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Understanding the Role of Locus Coeruleus Norepinephrine on Perceptual
Representations and Behavior


A Doctoral Dissertation in Partial Satisfaction
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**Dedication**

This work is wholeheartedly dedicated to my dad, Sena Yaghoubi, as without him, I would not be writing this work. To my dad for teaching me to follow my instinct and desire for research. To my mom, Sara Yaghoubi, for all her tough love and discipline. To my baby sister, Dana Yaghoubi, for kindly waiting for me to go home at the end of every week of graduate school. To my aunt, Susan Dehghan, for teaching me to appreciate maths and sciences from a very young age, for showing up at every school competition, and for always following up on my exam results. To my grandfather, Dr. Mahmoud Yaghoubi, for being an inspiration to pursue higher education, to be humble, and to give back to my community. To my cousin and best friend for life, Faezeh Bonyadinezhad, for all the emotional and mental health support. To my beautiful godparents, Dr. Nima Shojaee and Marzieh Vali, for their continuous support from high school to undergraduate and graduate school; they have played a key role in my personal and cultural development. And last but not least, to my fiancé, Dr. Arash Mirjalili, for his support, love, and encouragement.

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ABSTRACT OF THE DISSERTATION


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Perceptual processes are significantly modulated by the primary neurotransmitter,

Norepinephrine (NE). In the brain, the Locus Coeruleus (LC) nucleus located in the pons

of the brainstem houses NE production and serves the brain as its sole source of NE. The

LC-NE circuit has been shown to play a critical role in modulating various cognitive

functions, including sensory processing, perception, and perceptual behavior. However,

its complex circuitry, features, size, and location, have challenged our ability to

understand the underlying mechanisms of LC's modulatory role in the human brain. In

this dissertation, I investigate the relationship linking LC activity to sensory processing

and perception through a series of behavioral, neuroimaging, and physiological studies in

healthy young adults. Chapter 1 reviews the literature on LC's role in modulating

cognition, emphasizing the predominant models of LC's relationship with perceptual and

memory processes. Chapter 2 reports a behavioral, physiological, and neuroimaging

study designed to facilitate understanding LC's influence on human perceptual,

attentional, and decision-making processes. More specifically, behavioral and fMRI

paradigms were investigated in conjunction with suitable analytical approaches to address

how LC affects the sensory processing of perceptual stimuli in relevant sensory cortex

areas. Together, these chapters highlight key findings of LC literature in the context of

LC modulation of perceptual processes and behavior, examine influences of LC

engagement on behavioral and neural stimulus-response function in humans, and provide

an overview of current approaches for evaluating the LC activity related influences on

sensory representations and perceptual behavior.

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**General Introduction**

The Locus Coeruleus (LC) is a hyperpigmented nucleus in the pons of the brainstem that serves as the primary norepinephrine (NE) production center in the brain (Sharma et al., 2010). Modulations in Locus Coeruleus Norepinephrine (LC-NE) signaling are hypothesized to play a critical role in many key cognitive (Berridge & Waterhouse, 2003b; Sara, 2009; Usher et al., 1999) and autonomic functions (Aston-Jones et al., 1996; E. R. Samuels & Szabadi, 2008; E. Samuels & Szabadi, 2008), including attention (Aston-Jones et al., 2000; Mather et al., 2020), arousal (Aston-Jones, 2005; Aston-Jones et al., 1991; Breton-Provencher & Sur, 2019; Foote et al., 1980; Hussain et al., 2022; Maness et al., 2022; Sterpenich et al., 2006), and behavior (Aston-Jones et al., 2002, 2007; Gelbard-Sagiv et al., 2018; McBurney-Lin et al., 2022). LC neuron projections are broadly distributed across the central nervous system, innervating neural circuits and structures essential for alertness and cognition (Aston-Jones, 2005; E. R. Samuels & Szabadi, 2008; E. Samuels & Szabadi, 2008). Electrophysiological (Berridge & Foote, 1991; Berridge & Waterhouse, 2003a; Cedarbaum & Aghajanian, 1978; Foote et al., 1975, 1991), anatomical (Foote et al., 1983; Jedema & Grace, 2004; Moulton et al., 2014; Redmond & Huang, 1979; Sharma et al., 2010), and behavioral (Aston-Jones et al., 1991; Clewett et al., 2018; Gelbard-Sagiv et al., 2018; Mather et al., 2017, 2020; Rajkowski et al., 1994) studies, primarily done in non-human animal models, indicate that the LC system significantly contributes to sensory processing (Berridge & Waterhouse, 2003a; Foote et al., 1980; Hurley et al., 2004; Manunta & Edeline, 1997; Waterhouse & Navarra,

2019) of internal and external stimuli and that NE released from LC neurons can modulate sensory information processing via modulating memory (Chen & Sara, 2007; Jacobs et al., 2020; Sterpenich et al., 2006; Unsworth & Robison, 2017), attention (Aston-Jones et al., 2002; Mather et al., 2020; Snyder et al., 2012), perception (Markovic et al., 2014; McBurney-Lin et al., 2019; Noulhiane et al., 2007), and motor system (Kalwani et al., 2014; Maness et al., 2022), resulting in influences on behavior. For example, recordings from LC neurons in monkeys performing a visual discrimination task has shown that spontaneous and stimulus-evoked LC neural activity to be closely correlated with changes in behavioral performance on the task, such that epochs of moderate LC actively were associated with good performance and too high or low levels of LC activity were associated with poorer performance on the task (Usher et al. 1999). A similar role of LC on behavioral performance was observed in humans, where moderate levels of LC activity were associated with optimal performance on an auditory oddball discrimination task, and epochs of high LC activity were associated with poor task performance (Murphy et al. 2011).

Notably, disturbances of LC neurons are known to be closely associated with psychiatric disorders such as dementia; depression (Ressler & Nemeroff, 2000; Weiss et al., 1994); schizophrenia (Lohr & Jeste, 1988); bipolar disorder (Wiste et al., 2008); and attention and anxiety-related disorders, (Ressler & Nemeroff, 2000) such as ADHD (Darcq and Kieffer 2015) and PTSD (Aston-Jones et al., 1994). Furthermore, the integrity of LC neurons is essential for preserving normal cognitive functions during normal aging, as degradation of LC neurons occurs in neurodegenerative disorders like Parkinson's

(PD) (Chan-Palay & Asan, 1989; Del Tredici & Braak, 2013; Weinshenker, 2018; Zarow et al., 2003) and Alzheimer's disease (AD) (Mather & Harley, 2016; Tomlinson et al., 1981; Weinshenker, 2008). For example, in patients with Parkinson's, the LC-NE system has been shown to be implicated in inhibitory pathways, resulting in response inhibition deficits (O'Callaghan et al. 2021). And in patients with Alzheimer's disease, LC neuron degenerations, reduction in LC fiber density, and LC general volume has been shown to be correlated to pathological markers of Alzheimer's (Chen et al. 2022). In psychiatric disorders, the LC-NE system's role is more complex with various underlying implications, including dysregulation and overactivation of the LC-NE system (Ressler and Nemeroff 2000) as well as genetics effects (Bernard et al. 2011; Chandley et al. 2013; Naegeli et al. 2018; Valentino and Van Bockstaele 2008), which has further challenged our characterization of LC-NE circuit. Although remarkable progress has been made toward characterizing LC-NE circuit function, our lack of understanding of the exact underlying neural mechanisms of the LC-NE circuit and how it modulates the different cognitive processes has greatly limited our ability to develop therapeutic methods targeting dysregulations of the LC-NE circuit function.

In humans, our ability to characterize LC circuitry is vastly challenged by the complexity of this circuitry (Sharma et al., 2010), bi-directional interaction among various cognitive processes (Ester et al., 2014; Law & Gold, 2010; Lynch et al., 1991; Matthews & Meck, 2016; Merikle & Joordens, 1997; Purcell et al., 2010; Ratcliff & Smith, 2010; Rensink, 2013; Thielscher & Pessoa, 2007; Wittmann & Paulus, 2008), as well as anatomical constraints such as LC's small size and the location (deeply situated in

the pons of the brainstem near the wall of the fourth ventricle) (Sharma et al., 2010), and the divergent neural projections (Keren et al., 2009). Therefore, much of our understanding of LC activity and its modulatory effect on human cognition is derived from pupil size changes, as LC activity has been shown to correlate closely with pupil dilation (Hoffing & Seitz, 2015; Joshi et al., 2016; Joshi & Gold, 2020; Kuipers & Thierry, 2011; Murphy et al., 2011, 2014). Pupillometry is widely used as a proxy of LC-NE activity in humans and non-human models (Joshi et al., 2016; Murphy et al., 2014). It has been demonstrated that the pupillary response is closely associated with increased attention (Aston-Jones & Cohen, 2005), learning and memory (Chamberlain et al., 2006), perception (Oliva, 2019), and decision-making (de Gee et al., 2017). Although these fluctuations in pupil size are only partially due to LC-NE activity (de Gee et al., 2017; Reimer et al., 2016; Wang et al., 2012), converging evidence supports a strong link between changes in LC activity and changes in pupillary dilation (Murphy et al., 2014).

Today, it is well established that the LC-NE circuit is essential for normal cognitive function (Bekdash, 2021; Chalermpalanupap et al., 2013; Grueschow et al., 2022; Kelberman & Weinshenker, 2022; Mäki-Marttunen et al., 2020; Mather & Harley, 2016; Satoh & Iijima, 2019; Sundström et al., 2020; Vazey & Aston-Jones, 2012; Weinshenker, 2008; Zarow et al., 2003). Despite over 60 years of effort, however, fully characterizing this brainstem nucleus remains a challenge. With the advancement in cognitive neuroscience tools, such as imaging techniques (Hwang et al., 2022; Langley et al., 2017; Tona et al., 2017) for evaluating the relationship between LC's noisy activity and changes in behavior (Clewett et al., 2018; Gelbard-Sagiv et al., 2018; Lee et al.,

2018; Mather et al., 2020; Minzenberg et al., 2008; Nielsen & Mather, 2015), we have moved closer to characterizing the functions of LC. As discussed above, with LC's complex and significant role in normal aging and neurodegenerative disorders, researchers have remained eager to make progress toward a complete understanding of LC function, as successful progress on characterizing LC could potentially lead to the development of therapeutic methods for LC dysfunction (Bekdash, 2021).

This dissertation is focused on key LC research advancements (mostly in nonhuman models) and methods for understanding how LC modulates sensory processing and perception, with an objective to examine LC's role in perceptual representations and behavioral performance in healthy young humans:

- Chapter 1 reviews relevant LC literature, including functional anatomy and physiology of LC, to highlight how anatomical projections of LC contribute to LC's modulatory role in sensory processes. This leads to a selective review of how LC influences visual, auditory, and somatosensory sensory processes and perception. To gain an understanding of how changes in LC modulates sensory and perceptual process, I briefly discuss existing prevailing theories of LC function and the evidence supporting or challenging each theory.

- Chapter 2 presents a systematic behavioral and neuroimaging study that provides insight into suitable approaches for understanding how upregulated LC activity, via a handgrip manipulation, influences perceptual behavioral and neural representations. The paradigm discussed in this Chapter enables successful

estimation of behavioral and neural stimulus-response functions that show

sensitivity for capturing impacts of upregulated LC activity.

● Finally, an overall conclusion of the dissertation is presented with a focus on

accomplishments, limitations, and an introduction to an ongoing project designed

to characterize LC's relationship with memory and perceptual processes in older

adults.

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**Chapter 1: Locus Coeruleus Role in Perceptual and Sensory Processes**

**Introduction**

Sensing and interpreting environmental stimuli ultimately determines our interaction with the world; the result of this complex processing is called perception. The process of perception is subject to changes exerted by stimuli properties such as stimulus saliency (Endo, 1986; Liang et al., 2019; Li & Gilbert, 2002; Noesselt et al., 2008; Poirier et al., 2008; Qiu et al., 2022; Treue, 2003), novelty (Miller et al., 2015; Pascucci et al., 2019; Schomaker & Meeter, 2012; Schupp et al., 2006), relevancy (Egner & Hirsch, 2005; Hommel, 2007; Jin et al., 2018), etc., and importantly, the global arousal state of the brain (Csukly et al., 2009; Gelbard-Sagiv et al., 2018; Krishnamurthy et al., 2017; Mather & Sutherland, 2011; Murphy, Vandekerckhove, et al., 2014; Storbeck & Clore, 2008; Urai et al., 2017; van Kempen et al., 2019; Yao et al., 2016).

The global arousal state is, in part, controlled by the LC-NE neuromodulatory circuit (Aston-Jones & Cohen, 2005; McGinley et al., 2015). NE released from LC neurons has been suggested to profoundly impact sensory processing across different modalities by improving the signal-to-noise ratio (Foote et al. 1975; Waterhouse et al. 1990; Ciombor et al. 1999), lowering neural response thresholds (Waterhouse et al. 1990; Ciombor et al. 1999; Waterhouse et al. 1988), sharpening neural tuning curves (Edeline et al. 2011), and reducing neural response latency (Waterhouse et al. 1990; Ciombor et al. 1999), leading to LC-NE governing and changing sensory representations and perceptual behavior (Waterhouse and Navarra 2019; Aston-Jones and Cohen 2005; Poe et al. 2020).

This Chapter reviews the LC's anatomy and physiology role in the modulation of sensory processes, followed by a selective literature review on LC-NE influence on

sensory stimuli processing across the visual, auditory, and somatosensory modalities, followed by the neuroscience of LC in humans, which includes the methodology for assessing LC in human models as well as key theories of LC function.

**Locus Coeruleus Anatomy and Physiology**

Locus Coeruleus is a small nucleus situated in the upper part of the pons by the fourth ventricle (Sharma et al., 2010). Like many other neuromodulatory structures, such as the raphe nuclei that produce serotonin and the substantia nigra that produces dopamine, the LC nucleus is small in size; it contains approximately 50,000 neurons (Sharma et al., 2010). However,  with extensive axonal projections, LC effectively reaches the entire cerebral cortex as well as the hippocampus, amygdala, cerebellum, and the spinal cord via two ascending fiber systems: the dorsal noradrenergic bundle and the rostral limb of the periventricular pathway (E. R. Samuels & Szabadi, 2008; E. Samuels & Szabadi, 2008; Sharma et al., 2010). With LC's broad connection to these areas, it is hypothesized that LC modulates the autonomic functions, such as the fight-or-flight response, and a wide range of cognitive functions, including sensory processing and perception (Bouret & Sara, 2002; Gelbard-Sagiv et al., 2018; Markovic et al., 2014; Mather et al., 2016; Waschke et al., 2019).

 For more than five decades, LC was thought to be homogenous in its structure and functional influence, such that it projected its neurons through the cortex with and released NE with little to no regional specificity (Loughlin et al., 1982; Loughlin, Foote, & Bloom, 1986; Loughlin, Foote, & Grzanna, 1986; Waterhouse et al., 1983, 1993).

However, more recently, research on the organization of non-human LC projections has shown that LC differentially innervates brain regions like the orbitofrontal, medial prefrontal (Hirschberg et al., 2017), anterior cingulate cortex (Chandler et al., 2014), and hippocampus (Wagatsuma et al., 2018), which have different electrophysical and biochemical profiles. Specificity-related findings within LC's projection network argue for a more specific role of LC with respect to its efferent targets and NE release (Chandler et al., 2019; Totah et al., 2018). I use this foundation to gain insight into how LC functional anatomy and physiology contribute to its influence on perceptual representations and behavior.

**Efferent Pathways of Locus Coeruleus**

LC project widely across the cortical and subcortical regions of the brain (Figure 1.1). LC reaches most of the brain via three main efferent projection pathways originating from LC: the ascending projections to the cortex, the cerebellar pathway, and the descending pathway reaching the spinal cord (Szabadi, 2013). The ascending pathway includes projections to the ventral tegmental area, substantia nigra, amygdala, hippocampus, thalamus, basal forebrain, prefrontal cortex, and sensory cortices, including vestibular, somatosensory, auditory, and visual cortex (E. R. Samuels & Szabadi, 2008; E. Samuels & Szabadi, 2008). Within the LC nucleus, significant topographical organization has been observed (Loughlin et al., 1982; Loughlin, Foote, & Bloom, 1986; Mason & Fibiger, 1979; Schwarz & Luo, 2015; Van Bockstaele et al., 2001; Waterhouse et al., 1993). In general, projections to the hippocampus and septum originate from dorsal LC,

whereas projections to the spinal cord and cerebellum originate from ventral LC, projections to the thalamus arise from posterior parts of LC, and projections to the cortex and amygdala are shown to scatter from all parts of the LC nucleus (Loughlin, Foote, & Grzanna, 1986; Mason & Fibiger, 1979; Schwarz et al., 2015).

Projections of the ascending pathway are reported to be mostly related to the arousal state, sensory processing, and behavioral flexibility (McBurney-Lin et al., 2019; Szabadi, 2013). These relationships are in part supported by correlational analyses between LC activity and NE released in different brain areas, specific and non-specific molecular tracing studies, radioisotope studies, optogenetics approach, etc. (Berridge & Abercrombie, 1999; Gelbard-Sagiv et al., 2018; Hickey et al., 2014; Pickel et al., 1974; Simson & Weiss, 1987; Weiss et al., 1994). For instance, using fluorescence tagging coupled with messenger-Ribonucleic acid (mRNA) approaches, researchers have shown LC projections of the primary motor cortex, medial prefrontal cortex, orbitofrontal cortex, and anterior cingulate cortex are phenotypically distinct and have different electrophysical properties. Additionally, LC neuron populations innervating each of the aforementioned sub regions of the prefrontal cortex are different in their spontaneous firing patterns NE release in comparison to LC neurons innervating the primary motor cortex (Chandler et al., 2014, 2019). These anatomical organizations suggest the LC can profoundly influence sensory information processing.
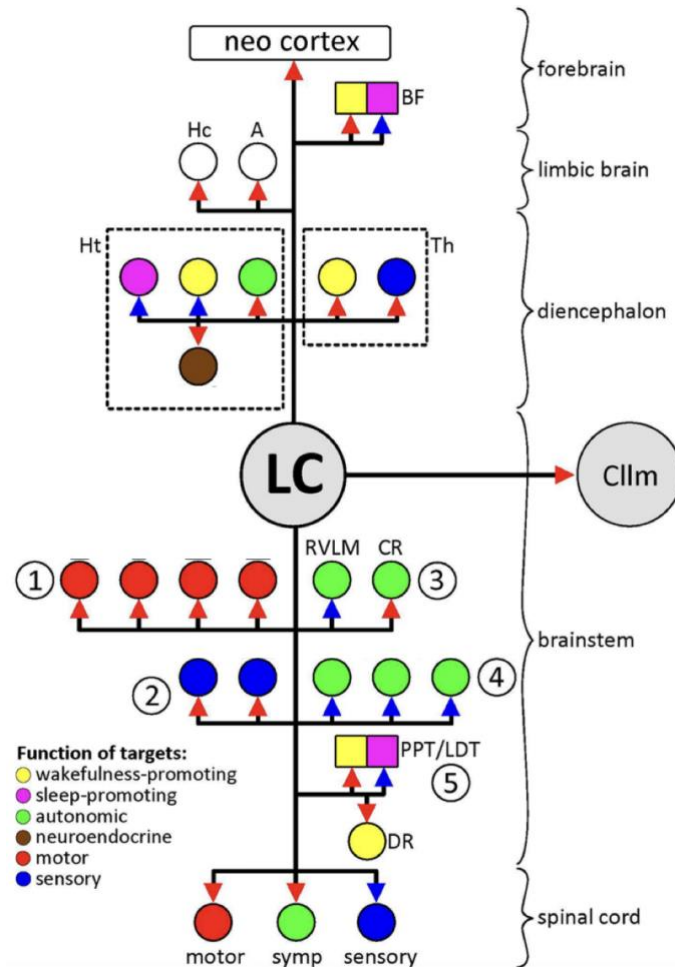
Figure 1.1. Efferents of Locus Coeruleus. Projections are represented by arrows. Red arrowheads depict excitatory inputs, and blue arrowheads depict inhibitory inputs. The numbers circled represent (1) motor; (2) sensory; (3 & 4) autonomic; (5) wakefulness-promoting/sleep-promoting functions. The LC exerts excitatory influence on the neocortex, hippocampus (Hc), Amygdala (A), Basal Forebrain (BF), Hypothalamus (Ht), Thalamus (Th), Brainstem, motor and sensory neurons of the brainstem, and motor and autonomic nuclei of the spinal cord. LC exerts excitatory and inhibitory influences on BF, Ht, Brainstem, autonomic nuclei, and wakefulness/sleeping nuclei within the brainstem. The figure is adapted from "Functional neuroanatomy of the central noradrenergic system" by Elmer Szabadi, 2013, Journal of Psychopharmacology, Volume 27, Issue 8. Copyright [2013] by the SAGE Publishing. Adapted with permission.

**Afferent Pathways of Locus Coeruleus**

In general, every area of the brain that receives input from LC also sends one back to LC (Arnsten & Goldman-Rakic, 1984; Arnsten & Pliszka, 2011; Cedarbaum & Aghajanian, 1978; Luppi et al., 1995); this includes the neocortex, with specific inputs to LC from the olfactory, somatosensory, visual, and auditory cortices, as well as the hypothalamus, the amygdala, the brainstem, and the spinal cord (Szabadi, 2013).

Out of all the major regions in the brain that project to LC, the LC nucleus is suggested to have its strongest reciprocal connection with the prefrontal cortex (Arnsten & Goldman-Rakic, 1984), which rules the brain by its powerful cognitive control function with respect to wakefulness (Horne, 1993; Zhang et al., 2014), attention (Knight et al., 1995; Rossi et al., 2009), behavioral flexibility (Anderson et al., 1999; Botvinick, 2008; Carlén, 2017; Cole et al., 2016; Donoso et al., 2014; Rougier et al., 2005; Szczepanski & Knight, 2014), and influencing sensory processing and perception (Burgess et al., 2007; Foxe & Simpson, 2002; Fuster, 2015; Hagen et al., 2002; Wood & Grafman, 2003). The majority of the neocortex projects to LC are reported to be excitatory inputs (Jodo & Aston-Jones, 1997) that are hypothesized to play a role in switching LC activation modes (Jodo et al., 1998).

There is also a strong reciprocal relationship between amygdala and LC, where amygdala densely projects back to the LC nucleus via its basal nuclei (Cedarbaum & Aghajanian, 1978). Considering the amygdala plays a primary role in fear and anxiety, the bidirectional connection between LC and amygdala argues for LC involvement in fear and anxiety (McDougle et al., 1995; Redmond & Huang, 1979). Although not a major

focus of this Chapter, emotionally arousing stimuli have been shown to engage LC, which in turn influences sensory processing, perceptual representations, and behavior (Llorca-Torralba et al., 2019; Morris et al., 2020).

Nuclei and neural clusters in the hypothalamus and the brainstem that receive inputs from LC are shown to densely project back to LC (Figure 1.2). With respect to the hypothalamus, the Lateral Hypothalamic (LH) and the Tuberomamillary nucleus (TMN) of the hypothalamus project excitatory input LC, promoting wakefulness (Szymusiak & McGinty, 2008) by increasing arousal and suppressing REM sleep (Bourgin et al., 2000), whereas the inhibitory projections of Ventrolateral Preoptic (VLPO) area are sleep-promoting (Cedarbaum & Aghajanian, 1978; Szymusiak & McGinty, 2008). These bi-directional projections of LC with sleep- and wakefulness-promoting nuclei and neural clusters modulate arousal-related cortical awareness, which in turn can also impact sensory processing and perception (Berridge & Waterhouse, 2003b). Sensory neurons of the dorsal horn in the spinal cord also send dense excitatory projections to the LC (Cedarbaum & Aghajanian, 1978). Projections arising from these neurons are shown to be implicated in somatosensory processing, with extensive evidence supporting LC activation via thermal and noxious stimuli (Elam et al., 1986; Hickey et al., 2014; H. Hirata & Aston-Jones, 1994; Viisanen & Pertovaara, 2007).
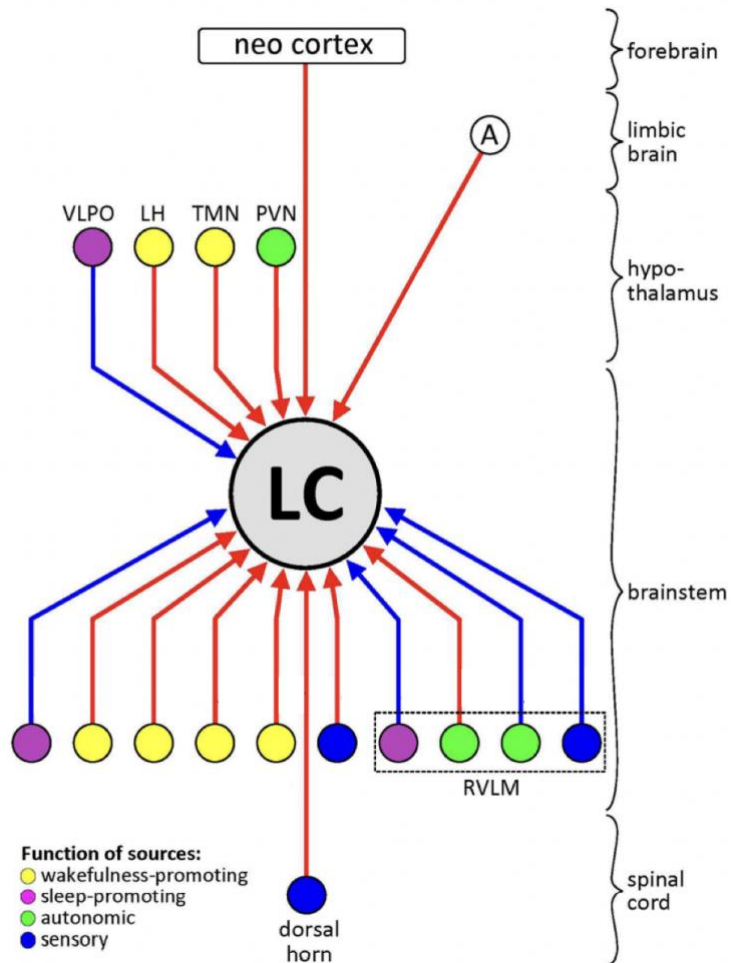
# AFFERENTS OF LOCUS COERULEUS



Figure 1.2. Afferents of Locus Coeruleus. Projections are represented by arrows. Red arrowheads depict excitatory inputs, and blue arrowheads depict inhibitory inputs. The figure is adapted from "Functional neuroanatomy of the central noradrenergic system" by Elmer Szabadi, 2013, Journal of Psychopharmacology, Volume 27, Issue 8. Copyright [2013] by the SAGE Publishing. Adapted with permission.

**Adrenoreceptors and NE Effect**

There are three main adrenoreceptor types in the brain: α1-, α2- and β-adrenergic

receptors (Berthelsen & Pettinger, 1977). All adrenoreceptor types are G-protein coupled

receptors, each consisting of multiple subtypes (Molinoff, 1984) with varying binding

affinity for NE (Greengrass & Bremner, 1979). Importantly, there is a differential

distribution of these receptor types in the brain (Reznikoff et al., 1986), playing a role in

the differential influence of LC in each target region of the brain (Benarroch, 2018). The

intracellular effects of NE on neurons are reported to be both inhibitory and excitatory

(McCormick & Prince, 1988). The α1- and β-adrenergic receptors are primarily present at

the postsynaptic sites influencing synaptic excitability and plasticity. In contrast, the α2-

adrenergic receptors reside at both presynaptic and postsynaptic sites and generally

inhibit neurotransmitter release. However, activation of the α2-adrenergic receptors

within the prefrontal cortex has been shown to increase cortical excitability by inhibiting

local hyperpolarization-gate cations (Arnsten et al., 2012). NE's primary effect is reported

to be a reduction in spontaneous neural activity and increasing responsiveness of sensory-

related neurons to sensory stimuli. NE has also been shown to impact synaptic plasticity

within cortical and subcortical areas of the brain (Benarroch, 2018; Hagena et al., 2016;

Lim et al., 2010; Lippiello et al., 2015).

**Animal Locus Coeruleus Physiology**

The electrophysiological properties of LC have been exclusively characterized within

non-human animal models. A series of studies using intracellular and extracellular

recordings have demonstrated that LC neurons exhibit two distinct modes of action:

phasic and tonic (Aston-Jones et al., 1991; Aston-Jones & Cohen, 2005; Reiner, 1986;

Usher et al., 1999; Waterhouse et al., 1998), which differ in NE-releasing properties and

spike discharge patterns. The next sections describe these modes in more detail.

**Tonic LC Mode**

LC tonic baseline activity is characterized by a sustained, irregular, and lower baseline frequency discharge (2-5 Hz), which has been suggested to be linearly related to the sleep-wake cycle and general arousal (Berridge & Abercrombie, 1999). Results from single and multiple unit extracellular recording of LC neurons in rats have shown that LC tonic discharge covaries with the sleep-wake cycle, where LC tonic discharge is during wakefulness, low during slow wave sleep, and extinguishes during paradoxical sleep (Aston-Jones & Bloom, 1981a). Furthermore, in rat models, LC tonic discharge during wakefulness is shown to be low during grooming and resting times and high with sensory-evoked interruptions such as unconditioned auditory, visual, or tactile stimuli to grooming, food, and consumption, or other behaviors (Aston-Jones & Bloom, 1981a). Similar results have been reported in cat (Rasmussen & Jacobs, 1986; Reiner, 1986) and monkey (Aston-Jones et al., 1994; Foote et al., 1980; Grant et al., 1988; Rajkowski et al., 1994) models, suggesting that high levels of LC tonic activity are associated with distraction, poor performance, and disengagement from tasks. The relationship between LC tonic and behavior has been further examined in non-human animal models performing simple cognitive tasks (Aston-Jones et al., 2000, 2002; Devilbiss & Waterhouse, 2004; Howells et al., 2012; Kane et al., 2017; Usher et al., 1999). For instance, in monkeys performing a visual detection task, where they were required to respond to infrequent visual stimuli (e.g., Gabor patches) while ignoring frequent visual distractor stimuli, periods of high LC tonic activity were consistently associated with more false alarm errors (Aston-Jones et al., 1997; Rajkowski et al., 1994; Usher et al.,

1999). Moreover, across the aforementioned studies, animals' ability to discriminate or detect infrequent stimuli from frequent distractors was hindered during periods of high LC tonic activity, which was demonstrated as a decrease in standard signal-detection measures such as d', and an increase in animals' task reaction-time variability (Aston-Jones et al., 1996; Jodo et al., 1998; Rajkowski et al., 1994). Together, these results argue that increased LC tonic activity is generally accompanied by disengagement and distractibility, resulting in poor behavioral performance. The next subsection covers the LC phasic activity mode in detail.

**Phasic LC Mode**

In contrast to tonic LC activity mode, in rats and monkeys, phasic LC is characterized by being shorter in duration but higher in frequency discharge (10-20 Hz) (Aston-Jones & Bloom, 1981a; Vazey et al., 2018) and can spontaneously occur but is also associated with focused attention, salient stimuli, and task-related decision-making (Aston-Jones & Bloom, 1981b; Aston-Jones & Cohen, 2005; Clayton, 2004), or shifts in behavioral strategy including task contingencies (Bouret & Sara, 2004, 2005).

LC phasic discharge appears to be most robust with moderate levels of LC tonic discharge and is less robust with low and high LC tonic responses (Devilbiss & Waterhouse, 2011; Rajkowski et al., 1994; Waterhouse et al., 1998). To that end, it could be said that phasic LC discharge is partially dependent on the LC tonic activity. This is further supported by studies showing external stimuli that elevate LC tonic discharge can

reduce LC sensory-driven phasic activity (Rajkowski et al., 1994; Valentino & Foote, 1988; Valentino & Wehby, 1988).

**LC Modulation of Sensory Processes and Perception**

LC-NE has been shown to modulate cognitive processes, including sensory processing and perception (Berridge & Waterhouse, 2003a). Below, the neuromodulatory impacts of the LC-NE circuit on visual, auditory, and somatosensory processes are reviewed.

**Visual**

The effects of LC-NE on visual processes and perception have been primarily examined using local administration of NE and LC stimulation in rats, cats, and monkeys (Rogawski & Aghajanian, 1980b). LC-NE impact has been examined in different parts of the visual pathway. For example, local administration of NE or electrical stimulation of LC has been shown to increase the magnitude of LGN neurons' response (Rogawski & Aghajanian, 1980a), which are responsible for transmitting information from the retina to the cortex. These results are also supported by in vivo tissue slice experiments conducted on cat and guinea pig tissue slices (McCormick et al., 1991).

Most of the studies that have employed local administration of NE have generally found an inhibitory effect on spontaneous activity within different layers of the visual cortex (Ego-Stengel et al., 2002; Kolta et al., 1987; McLean & Waterhouse, 1994; Olpe et al., 1980). With these predominantly inhibitory effects of LC on spontaneous activity within the visual cortex, no significant modulation of the signal-to-noise ratio was

observed (Sato et al., 1989; Videen et al., 1984). Albeit, studies report that the influences

of NE are highly dose-dependent (McLean & Waterhouse, 1994; Olpe et al., 1980).

Moreover, one study by (Kolta & Reader, 1989) has shown that noradrenergic

administration has an inhibitory effect on background neural activity, leading to an

enhancement of the signal-to-noise ratio. Additionally, few other studies in rat and cat

models have shown that NE increases the signal-to-noise ratio by positively impacting

just below the threshold neurons, increasing their visual responsiveness (Kasamatsu &

Heggelund, 1982; McLean & Waterhouse, 1994; Waterhouse et al., 1990)

**Auditory**

Much of what is known about LC's effect on auditory perception comes from

pharmacological manipulations of NE in squirrel monkeys, bats, and cats. While the main

effect of the LC-NE circuit on auditory processing is predominantly reported to be

inhibitory with no significant modulation of signal-to-noise ratio, i.e., both sensory-

evoked and spontaneous activity were inhibited (Chikamori et al., 1980; Foote et al.,

1975; Kossl & Vater, 1989; Manunta & Edeline, 1997), the inhibitory effects of LC-NE

on auditory cortical neurons appear to be dose-dependent, as the iontophoretic application

of different concentrations of NE has been shown to result in different inhibitory

magnitudes (Chikamori et al., 1980; Kossl & Vater, 1989; Manunta & Edeline, 1997,

1999).

Though LC-NE does not seems to widely modulate signal-to-noise ratio within

the auditory cortex, except for (Kossl & Vater, 1989), where iontophoretic application of

NE in anesthetized and unanesthetized has been shown to improve auditory cortical neurons' frequency selectivity for pure tones during the iontophoretic process and afterward (Manunta & Edeline, 1997, 1999). In a later study, (Edeline et al., 2011; Manunta & Edeline, 1997, 1999) LC stimulation was paired with auditory stimuli (e.g., pure tones) to understand the potential plasticity effects of LC. Results from this study showed an enhanced cortical auditory representation in the auditory cortex, with LC stimulation (100 Hz) paired with auditory stimuli resulting in a selective response tuning for a large population of auditory cortical and thalamus neurons. The selective response tuning of the auditory and thalamic neurons began during the LC stimulation and lasted for approximately 15 minutes after LC stimulation; this selectivity response onset and offset in both structures suggests that there is a bidirectional connection between the LC and the auditory cortex (Edeline et al., 2011). These mixed findings about the influence of LC-NE on sensory processing from the studies conducted by Manunta and Edeline et al. (Edeline et al., 2011; Manunta & Edeline, 1997, 1999) could be due to different pathways of LC to the auditory cortex (see Figure 1.1 and Figure 1.2) where pairing LC stimulation with pure tones engage thalamic pathways that are otherwise not engaged.

**Somatosensory**

Many studies have examined the LC-NE modulatory role on somatosensory processes in rats, cats, and monkeys (Devilbiss et al., 2006; Devilbiss & Waterhouse, 2004, 2011; Waterhouse et al., 1980, 1981, 1982; Waterhouse & Woodward, 1980). In-depth analyses of the effect of LC-NE on somatosensory processing were conducted by local

administration of glutamate (a major excitatory neurotransmitter), stimulating afferent

pathway (see Figure 1.2.), iontophoretic application of NE (Waterhouse et al., 1980), and

LC neuron stimulation in anesthetized or intact rats (Devilbiss & Waterhouse, 2011;

Hurley et al., 2004). Local administration of NE has been shown to increase target

sensory neurons' representations by inhibiting spontaneous activity more than those

evoked by sensory signals, resulting in an overall increased signal-to-noise ratio

(Armstrong-James & Fox, 1983; Castro-Alamancos & Gulati, 2014; Waterhouse &

Woodward, 1980). These results are largely within the Adaptive Gain Theory (Aston-

Jones & Cohen, 2005) framework that is discussed in the next section.

In a study by (Devilbiss et al., 2006), researchers used the rat vibrissae

somatosensory system to understand the influence of LC stimulation on sensory

representations of sensory input in ventral posteromedial (VPM) neurons of the thalamus.

Results from this study showed that LC neuron stimulation in rats resulted in an increased

NE level within trigeminal somatosensory nerves, which was accompanied by an overall

transmission of whisker pad sensory information, resulting in an inverted-U-shaped

relationship where no LC stimulation and high LC stimulation (~ 5 Hz) were associated

with poor ventral posteromedial (VPM) thalamic neuron responsiveness to synaptic

input, and moderate LC stimulation (~1 Hz) was associated with significantly increased

responsiveness of thalamic neurons to the synaptic input. Interestingly, a follow-up study

by (Devilbiss et al., 2012) showed when the LC-NE circuit is abnormally activated, i.e.,

as a result of high levels of stress, spontaneous activity is enhanced, and sensory-evoked

activity is inhibited, resulting in impairment of sensory information processing through poor signal-to-noise ratio.

Within somatosensory processing, LC-NE has been shown to also impact the fidelity of sensory representations by reducing spontaneous activity latency and inducing action potential in previously inactive neurons (Hurley et al., 2004). Other studies investigating the effects of LC-NE on somatosensory processing have shown that increased LC-NE activity inhibits spontaneous neural activity and facilitates sensory information processing (Devilbiss & Waterhouse, 2011; A. Hirata et al., 2006).

**Human Locus Coeruleus Neuroscience**

**Methods for Assessing LC Activity in Humans**

In humans, evaluating and assessing the dynamics of LC and its relationship with cognition in humans is primarily derived from pupillometry, which is used as an indirect marker of LC activity (Breton-Provencher & Sur, 2019; Frank & Nassar, 2016; Joshi et al., 2016; Murphy, O'Connell, et al., 2014), and magnetic resonance imaging (MRI) (Betts et al., 2019; Keren et al., 2009; Langley et al., 2017).

**Magnetic Resonance Imaging (MRI)**

For many years, imaging LC was challenging due to its small size and location, which does not provide any boundary landmarks for easy detection of LC structure on MRI images. However, with advancements in LC molecular components, LC has been shown to have different magnetic properties than its neighboring nuclei and structures, which

leads to a hyperintense signal in MRI images (Liu et al., 2020; Manaye et al., 1995; Mann & Yates, 1974). This has led to the detailed analysis of LC structure, development, and integrity with age and disease in humans (Betts et al., 2017, 2019; Langley et al., 2017; Liu et al., 2017; Priovoulos et al., 2018).

**Pupillometry**

Pupillometry has been a tested proxy of LC activity (Breton-Provencher & Sur, 2019; Frank & Nassar, 2016; Kalwani et al., 2014; Lanctot & Aleman, 2021). In animal models, cellular recording of LC has shown increased LC neural response to novel and infrequent stimuli in oddball paradigms and normal or weak neural response to infrequent or task-irrelevant stimuli (Aston-Jones & Cohen, 2005). In humans, it has been challenging to directly assess the moment-by-moment LC activity variation in response to task-related behaviors. To that end, pupillary dilation has been used as a proxy measure of LC phasic activity (Joshi et al., 2016).

**Behavioral Paradigms**

Oddball paradigms are commonly utilized to understand processes related to salient, emotional, or novel stimuli detection and discrimination. Traditional oddball paradigms include frequent and infrequent ("oddball") stimuli for detection or discrimination, and properties of the infrequent stimuli, such as novelty, saliency, or arousal valence, are often manipulated to address target research questions. More recently, oddball paradigms have been employed to modulate LC-NE signaling, as LC seems to robustly respond to

task-relevant salient or novel stimuli (Cerro et al., 2020; Kamp & Donchin, 2015; Krebs et al., 2018; Murphy, O'Connell, et al., 2014). Oddball tasks utilized in conjunction with isometric handgrip manipulation, a classical stress-inducing paradigm, can be a powerful tool to manipulate LC activity to investigate LC-related changes in cognitive processes (Mather et al., 2020; McAllister, 1979; Nielsen & Mather, 2015; Wallin et al., 1992). Over the past decade, there have been remarkable studies in humans using fMRI, and pupillometry, with behavioral paradigms designed to target and examine LC activity (Dahl et al., n.d.; Hussain et al., 2019, 2022; Jacobs et al., 2020; Liebe et al., 2022; Nielsen & Mather, 2015; Sara, 2015; Wainstein et al., 2022).

## Theories of LC Function

### Adaptive Gain Theory

The first theory is the Adaptive Gain Theory (Aston-Jones & Cohen, 2005), which seeks to explain the gain of cortical sensory and information processing to optimize behavior using phasic and tonic modes of LC activity. According to this theory, tonic LC activity serves the circuit as a general arousal regulator, where low and high LC tonic activity is hypothesized to be associated with poor performance that can lead to behavioral exploitation and exploration, and moderate levels of LC tonic are hypothesized to mediate optimal performance. Phasic LC mode is hypothesized to transiently emerge in response to task-relevant, salient, or novel stimuli, where it serves LC as a temporal attentional filter that enhances task-relevant stimulus processing and filters out task-irrelevant stimuli (Clayton et al., 2004; Eldar et al., 2013; Gilzenrat et al., 2010; Jepma &

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Nieuwenhuis, 2011; Kane et al., 2017; Usher et al., 1999). Overall, the relationship

between tonic LC and behavioral performance described by the Adaptive Gain Theory

closely resembled the (Yerkes & Dodson, 1908) inverted-U-shaped function (Figure

1.3), with LC tonic on the x-axis and behavioral performance on the y-axis (Aston-Jones

& Cohen, 2005).

One of the earlier studies that perhaps sparked the evolution of the Adaptive Gain

Theory collected recordings from LC neurons in monkeys performing a visual oddball

detection task (Rajkowski et al., 1994) where monkeys had to respond to infrequent

visual stimuli while refraining from responding to frequent stimuli. A clear correlation

between pupil sizes and periods of phasic and tonic activity was observed, where larger

and smaller pupil dilations were associated with tonic and phasic activity, respectively.

These studies led to multiple other studies examining LC phasic and tonic in animals

performing various cognitive tasks (Aston-Jones et al., 1994, 1997, 1999; Foote et al.,

1980). Results of those studies demonstrated that periods of goal-oriented and focused

attention were accompanied by phasic LC activity, and in contrast, periods of agitation

due to prolonged task performance were associated with high levels of tonic LC activity

and no significant phasic firing.

Although the authors themselves may not have explicitly mentioned it, as some of

those studies predate the Adaptive Gain Theory, much of the discussed literature on LC

modulation of sensory processes falls within the context of this theory. According to the

Adaptive gain theory, the LC-NE system modulates the gain of cortical sensory and

information processing to optimize behavior. To some extent, the auditory, visual, and

somatosensory processes literature discussed above supports at least the cortical gain

modulation part of the theory. Across the discussed studies looking at LC modulation of

sensory processes, NE has been shown to modulate the gain of sensory-evoked stimuli by

either decreasing spontaneous neural activity, which results in an overall increased

signal-to-noise ratio (or decreased signal-to-noise ratio if NE levels are too high),

increasing the magnitude of sensory neurons' responses, or improving selectivity

(Armstrong-James & Fox, 1983; Edeline et al., 2011; Manunta & Edeline, 1999;

Rogawski & Aghajanian, 1980b; Waterhouse & Woodward, 1980). Because tonic versus

phasic LC was not recorded in most of those studies, it cannot be said that those data

fully support the Adaptive Gain Theory. However, the gain effects of NE on sensory

processing are partially in alignment with the theory (for a detailed review, see (Berridge

& Waterhouse, 2003a)).

In humans, evidence for the Adaptive Gain Theory is derived from pupillometry

(Gilzenrat et al., 2010). Consistent with the Adaptive Gain Theory framework, an inverse

relationship between pre-stimulus and post-stimulus pupil dilation has been found, where

larger pupil dilations were evoked by oddball auditory stimuli that were in turn associated

with focused attention and exploitation in the oddball auditory paradigm, and overall

larger baseline (i.e., pre-stimulus) pupil dilation were associated with higher false alarm

rates and misses (Gilzenrat et al., 2010; Murphy et al., 2011). Similar findings were

reported within the visual perception (Einhäuser et al., 2008).

According to this theory, LC-NE modulates cortical gain. Some of the support for

this theorized role of LC modulation of the cortical gain comes from its relationship with

the P300 event-related potential (ERP), which is cortical activity recording peaks at about 300 milliseconds (Kamp & Donchin, 2015; Pineda et al., 1989). In monkeys, lesions to LC have been shown to negatively affect the magnitude of P300 (Pineda et al., 1989). Moreover, pharmacological reduction of LC activity via clonidine has been shown to exert similar influences on P300, such as reduced active cortical area and increased P300 latency (Swick et al., 1994). Additionally, the P300 has been demonstrated to correlate closely with pupillometry, which is considered to be an index measure of LC activity, and task performance on an auditory oddball task (Murphy et al., 2011), all following an inverted-U-shaped relationship. While the exact mechanisms by which the LC-NE circuit is connected to the P300 ERP are not yet understood, these multi-measure pieces of evidence support the LC's relationship with the P300 and fit within the Adaptive Gain Theory framework.

In humans, there are still key pieces of evidence required to fully test the Adaptive Gain Theory. For instance, both pupillometry and ERP are indirect measures of LC, which are confounded by other ongoing cognitive processes (Gilzenrat, 2006; Melnychuk et al., 2021). To fully test the Adaptive Gain Theory, a more systematic evaluation and granular timescale assessment of LC activity and its relationship with behavior are necessary, which has been challenging to understand in humans due limited noninvasive approaches to manipulate and record from LC. In Chapter 2, I discuss a study that provides a stepping stone toward examining the relationship between LC and behavior.
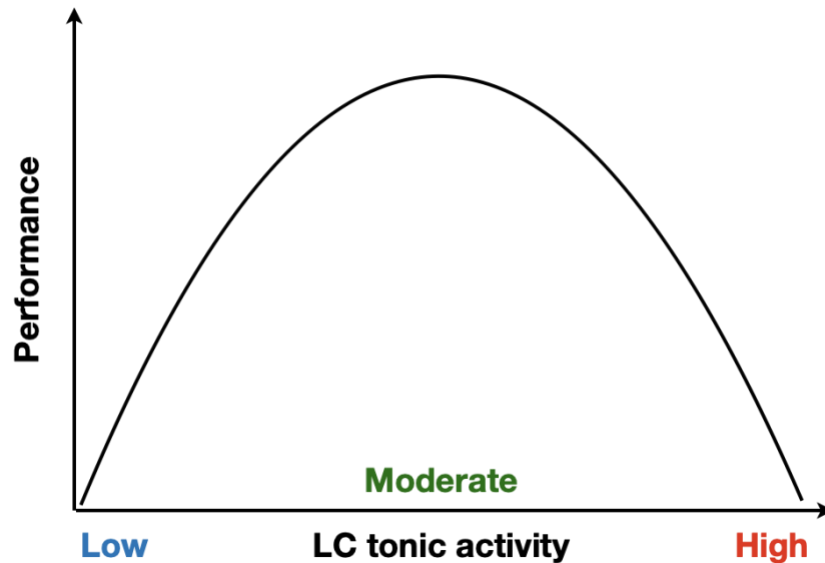
Figure 1.3. Yerkes-Dodson 1908 inverted-U-shaped curve (Yerkes & Dodson, 1908). Redrawn to represent the Adaptive Gain Theory (Aston-Jones & Cohen, 2005)

**Network Reset Theory**

In contrast to the Adaptive Gain Theory, which proposes that phasic LC activity facilitates focused attention leading to exploitation, the Network Reset Theory proposes that LC-NE neurons induce cortical arousal to reset and reorganize network activity accordingly when detecting salient, novel, uncertain, or emotional stimuli (Dayan & Yu, 2006; Sara & Bouret, 2012; Yu & Dayan, 2005). The Network Reset Theory does not address the distinct behavioral associations with the phasic or tonic response and appears to be primarily concerned with LC's role in attention, learning, and memory (Sara, 2015, 2016; Sara & Bouret, 2012; Yu & Dayan, 2005).

Specifically, LC activity has been shown to be related to specific aspects of learning (Sara & Segal, 1991). For example, in rats, LC neurons have been shown to activate in response to a stimulus with reinforcement stimulus, whereas their activity dissipated when the stimulus is presented at a behavioral level without any reinforcement,

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suggesting LC does not necessarily only mediate specific sensory processes but facilitates behavioral adaptation as a function of cognitive and stimulus significance (Aston-Jones et al., 1997; Sara et al., 1994; Sara & Segal, 1991; Vankov et al., 1995). Additional support for LC's role in learning and behavioral adaptation has come from pharmacological studies showing increased LC-NE activity facilitated behavioral adaptation (Devauges & Sara, 1990), for example, shifting from a strategy task to a visual discrimination task, whereas decreased LC-NE activity impaired animals behavioral adaptation to new contingencies (McGaughy et al., 2008).

Additionally, simultaneous recordings from LC neurons and prelimbic area in rats showed increased LC activity associated with behavioral responses that involved a reward compared to when the reward for behavior was delayed, suggesting that LC is involved in reward anticipation (Bouret & Sara, 2004).

In the human neuroscience literature, some support for the Network Reset Theory comes from empirical evidence for the relationship between LC and encoding of emotional or unexpected stimuli (Clewett et al., 2014; Sterpenich et al., 2006), and attention reorientation (Corbetta et al., 2008; Hermans et al., 2011).

While Network Reset Theory explains parts of LC's role in modulating cognitive functions, such as LC-induced cognitive shifts to reorganize and facilitate optimal behavior, it does not account for LC's role in sensory processing, perception, and perceptual behavior. A unified model of LC would require a detailed understanding of LC neural mechanisms underlying changes in attentional networks and cognitive functions.

**Discussion and Conclusion**

This Chapter reviewed LC anatomy and physiology and the routes by which they contribute to LC's influence on sensory processing and perception. The LC-NE circuit's role in cognitive functions and behavior has been challenging to study due to reasons including but not limited to LC's location (Liu et al., 2017), size (Sharma et al., 2010), and its wide projections (Keren et al., 2009) throughout the brain with each target differing in adrenergic receptor type and distributions (Vos et al., 1992), the excitatory and inhibitory inputs (Figure 1.1) and output (Figure 1.2), and its functional interaction with other neurotransmitters (Kim et al., 2016). Considering LC's broad projection throughout the cortex, it is often proposed that the LC serves the brain as the main hub where arousal signals get integrated to facilitate behavioral reactions accordingly (Aston-Jones & Cohen, 2005; Mather et al., 2016; Nieuwenhuis et al., 2005; Waterhouse & Navarra, 2019). Theoretical models such as the Adaptive Gain Theory posit that LC phasic mode is employed as a selective attentional filter in response to salient or high-priority stimuli and is particularly robust when LC tonic levels are moderate (Aston-Jones & Cohen, 2005). However, empirical evidence of LC activity and its behavioral impacts is very scarce in humans. To gain more insight into the LC-NE circuit's effects on cognitive processes and behavior, empirical evidence of a more granular timescale of LC activity in correspondence with behavioral performance is required.

Accessible measures and manipulations of LC activity have been some of the major limitations and constraints in developing and testing models of how LC modulates perceptual representations and behavior, which is further complicated by the interaction

between perception and other cognitive processes like attention, decision-making, learning, and memory. The extant literature is rich with empirical evidence of LC's neural and behavioral effects in non-human models (Aston-Jones & Cohen, 2005; Devilbiss & Waterhouse, 2011; McBurney-Lin et al., 2022; Poe et al., 2020). However, to date, no model has bridged the gap in understanding the neural mechanisms of LC across different cognitive functions, such as learning and memory versus sensory processing and perception, or between our understanding of LC humans versus animal datasets. Human LC research heavily relies on indirect measures of LC activity, like pupillary dilation, fMRI, or cortical event-related potentials (Murphy et al., 2011; Murphy, O'Connell, et al., 2014). Additionally, LC research in humans seems to be focused on LC influence on decisional processes (de Gee et al., 2014, 2017; Duzel & Guitart-Masip, 2013; Gilzenrat et al., 2010) and is vastly limited to general cognitive processes like perception. Today's technical advancements in neuroimaging sequences, preprocessing, and neuroimaging data analysis, along with computational fMRI models, provide a platform for identifying LC-related changes in perceptual representations, processes, and behavior-specific activity of LC.

Noninvasive behavioral and pharmacological paradigms are mostly indirect and have confounding variables associated with their employment. For example, pharmacological manipulations usually involve bi-directional modulation of NE levels by using clonidine, commonly used as a sedative (Hall et al., 2001), and reboxetine, which increases NE signaling by acting as a selective noradrenaline reuptake inhibitor (Wong et al., 2000). Systematically reducing LC-NE activity via clonidine is confounding by the

sedative effects of clonidine that can result in decreased vigilance and sleepiness (Gelbard-Sagiv et al., 2018; Hou et al., 2005; Morley et al., 1991) and is further modulated by the dose of clonidine used. Moreover, unlike the LC-NE signal that is suggested to be selective, pharmacological manipulation of NE is global within the central nervous system, impacting blood pressure, interactions among other neuromodulators such as serotonin, acetylcholine, neural networks, and behavioral processes (E. R. Samuels & Szabadi, 2008; E. Samuels & Szabadi, 2008). Nonetheless, pharmacological studies coupled with fMRI and behavioral paradigms provide the opportunity to test hypotheses and models of the relationship between modulated LC activity, which modulates NE levels, cognitive processes, and behavioral outcomes.

To model complex neuromodulatory activities of the LC-NE system, multi-level and multi-measure experiments are required to truly examine the dynamics of LC influence on the neural representation of related brain regions, as well as patterns of behavioral activity. This would include using high-resolution fMRI, EEG, and pupillometry coupled with systematic behavioral methodologies that give rise to multiple behavioral measures that can capture LC-NE influences. Although such experiments do not directly examine LC activity, they provide the opportunity to assess the dynamic effect of LC across multiple measures to understand the potential mechanism by which LC is involved in a particular cognitive function and behavior. Additionally, future studies should have within-subject designs that include the investigation of more than one cognitive function to facilitate the development of innovative models that can explain LC's role across multiple cognitive functions. This review is meant to highlight key

findings about the influences of LC on sensory processing and perception while also

alerting researchers of the need for further investigation of LC's influence on multiple

cognitive functions in humans.

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**Chapter 2: LC's Influence on Auditory Perceptual Behavior and Neural**

**Representations**

**Abstract**

Understanding the neuromodulatory role of the Locus Coeruleus-Norepinephrine (LC-NE) circuit on sensory processing and perception has been challenging in human models due to limited experimental approaches for recording and manipulating LC activity. In the current study, a novel perceptual discrimination task designed to extract sensitive stimulus-response function was used with an isometric handgrip manipulation to upregulate LC activity and high-resolution fMRI to comprehensively examine the consequences of LC engagement on perceptual behavior as well as on the neural representations of auditory perceptual stimuli in the primary auditory cortex. The reported auditory oddball discrimination paradigm allows for accurate estimation of behavioral and neural stimulus-response functions that can possibly capture influences of modulated LC activity. Reported findings provide insight into appropriate experimental paradigms and measures for a noninvasive approach to manipulate LC to study the influence of LC-NE upregulation on sensory representations and behavioral performance.

**Introduction**

The brain dynamically processes information in concert with other ongoing processes and the internal state variables, and changes in any of the variables of this rather complex equation result in different behavior. The internal arousal state plays a particularly important role in representing sensory information in the brain (Berridge & Waterhouse, 2003; Castro-Alamancos, 2002; Foote et al., 1980; Mayes, 2000; Sara, 2009; Sörensen et al., n.d.; Stitt et al., 2018; Waterhouse & Navarra, 2019), and it is heavily influenced by

primary neurotransmitters such as Norepinephrine (NE). In the brain, NE is primarily produced by the Locus Coeruleus (LC) nucleus in the pons of the brainstem, which has been shown to play a crucial role in cognitive and neural processes (Aston-Jones & Cohen, 2005; Berridge, 2005; Bouret & Sara, 2004; Mather et al., 2016). While tremendous effort has been put towards understanding LC's relationship with cognitive and neural functions such as sleep-wake cycles (Aston-Jones & Bloom, 1981), stress (Aston-Jones et al., 1994; Charney et al., 1990; Chen & Sara, 2007; Grueschow et al., 2021), attention (Aston-Jones et al., 1999; Mather et al., 2020; Sara, 2009), perception (Markovic et al., 2014; Mather et al., 2016; McBurney-Lin et al., 2019; Norman-Haignere et al., 2013), decision-making (Murphy et al., 2014; Nieuwenhuis et al., 2005; Reynaud et al., 2018), learning (Bouret et al., 2003; Bouret & Sara, 2004; Glennon et al., 2019), and memory (Clewett et al., 2018; Jacobs et al., 2020; Mather et al., 2016; Sara et al., 1994; Unsworth & Robison, 2017), very few studies have investigated the underlying mechanisms by which LC affects perceptual representations and performance in humans.

Perhaps, our limited understanding of LC's role in perception is in part due to the small size and location of LC, as well as a lack of noninvasive measures of LC, which particularly challenged our ability to test theory-driven hypotheses of LC, such as the modulation of signal-to-noise ratio. As a result, many great theories of LC driven by animal research have remained untested in human models.

To examine the relationship between LC and perception, in this study, a novel perceptual discrimination task was coupled with functional Magnetic Resonance Imaging (fMRI) to investigate the computational consequences of LC engagement on the sensory

representation through analyzing blood-oxygen-level-dependent (BOLD) signal changes

and patterns of activity in the primary auditory cortex, as well as examining changes in

perceptual behavior. Considering LC's role in modulation of signal-to-noise ratio in

sensory processes (Chapter 1), and the anatomical LC efferents (Figure 1.1) and afferents

(Figure 1.2), here, upregulated LC activity is hypothesized to result in enhanced sensory

representations within the auditory cortex, and positively impact perceptual behavior. To

test these hypotheses, a novel auditory oddball paradigm was developed and used in

conjunction with univariate and multivariate analyses of high-resolution fMRI, which

enable estimation of averaged neural activity and patterns of neural activity to examine

the influence of upregulated LC activity on sensory representations in human primary

auditory cortex. The novel Auditory Oddball Discrimination (AOD) task used in this

study included a stimulus sensitivity manipulation, such that multiple levels of oddball

stimulus were presented for discrimination. The employed behavioral paradigm paired

with neural activity measures facilitated a sensitive estimation of behavioral and neural

stimulus-response functions, which can more easily capture the neuromodulatory

influences of LC. Results from this study show a successful estimation of behavioral and

neural stimulus-response functions, where behavioral performance, averaged auditory

cortex BOLD signal, as well as decodability of the BOLD signal associated with oddball

levels, increase as a function of Oddball Stimulus Level, and show susceptibility to

capture changes change resulting from factors such as the employed handgrip

manipulation. These findings provide valuable methodological insight into experimental

design and computational analysis factors that play a key role in researching the relationship among LC, sensory processing, and behavioral outcome.

**Methods**

**Participants**

Thirty-one healthy undergraduate students were recruited from the University of California, Riverside ((17 F), $M_{age} = 24.5$, $SD_{age} = 4.4$ yrs.) to participate in this study. All participants provided written informed consent approved by the University of California, Riverside's Institutional Review Board and received monetary ($10 per hour) compensation for their participation in this study. All participants reported normal or corrected-to-normal vision, had no history of psychiatric or neurological disorders and were not taking any psychoactive drugs.

Data from 5 participants have been excluded: one participant due to later diagnosis with ADHD and consumption of related medication, and four participants' datasets due to failed fMRIprep preprocessing (potentially due to different orientations of the AP/PA field maps). The total number of participants reported in this study across all analyses is 26.

## Procedure

### Overall Procedure

Upon arriving for the experiment, participants provided written informed consent, completed an MRI safety questionnaire, and provided basic demographic information. Next, participants were given instructions on performing the auditory oddball discrimination task with instructions on squeezing or holding the squeeze ball. To familiarize participants with the auditory oddball discrimination task and ensure correct performance on the Squeeze or hold (hereon referred to as the Control) procedure, they completed ten task practice trials and practiced holding or squeezing the squeeze ball. All participants were given the exact verbal instructions for the Squeeze or the Control experimental session.

Scanning procedures took approximately 1 hour. Inside the MRI scanner, participants first completed the anterior-posterior (AP) and posterior-anterior (PA) field maps, which were then followed by a resting state (RS) functional scan (Figure 2.1). Participants were then given a squeeze ball and were instructed to bring it up to their chest and squeeze or hold it, as a control, for 18 seconds and rest for a short period. The squeeze-and-rest or control-and-rest periods occurred five times (Figure 2.1). Upon completion of the Squeeze or the Control session, the squeeze ball was replaced with a response button box, and participants completed three runs of the auditory oddball discrimination task (Figure 2.3). After the first three task runs, participants completed two rounds of an 18-second long squeeze or hold period followed by a 2-minute long

resting state. Following that, participants completed three more runs of the auditory

oddball discrimination task. Between each run, participants were allowed to close their

eyes and rest for a short time (>2 minutes) and were reminded to keep their heads as still

as possible.

**Squeeze Session**

Following the initial resting state, participants underwent a series of squeezing the

squeeze ball with their maximum strength and then resting (Figure 2.2). The squeeze

duration was always 18 seconds and the resting state period had durations of one-, two, or

five-minute-long (Hussain et al., 2019; Mather et al., 2020; Nielsen & Mather, 2015). A

total of five squeeze-and-rest iterations were completed before beginning the AOD task

(Figure 2.1).

**Control Session**

The control session procedure was the same as the squeeze session in structure, except

participants did not squeeze the ball; instead, they held the squeeze ball without exerting
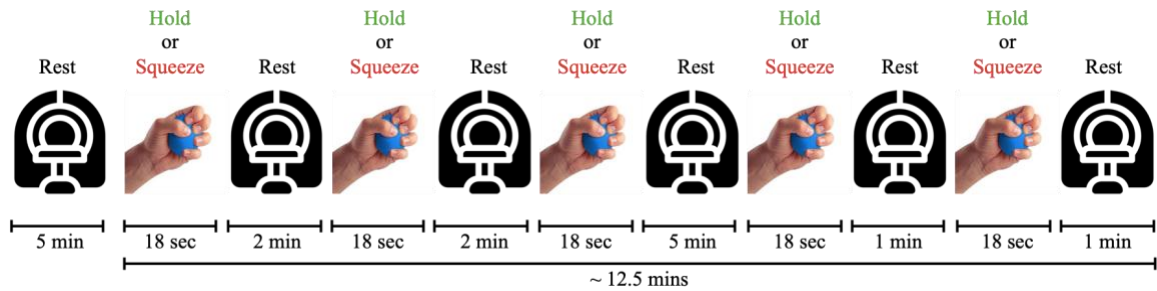
any force (Figure 2.1).

Figure 2.1. Squeeze/Hold (Control) session procedures. The experimental session began with a 5-minute resting state followed by five iterations of an 18-second squeeze or hold (control) period followed by a two-, two-, five-, one-, and one-minute, respectively. The schematic is not drawn to scale.
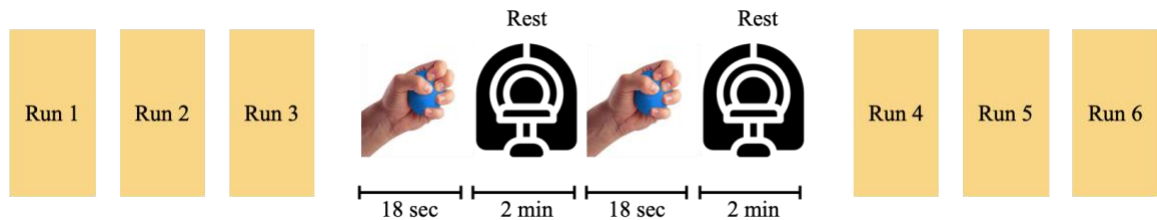


Figure 2.2. General schematic of auditory oddball discrimination task's experimental runs 1-3, followed by the mini-squeeze or mini-hold period, followed by experimental runs 4-5. The schematic is not drawn to scale.

After completing all task runs, scanning concluded with a T1-weighted and a T2-weighted high-resolution neuroanatomical scan, the second round of AP/PA field map scans, and a Neuromelanin or Diffusion Tensor Imaging (DTI) scan. To keep scanning hours short, the Neuromelanin scan was collected during the first session, and the DTI scan was collected during the second session.

**Auditory Stimuli**

The auditory stimuli consisted of five consecutive tones with 100 ms per auditory tone and an inter-stimulus-interval duration of 400 ms. The frequent trial stimulus consisted of five 1000 Hz tones, while the oddball trial stimulus included a single odd tone  (1004,

1008, 1016, 1032, 1064, 1128Hz) embedded in four 1000 Hz tones (Figure 2.3). In

addition to the oddball and frequent trials, a number of blank trials (no auditory stimuli)

were included in our design to examine the sound-sensitive (frequent and oddball) voxels

in the auditory cortical area. The position of the oddball was never in the sound

sequence's first or last tone. The stimulus was presented for a duration of 2.5 seconds,

and participants had a response window of 1.9 seconds to indicate whether a trial was

oddball or frequent using a 2-button MRI-compatible response box (reponsepixx from

VPixx Technologies, Vision Science Solutions, Quebec, Canada). Following each

response, participants were given text feedback (correct, incorrect, missed) on the screen.

On blank trials, no auditory stimuli were presented; participants were given text

information on the screen to press a particular button. The stimulus and paradigm were

programmed (Aaron Seitz) in MATLAB (2015b) using Psychtoolbox, version 3.0

(Kleiner et al., 2007).

**Task Design**

The overall structure of the experiment was a 1 (discriminate frequent or oddball) x 2

(arousal condition: Squeeze vs. Control) within-participant design, with oddball including

multiple stimulus levels. There was a total of 234 trials per session, which were

subdivided into six runs of 39 trials each. Each experimental run consisted of oddball,

frequent, and blank trials with a proportion of 24:9:6, respectively. The task was designed

to include multiple levels of Oddball Stimulus Level with an equal number of oddball

trials per each oddball level (Figure 2.3). Each participant performed a total of two

sessions under two conditions and on two different days: one with squeezing a squeeze

ball, alternating with rest periods, and another with only holding the squeeze ball and

alternating with resting periods. The experimental session order (Squeeze vs. Control)
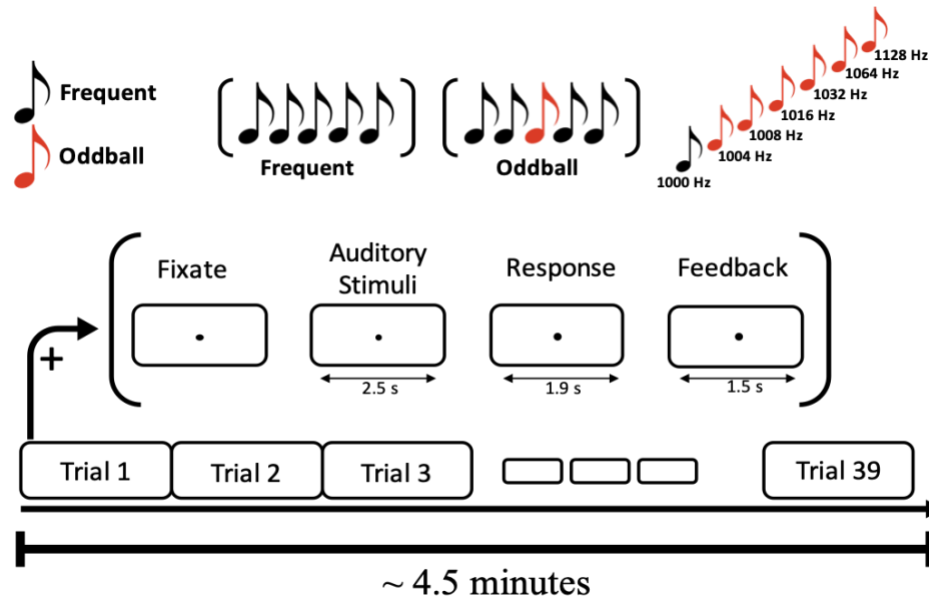
was counterbalanced across all participants.



Figure 2.3. Task design schematic. Depicting Frequent vs. Oddball trials, Oddball tone
saliency levels, task procedure, and experimental run design.

The within-participant experimental design employed in this study required each

participant to complete two sessions corresponding to two conditions: squeezing a

squeeze ball to upregulate LC arousal levels or simply holding the squeeze ball without

exerting any force to understand base LC arousal levels. The order of the experimental

sessions was counterbalanced across all participants.

**Neuroimaging**

**MRI Data Acquisition**

All neuroimaging data were acquired on a 3T Siemens PRISMA scanner (Prisma, Siemens Healthineers, Malvern, PA) equipped with a 64-channel receive-only head coil located at the University of California, Riverside Center for Advanced Neuroimaging. The high-resolution T1-weighted and T2-weighted scans were collected using an MP-RAGE sequence (TE/TE/inversion time = 3.02/2600/800 ms, flip angle =8°, voxel size = 0.8×0.8×0.8 mm$^3$), which were used to aid functional image co-registration to common space.

Functional images for experimental the six experimental runs (138 volumes each) of the auditory oddball discrimination tasks were acquired using one echoplanar imaging sequence (TR/TE = 2000/32 ms, FOV = 224×196 mm$^2$, matrix size = 112×98, slice thickness 3 mm, 52 slices, flip angle = 69 degrees, multiband factor = 2, GRAPPA = 2, bandwidth = 1440 Hz/Px, phase encoding direction was anterior-posterior. The RS, DTI, or the Neuromelanin data were not analyzed or reported on in this dissertation (see (Hussain et al., 2022) for the RS and the Neuromelanin examination).

**Preprocessing**

Prior to any preprocessing steps, all functional and anatomical images were reorganized into Brain Imaging Data Structure (BIDS) to simplify data analysis and data sharing (K. J. Gorgolewski et al., 2016, 2017). The functional data underwent standard preprocessing

using the fMRIprep (Esteban et al., 2019) 21.0.1, which is based on Nipype 1.6.1 (K. J. Gorgolewski et al., 2011). For each experimental session, the T1-weighted images were corrected for intensity non-uniformity using N4BiasFieldCorrection (Tustison et al., 2010), distributed using ANTs 2.3.3. The T1-weighted images were skull-stripped using antsBrainExtraction.sh (ANTs 2.3.3), using OASIS30ANTs as the target template. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (MNI152NLin2009cAsym) (Fonov et al., 2009) was performed through nonlinear registration with antsRegistration (Avants et al., 2008) using skull-stripped versions of the T1-weighted images and template.

The T1w-reference was then skull-stripped using antsBrainExtraction.sh (ANTs 2.2.0), using OASIS as the target template. Spatial normalization to the ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov, Evans, McKinstry, Almli, & Collins, 2009) was performed through nonlinear registration with antsRegistration (ANTs 2.2.0; Avants, Epstein, Grossman, & Geea, 2008), using brain-extracted versions of both T1w volume and template. Brain tissue segmentation of cerebrospinal fluid, white matter (WM), and gray matter (GM) were performed on the brain-extracted T1w using fast (FSL 5.0.9; Zhang, Brady, & Smith, 2001).

Because each participant briefly rested between each experimental run (1-2 minutes) and performed either a squeeze or control interval between experimental runs 3 and 4, the following preprocessing steps were performed for each auditory oddball discrimination run to minimize any potential loss of signal as a result of co-registration of all the runs' data. First, a reference volume and its skull-stripped version were generated

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using a custom methodology of fMRIPrep. Head-motion parameters concerning the BOLD reference (transformation matrices and six corresponding rotation and translation parameters) were estimated before any spatiotemporal filtering using mcflirt (Jenkinson et al., 2002). BOLD runs were slice-time corrected to 0.955 (0.5 of slice acquisition range 0s-1.91s) using 3dTshift from AFNI (Cox & Hyde, 1997). The BOLD time series (including slice-timing correction when applied) were resampled onto their original, native space by applying the transformation to correct head motion. These resampled BOLD time series are referred to as preprocessed BOLD in original space or just preprocessed BOLD. The BOLD reference was then co-registered to the T1-weighted reference using FreeSurfer mir_coreg (Fischl, 2012), followed by flirt (Jenkinson & Smith, 2001) with the boundary-based registration cost function. Co-registration was configured with six degrees of freedom to account for distortions remaining in the BOLD reference.

Additionally, a set of physiological regressors were extracted to allow for component-based noise correction. Principal components are estimated after high-pass filtering the preprocessed BOLD time series using a discrete cosine filter with a 128s cut-off. No additional susceptibility distortion processing was performed. The BOLD time series were resampled to MNI152NLin2009cAsym standard space, generating a preprocessed BOLD run in MNI152NLin2009cAsym space. All functional volumes were then smoothed using a Gaussian kernel with full width at half maximum of 4 mm$^3$ using SPM12 (Wellcome Trust Centre for Neuroimaging, London, UK).

**Region of Interest (ROI)**

An ROI mask was constructed for the bilateral primary auditory cortical areas by combining the Anterior Transverse Temporal Gyrus of Heschl, the Lateral aspect of the Superior Temporal Gyrus, and the Transverse Temporal Sulcus (Destrieux et al., 2010) using parcellated grey matter from the high-resolution T1 anatomical scan.

To construct the primary auditory mask, the participants' high-resolution anatomical scan was used to reconstruct each hemisphere using Freesurfer's (http://surfer.nmr.mgh.harvard.edu/) recon-all function (i.e., reconstruction) called through custom-made shell scripts in anaconda virtual environment (Python Version 3.1). Using the landmark labels from the recon-all outputs, the labels G_temp_sup-G_T_transv, G_temp_sup-Lateral, and S_temporal_transverse were combined across both hemispheres to generate the primary auditory cortex mask. The ROI mask was generated in the native (participant) space and then transformed into the MNI space using FSL's FNIRT function (Smith et al., 2004).

**Analyses**

**Software and Equipment**

The auditory oddball discrimination task was programmed by Aaron Seitz in MATLAB 2015b (MathWorks, Natick, MA, USA) using Psychtoolbox version 3.0 and was revised for compatibility with the MRI system (3T Siemens PRISMA scanner equipped with VPIXX eye-tracking system, responsePIXX by Vision Science Solutions) by Xu Chen.

Multiple neuroimaging software packages were used to conduct and analyze data from this study, including but not limited to FSL (Smith et al., 2004; Woolrich et al., 2009), SPM (Penny et al., 2011), FreeSurfer (Desikan et al., 2006; Fischl, 2004; Fischl et al., 2002; Reuter et al., 2010, 2012), MRIcroGL (Rorden & Brett, 2000), and fMRIPrep (Esteban et al., 2019) that were implemented across MATLAB (Version 2018b) and Python (Version 3.6) to perform preprocessing, create ROI masks, and perform univariate and multivariate analyses.

**Data Cleaning**

Trials with a response time shorter than 100 ms after the start of the response window and missed response trials were excluded from all analyses (3519 trials/12168 total trials across all participants). Blank trials were only used for creating the sound-sensitive functional mask and have not been included in any data analyses beyond the GLM performed on the data (see below).

**Behavioral Data Analysis**

Each participant's behavioral performance was calculated based on correct decisions on "oddball" and "frequent" trials. For the frequent trials and each of the oddball trials (1004, 1008, 1016, 1032, 1064, 1128Hz), accuracy is calculated as the number of correct trials per each label (frequent, oddball: 1004, 1008, 1016, 1032, 1064, 1128Hz) over the total number of trials per label multiplied by 100. Behavioral psychometric functions for

each of the conditions (Squeeze vs. Control) were acquired by averaging accuracy per label across all trials within each experimental session.

For each trial, reaction time was measured as the time a response button was pressed minus the start of the response window. Reaction time provides insight into decision-making time and its corresponding function per frequent trials, and each of the oddball level trials is calculated as the average reaction time per label (frequent, oddball: 1004, 1008, 1016, 1032, 1064, 1128Hz).

**Univariate fMRI Analyses**

The functional MRI (fMRI) data were analyzed to estimate a neural stimulus-response function for the Squeeze versus Control sessions across the primary auditory cortex using a parametric GLM implemented in SPM12. Separate event-related regressors were created by modeling the onset times of the auditory oddball discrimination task's auditory stimuli and overlapped with a stimuli duration of 2.5 seconds. Each task regressor was convolved with a canonical hemodynamic response function. Six motion nuisance regressors were added (one for each run) within a single experimental session. Next, for each participant, single contrasts were performed for sound (frequent and all oddball levels) and oddball (for all oddball levels) to create a sound-sensitive mask and an oddball-sensitive mask within the defined A1 ROI. Both functional masks were combined to extract blood oxygenation level-dependent (BOLD) responses to frequent and oddball trials. Across all participants, for each trial, the average BOLD signal (across voxels and time within the ROI mask) was extracted one TR before and four TRs after

stimulus onset. Across all participants and all trials, any missed trials or trials with a

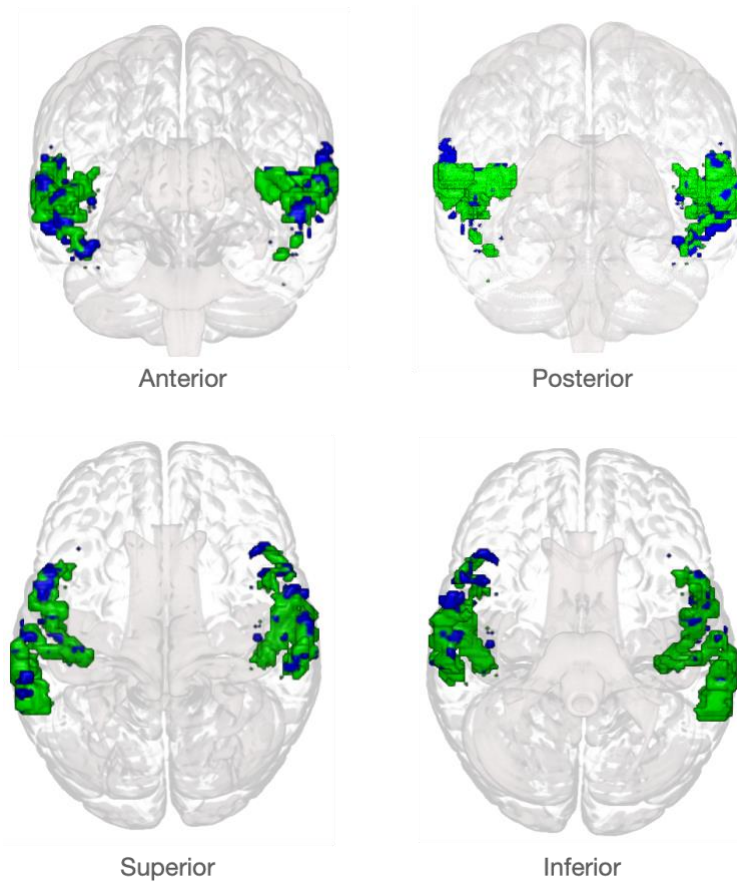response time of shorter than 0.1 seconds were excluded (3519/12168).



Figure 2.4. A single-subject example of the primary auditory cortex mask. The green voxels show the sound-sensitive functional mask, and the blue voxels show the oddball-sensitive functional mask.

**Multivariate fMRI Analyses**

To investigate the neural representations of the auditory oddball stimuli in the auditory

cortex, multivariate pattern analysis approaches were used to examine relative similarity

patterns of neural activity across experimental conditions and oddball levels. The

multivariate analyses reported were performed using The Decoding Toolbox (TDT)

(Hebart et al., 2015), which is a neuroimaging toolbox that is implemented on MATLAB

and is developed based on multivariate approaches established by Haxby and colleagues (Haxby, 2012; Haxby et al., 2001). The GLM models from the Univariate analyses were used to conduct cross-validated searchlight analyses on the sound-sensitive and oddball-sensitive ROI masks within the primary auditory cortex. A configuration variable matrix containing estimated betas from the standard general linear model, information per decoding label, and experimental run information was created. Then, a multiclass classification approach using the commonly used support vector multinomial classifier from LIBSVM (Chang & Lin, 2011) was used to run a cross-validated leave-one-run-out searchlight (3-voxel in radius searchlight, voxel size $= 2{\times}2{\times}2$ mm$^3$) decoding analysis among the regressors blank, frequent, oddball-o4, -o8, -o16, -o32, -o64, and o-128 (8-way classification). TDT outputs a series of estimations from the decoding analysis, including accuracy minus chance level per decoding of each of the regressors. Decoding analyses were run for each subject and session in each auditory functional mask.

**Statistical Analyses**

Statistical analyses were performed using JASP (JASP Team (2021). JASP (Version 0.15) [Computer software]. All the statistical analyses were performed on cleaned data (See Data Cleaning under Methods). For all the Repeated Measures ANOVA tests, if Mauchly's test of sphericity indicated that the assumption of the sphericity test is violated ($p < .05$), the Greenhouse-Geisser-corrected degrees of freedom are reported. Any significant interactions were followed by post hoc analyses (e.g., t-tests), reported in the

main text as well as the Chapter's Supplementary Figures. Error bars are within-subject standard error, which is calculated as:

$$\frac{Standard\ deviation\ (Mean\ corrected\ data)}{\sqrt{Sample\ size}}$$

**Behavioral Measure - Accuracy**

To examine main and interaction effects, a 2 (Conditions: Squeeze and Control) by 6 (Oddball Level 1004, 1008, 1016, 1032, 1064, and 1128 Hz) Repeated Measures ANOVA (RM-ANOVA) was performed on average percent correct across all participants for each Oddball Stimulus Level within each experimental session (Squeeze and Control), with the experimental session order accounted for as the between-subject factor.

To examine the longevity of the experimental Condition (i.e., Squeeze) effect on behavioral accuracy, data from runs were binned and averaged based on post-squeeze or control interval time. For instance, runs 1 and 4 were performed early-post-squeeze or -control interval, compared to runs 2 and 5, performed mid-post-squeeze or -control interval, and runs 3 and 5 performed late-post-squeeze or -control session. A 2 (Conditions: Squeeze and Control) by 3 (Condition Intervals: Early-, Mid-, Late-post-condition) by 6 (Oddball Levels: 1004, 1008, 1016, 1032, 1064, and 1128 Hz) RM-ANOVA was performed on the averaged and binned accuracy data, with experimental session order accounted for as the between-subject factor.

**Behavioral Measure - Reaction Time**

To examine main and interaction effects, similar to the behavioral accuracy analysis, a 2 (Conditions: Squeeze and Control) by 6 (Oddball Levels: 1004, 1008, 1016, 1032, 1064, and 1128 Hz). RM-ANOVA was performed on average reaction time across all participants for each Oddball Stimulus Level within each experimental session (Squeeze and Control), with the experimental session order accounted for as the between-subject factor.

Further, to examine the longevity of the experimental Condition (i.e., squeeze) effect on reaction time, similar to the behavioral accuracy data, a 2 (Conditions: Squeeze and Control) by 3 (Condition Intervals: Early-, Mid-, Late-post-condition) by 6 (Oddball Levels: 1004, 1008, 1016, 1032, 1064, and 1128 Hz) RM-ANOVA was performed on the averaged and binned reaction-time data, with experimental session order accounted for as the between-subject factor. The reaction time data were submitted to all statistical analyses without any data transformation procedure (i.e., no lon transformation was performed).

**Univariate fMRI Analyses**

To examine the main effect of the experimental Condition (i.e., squeeze) and Oddball Stimulus Level on the average BOLD signal from the auditory cortex, two different RM-ANOVA analyses were performed.

First, a 2 (Conditions: Squeeze and Control) by 6 (Oddball Levels: 1004, 1008, 1016, 1032, 1064, and 1128 Hz) RM-ANOVA was performed on the peak auditory

BOLD signal averaged across all trials per each Oddball Stimulus Level and across all participants, with experimental session order accounted for as the between-subject factor. A similar analysis was performed on the peak LC BOLD signal average across all trials per each Oddball Stimulus Level and across all participants.

**Multivariate fMRI Analyses**

A 2 (Conditions: Squeeze and Control) by 6 (Oddball Levels: 1004, 1008, 1016, 1032, 1064, and 1128 Hz) RM-ANOVA was performed on average decoding accuracy across all subjects for each Oddball Stimulus Level, with experimental session order accounted for as the between-subject factor.

Additionally, to examine the relationship between decoding accuracy for each Oddball Stimulus Level and the magnitude of the auditory BOLD signal, correlation coefficient and statistical significance (p-value) were extracted by using a linear model fitted to across-subject average data for the peak auditory BOLD signal and across-subject average decoding accuracy data for each oddball level, and in each experimental Condition. To maximize statistical analysis power, this analysis was performed on across-subject average data, as there were several zero values for decoding accuracy or peak auditory BOLD signal across the different oddball trials and participants.

**Results**

**Behavioral Analyses**

Performance accuracy, calculated as percent correct (See Behavioral Data analysis under Methods), increased as a function of Oddball Stimulus Level (Figure 2.5). A main effect of Oddball Stimulus Level on performance was observed ($F(2.603, 62.478) = 180.1$, p <0.001, $\eta^2 = 0.777$), confirming that, as expected, discriminating oddball trials become easier as a function of Oddball Stimulus Level. A potential influence of the Condition on behavioral performance was expected, such that the Squeeze would positively impact behavioral performance (i.e., accuracy and reaction time) compared to the Control session. However, no significant main effect of the Condition ($F(1,24)= 0.114$, p= 0.738, $\eta^2 = 0.000$) or experimental session ($F(1,24)= 0.001$, p=0.970, $\eta^2 = 0.000$) was observed on performance accuracy. No significant interaction effects were observed between Condition and Order ($F(1,24)= 0.055$, p= 0.817, $\eta^2 = 0.000$), Oddball Stimulus Level and Order ($F(2.603,62.478)= 0.222$, p= 0.855, $\eta^2 = 0.000$), or amongst Condition, Oddball Stimulus Level, and Order ($F(3.047,73.127)= 1.049$, p= 0.377, $\eta^2 = 0.001$). These analyses were followed up by analyzing the longevity of the experimental condition effect by evaluating performance on runs performed early-, mid-, and late-post-condition (Squeeze or Control). Importantly, results from this analysis revealed a significant main effect of Post-Condition Interval ($F(1.633,39.192)= 4.447$, p= 0.024, $\eta^2 = 0.003$) and Oddball Stimulus Level ($F(2.892, 69.405)=136.508$, p < 0.001, $\eta^2 = 0.590$), suggesting a statistically significant difference amongst the three post-condition intervals with early-

post-condition interval performance being highest and late-post-condition performance being the lowest (Figure 2.6), as well as confirming that performance statistically increases as a function of Oddball Stimulus Level. However, no significant main or interaction effects were observed on Condition ($F_{(1,24)}$= 1.582, p= 0.221, $\eta^2$=0.000), or between Post-Condition Interval and Condition (i.e., Squeeze or Control) ($F_{(1.926,46.231)}$= 0.180, p= 0.836, $\eta^2$= 0.000) and Condition and Oddball Stimulus Level ($F_{(3.215,7.151)}$= 1.963, p= 0.122, $\eta^2$= 0.003), or amongst Post-Condition Interval, Condition, and Oddball Stimulus Level ($F_{(6.785, 162.830)}$= 0.537, p= 0.801, $\eta^2$= 0.001), Post-Condition Interval, Condition, Oddball Stimulus Level, and Order ($F_{(6.785, 162.830)}$=1.518, p= 0.163, $\eta^2$= 0.003). While a significant main effect of Post-Condition Interval was observed, the lack of statistical interaction between the Post-Condition Interval and Condition suggests that Squeeze did not affect experimental runs performed immediately after the Squeeze session compared to the experimental runs performed mid- and late-post-squeeze interval (See Figure 2.6).
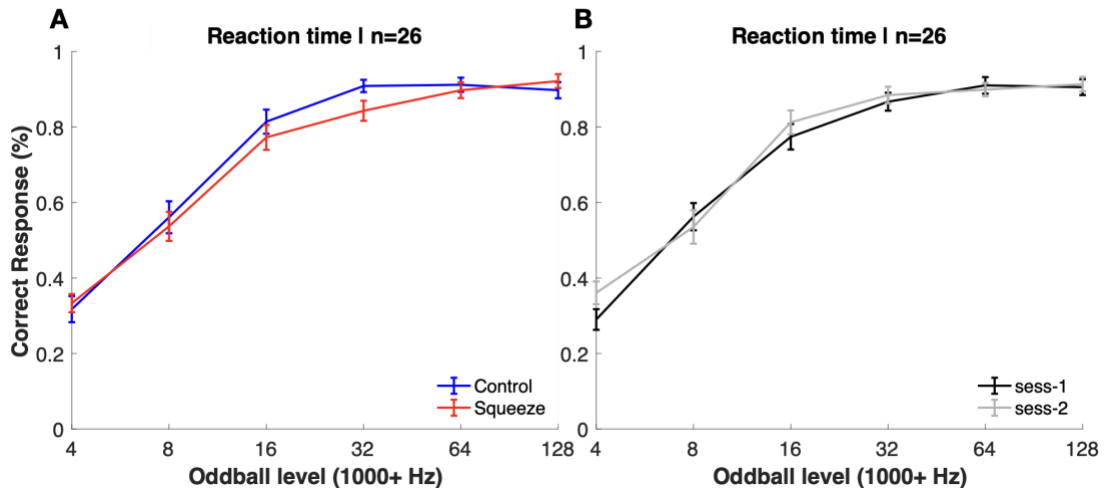
Figure 2.5. Behavioral performance on the AOD task as a function of (A) Squeeze and Control and (B) experimental session. A main effect of Oddball Stimulus Level ($F_{(2.603, 62.478)}$ = 180.1, $p < 0.001$, $\eta^2 = 0.777$) was found. No statistically significant main effects of (A) squeeze ($F_{(1,24)}$ = 0.114, $p = 0.738$, $\eta^2 = 0.000$) or (B) session ($F_{(1,24)}$ = 0.001, $p = 0.970$, $\eta^2 = 0.000$) were observed on participants' (n=26) behavioral performance. Error bars represent within-subject standard error.
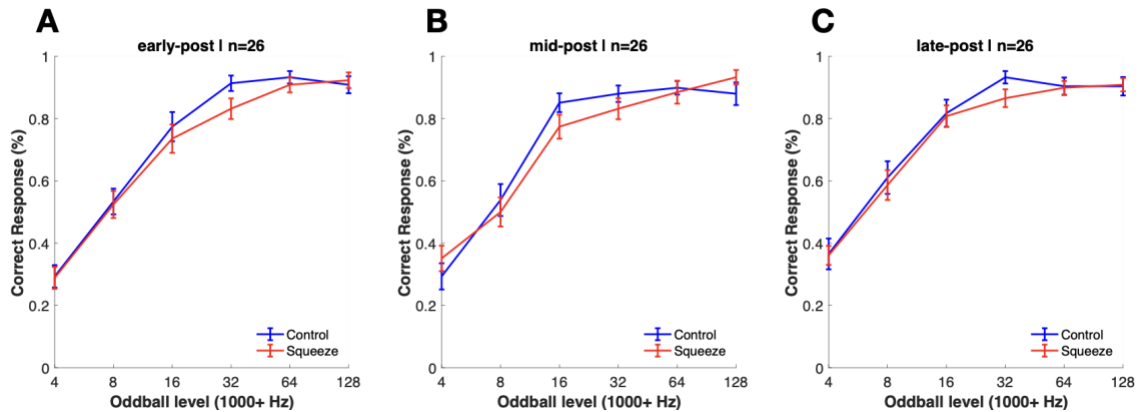


Figure 2.6. Behavioral performance on the AOD as a function of Squeeze (represented in red) and Control (represented in blue), separated by post-condition interval (Squeeze or Control). Representing averaged performance on runs 1 and 4 performed early-post-condition (A), runs 2 and 5 performed mid-post-condition (B) and runs 3 and 6 performed late-post-condition (C). A significant main effect of Oddball Stimulus Level ($F_{(2.892, 69.405)}$ = 136.508, $p < 0.001$, $\eta^2 = 0.590$), and of the Post-Condition Interval ($F_{(1.633,39.192)}$ = 4.447, $p = 0.024$, $\eta^2 = 0.003$) was observed. But, no significant main effects were observed for Condition ($F_{(1,24)}$ = 1.582, $p = 0.221$, $\eta^2 = 0.000$). Error bars represent within-subject standard error.

Reaction time, measured as the time between the onset of the response window and the response button press, decreased as a function of the Oddball Stimulus Level (Figure 2.7). A statistically significant main effect of Oddball Stimulus Level was observed on reaction time ($F_{(2.288, 54.913)}=31.043$, $p < 0.001$, $\eta^2= 0.168$) with an interaction effect between Oddball Stimulus Level and Order ($F_{(2.288, 54.913)}=3.722$, $p=0.025$, $\eta^2=0.020$) (See Table S2.1 for follow up post hoc comparisons). However, despite expecting a main effect of the Condition on reaction time, no significant main effects of the Condition ($F_{(1,24)}= 0.604$, $p=0.445$, $\eta^2=0.002$) or experimental Session ($F_{(1,24)}=2.318$, $p=0.141$, $\eta^2=0.007$) were observed (Figure 2.7). These statistical results suggest that the squeeze paradigm used in this study did not significantly impact reaction time on task and that no significant differences occurred across the two sessions. No significant interaction effects were observed between Conditions and Order ($F_{(1,24)}=0.023$, $p= 0.881$, $\eta^2=0.000$), or amongst Conditions, Oddball Stimulus Level, and Order ($F_{(3.932,94.371)}=0.568$, $p= 0.683$, $\eta^2=0.002$).

To further examine the main effects of Condition that could have dissipated with time on task, an RM-ANOVA was performed on averaged reaction time for each Oddball Stimulus Level on runs performed early-post-squeeze, mid-post-squeeze, and late-post-squeeze (see Statistical Analyses under Methods for details). Results from the RM-ANOVA revealed a statistically significant main effect of Oddball Stimulus Level ($F_{(2.288,54.903)}= 29.799$, $p < 0.001$, $\eta^2= 0.127$), showing that reaction time significantly decreases a function of Oddball Stimulus Level. These results are in alignment with behavioral accuracy performance and demonstrate that the employed auditory oddball

discrimination paradigm sensitively estimates behavioral stimulus-response functions and

is suitable to reflect any behavioral variability, making the paradigm an appropriate

candidate for examining variability induced by factors such as the LC-NE upregulation.
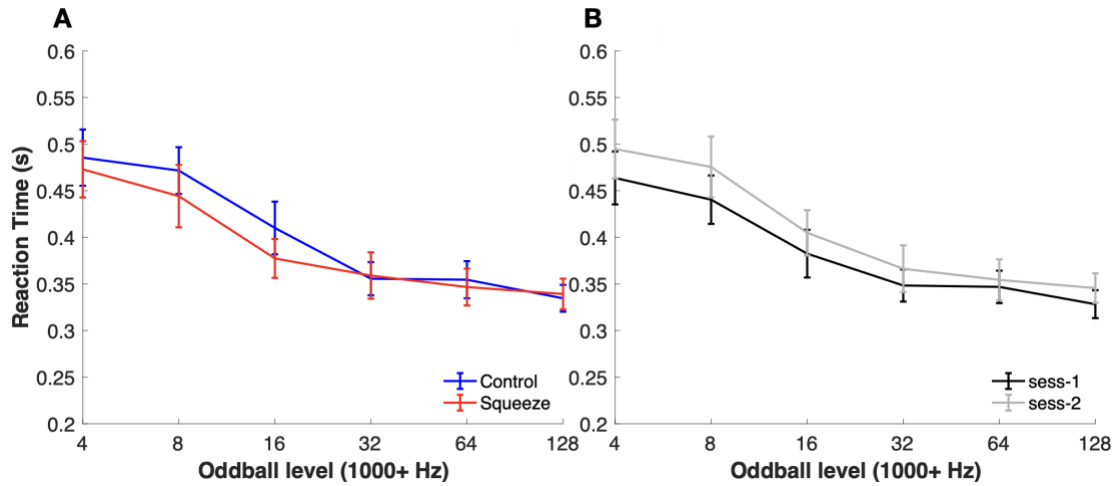


Figure 2.7. Behavioral reaction time in response to oddball levels as a function of (A) squeeze and Control and (B) experimental session. There were no main effects of (A) squeeze or (B) experimental session on participants' (n=26) reaction time. Error bars represent within-subject standard error.
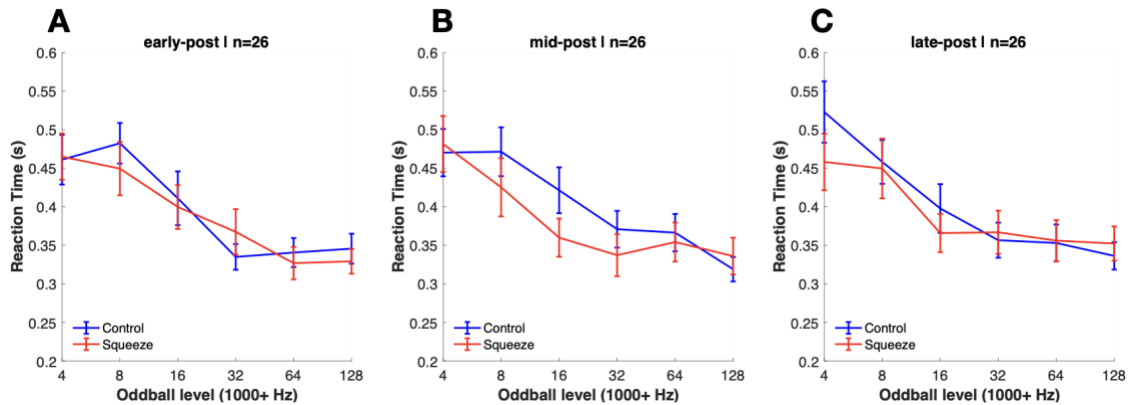
Figure 2.8. Behavioral reaction time as a function of Oddball Stimulus Level for the Squeeze (represented in red) and the Control (represented in blue) Condition. Representing averaged reaction time on runs 1 and 4 performed early-post-condition (A) runs 2 and 5 performed mid-post-condition (B), and runs 3 and 6 performed late-post-condition (C). A statistically significant main effect of Post-Condition Interval (i.e., early-, mid-, and late-post-squeeze or -post-control) $(F(1.919,46.053)=55.508, p < 0.001, \eta^2 =0.016)$, as well as a significant interaction between Post-Condition Interval and Oddball Stimulus Level $(F(6.686, 160.463)=3.338, p=0.003, \eta^2 = 0.015)$, were observed. Error bars represent within-subject standard error.

**Univariate fMRI Analyses**

To examine averaged neural activity related to the auditory oddball stimuli in the primary

cortex, a conventional univariate analysis approach was used to estimate the BOLD

signal in the auditory cortex as a function of oddball levels and squeeze or control

conditions. Auditory stimuli evoked changes in the BOLD signal within the primary

auditory cortex mask at 6 seconds post-stimulus onset under both the Squeeze (Figure

2.9.A) and the experimental Control sessions (Figure 2.9.B). Peak (i.e., max value across

1TR before stimulus onset and 4 TRs after stimulus onset) auditory BOLD signal

revealed a significant main effect of Oddball Stimulus Level $(F(4.00, 95.996)=11.461, p$

$< 0.001, \eta^2= 0.111)$, such that larger deviations in the percent signal change in auditory

cortex were observed as a function of Oddball Stimulus Level (Figure 2.10). Other

significant effects included a significant interaction effect between Oddball Stimulus

Level and Condition ($F(3.644, 87.460)=2.653$, $p=0.043$, $\eta^2= 0.031$) that was followed up

by post hoc testing (pairwise t-tests) using the Holm correction. Post hoc comparisons

revealed no statistically significant differences between pairs of Oddball Stimulus Level

auditory BOLD corresponding to the Squeeze and the Control Condition (See Table S2.3

for post hoc comparisons). No statistically significant effects were observed for

Condition ($F(1,24)=0.293$, $p=0.593$, $\eta^2= 0.001$), and no significant interactions were

observed for Condition and Order ($F(1,24)=0.449$, $p=0.509$, $\eta^2= 0.002$), Stimulus

Oddball Level and Order ($F(4.00, 95.996)=1.729$, $p=0.150$, $\eta^2= 0.017$), or among

Condition, Stimulus Oddball Level, and Order ($F(3.633, 87.460)=0.613$, $p=0.639$, $\eta^2=$
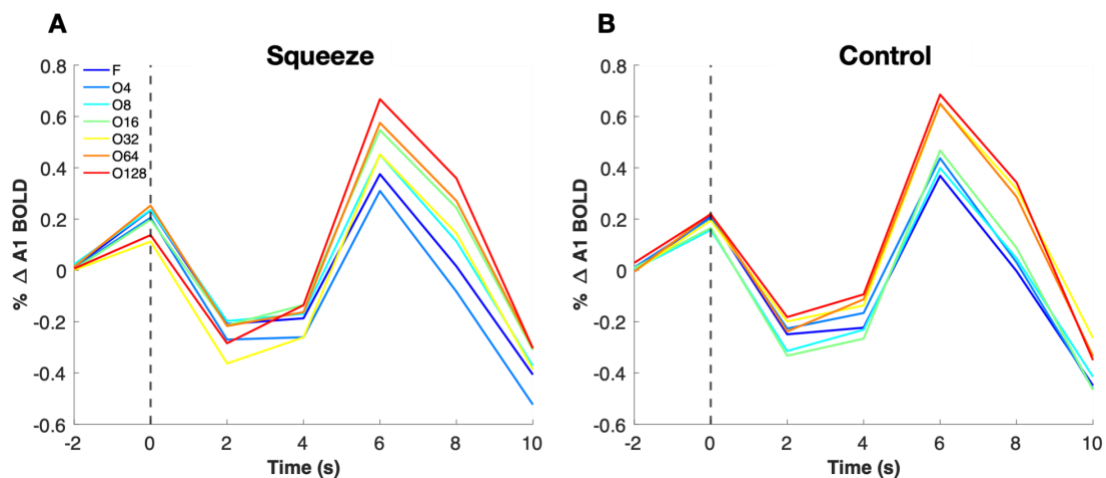
$0.007$).



Figure 2.9. Percent change in auditory cortex BOLD signal during the Squeeze (A) and
Control (B) experimental session. The dashed line represents stimulus onset.
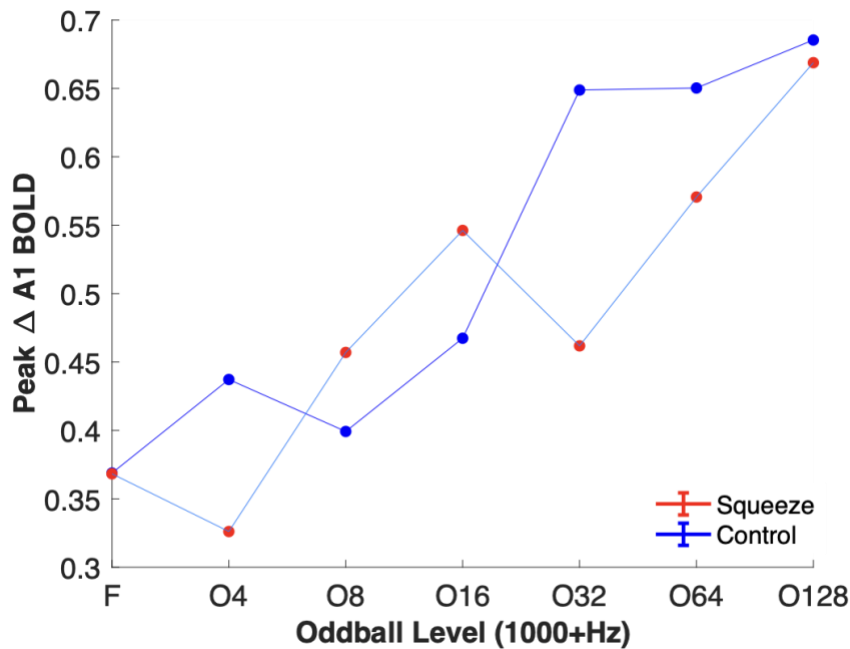
Figure 2.10. Peak changes in the auditory cortex BOLD signal are plotted as a function of the Squeeze (in red) and Control (in blue). A significant main effect of Oddball Stimulus Level ($F_{(4.00, 95.996)}$=11.461, $p < 0.001$, $\eta^2 = 0.111$), as well as interaction effect between Oddball Stimulus Level and Condition ($F_{(3.644, 87.460)}$=2.653, $p=0.043$, $\eta^2 = 0.031$) were observed.

Results from RM-ANOVA analysis performed on peak LC BOLD signal per Oddball Stimulus Level across all subjects showed no significant main or interaction effects of Condition ($F_{(1,24)}$=0.049, $p=0.827$, $\eta^2 = 0.000$), Oddball Stimulus Level ($F_{(4.431, 106.347)}$=1.685, $p=0.152$, $\eta^2 = 0.028$), or between Oddball Stimulus Level and Order ($F_{(4.396, 105.515)}$= 0.163, $p= 0.975$, $\eta^2 = 0.003$), and amongst Condition, Oddball Stimulus Level, and Order ($F_{(3.937, 94.481)}$= 1.103, $p= 0.360$, $\eta^2 = 0.017$) were observed, suggesting no direct relationship between LC BOLD and the Condition, or the Oddball Stimulus Level (Figure 2.11). No significant interactions were observed between Condition and Order ($F_{(1,24)}$=0.594, $p=0.448$, $\eta^2 = 0.002$), Oddball Stimulus Level and

Order (F(4.431, 106.347)=1.268, p=0.286, $\eta^2$= 0.021), or among Condition, Oddball

Stimulus Level, and Order (F(3.754, 90.100)=1.650, p=0.172, $\eta^2$= 0.022).

The relationship between the estimated LC BOLD signal and the Oddball

Stimulus Level was not as clear as the relationship that was observed between the

auditory cortex BOLD signal and Oddball Stimulus Level (See Figure 2.9.A and 2.9.B).

For example, the LC BOLD signal did not increase or decrease as a function of the

Oddball Stimulus Level. Despite the baseline corrections applied to the BOLD data, one

can visually observe significant variability in LC BOLD at the stimulus onset point. I

suspect these could be due to a combination of noise sources, including both not limited

to cerebrospinal fluid (CSF) noise and MRI-related acoustic noise (T. T. Liu, 2016).

These findings were reproduced across two different preprocessing pipelines (Mahsa

Alizadeh Shalchy, 2021), providing evidence for the robustness of our analytical process
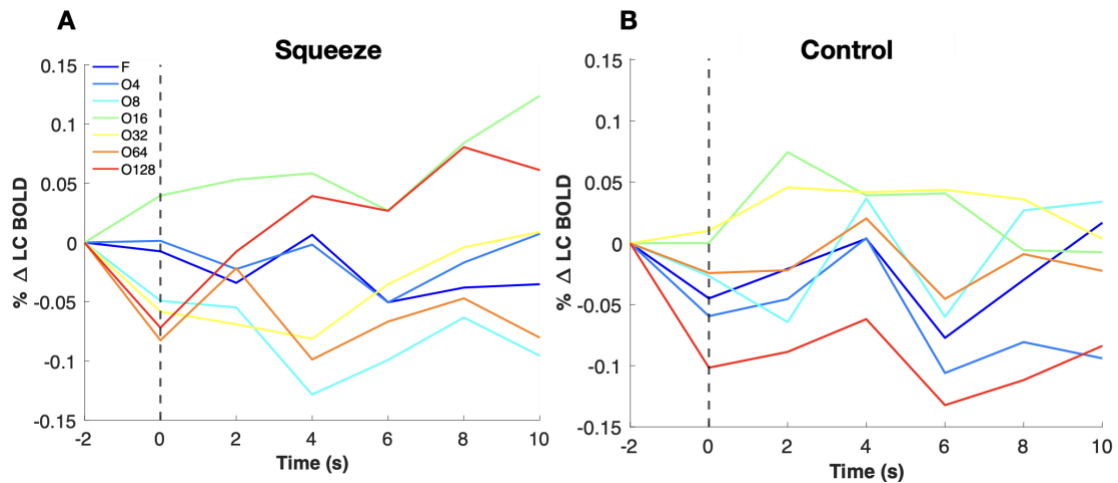
of the data.



Figure 2.11. Percent change in LC BOLD signal during the Squeeze (A) and Control (B)
experimental session. The dashed line represents stimulus onset.

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**Multivariate fMRI Analyses**

While conventional univariate analyses detect averaged regional activation differences, they lack granularity in detecting changes in activation patterns. Regardless of average activation levels from univariate analyses, MVPA approaches are thought to detect representational differences across experimental conditions (Kriegeskorte et al., 2008). The multivariate analysis thus measured the decodability of each oddball level based on their patterns of voxel activation within the given ROI. A cross-validation decoding approach was employed using a Linear Support Vector multi-nominal classifier that trained on 5 out of 6 runs and tested on one run (see Methods for details). To avoid misinterpretation of decoding accuracy, decoding accuracy minus decoding chance level (chance level = 12.5% in the 8-way multiclass classification) is reported in figures and analyses (Figure 2.12). Within each experimental Condition and each Condition (Figure 2.12), the average percent decodability accuracy minus chance is plotted, with the error bars showing the mean of averaged within-subjection error of decoding accuracy across all subjects. No significant main effect of the Condition was observed on the decodability accuracies across conditions ($F(1,24) = 0.044$, p= 0.836, $\eta^2 = 0.00$). However, RM-ANOVA results revealed a significant main effect of Stimulus Oddball Level on decoding accuracy ($F(4.396,105.515) = 3.107$, p=0.015, $\eta^2 = 0.053$), such that decoding accuracy for oddball 1128 Hz was higher than for Oddball 1008 Hz. There was no significant interaction between Stimulus Oddball Level and the Condition ($F(3.937,94.481) = 0.484$, p=0.743, $\eta^2 = 0.008$), or amongst the Stimulus Oddball Level, Condition, and Order ($F(3.937,94.481) = 1.103$, p=0.360, $\eta^2 = 0.017$). The decoding

accuracy of the blank and the frequent conditions within both the Squeeze and the

Control sessions were significantly higher than the oddball conditions (Table 2.1).

Following these results, a correlation analysis was performed between an across-subject average of peak auditory BOLD signal and across-subject average decoding

accuracy for each Oddball Stimulus Level and Condition to examine the extent to which

decoding accuracy for higher oddball levels could be simply due to an overall increase in

BOLD signal magnitude. Results from this correlation analysis showed that this was not

the case in either the Squeeze (R= 0.0013, p= 0.2488) or the Control (R= -0.0116, p=
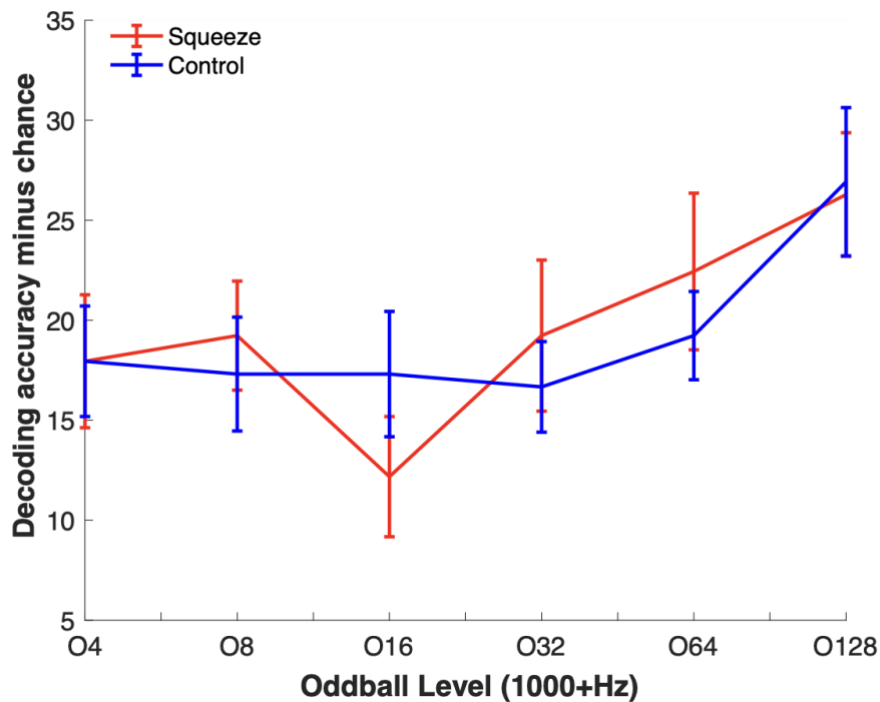
0.5806) conditions (Figure 2.13).



Figure 2.12. Decoding accuracy minus chance for the Squeeze versus Control experimental session within the hybrid auditory cortex mask. A significant main effect of Stimulus Oddball Level (F(4.396,105.515)= 3.107, p=0.015, $\eta^2 = 0.053$) was observed. Error bars represent within-subject standard error.

|                | Squeeze |          | Control |          |
|----------------|---------|----------|---------|----------|
|                | Blank   | Frequent | Blank   | Frequent |
| **Mean**           | 92.95   | 46.80    | 93.60   | 48.08    |
| **Standard error** | 2.30    | 3.21     | 2.08    | 3.74     |

Table 2.1. Average decoding accuracy minus chance for the blank and the frequent conditions in the Squeeze versus Control experimental session.
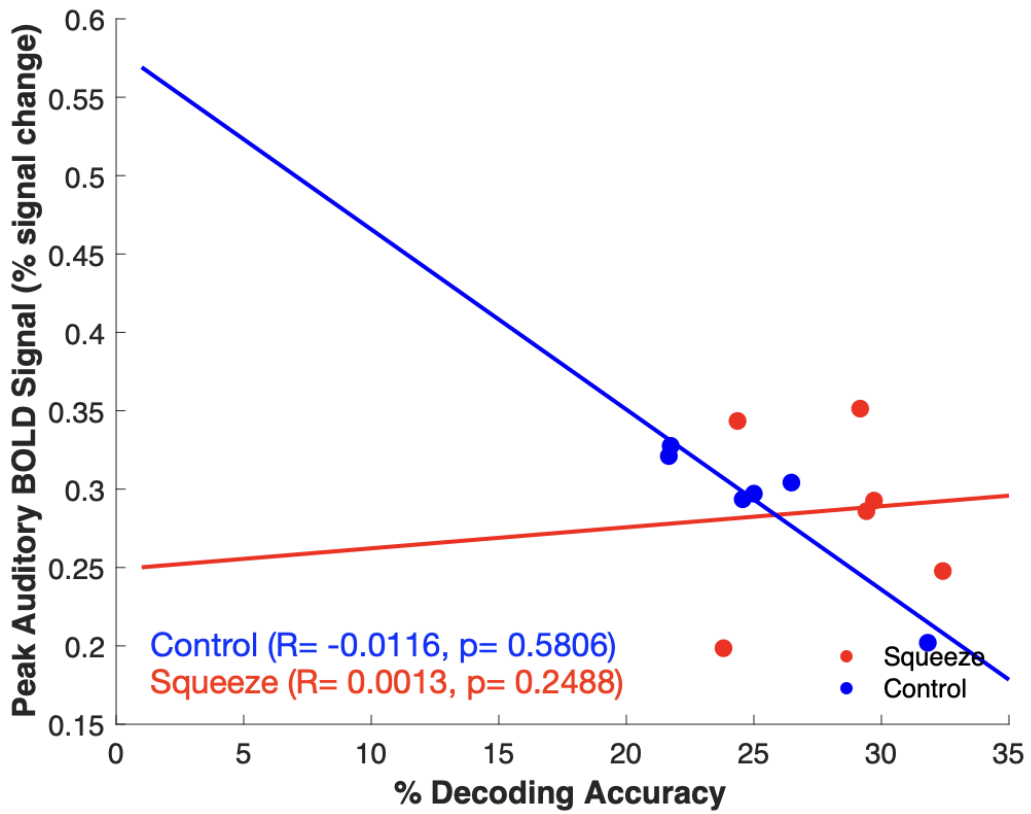


Figure 2.13. Correlation plot between averaged Decoding Accuracy and Peak Auditory BOLD Signal.

**Discussion**

Paradigms for examining how the LC-NE system influences perceptual representations and behavior in humans are scarce. In this study, a novel auditory oddball discrimination paradigm, designed to facilitate sensitive estimation of the behavioral and neural stimulus-response functions, was used conjunction with a handgrip LC manipulation paradigm to examine the influence of LC upregulation on sensory representations and behavioral performance. Upregulated LC activity (via handgrip manipulation) was predicted to increase behavioral accuracy, decrease reaction time, and increase auditory BOLD signal. To test this, a novel Auditory Oddball Discrimination task was designed to include attributes of an oddball paradigm to modulate LC-related arousal, such as the typical 80:20 frequent to infrequent stimuli ratio as well as a sensitivity stimulus range attribute that would more robustly capture behavioral and neural variability. Although the reported behavioral and neural stimulus-response functions were statistically not significant between the two conditions, possibly due to a weak handgrip manipulation for young adults, the employed auditory oddball discrimination paradigm demonstrates viability to reliably extract behavioral and neural stimulus-response functions that may be susceptible to changes resulting from LC manipulations.

Within behavioral measures, performance accuracy increases and reaction time decreases as oddball levels deviate from frequent auditory stimuli, supporting the paradigm's utility in terms of its sensitivity for capturing trial-by-trial changes in behavior performance, and creating psychometric functions that may be more susceptible to influences of modulated LC activity. Similarly, the neural stimulus-response function

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extracted from the auditory cortex shows a main effect of Oddball Stimulus Level; changes in the auditory BOLD signal increased as a function of stimulus level, which provides support for the reported paradigm's capability to capture changes in neural representations. Although no statistically significant main effect of the Condition was observed on the auditory BOLD signal, the neural stimulus-response function for each Oddball Stimulus Level was visually more clearly different between Squeeze and Control (Figure 2.9). Similarly, no significant effect of the Condition was found on LC BOLD signal change, which could be due to lack of handgrip impact as well as physiological and scanning noise. Further research on imaging procedures, image processing, and particularly data denoising can optimize examining LC's activity in response to the auditory oddball stimuli. Overall, considering that influences of LC on behavioral and neural measures could be complex, further data analyses, including analyzing the variability of these behavioral and neural measures, are needed to fully examine effects of Condition on behavioral measures, auditory and LC BOLD signal.

The use of multiple different Oddball Stimulus Levels, the employed task may be viewed as a frequency discrimination task, which could be correct as some used the task names oddball auditory discrimination and frequency discrimination interchangeably (Beauchamp & Stelmack, 2006). Generally, oddball paradigm focuses on salient oddball stimuli, whereas frequency discrimination paradigms are focused on thresholds. However, many frequency discrimination procedures commonly employ an oddball paradigm to estimate frequency thresholds (Gaál et al., 2007; Menning et al., 2000; Novitski et al., 2007) with a rather lower number of trials (25-39 trials) compared to 120+

trials (Amitay et al., 2006). Despite the novel oddball sensitivity attribute of the employed auditory oddball discrimination task, the general procedure of the AOD task used in this study is still in alignment with the oddball paradigm's established attributes, such as response evaluation to frequent (high probability) stimuli versus oddball (lower) probability stimuli.

Our study had several limitations. Although the utilized isometric handgrip manipulation was previously employed to upregulate LC phasic activity (Nielsen & Mather, 2015) for investigating LC's influence on behavior, no significant influence of the handgrip was observed on any of the behavioral or neural measures. This could be because the handgrip manipulation paradigm utilized was not systematically controlled across all participants, i.e., participants did not squeeze the ball with a controlled percentage of their maximum volumetric contraction force, which could have allowed squeezing the ball at a comfortable level. A total of two short handgrip sessions were used across all runs within a single session (See Methods), hypothesizing its effects to run through a period of 15-20 minutes per the limited reported literature (McAllister, 1979; Nielsen et al., 2015; Nielsen & Mather, 2015; Robertson et al., 1979). To address any reduction of the handgrip manipulation impact and to control for the influences of handgrip on upregulating LC, it would be best to employ a trial-by-trial handgrip manipulation with Squeeze and Control (i.e., no squeeze) within the same experimental session. Overall, the reported findings in the context of the isometric handgrip manipulation could be due to several factors, including but not limited to individual differences, the average age of the participants, and squeezing strength.

Additional analysis of fMRI data during periods of Squeeze or Control can further help to confirm whether participants performed the squeeze interval, as well as examine any detectable relationships between the primary motor cortex (M1) BOLD signal and LC BOLD signal. Considering LC neurons have been shown to have a bidirectional connection with M1 (Sharma et al., 2010) on sessions with successful handgrip performance, shown via increased M1 BOLD signal compared to the control session (i.e., holding the squeeze ball), theoretically, I would expect to observe an increased LC BOLD signal associated with several TRs post-squeeze onset. However, while previous electrophysiological studies of LC neurons have shown LC to robustly respond to task-relevant motor actions such as pressing a response bar (Aston-Jones et al., 1994), several studies have shown that LC modulation occurs more rapidly and robustly in the medial prefrontal cortex compared to M1 and other sensory cortices (Chandler et al., 2014); therefore, nonsignificant associations between M1 BOLD and LC BOLD could be observed. Regardless, fMRI analysis of M1 activity during squeeze and control intervals would be informative regarding the employed experimental design and will be conducted in the near future.

It is worth noting that LC-NE arousal is confounded by factors such as age (Keren et al., 2009; K. Y. Liu et al., 2019; Manaye et al., 1995; Mann, 1983; Mouton et al., 1994; Tejani-Butt & Ordway, 1992), arousal-related gender impacts (Walter et al., 2008; Zhang et al., 2016), sleep patterns (Jones et al., 1977), hormonal cycles and difference (Herrera et al., 2019; Jedema & Grace, 2004; Moulton et al., 2014; Samuels & Szabadi, 2008), etc.; therefore, a more systematic behavioral manipulation is needed to successfully

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manipulate LC activity and capture its influence on behavioral and neural measures. Future studies should test other behavioral approaches for upregulating LC activity. For instance, the IAPS (International Affective Picture System) is a collection of pictures designed to elicit certain responses for psychological studies (Lang, Bradley, and Cuthbert, 2008). Similarly, the IADS (International Affective Digitized Sounds) is a set of acoustics and auditory stimuli conceived to evoke similar reactions (Soares et al., 2013). Both approaches are commonly used as effective arousal manipulations within a wide range of cognitive tasks (Bradley, 2014; Dietz & Lang, 1999; Koelstra et al., 2012; Lang et al., 1997; Marchewka et al., 2016; Noulhiane et al., 2007; Sutherland & Mather, 2012; Viinikainen et al., 2012). Other stress-inducing approaches, such as using a cold pressor paradigm (Mourot et al., 2009), and delivering milliamps-electrical shocks within expected and unexpected shock stimuli paradigm, could also be employed as methods to upregulate LC activity (Gaebelein et al., 1974). Another limitation in the design of our study was the lack of recording general physiological measures, such as respiratory and cardiac measures. These measures can address signal-to-noise issues (Hutton et al., 2011) of imaging regions like LC, which is situated by the lateral wall of the fourth ventricle and is highly susceptible to physiological noise.

**Conclusion**

This study provides valuable experimental methodology insights into experimental paradigms for investigating the relationship among the LC, sensory processing, and behavior. We tested a paradigm suitable to systematically study behavioral and neural

stimulus-response functions that are susceptible to possible impacts of arousal. We found that, across younger adults, the handgrip manipulation did not significantly impact the behavioral or the neural stimulus-response functions, which suggest that perhaps more systematic approaches for behaviorally manipulating LC are necessary to examine LC engagement consequences on perceptual behavior and corresponding neural representations. These findings may be found in conflict with the previously found effects of the isometric handgrip on behavior, as no effects of the handgrip manipulation were observed on the analyzed behavioral or neural measures (Mather et al., 2020). However, further behavioral and neural data analyses, including analyzing main effects of Condition on the variability found across accuracy, reaction time, auditory and LC BOLD, are needed to fully examine the viability of the employed handgrip manipulation.

Overall, the reported behavioral paradigm demonstrates the viability of the auditory oddball discrimination task to systematically capture trial-by-trial changes in behavior and neural measures in response to a range of stimulus levels, resulting in psychometric and neurometric functions that may be more susceptible to changes induced by modulated LC activity. Further research on behavioral methods to sufficiently manipulate LC in conjunction with the reported novel auditory oddball discrimination task could facilitate examining the relationship between LC and behavior.

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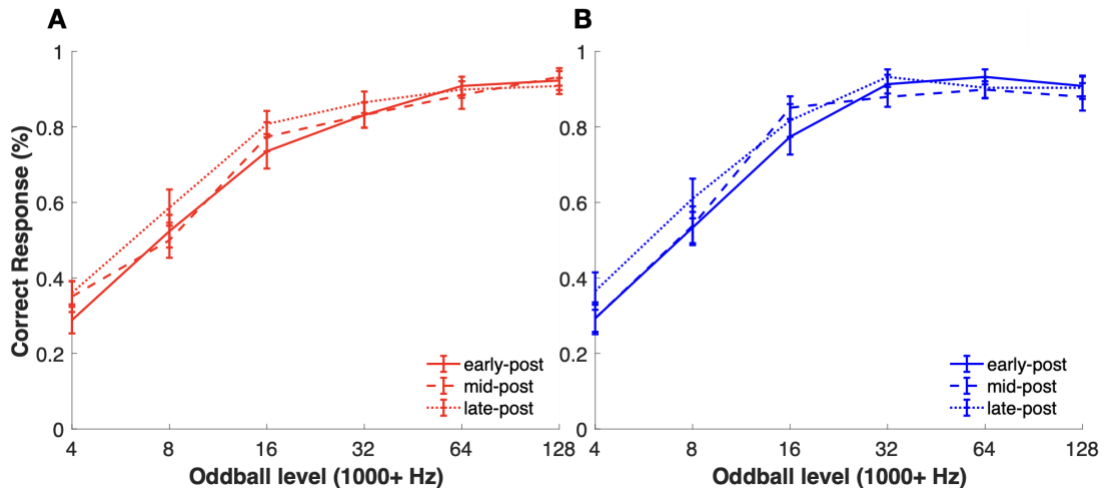
## Supplementary Figures



Figure S2.1 Behavioral performance on the AOD as function of Squeeze (A) and Control (B), separated by post-condition interval. Averaged performance on runs 1 and 4 performed early-post-condition (solid line), runs 2 and 5 performed mid-post-condition (dashed line), and runs 3 and 6 performed late-post-condition (dotted line). A significant main effect of Oddball Stimulus Level ($F(2.892, 69.405)= 136.508$, $p < 0.001$, $\eta^2 = 0.590$), and Post-Condition Interval ($F(1.633, 39.192)= 4.447$, $p= 0.024$, $\eta^2 = 0.003$) was observed. Error bars represent within-subject standard error.

| Post Hoc Comparisons - Order ✱ Oddball Stimulus Level | | Mean Difference | SE | t | p holm |
|---|---|---|---|---|---|
| **Control First, O4** | Squeeze First, O4 | 0.096 | 0.043 | 2.222 | 1.000 |
| **Control First, O8** | Squeeze First, O8 | 0.073 | 0.043 | 1.700 | 1.000 |
| **Control First, O16** | Squeeze First, O16 | 0.006 | 0.043 | 0.140 | 1.000 |
| **Control First, O32** | Squeeze First, O32 | 0.001 | 0.043 | 0.025 | 1.000 |
| **Control First, O64** | Squeeze First, O64 | 0.033 | 0.043 | 0.777 | 1.000 |
| **Control First, O128** | Squeeze First, O128 | -0.003 | 0.043 | -0.068 | 1.000 |

*Note.* **Results are averaged over the levels of: Condition**
*Note.* **P-value adjusted for comparing a family of 66**
 **\* p < .05, \*\* p < .01, \*\*\* p < .001**

Table S2.1. Post Hoc Comparison - Oddball Stimulus Level ✱ Order interaction effect on reaction time data. Since multiple measures are tested, the reported p-value is Holm corrected to control the family-wise error rate.

| Post Hoc Comparisons - Condition ✳ Oddball Stimulus Level | | | | | |
|---|---|---|---|---|---|
| | | Mean Difference | SE | t | p holm |
| Squeeze, O4 | Control, O4 | -0.067 | 0.070 | -0.958 | 1.000 |
| Squeeze, O8 | Control, O8 | 0.076 | 0.070 | 1.086 | 1.000 |
| Squeeze, O16 | Control, O16 | 0.105 | 0.070 | 1.502 | 1.000 |
| Squeeze, O32 | Control, O32 | -0.186 | 0.070 | -2.665 | 0.372 |
| Squeeze, O64 | Control, O64 | -0.046 | 0.070 | -0.658 | 1.000 |
| Squeeze, O128 | Control, O128 | -0.003 | 0.070 | -0.038 | 1.000 |
| *Note.* **P-value adjusted for comparing a family of 66** | | | | | |
| *Note.* **Results are averaged over the levels of: Order** | | | | | |

Table S2.3. Post Hoc Comparison – Condition ✳ Oddball Stimulus Level interaction effect on peak auditory BOLD signal. Since multiple measures are tested, the reported p-value is Holm corrected to control the family-wise error rate.
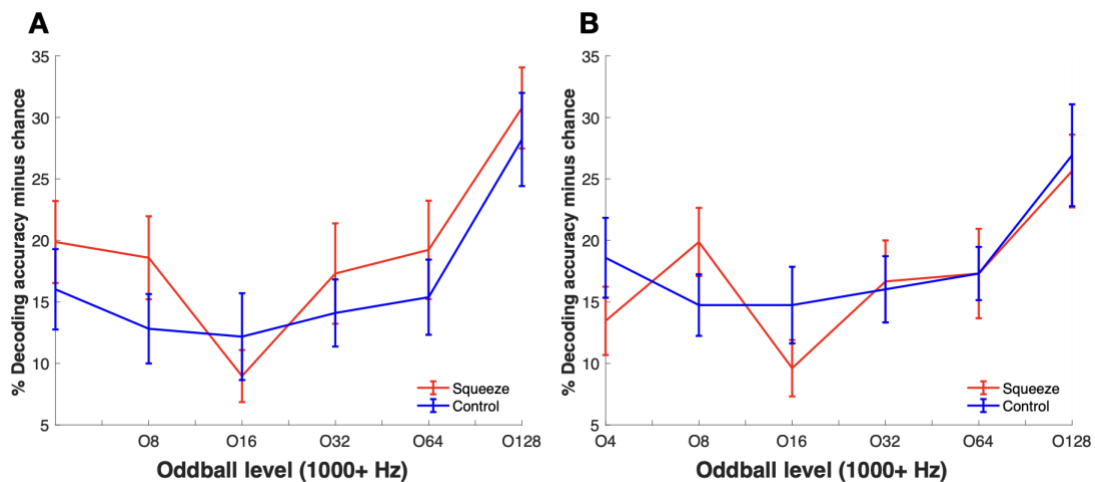


Figure S2.2. Decoding accuracy minus chance for each oddball condition within the (A) sound-sensitive voxels and (B) oddball-sensitive voxels of the primary auditory cortex mask. Error bars represent within-subject standard error.

**General Discussion and Conclusion**

This dissertation serves as the first few steps of an ambitious ladder that aims to examine how changes in LC activity impacts perceptual representation and behavioral performance. Experiments performed in chapter 2, partially published and discussed in (Hussain et al., 2019, 2022; Yaghoubi et al., 2019), used a novel auditory oddball discrimination paradigm in conjunction with fMRI and pupillometry (discussed elsewhere, Alizadeh Shalchy, 2021) to develop a suitable paradigm for studying computational consequences of LC engagement on perceptual neural representation and behavioral performance. First, I reviewed the LC-NE circuit anatomy and physiology, with emphasis on examining anatomical routes that could contribute to LC's modulation of sensory processing and perception. I then reviewed the key findings on how LC modulates sensory processes across different modalities, and although those were primarily done in nonhuman animals, the literature discussed revealed consequences of LC engagement on sensory stimulus processing, which led to a discussion of existing models of LC function that successfully explain parts of LC's role in cognition but are limited to either certain cognitive processes, such as the Network Reset Theory's explanation of LC involvement in memory processes, or animal models.

The different results observed along with limitations methodological approaches for understanding the underlying neural mechanisms of LC, especially in humans, has made it difficult to model the modulatory effects of LC-NE on perception and sensory processing. To address some of these limitations, we have successfully developed and tested a paradigm designed to enable sensitive estimation of neural, physiological, and

behavioral stimulus-response functions, which can capture variability exerted by modulatory influences such as the LC-NE. We found our novel AOD task allows for the estimation of behavioral and neural stimulus-response functions, however, the handgrip manipulation, as employed in this study, did not sufficiently upregulate LC activity (evaluated via LC BOLD in this study and by pupillary response elsewhere (Mahsa Alizadeh Shalchy, 2021)) to the point that we could systematically test LC's influence on sensory processing within auditory cortex. Future research requires a more robust paradigm to modulate LC activity and characterize its related influences on behavior. We are currently engaged in a project that aims to use neuroimaging, pupillometry, and behavioral measures to investigate individual differences in LC structure and how LC moderates perceptual and memory processes in older adults. Guided by the experimental design and study presented in Chapter 2, our research group initiated a sister project where we employed a within-subject design to systematically manipulate LC activity using a handgrip stressor and examine its relationship with neural activity within relevant brain areas and behavioral performance on two visual and two memory tasks. The first objective of this study is to characterize the relationship between LC and perceptual processes by examining variation in LC activity and its related changes in behavioral and neural processes involved in visual and auditory perception. This objective is achieved by participants performing an Auditory Oddball Discrimination (AOD) task (Figure 3.1) and a Visual Oddball Discrimination (VOD) task (Figure 3.2) with a low and a high grip manipulation targeted to modulate LC-NE signaling. To address the experimental design limitations presented in Chapter 2, LC activity is manipulated via the handgrip stressors

on a trial-by-trial basis, where participants are instructed to squeeze a dynamometer with a low or a high grip strength that is calculated to be 5% or 40% of the individual's maximum volumetric contraction (MVC) force. We note that the advantages of these two novel auditory and visual oddball paradigms are numerous outcome measure (hit rate, reaction time, confidence, neural activity, pupillary dilation, etc.) that enables evaluating how each behavioral, physiological, and neural measure is impacted by our experimental manipulations and the extent to which they are differently encoded as a function of oddball saliency.

On a behavioral level, we expect participants' behavioral performance on the AOD and VOD task to increase (accuracy and signal detection theory sensitivity measure dprime (d')(Hawkes & McNicol, 1973)) and reaction time (RT) to decrease as a function of oddball saliency. Despite the results we reported in Chapter 2, based on theoretical models of LC and the testing population age range, we expect to see increased behavioral measure variance associated with the high grip trials. Stimulus saliency and novelty have been thought to correlate positively with pupil dilation (Liao et al., 2016); therefore, we expect a systematic change in pupillary dilation as a function of increased oddball saliency across both AOD and VOD tasks. Within the neural activity measures, we hypothesize that averaged BOLD activity in the auditory and visual cortex increases as a function of auditory and visual stimulus saliency, respectively. Considering the systematic trial-by-trial manipulation of LC via the handgrip stressor, we expect to observe more and less average BOLD variability associated with high and low-level handgrip manipulation, respectively.

The second objective of this project is to examine how variations in LC activity influence behavioral processes involved in episodic memory and working memory, which is achieved by testing subjects performing a Mnemonic Similarity Task (MST) and a Change Detection Task (CDT) with a low and a high handgrip manipulation that is known to influence LC activity. To better compare the influence of our experimental manipulation on the different cognitive processes, the general structure of these paradigms (AOD, VOD, CDT, MST) is designed to be as similar as possible. As LC neurons reduce as a function age, we hypothesize significant relationships between LC structural integrity and performance on memory tasks (Betts et al., 2017; Dahl et al., n.d.).

In conclusion, the results reported in this dissertation together with the discussed ongoing project that has employed multi-level examinations of LC activity-related changes in perceptual and memory processes, will provide a more comprehensive understanding of LC's role in perception and memory. Results from this project will have far-reaching implications: the experimental design of this project, in conjunction with state-of-the-art neuroimaging procedures, pupillometry, and computational approaches to data analysis, will allow the investigation of a complex underlying mechanism by which LC mediates perception and memory processes in older adults.

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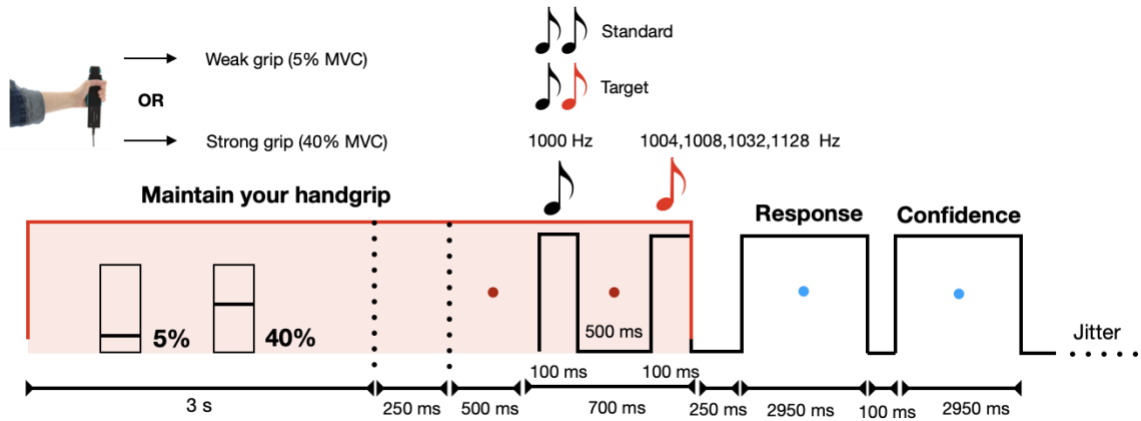
Figure 3.1. Schematic representation of the auditory oddball discrimination (AOD) task.
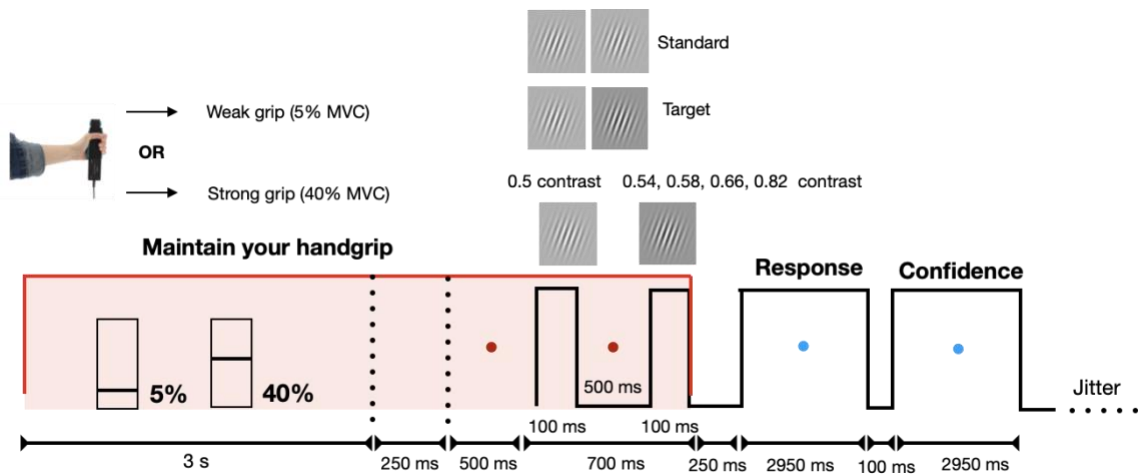


Figure 3.2. Schematic representation of the visual oddball discrimination (VOD) task.