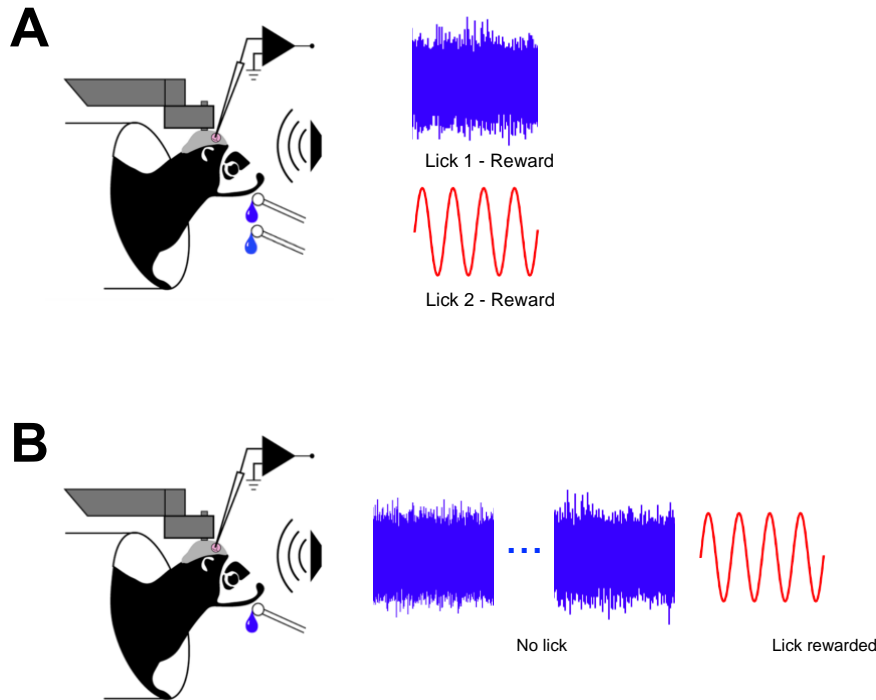
Figure 1. Behavioral tasks for the ferrets. Ferrets were trained and recorded in a head-restrained setting. A: in the 2AFC task, two water spouts were placed in front of the ferret. Each trial included either a pure tone stimulus or a TORC stimulus. Ferrets should lick to one water spout when they heard the pure tone, and lick to the other water spout when they heard the TORC. B: in the go/no-go task, only one water spout was placed in front of the ferret. Each trial included 1-4 TORCs and one pure tone stimulus. Ferrets should lick when they heard the pure tone (the target stimulus) while restraining licking when they heard the TORCs (the non-target stimulus).

2.2 Training procedures

For the go/no-go task, training started with pairing water reward with a pure tone. After that, the ferrets learned to lick to a water spout after they heard the pure tone to obtain water. The response window was around 0.1-2 s from the tone onset. In the next stage, non-target stimuli (TORCs) were gradually added before the target tone. At the beginning, the non-target stimuli were presented at a low intensity level (50 dB

relative attenuation), and then the level gradually increased to match that of the target

stimuli (65dB). The number of TORC stimuli in each trial was 1-2 at first, and

gradually increased to 1-4 when ferrets could better withhold licking during the

TORC stimuli.

For the 2AFC task, training started with pairing water with one of the stimuli (for

example, the pure tone). Then ferrets learned to lick to one of the two water spouts

when they heard the pure tone. In separate training sessions, ferrets were trained to

lick to the other water spout when they heard the TORC stimuli. The response

window for both conditions was 0.1-2 s from sound onset. At the beginning, each

training block contained only one type of stimuli (either TORCs or tones), and ferrets

only need to lick to one water spout during that block. When the ferrets learned two

ways of licking to the corresponding stimuli in separate blocks, the number of trials

per block was gradually reduced. Ferrets learned to switch licking in different blocks,

and then eventually they could perform the 2AFC task on a trial-by-trial basis.

2.3 Surgeries

For the go/no-go task, the training started in a freely moving setting. Once they

reached a consistent and acceptable performance, ferrets were then implanted with a

stainless steel headpost in sterile surgeries. The headpost was attached to the sagittal

interparietal suture of the skull. For the 2AFC task, ferrets were implanted first and

then started to be trained in a head-restrained setting. During the surgery, ferrets were

anesthetized with a combination of ketamine (35 mg/kg intramuscularly) and

dexmedetomidine (0.03 mg/kg subcutaneously) for induction. During the surgery, the

deep level of anesthesia was maintained with 1-2% isoflurane throughout the surgery.

Ferrets were also medicated with atropine sulfate (0.05 mg/kg subcutaneously) to

control salivation and to increase the heart rate and respiratory rate.

Electrocardiogram (ECG), pulsation, and blood oxygenation level were monitored

during the surgery, and the rectal temperature was maintained at ~38°C. In the sterile

surgery, the skull was exposed by making a midline incision in the scalp and

dissecting both temporal muscles from the insertion in the sagittal interparietal crest

down to the level of the zygomatic arch. The headpost was secured in the skull with

titanium screws and a light curing microglass composite material (Charisma), leaving

small (2-3 mm2) cavities for easy access to the auditory and frontal cortices in both

hemispheres. After the surgery, antibiotics (cefazolin, 25 mg/kg subcutaneously) and

analgesics (dexamethasone 2 mg/kg subcutaneously and flunixin meglumine 0.3

mg/kg subcutaneously) were administered to the ferret.

Ferrets were allowed to recover for ~2 weeks and then were habituated in a head-

restrained setting. They were placed in a customized Lucite horizontal cylindrical

holder for approximately 1-2 weeks. Then they either were re-trained on go/no-go

task paradigm or started to be trained on the 2AFC task paradigm for the auditory

discrimination task while restrained in the holder until they reach satisfactory

behavioral performance. Before the recording sessions, small craniotomies were

made over the frontal cortex. The compose material of the head cap allowed the

craniotomies to remain well protected from the environment. Once the craniotomies

were open, the wells in the head cap implant were sealed between experiments with vinyl polysiloxane impression material (EXAMIX NDS; GC America, Inc.). The wells and craniotomies were cleaned and treated with topical antiseptic drugs (povidone-iodine) and antibiotics (cefazolin or enrofloxacin, 0.2 ml) at least once per week. The skin surrounding the head cap implant was cleaned three times per week with saline and treated with povidone-iodine and silver sulfadiazine cream ointment.

2.4 Electrophysiological recordings

Electrophysiological experiments with behavior tasks were conducted in a double-walled sound-attenuating chamber. In the electrophysiological recordings, tungsten microelectrodes (FHC) with high impedance (2-6 MΩ at 1kHz) were used to measure the extracellular activity. In each recording session, four electrodes were arranged in a square with 0.5 mm distance from their nearest neighbor. The four electrodes were independently advanced using an EPS drive system (Alpha Omega) to penetrate through the dura into the cerebral cortex. Electrodes were slowly and independently advanced until good spike isolation was found in most electrodes. The neuronal data were recorded with an AlphaLab SnR data acquisition system (Alpha Omega). Continuous signals were recorded at a sampling rate of 22,000 Hz and then amplified. Additionally, in 8 recording sessions, the data acquisition was performed using a 24-electrode linear array (Plexon U-probe) with 75 μm between electrodes. Plexon and Triangle BioSystems International 1× headstages was used. The signals were amplified with Plexon preamplifiers and recorded using MANTA v.1.0 (Englitz et al.,

2013), an open-source data acquisition suite written for MATLAB (MathWorks, Natick, MA). Single units were sorted with a custom software written in MATLAB. Single units were isolated by *k*-means clustering. Usually one or two single units could be isolated per recording electrode. The presentation of auditory stimuli, the acquisition of animal behavior, and the delivery of liquid reward were controlled by a customized MATLAB software (Behavioral Auditory PHYsiology (BAPHY)).

As discussed above, the anatomical localization of ferret frontal cortex remains debatable. Previously, anatomical and behavioral studies of ferrets have suggested that the dorsolateral frontal cortex of ferrets located on the rostral anterior sigmoid (ASG) and orbital gyrus (OBG), which have reciprocal connection with the mediodorsal nucleus of the thalamus (Duque & McCormick, 2009; Francis et al., 2018; Fritz et al., 2010; Zhou et al., 2016). According to the ferret brain atlas (Radtke-Schuller, 2018), these regions locate at approximately 25-30 mm relative to caudal crest, 1-3 mm from the midline. In the electrophysiological recordings, electrodes were targeted at these locations.

2.5 Stimuli

All acoustical stimuli were presented at 65 dB sound pressure level (SPL). Sounds were digitally generated at 40 kHz with custom-made MATLAB functions and A/D hardware (PCI-6052E; National Instruments) and presented with a free-field speaker positioned in front of the ferret. Pure tones (5 ms onset and offset ramps) were used

as the only target stimuli in the positive reinforcement go/no-go task, and used as one

of the target stimuli in the 2AFC task. The frequency of the tone was randomly

chosen in each recording session. Thirty distinct TORCs were used as non-target

stimuli in the go/no-go task, and used as one of the target stimuli in the 2AFC task.

Each TORC was composed of a broadband noise with 5-octave width and dynamic

spectrotemporal profile. The superposition of the envelopes of the six temporally

orthogonal ripples (for 4-24 Hz TORCs) or 12 temporally orthogonal ripples (4-48 Hz

TORCs). Ripples composing the TORCs had linear sinusoidal spectral profiles, with

peaks equally spaced at 0-1.2 cycles per octave. The envelope drifted temporally up

or down the logarithmic frequency axis at a constant velocity (Depireux et al., 2001).

The envelope of these ripples drifted temporally up or down the logarithmic

frequency axis at a constant velocity (4-48 Hz or 4-24 Hz). The 5-octave spectrum of

TORCs could be varied in several ranges and was randomly chosen in each recording

session.

2.6 Data analysis

Offline data analyses were performed with custom-made MATLAB and R scripts.

Figures were created using MATLAB (R2018a) functions and Microsoft Excel.

Single-unit neural responses to task stimuli were measured by the computing the

peristimulus time histogram (PSTH) responses to the auditory stimuli. Spikes were

grouped into 100-ms bins to calculate the mean firing rate for each condition. Units

were considered showing behavior-related response when there were at least two consecutive 100-ms bins showing significant difference in firing rate from baseline in the PSTH in response to either sound ($p < .05$, independent sample t-test with Bonferroni corrected p value). For each unit, averaged firing rates were normalized by subtracting the baseline firing rate (the average firing rate during the 300-ms period preceding stimulus onset) and then dividing by the baseline firing rate of the unit.

Chapter 3: Results

3.1 Behavioral performance

One of the ferrets was trained in a freely moving setup before the implant surgery.

After reaching an acceptable behavioral performance for consecutive training

sessions, the ferret received a surgery to implant a headpost on the skull. After the

surgery, the ferret was habituated and re-trained on the task in a head-fixed holder.

The other ferrets were implanted first, and then habituated and trained on behavioral

tasks.

Behavioral performance was evaluated using the percentage of correct response,

which was calculated as the percentage of trials with correct response versus trials

with either correct or incorrect response. When no response was given in a particular

trial, it did not count towards the total accuracy rate. Because the performance was

gradually increasing and sometimes not very stable during training only sessions,

only behavioral sessions with electrophysiological recordings were included. In

general, the behavioral performance of the ferrets became stable before the

electrophysiological recording stated. The behavioral performance for each individual

ferret was shown below in Table 1 (the 2AFC task) and Table 2 (the go/no-go task)

and Figure 2.

An independent sample t-test was conducted to examine the difference in the

percentage of correct response between the two tasks. The accuracy rate did not show

significant difference between the 2AFC task ($M = 79.5\%$, $SD = 7.0\%$) and the go/no-go task ($M = 82.5\%$, $SD = 9.8$), $t_{111} = 1.90$, $p = .06$. The accuracy rate was also compared between individual ferrets for each task. In the go/no-go task, the behavioral response differed significantly between the two ferrets, $t_{70} = 2.21$, $p < .05$. In the go/no-go task, the behavioral response did not significantly differ between the two ferrets, $t_{39} = 1.90$, $p = .07$.

Table 1

Percentage of correct responses in the 2AFC task (mean ± SD)

	Accuracy (%)
Ferret C	81.0 ± 6.4
Ferret S	77.4 ± 7.4
Average	79.5 ± 7.0

Table 2

Percentage of correct responses in the go/no-go task (%, mean ± SD)

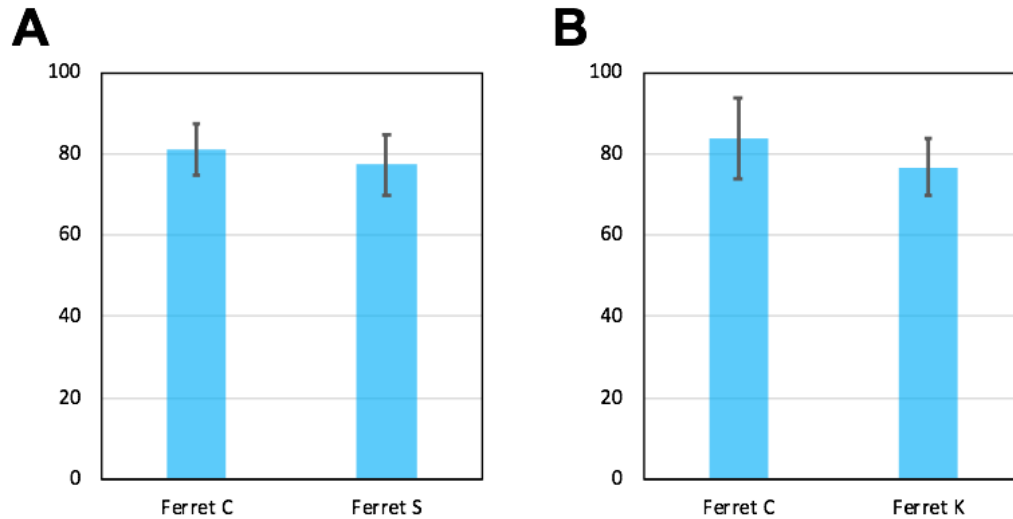|	Accuracy (%)
Ferret C	83.9 ± 9.9
Ferret K	76.8 ± 7.2
Average	82.5 ± 9.8

Figure 2. Behavioral performance (percentage of correct responses) in the 2AFC task (A) and the go/no-go task (B).

3.2 Single unit activity

Single unit activity was recorded from ferret frontal cortex when they were performing the behavioral task or passively listening to the auditory stimuli before and after the behavior session. Examples of single unit activity in the 2AFC task and the go/no-go task were shown in Figure 3 and Figure 4 respectively.

Single units in the frontal cortex displayed various spiking pattern and temporal dynamics in response to auditory stimuli in the two behavioral paradigms. The figures below showed the raster plots and PSTHs of frontal neurons during either the go/no-go task or the 2AFC task. Each row shows the raster and PSTH for a single unit across three sessions (the passive session before the behavior session, the behavior session, and the passive session after the behavior session). In each panel, a raster plot

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at the top shows the spike events for each category of stimuli for all trials, and the PSTH at the bottom shows mean firing rate for each category.

As in the single unit examples, most of the single units showed little or no response changes to auditory stimuli during the passive sessions. In both tasks, neurons showed more response during behavior. In the examples, neurons have different response latency and duration. The latency may vary from immediately after stimulus onset, to during or after the licking responses. They may have similar response strength and latency to both auditory stimuli, or have biased response towards one of the stimuli, or only respond to one stimulus category.

In the 2AFC task, many units responded to both categories of auditory stimuli when the ferret was performing the behavioral task, as the two examples show below in Figure 3. However, the average firing rate, latency, and duration of response may vary among individual units. As the first example shows, the response may be equivalent to both stimulus categories. The peak of response was relatively late (about 0.7s after stimuli onset) and also showed not difference between the two stimulus categories. The second single unit example represents another case in which the firing rate was higher to one stimulus category. In this example, the firing rate was higher in response to the pure tone stimuli than that to the TORC stimuli. The duration of response was also different between the two stimulus categories. The firing rate in response to the TORC reached a peak at about 0.2 s after stimulus onset,

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and then quickly decreased (< 0.5 s), whereas the response in response to the pure

tone reached a peak at the similar time, but lasted longer (until around 0.7 s).

In the go/no-go task, many units also responded to both stimulus categories (Figure

4). As the first example shows, the neuron had similar firing rate and latency in

response to the TORC and pure tone stimuli. In addition, more units showed biased

response towards one of the stimulus categories. Most of those units showed higher

firing rate in response to the target stimulus than to the non-target stimulus. The

second single unit example represents the neurons that showed significant response in

response to the pure tone stimuli but had little or no response to the TORC stimuli.

In both tasks, there were few neurons that showed response during the sessions when

the auditory stimuli were passively presented to the ferret (passive sessions before

and after the behavior session). The two figures showed two examples of such

neurons that respond to passively presented auditory stimuli.

Figure 3. Single unit examples of frontal neurons in the 2AFC task. In each panel, a raster plot at the top shows the spiking activity for all trials, and the PSTH at the bottom shows mean firing rate for each category. Different colors represent different stimulus categories. Each row shows the raster and PSTH for a single unit across three sessions (the passive session, the behavior session, and the second passive session).
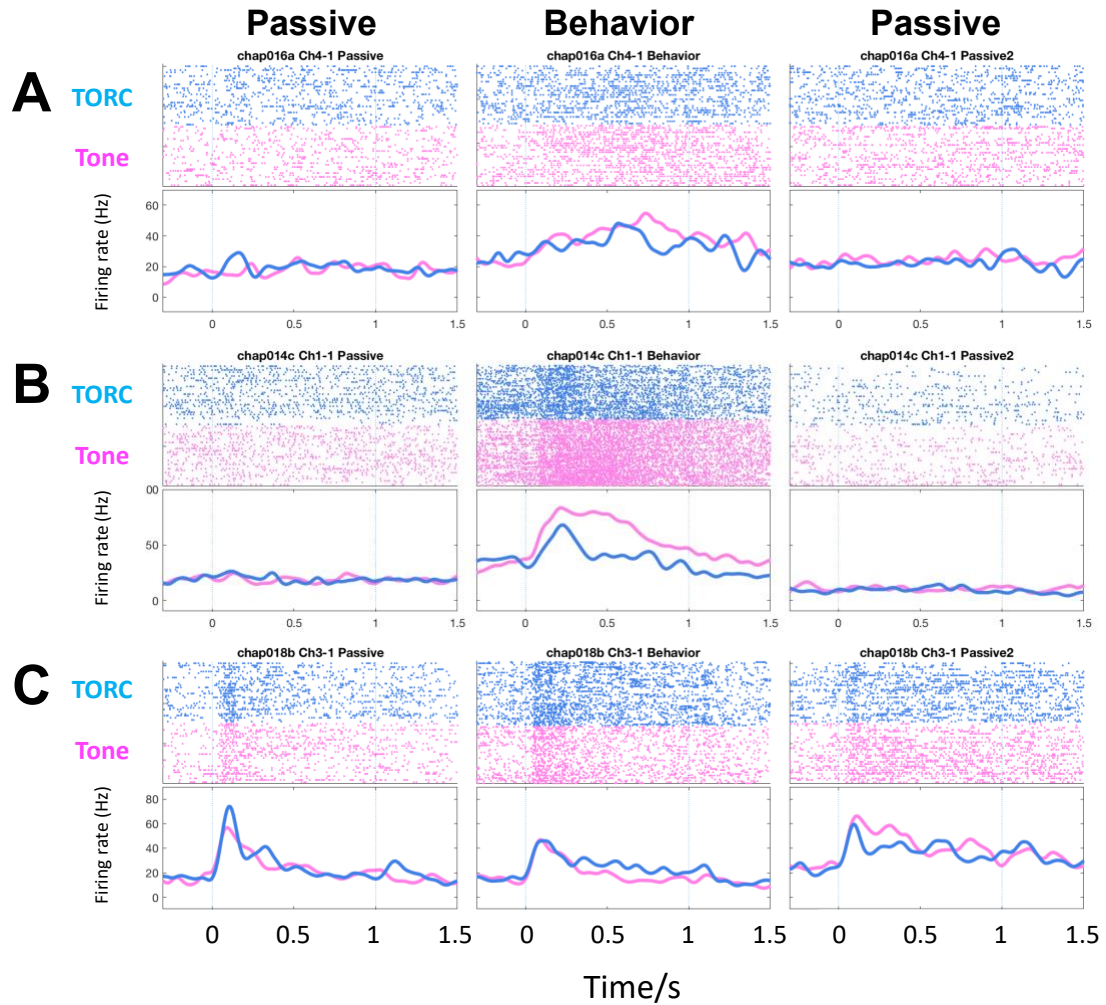
Figure 4. Single unit examples of frontal neurons in the go/no-go task. In each panel, a raster plot at the top shows the spiking activity for all trials, and the PSTH at the bottom shows mean firing rate for each category. Different colors represent different stimulus categories. Each row shows the raster and PSTH for a single unit across three sessions (the passive session, the behavior session, and the second passive session).
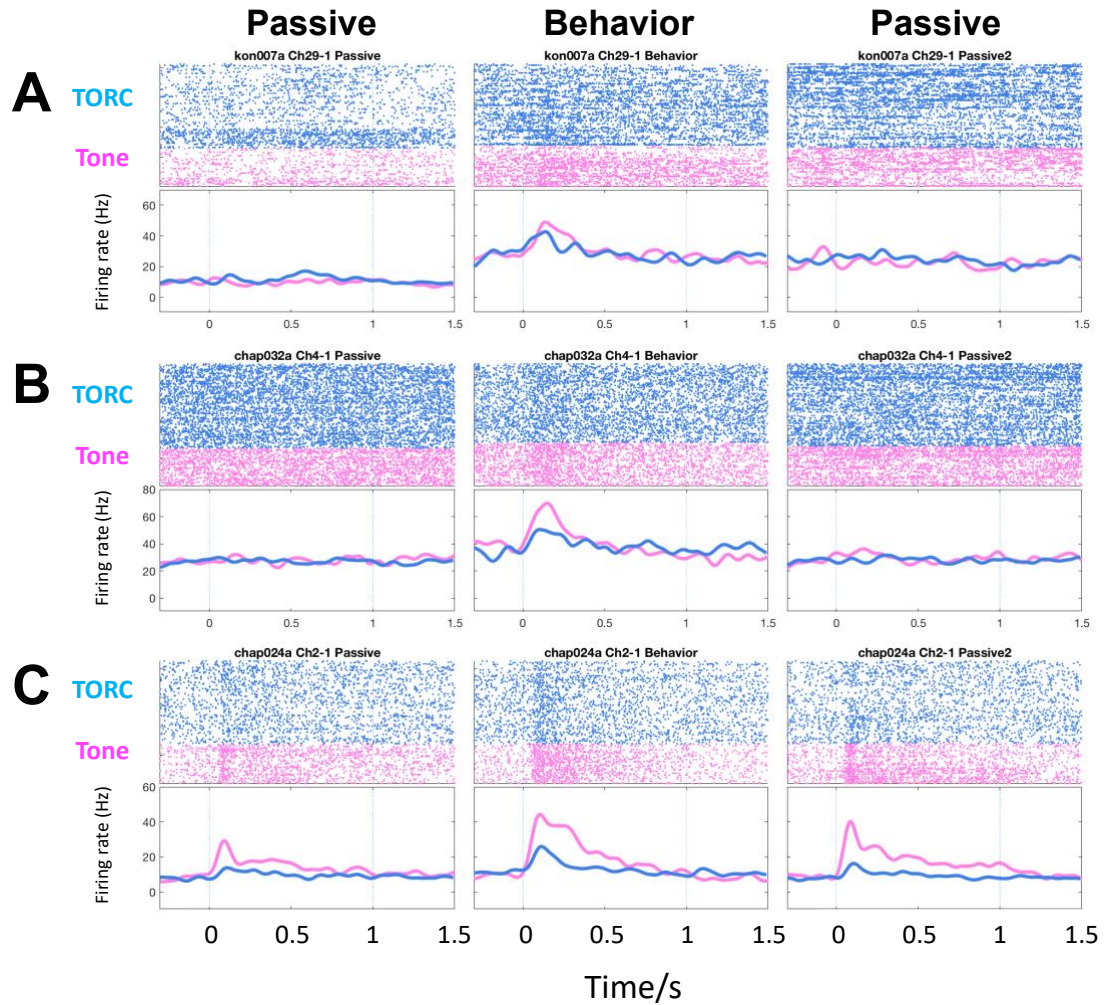
Because most of the neurons only showed significant response change during behavioral task performance, subsequent analyses and comparisons focused on the neural response to auditory stimuli during the behavioral sessions for both tasks.

Figure 5 showed the number of single units that had significant firing rate change in response to the either one or both categories of stimuli, or no significant firing rate change to either stimulus category. The significance of response was calculated by binning the firing rate during the time from stimulus onset to stimulus offset (1 s in total) in 100 ms time windows. For each category of stimuli, the firing rate was compared to the baseline firing rate (0.3 s before each trial) with independent sample *t*-test. If two consecutive windows showed significant difference compared to the baseline firing rate, then the neuron was considered as showing significant response change to that stimulus category.

In the 2AFC task, 127 of 335 units showed significant response to both TORC and pure tone stimuli. 136 units had significant response only to one of the stimulus categories, among which 69 units had significant response to the pure tone and 67 to the TORC stimuli. 72 units showed no significance to either stimulus category.

In the go/no-go task, 70 of the 301 units showed significant response to both TORC and pure tone stimuli. 125 units showed significant response to the target stimuli (the

pure tones) and 28 units showed significant response to the non-target stimuli (the TORC stimuli). 78 units showed no significance to either stimulus category.

A chi-square test of independence was performed to examine the difference in the numbers of units showing significance to each stimulus category between the two tasks. The relation between task paradigms and response to different stimuli was significant, $\chi_2 = 47.23$, $p < .001$. In general, in the 2AFC task, more units showed significant response to both stimulus categories, whereas in the go/no-go task, more units showed significant response only to the target stimuli.

Figure 6 and Figure 7 below showed the averaged normalized PSTHs for single units with significant modulation during behavioral sessions. The firing rate for each individual unit was normalized by subtracting the baseline firing rate (300 ms before each trial to the start of the trial) and then dividing by the baseline firing rate of the unit. Only single units with significant increased or decreased response to at least one of the stimulus categories were included. Figure 6 included the units with significant increased response, whereas Figure 7 included units with significant decreased response. For neurons with increased response, in the 2AFC task, the patterns for the firing rate were generally similar for the two stimulus categories in terms of the amplitude of modulation, response latency and duration. In the go/no-go task, the firing rate in response to the target stimuli (pure tones) was higher than that to the non-target stimuli (TORCs). And the response also sustained for longer before returning to the baseline level. The PSTHs of neurons with decreased response

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showed comparable patterns. In the 2AFC task, the averaged PSTHs showed similar amplitude of behavioral modulation and response latency to the two categories of stimuli. In the go/no-go task, the neurons also showed similar firing rate change in response to the target stimuli as that in the 2AFC task, but almost no change in response to the non-target stimuli were shown in the averaged PSTH.

A

B

72   127   67   69

both   tone   torc   none

78   70   28   125

both   tone   torc   none

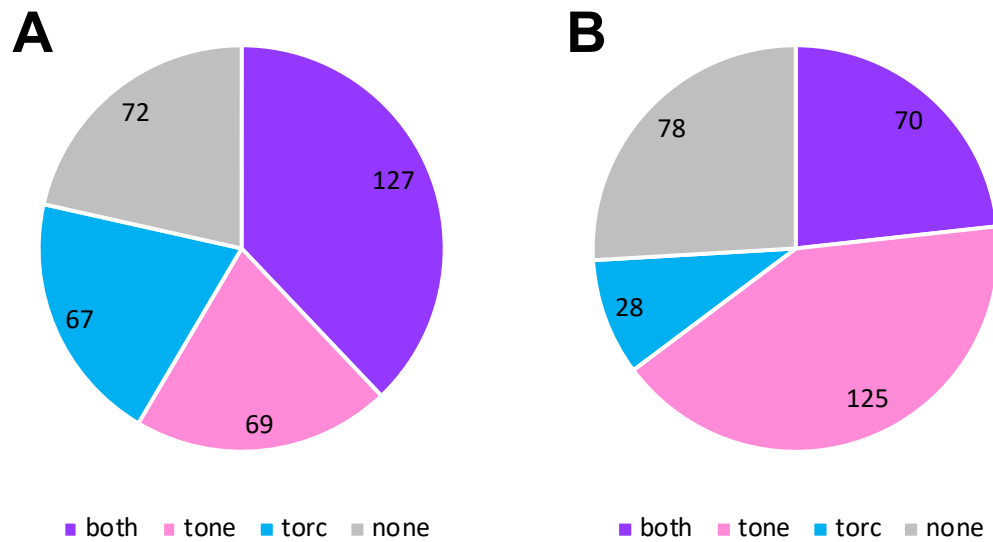*Figure 5.* Number of single units showing significant response during behavioral tasks. A: the 2AFC task. B: the go/no-go task.

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Figure 6. Population averaged PSTHs for neurons with increased response after stimulus onset in the 2AFC task and the go/no-go task. A: the 2AFC task. B: the go/no-go task. Different colors represent the averaged normalized firing rate to different stimulus categories.
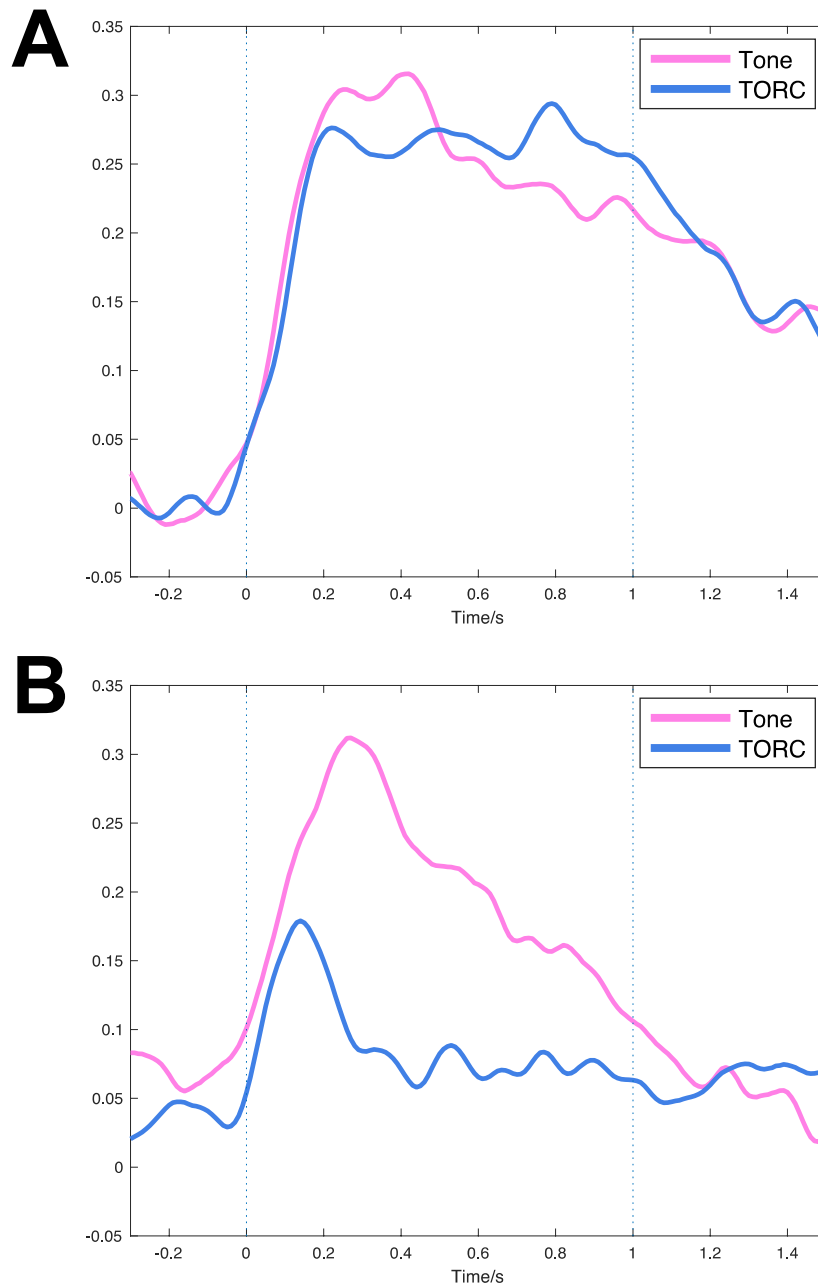
Figure 7. Population averaged PSTHs for neurons decreased response after stimulus onset in the 2AFC task and the go/no-go task. A: the 2AFC task. B: the go/no-go task. Different colors represent the averaged normalized firing rate to different stimulus categories.
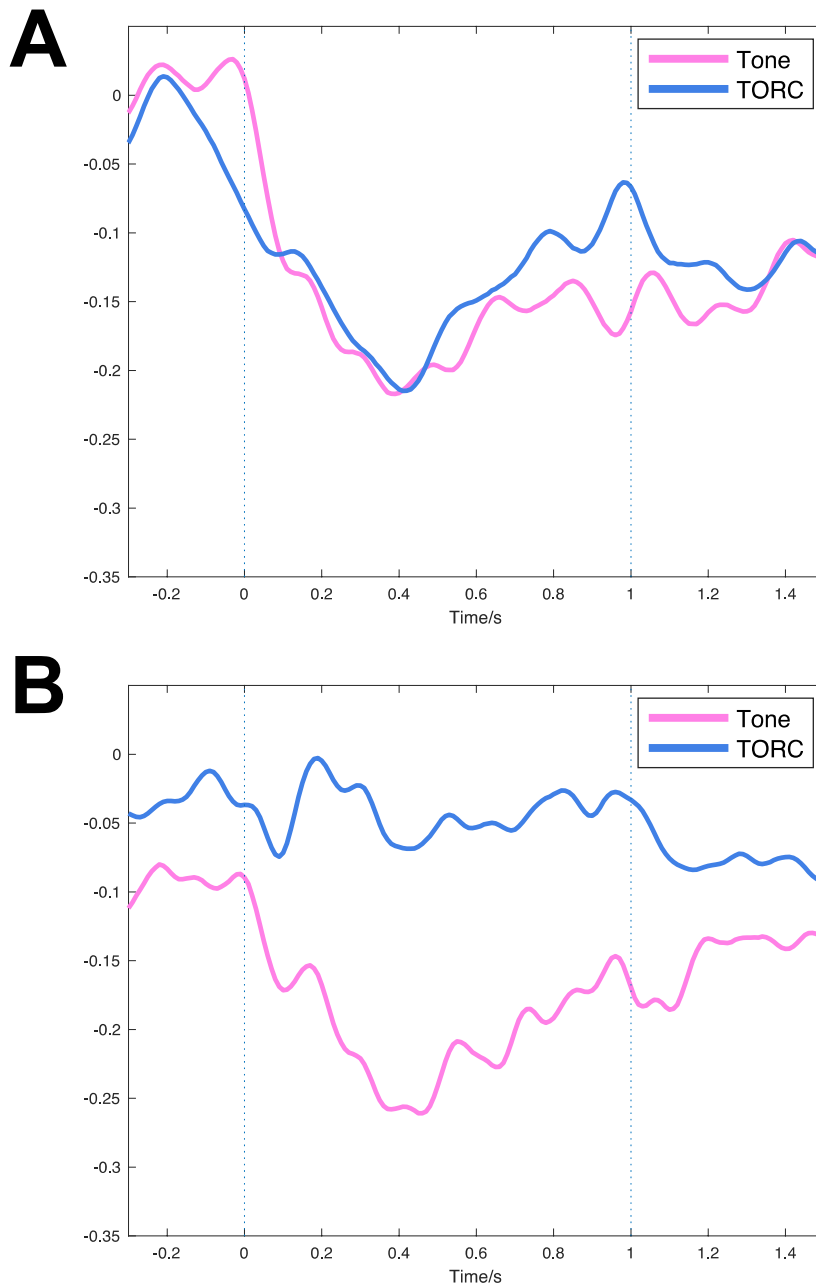
3.4 Behavioral modulation and the selectivity of response

To quantitatively evaluate the behavioral modulation between the two tasks, the firing rate change in response to each stimulus category was calculated and compared between the two tasks. The relative firing rate change was computed as the firing rate during auditory stimulus minus the baseline firing rate (300 ms before the trial to when trial starts), then divided by the baseline firing rate ((FR_{stim} - FR_{base})/FR_{base}). The firing rate changes to the pure tone stimuli versus the firing rate change to the TORC stimuli were plotted for the 2AFC task and go/no-go task respectively in Figure 8. In general, in the go/no-go task, the response change to tone was higher than the response change to TORC, whereas in the 2AFC task, no such bias was found.

To quantify the difference in firing rate (FR) change in response to the two stimulus categories, the selectivity to the two types of stimuli was calculated as the difference between the response to tone and the response to TORC, and normalized by dividing by the baseline firing rate ((FR_{tone} - FR_{TORC})/FR_{base}). For both tasks, the histogram of response selectivity was shown in the figure above. The mean selectivity in the 2AFC task is -0.0012. The mean selectivity in the go/no-go task is 0.0873. The selectivity was significantly higher in the go/no-go task than in the 2AFC task (independent sample t-test, t_{634} = 3.96, $p < .001$).
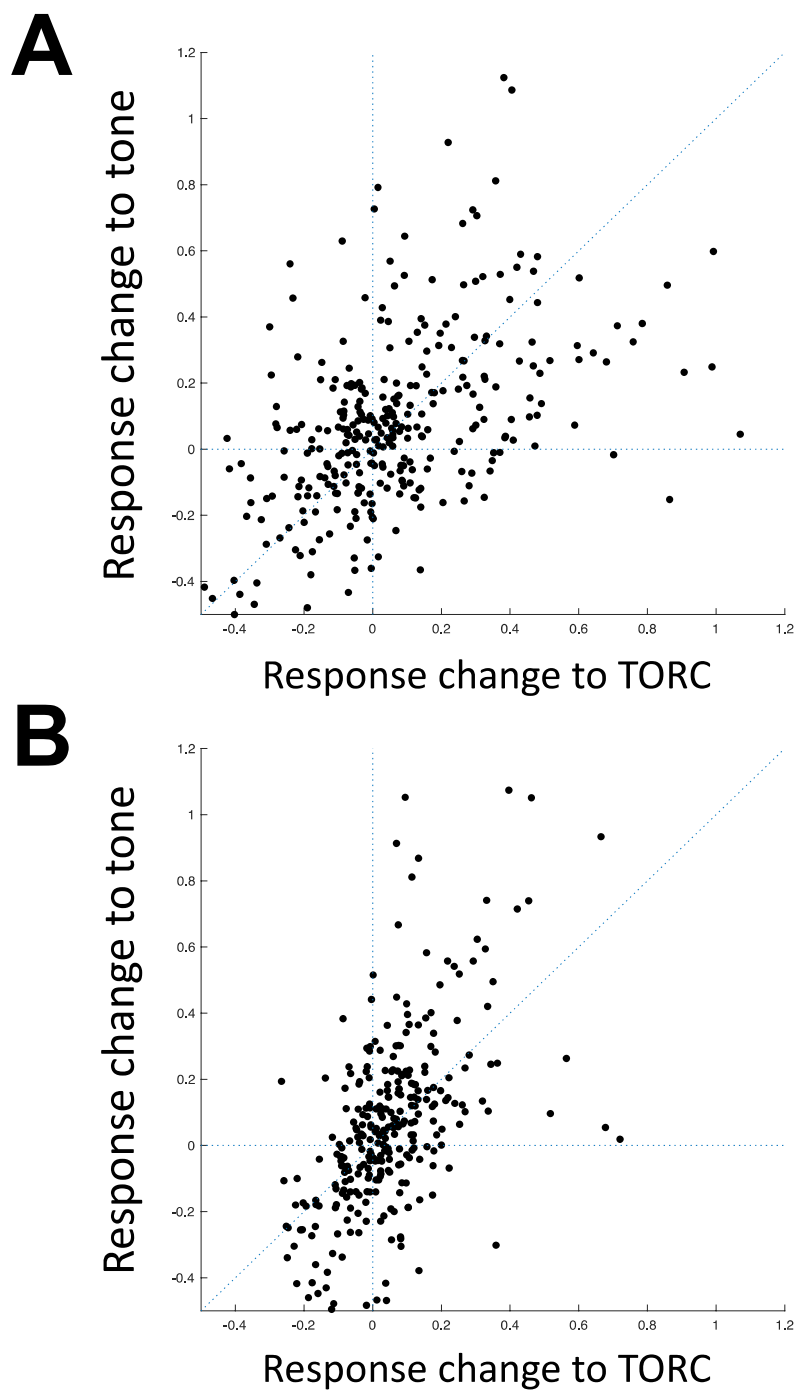
Figure 8. Firing rate changes to the pure tone stimuli versus to the TORC stimuli in the two tasks. Each dot represents the data from one single unit. A: the 2AFC task. B: the go/no-go task.
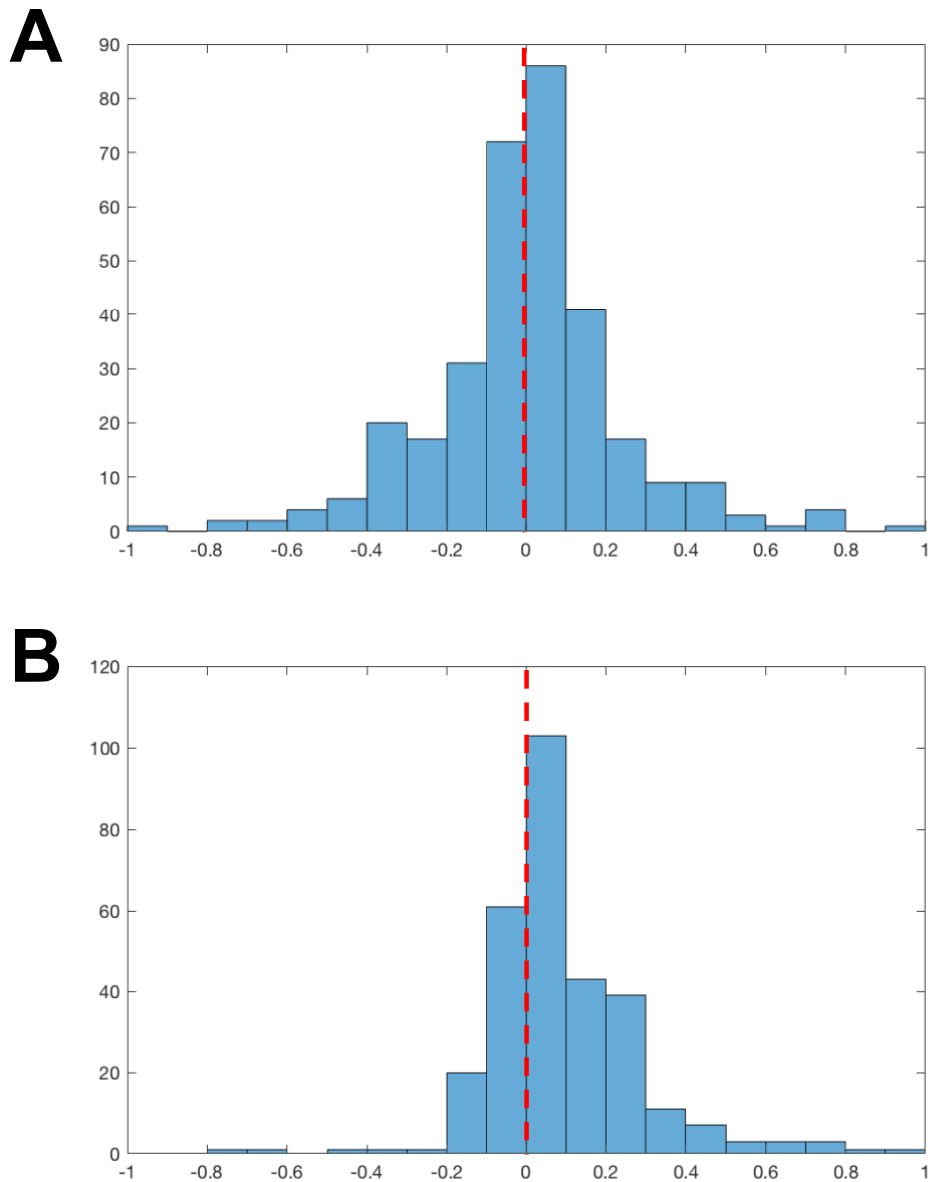
Figure 9. Histograms of response selectivity (normalized FR to tones minus normalized FR to TORCs) in the two tasks. A: the 2AFC task. B: the go/no-go task.

3.5 Dynamics and classification of single units in the 2AFC task

The single unit examples indicated that frontal neurons had diverse response latency and spiking patterns during behavior. Therefore, in the subsequent analysis, the single

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units were grouped based on the response latency and temporal dynamics. The following analysis only focused on the 2AFC data set because of its more balanced task structure and neural response patterns.

Table 3 shows the numbers of single units that exhibit significant task modulation at different time windows. Specifically, for each unit, the firing rate was compared at four consecutive time windows: (1) immediately at stimulus onset (0-100 ms after stimulus onset), (2) from stimulus onset to the behavioral response (from 100 ms after stimulus onset to 100 ms before the first licking response), (3) immediately before a licking response (from 100 ms before the first licking response to the time of the licking response), and (4) after a licking response (from the first licking response to the entire continuous licking period). For each time window, the averaged firing rate for each stimulus type was compared to the baseline firing rate before stimulus onset (One-way ANOVA, and simple effects were tested by Tukey's HSD test). To control the effect of rewards, only correct trials were used. Therefore, in each trial, the behavioral response was correct and rewarded with water. The proportions of units showing significant difference in firing rates to the two stimuli (the number of units showing different activity between two stimuli divided by the number of units showing task modulation) were also shown in Figure 8. From stimulus onset to a response was give, then to the after-response period, although the total number of units showing task modulation increased, the proportion of units showing different activity to the two stimuli decreased. This result indicated that the selectivity of the

neural response at population level may decrease over the time course since stimulus onset.

Table 3

The numbers of single units showing significant task modulation and difference between two types of stimuli

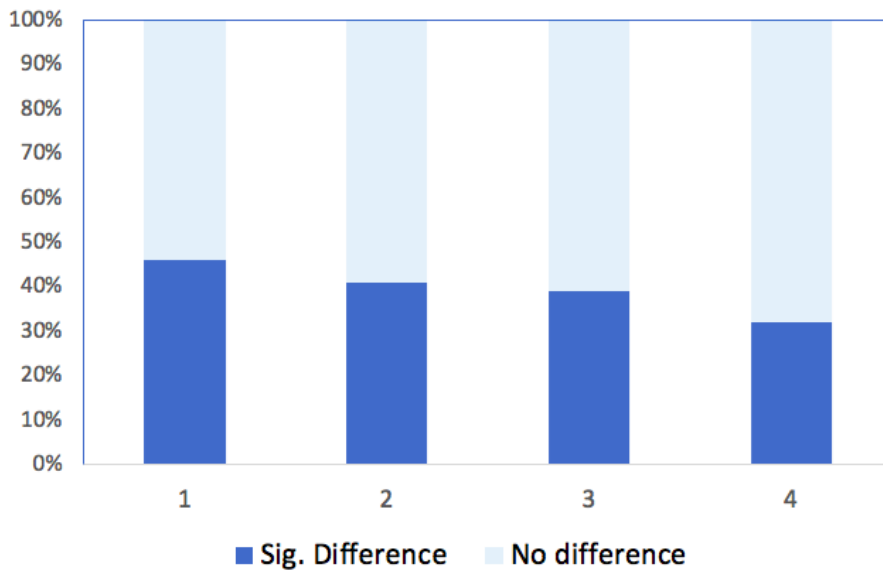|	Stim. Onset	Stim-response	Before response	After response
# of units showing task modulation	26	100	90	134
# of units showing difference between 2 stimuli	12	41	35	43
Proportion of units showing difference	46.2%	41.0%	38.9%	32.1%

Figure 10. Proportions of units showing significantly different activity between two stimuli in four consecutive time windows. Column 1-4 (x axis) corresponds to the four windows described above

This may indicate that neurons with different latency may also show different selectivity to the stimuli. For simplicity, in the following analysis, the first three windows were combined as one grouping factor. Single units were then classified into three categories: (1) neurons with only significant modulation before the licking response (Group 1), (2) neurons with only significant modulation after the licking response (Group 2), and (3) neurons with significant modulation both before and after licking response (Group 3). Figure 9 showed the differences in firing rate in response to the two categories of stimuli based on this classification. The averaged absolute values of the difference in normalized firing rate were plotted over time. The response of Group 1 neurons showed greater selectivity than those in Group 2 during time windows with significant task modulation (independent sample *t-test*, $p < .05$). The comparison between Group 1 and Group 2 showed that the two groups of neurons with different response latency also had different selectivity of response. This indicated that neurons that responded earlier after stimulus onset also exhibited larger selectivity to one of the stimulus categories. For Group 3 neurons, the response selectivity was larger before the lick than that after the lick (paired sample *t-test*, $p < .05$). This result showed that for neurons with sustaining response, the selectivity decreases over the time course since stimulus onset.
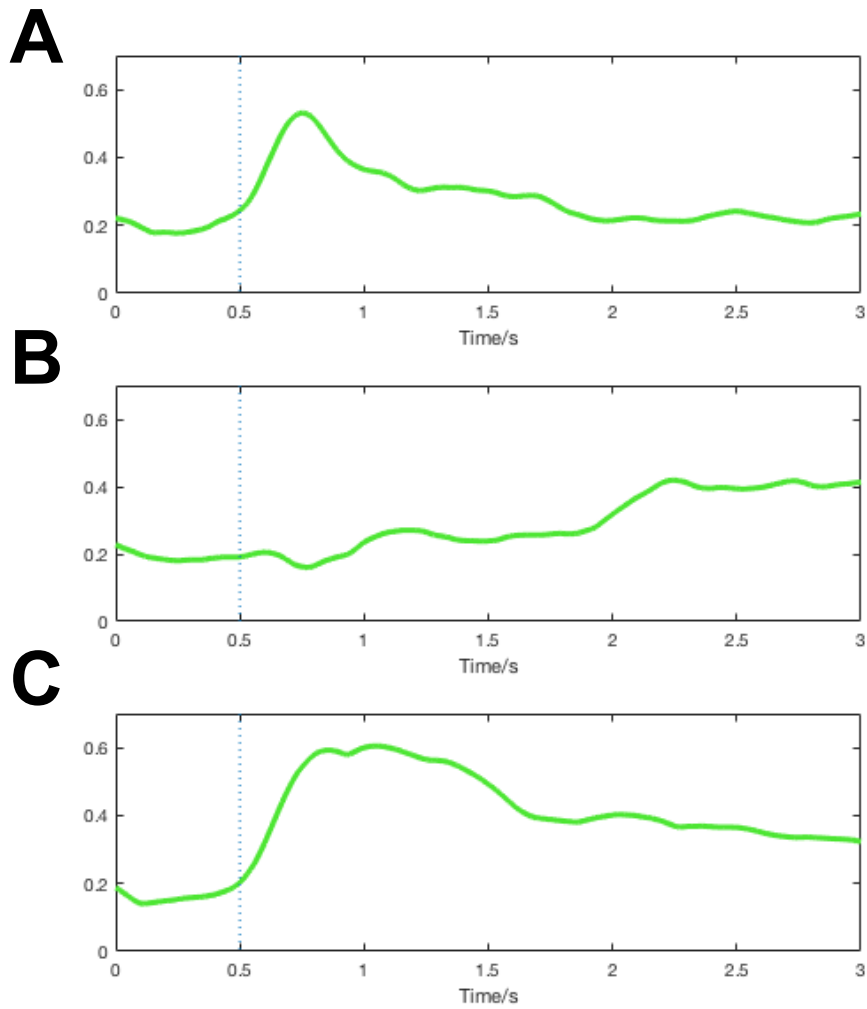
Figure 11. Dynamics of response selectivity to stimuli during behavior for three categories of single units. A: neurons with only significant modulation before the licking response; B: neurons with only significant modulation after the licking response; C: neurons with significant modulation both before and after licking response. Colors indicate separate stimuli.

Chapter 4: Discussion

4.1 Behavioral task paradigms and task reward structures

In this study, ferrets were trained on an auditory discrimination task with two different behavioral paradigms: the positive reinforcement go/no-go paradigms and the 2AFC paradigm. The auditory stimuli used in both paradigms were the same, therefore the requirement at the perceptual discrimination level was also the same for both tasks. However, the requirement for behavioral response or motor action was different in the two paradigms. In both task paradigms, the discrimination task was relatively easy at the sensory or perceptual level, because the difference between two categories of auditory stimuli were clear. The ferrets could easily discriminate the pure tone stimuli and the TORC stimuli after a short period of training. The behavioral performance was evaluated by the percentage of accuracy response. The analysis of behavioral performance during recording sessions showed that the average accuracy rate was higher than 75% for all ferrets in either the 2AFC task or the go/no-go task. The behavioral performance did not differ significantly between the two tasks. The behavioral results indicated that ferrets could be trained to perform the tasks in a head-restrained setting and achieve satisfactory behavioral performance in both tasks after a certain level of training with positive reinforcement.

Compared to the previous studies with conditioned avoidance go/no-go tasks (Elgueda et al., 2019; Francis et al., 2018; Fritz et al., 2010), one advantage of the

current positive reinforcement tasks is that they both provided a measure of the reaction time. One question of interest in behavioral tasks is how the neural activity is associated with the perceptual decision. However, in the conditioned avoidance go/no-go task, the time of the actual decision or response could not be directly measured. The ferrets were trained to freely lick to receive water at the non-target stimuli, whereas to restrain licking after they hear the target stimuli. In other words, the target stimuli (the pure tone) required a "no-go" response. Therefore, in conditioned avoidance paradigm, the actual reaction time for the no-go decision was not clear. Although it could be estimated from the licking activity and relative licking rates, this paradigm did not directly measure when the actual no-go decision was made. In the positive reinforcement of the go/no-go task, although there is still not a direct measure of the reaction time for the no-go response, the reaction time for the go response (response to the target stimuli) could be measured directly as the time from target stimulus onset to the time of the first licking response. In the 2AFC task, the reaction time for both stimulus categories could be measured with this method. Knowing the accurate reaction time would provide a way to measure to how the frontal activity is related to the correct and incorrect behavioral response.

In addition, as previously discussed, although the two task paradigms require some common cognitive functions of the frontal cortex, they highlighted different aspects. The 2AFC task emphasizes the selection and decision-making processes, whereas the go/no-go task requires more inhibitory control. Moreover, the perceptual decision process may also be influenced by the task paradigms. In the go/no-go task, the

response tendency may be vulnerable to the animal's motivation and state, whereas the 2AFC task is more immune to the changing of decision criterion (Carandini & Churchland, 2013). However, in the current study, it is difficult to separate the influence from all those contributing factors with the relatively simple experiment design. Therefore, in animal behavior studies, different factors need to be taken into consideration when designing the behavioral task.

4.2 Neural correlates of task-relevant auditory signals

Single units in ferret frontal cortex showed differential response strength and selectivity during the two different behavioral tasks. In the go/no-go task, the frontal units responded more selectively to the target stimuli (the pure tone stimuli) compared to the non-target stimuli (the TORC stimuli). In the 2AFC task, the neural response in ferret frontal cortex did not show a systematical bias towards either category of stimuli.

Although the sensory discrimination was the same in both tasks, the difference in task reward structures may be the factor that led to the distinct response pattern of frontal neurons. However, the underlying mechanism for this difference remains unclear. One plausible explanation is that in the positive reinforcement go/no-go task, only the target stimuli were paired with reward. The anticipation for reward could lead to the relatively higher response. Another possible factor is that the target stimuli required a motor action (i.e., licking towards an water spout). Therefore, the frontal

response to the target stimuli may be associated with the preparation of the motor action. However, in the conditioned avoidance task with the same two stimuli (Elgueda et al., 2019; Fritz et al., 2010), when the reward was delivered continuously during both target and non-target stimuli, the neural response in ferret frontal cortex also showed a strong bias towards the target stimuli. Indeed, even fewer neurons responded to the non-target stimuli, compared to the positive reinforcement version of the go/no-go task in this study. If the activity in frontal neurons was primarily associated with reward, the response should not be weaker for the non-target stimuli. Moreover, no extra motor action was required for the target stimuli. The ferret could lick freely during the non-target stimuli and target stimuli, but only had to stop licking after the target stimuli. If the frontal activity was primarily related to motor activity, then similar response should be observed throughout the non-target stimuli and the target stimuli. Therefore, the selective response in frontal neurons was not likely to be completely due to the anticipation for rewards or the preparation for motor actions.

Attentional effect may be another plausible factor that contribute to the selective response towards the target stimuli. In the go/no-go task, the ferret might pay more attention to the target stimuli, because it required a motor action and was predicting a potential reward. However, it is difficult to quantitatively measure the level of attention, and at the same time, many other factors also contributed to the attention level at the same time, such as the motivation to perform the task, the extent of thirst, and the amount of the reward. Therefore, it may be difficult to quantify the

association between frontal activity and the attention level. Consequently, it could not be concluded that the effect was primarily due to attention.

4.3 Dynamics of frontal neurons during behavioral tasks

In both tasks, frontal neurons showed heterogeneous response patterns and dynamics. Despite some neurons that did not show any significant response change during the behavioral tasks, most of the frontal neurons showed a diverse range of latency, strength, and selectivity in response to different task-relevant stimuli and behavior-relevant variables.

Although the functional role of individual frontal neurons remains unclear, it has been suggested that the neural response in the frontal cortex may be associated with preparing for an action or receiving a reward. In this study, when an auditory stimulus required a corresponding behavioral action, a large portion of the neurons showed response before or after the actual response, and many showed response after receiving the reward. However, in the current study, it was not feasible to separate the activity that was associated with the decision response, the motor action, and receiving the reward. When the ferret made a correct decision, the water was delivered as the rewards, and the ferret continued to lick to drink the water. In this case, all these three components happened at the same time. Other task-related variables, such as the level of attention, motivation, and task difficulty, should also be controlled or parametrically manipulated. Therefore, future studies need to consider the design for collecting the decision response and delivering the reward to make sure

that these factors are not confounding. Future studies could use experiment designs that allow the separation of attentional effect and decision related responses. A multiple-choice behavioral paradigm with parametric changes in task difficulty could be useful in separating the effect of decision from attention.

Chapter 5: Future directions

5.1 Top-down modulation in auditory areas

One question that remains to be answered is how the different task paradigms and task reward structures would influence the top-down modulation in sensory areas. In previous studies, differential receptive field changes in the previous auditory cortex were observed in different task reward paradigms (David et al., 2012). The functional connectivity between frontal cortex and auditory cortices also changed during behavioral tasks (Elgueda et al., 2019; Fritz et al., 2010). These findings indicated that different task-reward structures could influence the top-down modulation signals from the frontal cortex to the auditory areas.

Simultaneous recordings from multiple brain areas during behavioral task performance could provide an understanding to the neural mechanism of top-down modulation. Recordings from different orders of auditory cortices could provide an estimate of the receptive field changes during different behavioral tasks, therefore indicates how the task reward structure could influence sensory processing. Another measure is to calculate the functional connectivity from the neural data recorded in the two areas. One method is to calculate the Granger causality in the local field potential (LFP) data. Granger causality is a statistical analysis that allows the statistical testing of whether one time series could forecast another time series (Seth et al., 2015). Previous studies have shown that the top-down causality changed in the

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behavioral tasks (Elgueda, 2016). Investigating the receptive field property changes in auditory areas and the functional connectivity between frontal and auditory cortices in different behavioral tasks and contexts could provide an understanding to the neural mechanisms of top-down modulation.

5.2 Simultaneous recordings and large-scale neural data

The current multiple-electrode technology has enabled simultaneous recordings from large amounts of single neurons. In the past few decades, the number of neurons that could be simultaneously recorded from significantly has increased. Now it is possible to recorded from hundreds of neurons simultaneously (Gao & Ganguli, 2015; Stevenson & Kording, 2011). The availability of large-scale neural data sets also posed challenges to the development of data analysis techniques. A key effort is to shift from single neuron analyses to population level analyses. Population recordings enabled the analysis of behavior-relevant events on a trial-by-trial basis. Some task- or behavior-related variables, such as the reaction time for each trial, would provide more information if analyzed on a trial-by-trial basis, compared to trial averaged analyses. In single-trial analysis, large-scale recordings provided the statistical power that could not be achieved by recording from a single neuron (Cunningham & Yu, 2014). Therefore, large-scale recordings could be a powerful method to understand the temporal dynamics of decision processes.

5.3 Representation of task variables and mixed selectivity

Neurons in higher order brain areas often show highly heterogeneous and complex response patterns. However, such heterogeneity was sometimes neglected in data analyses. Traditional methods usually focus on selecting single neurons based on certain criteria or averaging across the entire neuron population. Recent studies suggested that the neurons in higher order areas may encode several different task variables simultaneously, and therefore display mixed selectivity (Kobak et al., 2016; Raposo et al., 2014; Rigotti et al., 2013). One approach to analyze the neural population data with heterogenous response is to use dimensionality reduction methods (Cunningham & Yu, 2014; Kobak et al., 2016). Dimensionality reduction methods, such as principal component analysis (PCA), could extract the shared latent variables among the neuron population, thus examine the population response structure. A relatively new dimensionality reduction technique, demixed principal component analysis (dPCA), could also be applied to the frontal neuron data set. The dPCA approach also focuses on decomposing population activity into fewer components, but it also exposes the dependency of the neural representation of task variables (Kobak et al., 2016). Applying those approaches to the analyses of population data could provide a better understanding to the features of neural activity at population level.

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