1-1-2021

Pharmacological manipulation of NMDA receptor activation and synaptic norepinephrine levels: Effects on sustained attention in male rats

Zach V. Redding
University of Mississippi

PHARMACOLOGICAL MANIPULATION OF NMDA RECEPTOR ACTIVATION AND SYNAPTIC NOREPINEPHRINE LEVELS: EFFECTS ON SUSTAINED ATTENTION IN MALE RATS

A Dissertation
presented in partial fulfillment of requirements
for the degree of Doctor of Philosophy
in the Department of Psychology
The University of Mississippi

by

ZACHARY V. REDDING

May 2021

ABSTRACT

Impaired attention is common in many neurological disorders. Normal attention promotes the selective processing of important sensory information. This selective processing relies on neurotransmitters, like glutamate, and neuromodulators, like norepinephrine, acting in frontal, parietal, and visual cortices. We tested treatments targeting the glutamatergic and noradrenergic systems using a rat model of attentional lapses.

Rats were trained to respond quickly to stimuli in a two-choice reaction time task (2CRTT). Response times were split into initiation time (IT) and movement time (MT). Performance measures were derived from IT and MT distributions. IT mode represents sensorimotor processing speed when rats are attentive. IT deviation from mode (devmode) measures distribution skew which is thought to reflect attentional lapses. Altered MT mode or trials completed could reflect drug-induced side-effects. We tested the NMDA receptor co-agonist, D-serine, in a group of rats. We then tested a combination treatment of D-serine and the norepinephrine reuptake inhibitor, atomoxetine (ATX). New rats were used in a follow-up test. Data were analyzed using linear mixed models or repeated measures ANOVA.

We did not find an effect of D-serine on IT mode; however, the highest dose (300 mg/kg) reduced IT devmode. The initial test of the combination treatment (100 mg/kg D-serine with 0.5 mg/kg ATX) did not reveal an effect on IT mode; however, the combination treatment reduced IT devmode with no effect following either drug alone. The follow-up test (125 mg/kg D-serine with 0.3 mg/kg ATX) did not reveal an effect on IT mode; however, IT devmode was reduced

following ATX or the combination treatment. Importantly, the combination treatment reduced IT devmode more than either drug alone. Furthermore, the combination treatment did not increase MT mode or trials completed compared to ATX alone.

Activating NMDA receptors with D-serine appears to reduce attentional lapses without affecting sensorimotor processing speed. The present findings also support the efficacy of a combination treatment comprising D-serine and ATX. This combination treatment does not appear to increase unwanted side-effects associated with ATX. Taken together, these findings suggest that simultaneously targeting glutamate and NE systems could be a safe and effective strategy for treating impaired attention.

LIST OF ABBREVIATIONS OR SYMBOLS

2CRTT – Two-choice reaction time task

5CSRTT – Five-choice serial reaction time task

ADHD – Attention-deficit/hyperactivity disorder

ATX – Atomoxetine

CPT – Continuous performance task

DAN – Dorsal attention network

devmode – Deviation from the mode

ECoG – Electrocorticography

ED – Effective dose

EEG – Electroencephalography

FEF – Frontal eye field

fMRI – Functional magnetic resonance imaging

GABA – Gamma-aminobutyric acid

GANE – Glutamate amplifies noradrenergic effects

i.p. – Intraperitoneal

IPS – Intraparietal sulcus

IT – Initiation time

LC – Locus coeruleus

LFP – Local field potential

LIP – Lateral intraparietal area

MT – Movement time

MUA – Multi-unit activity

NE – Norepinephrine

NMDA – *N*-methyl-D-aspartate

PET – Positron emission tomography

RT – Response time

RTV – Response time variability

s.c. – Subcutaneous

τ – Tau, a measure of distribution skew

TMS – Transcranial magnetic stimulation

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

CHAPTER 1 - INTRODUCTION

Goal-directed behavior depends on the ability to detect relevant information in the environment. Attention adjusts our receptivity to competing sources of sensory stimulation, increasing the likelihood that relevant information is processed efficiently and therefore perceived (Buschman & Kastner, 2015; Parasuraman et al., 1998). Sustained attention requires the maintenance of selective sensory processing over time, a function that is often impaired in individuals with attention deficit/hyperactivity disorder (ADHD; Huang-Pollock et al., 2012; Kofler et al., 2013; Tamm et al., 2012) or schizophrenia (Cornblatt & Malhotra, 2001; Liu et al., 2002; McCleery et al., 2015; Nuechterlein et al., 2004, 2015). The development of safe and effective treatments for impaired attention requires 1) an appropriate animal model for translational research and 2) an understanding of how neurotransmitter and neuromodulator systems affect patterns of neural activity that underlie the processing of selected sensory information.

This introduction begins by describing the tasks and parameters used to study sustained attention in humans and rodents. Several sections then cover brain networks and neurochemical systems that are relevant to the present research. *First*, evidence is presented to illustrate the modulation of neural activity in frontal, parietal, and visual cortical areas of the visual processing system during attention. Briefly, top-down feedback is generated in these areas when visuospatial attention is oriented endogenously (i.e., in the absence of visual stimulation). Top-

down feedback subsequently affects patterns of sensory-driven neural activity to facilitate the bottom-up processing of selected sensory information. Sensory processing during attention could be affected by changes in neural firing rates, neural synchronization, or network-level noise correlations. Each of these concepts is briefly described below. The *second* major section then describes possible roles for the activation of *N*-methyl-D-aspartate (NMDA) receptors and norepinephrine (NE) release in the modulation of endogenous and sensory-driven neural activity during visuospatial attention.

Sustained Attention

The Study of Sustained Attention in Humans

Sustained attention is often studied in humans using discrimination tasks such as the continuous performance task (CPT) first introduced by Rosvold and colleagues (1956). Participants orient attention to a stream of continuously presented stimuli, responding by key press to targets while withholding responses to non-targets. Accuracy, omissions, and target discrimination scores (including d') are often used in CPTs to measure sustained attention (Riccio et al., 2002). More recently, intraindividual reaction time (RT) variability (RTV) has been used to measure sustained attention in these tasks. In particular, measures of RTV that reflect the positive skew of RT distributions are increasingly emphasized in clinical research (Kofler et al., 2013; Tamm et al., 2012). For example, the ex-Gaussian measure, tau (τ), reflects the influence of unusually slow responses that increase positive skew in RT distributions. These slow RTs are thought to be caused by lapses in attention (Leth-Steensen et al., 2000).

The Study of Sustained Attention in Rodents

The development of rodent behavioral models for sustained attention research has largely paralleled the development of tasks and measures for clinical research. Spatial discrimination tasks such as the five-choice serial reaction time task (5CSRTT) and the five-choice CPT were adapted from human paradigms like the CPT (Bari et al., 2008; Carli et al., 1983; Robbins, 2002; Young et al., 2009). Behavioral measures include accuracy and d' (Bhakta & Young, 2017; Robbins, 2002). As seen in clinical research, recently developed measures of RTV have been used to study sustained attention in rats (Hausknecht et al., 2005; Redding et al., 2019; Sabol et al., 2003).

The model developed by Sabol and colleagues (2003) uses the positive skew of RT distributions in rats performing a spatial discrimination task called the two-choice reaction time task (2CRTT). To account for the full-body movements required for responding in rodent tasks, RT is split into initiation time (IT) and movement time (MT). Analyses focus on the distribution of ITs to isolate effects on attentional processes from effects on movement speed, motivation, or sedation (MT). The difference between the mean and the mode of an IT distribution is referred to as deviation from the mode (devmode). Like ex-Gaussian τ, devmode measures positive distribution skew and therefore reflects the occurrence of slow ITs that are thought to be caused by lapses in attention. Measures of RTV that account for the skew of distributions (including IT devmode) are analogous to techniques currently used in clinical research (Tamm et al., 2012; Kofler et al., 2013) and could prove to be valuable tools for translational sustained attention research.

Extensive research in humans and rodents has been conducted to study sustained attention, leading to the development of current behavioral measures such as intraindividual variability of RT distributions. Research using these measures in translational rodent models

could lead to the development of safer and more effective pharmacological treatments for people experiencing impaired attention due to ADHD, schizophrenia, or other neurological disorders. The success of such research depends on understanding 1) how neural activity is modulated during attention in the interconnected brain regions responsible for processing sensory information and 2) how neurotransmitters and neuromodulators promote these processes. These concepts are described in the following sections.

Modulation of Neural Activity During Attention

The brain has a limited capacity to process visual sensory information, meaning that we cannot simultaneously perceive all the information present in most naturalistic scenes (Broadbent, 1958; Schneider & Shiffrin, 1977; Tsotsos, 1990). A *content filter* is needed to increase the likelihood that important sensory information is processed efficiently. Visuospatial attention provides a content filter for perception when we know in advance which stimuli are important and where to look for them. The advantage of attention can be seen in the more efficient processing of sensory information at attended visual field locations (e.g., Albares et al., 2011; Anton-Erxleben & Carrasco, 2013; Bashinski & Bacharach, 1980; Carrasco et al., 2004; Eriksen & Hoffman, 1973; Lee et al., 1997; Posner, 1980; Treisman & Gelade, 1980). Attention depends on a complex network of brain areas that includes cortical and subcortical structures (Kastner & Pinsk, 2004; Langner & Eickhoff, 2013). Here we will focus on frontal, parietal, and visual cortical areas involved in the processing of visual sensory information. Neural activity in these areas is selectively modulated in humans performing visuospatial attention tasks, meaning that patterns of neural activity change to reflect the orienting of attention toward specific visual field locations.

A network of dorsal frontal and parietal cortical regions referred to as the dorsal attention network (DAN; Corbetta & Shulman, 2002) is thought to initiate and maintain control over the orienting of visuospatial attention (Corbetta & Shulman, 2002; Kanwisher & Wojciulik, 2000; Kastner & Ungerleider, 2000; Petersen & Posner, 2012). Consistent with this thinking, human subjects exhibited increased frontal and parietal activity in positron emission tomography (PET; (Corbetta et al., 1993; Coull & Nobre, 1998; Nobre et al., 1997) and functional magnetic resonance imaging (fMRI; Beauchamp et al., 2001; Maurizio Corbetta et al., 1998; Coull & Nobre, 1998; Gitelman et al., 1999; Huddleston & DeYoe, 2008; Perry & Zeki, 2000; Serences & Yantis, 2007; Szczepanski et al., 2010; Vandenberghe et al., 2001; Wojciulik & Kanwisher, 1999; Yantis et al., 2002) scans taken during tasks in which attention was voluntarily oriented in space. Topographic mapping techniques paired with fMRI during the orienting of spatial attention (Saygin & Sereno, 2008; Sereno et al., 2001; Silver et al., 2005) revealed retinotopic modulation corresponding to attended locations in contralateral frontal and parietal cortices. Frontal areas include the frontal eye fields (FEF) and the junction between precentral gyrus and inferior frontal sulcus, and parietal areas include parts of the intraparietal sulcus (IPS) and superior parietal lobule. Retinotopic modulation of neural activity in the DAN is consistent with proposed "salience maps" in frontal (Thompson & Bichot, 2005) and parietal (Colby & Goldberg, 1999; Gottlieb et al., 1998) areas that could be involved in assigning priority to sensory information at attended locations.

During attention, neural activity is also modulated in retinotopically organized visual cortical areas within the occipital and temporal lobes. For example, fMRI activity in primary and extrastriate visual cortical areas was increased when attention was directed or cued toward a corresponding visual field location (Beauchamp et al., 1997, 2001; Gitelman et al., 1999; S.

Kastner et al., 1998; Wojciulik & Kanwisher, 1999). Increased activity measured by fMRI (Brefczynski & DeYoe, 1999; Maurizio Corbetta et al., 1998; Coull & Nobre, 1998; Gandhi et al., 1999; Perry & Zeki, 2000; Saygin & Sereno, 2008; Serences & Yantis, 2007; Silver et al., 2005; Yantis et al., 2002) or PET (Coull & Nobre, 1998; Vandenberghe et al., 2001) displayed retinotopic specificity in the hemisphere contralateral to attended locations. In contrast, extrastriate areas ipsilateral to attended locations demonstrated reduced fMRI activity (Perry & Zeki, 2000). These studies suggest that attention's effects on sensory processing involve the selective modulation of neural activity in visual cortical areas, including enhancing activity representing attended sensory information and suppressing activity representing unattended or ignored sensory information.

Importantly, the imaging studies described above did not separate the *endogenous* neural activity generated during the orienting of attention in the absence of visual stimulation from the *sensory-driven* neural activity generated when the effects of attention interact with visual stimulation (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). When attention is voluntarily oriented in the absence of visual stimulation, top-down feedback in frontal, parietal, and visual cortical areas is thought to reflect preparation for the processing of expected stimuli (targets). Successful maintenance of top-down feedback could therefore increase the likelihood that selected sensory information is processed efficiently. During the ensuing visual stimulation, top-down feedback influences the bottom-up processing of sensory information. The modulation of sensory-driven neural activity could increase the efficiency of processing for selected sensory information. The interaction between top-down and bottom-up influences could therefore determine what we perceive. The following sections detail the evidence for this line of reasoning. *First*, evidence is presented for the modulation of purely

endogenous neural activity in frontal, parietal, and visual cortical areas during attention. *Second*, evidence is presented to demonstrate that the modulation of endogenous neural activity involves top-down feedback between frontal, parietal, and visual cortical areas. *Third*, evidence is presented for top-down feedback leading to the modulation of sensory-driven neural activity in frontal, parietal, and cortical areas. *Finally*, evidence is presented for the modulation of sensory-driven neural activity in frontal, parietal, and visual cortical areas during visuospatial attention. Endogenous neural activity influencing the bottom-up processing of sensory information via top-down feedback illustrates how attention, when properly functioning, allows us to perceive important stimuli in cluttered environments.

Modulation of Endogenous Neural Activity During Attention

Event-related analyses of fMRI data (Buckner et al., 1996; Buckner, 1998) and neurophysiological recordings have been used to demonstrate the modulation of purely endogenous neural activity in frontal, parietal, and visual cortical areas of subjects performing visuospatial attention tasks. In visuospatial cueing tasks, subjects must maintain gaze at a central fixation point. A cue informs the subject where a target is likely to appear; however, the cue disappears, forcing the subject to maintain covert attention (without eye movements) at the cued location for a short delay without visual stimulation. The subject must then respond to a target at the cued location within a predetermined time limit. When subjects covertly oriented attention to cued locations in the absence of visual stimulation (i.e., after the cue disappeared but prior to the appearance of the target), fMRI activity was increased in regions corresponding to the FEF (Astafiev et al., 2003; Corbetta et al., 2002; Egner et al., 2008; Hopfinger et al., 2000; Kastner et al., 1999; Sapir et al., 2005). In contrast, one study using intracranial electrocorticography (ECoG) recordings from the surface of the brain in humans with epilepsy revealed no attentional

modulation of neural activity recorded at FEF electrodes during the delay period of a cued spatial attention task without visual stimulation (Martin et al., 2019). Despite this null finding, imaging studies consistently demonstrate spatially specific modulation of endogenous neural activity in human FEF during visuospatial attention.

Imaging of the parietal cortex has also revealed modulation of endogenous neural activity during visuospatial attention. For example, event-related fMRI demonstrated increased activity in IPS areas following cues that oriented covert attention to a corresponding location in the visual field in the absence of visual stimulation (Astafiev et al., 2003; Corbetta et al., 2000; Corbetta et al., 2002; Egner et al., 2008; Hopfinger et al., 2000; Kastner et al., 1999; Sapir et al., 2005). The extent of this modulation was shown to be specifically related to the use of the cue to orient spatial attention (Sapir et al., 2005). Intracranial ECoG recordings from human epilepsy patients revealed similar spatially specific enhancement in posterior IPS during the delay period following cue presentation in the absence of visual stimulation (Martin et al., 2019). Together, these findings support the thinking that visuospatial attention involves the modulation of endogenous neural activity in the parietal cortex.

Event-related fMRI also revealed modulation of endogenous neural activity in the visual cortices during attention. Endogenous activity was increased in human V1, V2, and V3 following an auditory cue that oriented covert attention to detect an ensuing low-contrast patterned annulus centered around the fixation point (Ress et al., 2000). The extent of this modulation was associated with the ability to discriminate the target pattern. Other studies using cued visuospatial attention tasks reported similar modulation of neural activity in human extrastriate (Corbetta et al., 2002; Egner et al., 2008; Hopfinger et al., 2000; Kastner et al., 1999; Ruff et al., 2006; Sapir et al., 2005; Silver et al., 2007) and primary visual cortical areas (Kastner et al.,

1999; Silver et al., 2007) corresponding to a specific cued location prior to the presentation of a target stimulus at that location. Consistent with the idea that the modulation of endogenous neural activity reflects the orienting of attention in space, the locus of attention could be predicted from fMRI activity in extrastriate visual areas during the preparatory period prior to visual stimulation (Sylvester et al., 2007). These findings are supported by intracranial ECoG recordings from epilepsy patients performing a cued visuospatial attention task. Spatially specific enhancement of activity was recorded from dorsal extrastriate electrodes during the delay period following cue presentation in the absence of visual stimulation (Martin et al., 2019). Together, these findings demonstrate spatially specific modulation of endogenous neural activity in extrastriate and primary visual cortical areas during visuospatial attention.

In summary, event-related neuroimaging and neurophysiological recordings in humans have revealed modulation of neural activity in frontal, parietal, and visual cortical areas during the orienting of visuospatial attention without visual stimulation. The modulation of endogenous neural activity in these areas corresponds topographically with the allocation of attention in space. In other words, increased activity occurs in areas representing attended visual field locations. The available evidence supports the thinking that attention's effects on sensory processing involve the selective modulation of endogenous neural activity throughout frontal, parietal, and visual cortical areas of the visual processing system.

Top-Down Feedback and Effects on Bottom-Up Processing

Modulation of Endogenous Neural Activity via Top-Down Feedback

The modulation of endogenous neural activity during attention (described above) is thought to involve top-down feedback within frontal, parietal, and visual cortical processing

areas. Consistent with this thinking, the voluntary orienting of visuospatial attention is characterized by feedback originating in frontal cortex and flowing in a top-down direction to parietal cortex (Buschman & Miller, 2007), potentially via direct connections between these areas (Cavada & Goldman-Rakic, 1989; Stanton et al., 1995; Szczepanski et al., 2013). Top-down feedback from DAN areas also modulates neural activity in extrastriate and primary visual areas corresponding to attended locations (Kastner et al., 1999; Moore & Armstrong, 2003). This feedback could occur via direct cortico-cortical connections (Blatt et al., 1990; Felleman & Van Essen, 1991; Lewis & Van Essen, 2000; Selemon & Goldman-Rakic, 1988; Stanton et al., 1995; Ungerleider et al., 2008) or cortico-thalamic loops involving the pulvinar nucleus of the thalamus (Huerta et al., 1986; Jones, 2001; Shipp, 2003).

Consistent with the thinking that neural activity in higher-order areas influences neural activity in lower-order areas, Ekstrom and colleagues (2008) reported that electrical stimulation of the monkey FEF in the absence of visual stimulation enhanced fMRI activity in the lateral intraparietal area (LIP), an area thought to correspond with human IPS (Sereno et al., 2001; Van Essen et al., 2001). Top-down modulation of endogenous neural activity has also been demonstrated using transcranial magnetic stimulation (TMS) in combination with functional imaging or electroencephalography (EEG) in humans. For example, Paus and colleagues (1997) reported increased PET activity in superior parietal and parieto-occipital areas following TMS over the FEF. TMS over the FEF (Ruff et al., 2006) or IPS (Ruff et al., 2008) also enhanced fMRI activity in V1, V2, V3, and V4 independent of visual stimulation. Taylor and colleagues (2007) used TMS to stimulate the FEF and EEG to record neural activity in visual cortical regions during a cued visuospatial attention task. The FEF was stimulated following cue presentation, enhancing event-related potentials measured by EEG over corresponding

extrastriate visual areas prior to target presentation. In another study, TMS over the FEF increased the excitability of extrastriate middle temporal area neurons as indicated by a lower threshold of TMS stimulation over this area needed to induce visual perception (Silvanto et al., 2006). Granger causality analyses performed on event-related fMRI signals during the purely endogenous orienting of visuospatial attention were also consistent with top-down feedback from FEF to IPS and from FEF and IPS to occipital visual areas (Bressler et al., 2008). These findings are all consistent with the thinking that top-down feedback supports the modulation of endogenous neural activity that takes place in frontal, parietal, and visual cortical processing areas during attention.

Top-down Feedback Influences Bottom-Up Sensory Processing

Incoming sensory information is communicated in a bottom-up direction as indicated by the time course of initial responses to visual stimulation across primary visual, extrastriate visual, and parietal cortices (Martin et al., 2019). Visual information relayed through the thalamus is transmitted via feedforward connections across multiple hierarchical levels of visual, parietal, and frontal cortices (Ungerleider et al., 2008; Ungerleider & Haxby, 1994). Top-down feedback associated with the modulation of endogenous neural activity could influence bottom-up sensory processing via effects on sensory-driven neural activity in these cortical areas of the visual processing system. Consistent with this thinking, fMRI in monkeys revealed modulation of sensory-driven responses in V1, V2, V3, V4, and middle temporal areas following electrical stimulation of the FEF (Ekstrom et al., 2008). TMS has also been used to experimentally link top-down feedback with the modulation of bottom-up processing in humans performing visuospatial attention tasks. For example, following the covert orienting of visuospatial attention, TMS over the FEF modulated visually evoked potentials recorded by EEG over posterior visual

cortical areas (Taylor et al., 2007). TMS over the FEF while subjects prepared to discriminate a target's direction of motion similarly increased visually evoked potentials over occipitotemporal areas (Morishima et al., 2009). Furthermore, TMS over the FEF reduced RTs for validly cued trials during a cued visuospatial attention task, analogous to the effects of attention (Grosbras & Paus, 2002). Together, these findings support the notion that top-down feedback from higher-order areas influences the bottom-up processing of attended sensory information.

Modulation of Sensory Driven Neural Activity During Attention

Consistent with the idea that sensory processing is influenced by top-down feedback that occurs during the voluntary orienting of attention, human imaging studies have demonstrated modulation of sensory-driven neural activity in frontal, parietal, and visual cortical areas following the presentation of targets in cued visuospatial attention tasks. Event-related fMRI revealed increased activity in FEF (Corbetta et al., 2002; Kastner et al., 1999; Kincade et al., 2005), IPS (Corbetta et al., 2000; Corbetta et al., 2002; Kastner et al., 1999; Kincade et al., 2005), and extrastriate visual cortical (Corbetta et al., 2002; Corbetta et al., 2000; Dugué et al., 2020; Hopfinger et al., 2000; Kastner et al., 1999; Kincade et al., 2005) areas corresponding to a cued location following the presentation of a target at that location. In contrast to these studies, Martin and colleagues (2019) reported no modulation of sensory-driven activity in intracranial recordings from the topographic FEF areas of epilepsy patients during the presentation of a target at a previously cued location. Despite this one null result, findings from fMRI agree with the thinking that attention's effects on sensory processing and perception involve top-down feedback-mediated effects on sensory-driven neural activity in frontal, parietal, and visual cortical areas of the visual processing system.

How Is Neural Activity Modulated During Attention?

Findings from the imaging and neurophysiological studies described above support the thinking that top-down feedback generated during the modulation of endogenous neural activity in frontal, parietal, and visual cortical areas affects subsequent sensory-driven neural activity in these areas. These ideas provide a basic blueprint for how attention could affect sensory processing and perception. *First*, the modulation of endogenous neural activity and the associated top-down feedback could function as a *content filter* for perception. This content filter could increase the likelihood that selected sensory information is processed efficiently. *Second*, the resulting modulation of sensory-driven neural activity could enhance the efficiency of processing for selected sensory information.

Due to the low temporal resolution of fMRI or PET and the low spatial resolution of ECoG or EEG, the findings described above cannot explain how neural activity is modulated in individual neurons. Understanding how exactly neural activity is modulated during attention could be critical for detailing the etiology of disordered attention in different clinical populations and advancing the development of effective treatments. There are at least three ways that neural activity could be modulated during attention to facilitate the processing of selected sensory information. 1) Neural *firing rates* across frontal, parietal, and visual cortical areas could be modulated to promote the communication of selected sensory representations, while suppressing the communication of competing representations. 2) Sensory processing could be affected via modulation of the *synchronization* of rhythmic firing between selected neurons across these cortical areas. 3) Sensory processing could be affected via modulation of the trial-to-trial variability in sensory-driven firing rates of individual neurons and the *noise correlations* in populations of neurons representing attended sensory information. Modulation of firing rates and synchronization have been demonstrated during purely endogenous orienting and during the

processing of attended visual stimuli. Firing rate variability is also modulated during attention; however, these effects are implicitly sensory-driven. The following sections explain how the modulation of firing rates, gamma synchronization, and noise correlations could affect sensory processing. These sections also outline evidence for the modulation of each of these aspects of neural activity during attention, consistent with the thinking that each could be involved in determining what sensory information we are able to perceive.

Modulation of Neural Firing Rates During Attention

Precise coding of information in the brain depends on the spatiotemporal pattern of action potentials fired within a network of neurons (Georgopoulos et al., 1986; Paradiso, 1988; Shadlen & Newsome, 1994). In other words, the information contained in a neural "population code" depends on the firing rates of many neurons, but also on which neurons increase or decrease their firing rates in relation to other neurons in the population. The modulation of firing rates in cortical processing areas during attention could therefore affect the coding of sensory information to influence what we perceive (Reynolds & Heeger, 2009).

The following section details evidence for the modulation of endogenous firing rates during attention. This is followed by evidence linking the modulation of sensory-driven firing rates with top-down feedback, suggesting that the modulation of endogenous firing rates during attention could influence subsequent sensory processing. In support of this thinking, evidence is presented for the modulation of sensory-driven firing rates during attention.

Modulation of Endogenous Firing Rates

The fine temporal and spatial resolution of single-unit (i.e., single neuron) electrophysiological recordings in monkeys permits the isolation of purely endogenous firing

rate modulation in neurons throughout frontal, parietal, and visual cortical areas of the visual processing system. In addition to its role in the orienting of visuospatial attention (Awh et al., 2006), the FEF is an important part of the oculomotor system involved in directing saccadic eye movements (Paus, 1996). One way to identify FEF neurons in monkeys is by electrical stimulation and observation for resulting saccades (Robinson & Fuchs, 1969). The distribution of saccade endpoints within the visual field triggered by stimulating a FEF neuron delineates that neuron's "response field". Consistent with the role of the FEF in orienting visuospatial attention, spatial cues that oriented covert attention inside the response fields of recorded FEF neurons increased the firing rates of these neurons prior to the presentation of the expected stimulus (Armstrong et al., 2009; Zhou & Thompson, 2009). In contrast, firing rates were reduced when cues oriented attention outside the response fields of recorded FEF neurons (Armstrong et al., 2009). Consistent with a proposed salience map of the visual field in the FEF (Thompson & Bichot, 2005), Astrand and colleagues (2016) showed that a machine-learning algorithm could reliably decode the location of attention in continuous two-dimensional coordinates from multi-unit activity (MUA; i.e., activity recorded simultaneously from multiple neurons) during the delay period of a cued visuospatial attention task in the absence of visual stimulation. The accuracy of decoding was reduced on trials in which monkeys missed the target or produced false alarms, further supporting the notion that the modulation of firing rates in FEF neurons is a signature of visuospatial attention. In contrast to FEF neurons, neurons in parietal and visual cortical areas are typically identified based on their "receptive fields". The receptive field of a neuron describes the portion of the visual field inside which stimulus presentation evokes responses in the neuron. In a visuospatial cueing task, firing rates were increased in LIP neurons with receptive fields overlapping a cued location prior to the presentation of the target stimulus

(Saalmann et al., 2018). Firing rates were similarly enhanced in monkey V4 (Luck et al., 1997; Saalmann et al., 2018) and V2 (Luck et al., 1997) neurons during the period after a cue oriented covert attention to the receptive fields of recorded neurons but before the appearance of the expected target stimulus. These findings support the thinking that attention involves the spatially specific modulation of endogenous neural firing rates in topographically organized frontal, parietal, and visual cortical areas.

Top-Down Feedback Influences Sensory-Driven Firing Rates

Endogenous neural activity mediated by top-down feedback in DAN and visual cortical areas is thought to influence the subsequent processing of sensory information (as detailed above), acting as a content filter to facilitate the perception of stimuli at attended locations (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Consistent with this thinking, experimental evidence for the top-down modulation of sensory-driven firing rates has been demonstrated using direct electrical stimulation of neurons in monkey DAN areas and electrophysiological recordings from visual cortical neurons. For example, stimuli of varying orientations were presented inside of both the response fields of stimulated FEF neurons and the receptive fields of recorded V4 neurons. Analogous to the modulation of sensory-driven firing rates following the orienting of spatial attention, electrical stimulation of FEF neurons increased firing rates of V4 neurons in response to stimuli with preferred orientations (Armstrong & Moore, 2007; Armstrong et al., 2006; Moore & Armstrong, 2003). Interestingly, Schafer & Moore (2011) operantly conditioned monkeys to increase firing rates in neurons in their own FEF. This endogenous modulation of firing rates in FEF neurons increased the sensory-driven firing rates of these same FEF neurons following the presentation of target stimuli in a visuospatial attention task.

Top-down feedback can also suppress the firing rates of neurons representing unattended or ignored information. For example, stimulation of FEF neurons with response fields that do not overlap the receptive fields of recorded V4 neurons led to suppression of firing rates in response to a stimulus with the preferred orientation of the recorded V4 neurons (Armstrong et al., 2006; Moore & Armstrong, 2003). In other words, V4 neurons normally show enhanced firing rates in response to stimuli with orientations close to their preferred orientation. This enhanced response was attenuated when FEF stimulation caused attention to be oriented outside of the receptive fields of the recorded neurons.

Consistent with effects of top-down feedback on bottom-up processing in the visual cortex, the modulation of sensory-driven firing rates in monkey V4 neurons was reduced following FEF lesions (Gregoriou et al., 2014). Other lines of evidence also support the thinking that sensory processing is modulated via top-down feedback. For example, stimulation of FEF neurons increased the discriminability of stimulus orientation based on decoding the sensory-driven firing rates of V4 neurons (Armstrong & Moore, 2007). Behaviorally, FEF stimulation improved accuracy and sensitivity at corresponding visual field locations (Moore & Fallah, 2001, 2004), consistent with the enhancement of feature discrimination that occurs during visuospatial attention (McAdams & Maunsell, 1999; Spitzer et al., 1988). Together, these studies demonstrate that top-down feedback can influence the bottom-up processing of sensory information by enhancing or suppressing sensory-driven firing rates in neurons representing attended or unattended information, respectively.

Modulation of Sensory-Driven Firing Rates

Consistent with the thinking that top-down feedback generated during attention influences bottom-up processing, sensory-driven firing rates of neurons in DAN and visual

cortical areas are modulated in visuospatial attention tasks. In another type of visuospatial cueing task, a cue orients attention to a stimulus that is already present in the visual field to detect a subsequent change in a predetermined feature of that stimulus (e.g., color, contrast, shape). In this type of task, firing rates were increased in FEF neurons with response fields overlapping the cued location prior to the stimulus change (Gregoriou et al., 2009). In other words, the stimulus was already present prior to the appearance of the cue, leading to sensory-driven responses in the corresponding neurons; however, when attention was oriented to the visual stimulus by the cue, firing rates were increased even further. These enhanced sensory-driven firing rates likely reflect the influence of top-down feedback. Other studies demonstrated persistent increases in sensory-driven firing rates in monkey FEF (Armstrong et al., 2009; Chang et al., 2012; Fiebelkorn et al., 2018; Monosov & Thompson, 2009; Thompson et al., 1997, 2005), LIP (Bushnell et al., 1981; Fiebelkorn et al., 2018), V4 (Buffalo et al., 2010; Fries et al., 2008; Fries et al., 2001; Gregoriou et al., 2009; Luck et al., 1997; Vinck et al., 2013), V2 (Buffalo et al., 2010; Luck et al., 1997), and V1 (Buffalo et al., 2010; Chalk et al., 2010; Herrero et al., 2008; Herrero et al., 2013) neurons when attention was oriented to a visual stimulus overlapping the response fields or receptive fields of the recorded neurons. Additionally, decoding of MUA from topographic lateral PFC areas just anterior to the FEF reliably predicted the location of attention as monkeys focused on a stimulus to detect a subsequent change in its orientation (Tremblay et al., 2015). This finding is consistent with the thinking that the modulation of sensory-driven neural firing rates in topographically organized cortical areas of the visual processing system reflects the orienting of attention based on spatial information. Taken together, the evidence described above supports the thinking that attention's effects on sensory processing and perception involve the modulation of sensory-driven firing rates of neurons in frontal, parietal, and visual cortical areas.

Summary

Information coding in frontal, parietal, and visual cortical networks in the visual processing system depend on the pooled firing rates of many neurons processing visual sensory information. During the endogenous orienting of attention prior to visual stimulation, firing rates are enhanced in frontal, parietal, and visual cortical neurons corresponding to attended locations, while firing rates are even reduced in some FEF neurons corresponding to unattended or ignored locations. During attention, top-down feedback associated with the modulation of endogenous neural activity is thought to influence bottom-up sensory processing. Experimental evidence supports this thinking, demonstrating that top-down feedback induced via electrical stimulation modulates sensory-driven firing rates. Modulation of sensory-driven firing rates has also been reported in frontal, parietal, and visual cortical areas during visuospatial attention, mirroring the effects of electrically induced top-down feedback. These pieces of evidence are consistent with the thinking that top-down feedback generated during the orienting of visuospatial attention promotes the modulation of sensory-driven firing rates in cortical areas of the visual processing system, thereby determining what we perceive of the world.

Modulation of Gamma Synchronization During Attention

In addition to the modulation of firing rates, selective sensory processing during visuospatial attention could involve the modulation of neural synchronization (Ainsworth et al., 2012; Buehlmann & Deco, 2008) in frontal, parietal, and visual cortical areas of the visual processing system. Cortical neurons display oscillatory activity in the gamma frequency range (30-90 Hz) with increased coherence during the processing of visual sensory information (Brunet et al., 2015; Brunet & Fries, 2019; Gray & Singer, 1989; Gray et al., 1989; Roberts et al., 2013). The synchronization of gamma frequency neural activity has been proposed to facilitate

perception by integrating sensory representations across different cortical areas (Crick & Koch, 1990; Engel et al., 1992, 2001; Gray et al., 1989; Maldonado et al., 2000; Roelfsema et al., 1997; Singer & Gray, 1995).

Gamma-band synchronization can be measured using MUA, the power of local field potentials (LFP) in the gamma frequency band, or the coherence between these measures within and between cortical regions (e.g., spike-field coherence). Recordings of MUA reflect the spiking (i.e., action potentials or outputs) of multiple neurons, while LFPs primarily reflect the combined synaptic transmembrane currents (i.e., dendritic activity or inputs) within a short distance of recording electrodes (Buzsáki et al., 2012). Spectral analyses of LFPs are used to determine the power of oscillations within selected frequency bands. While attention also appears to involve the synchronization of neural activity in other frequency bands, especially for top-down control (for reviews see Buschman & Kastner, 2015; Fiebelkorn & Kastner, 2019; Gaillard & Ben Hamed, 2020), we will focus on the gamma frequency band due to its proposed involvement in bottom-up sensory processing.

According to the *Communication through Coherence* theory, gamma synchronization *within* and *between* groups of neurons could lead to more effective communication of selected information (Fries, 2015). Excitatory-inhibitory or pyramidal-interneuron gamma models (Börgers & Kopell, 2003; Brunel & Wang, 2003; Geisler et al., 2005; Tiesinga & Sejnowski, 2009; Whittington et al., 2000) describe how gamma synchronization could arise *within* a group of neurons via a cyclical process involving the firing of pyramidal neurons that release the excitatory neurotransmitter, glutamate, followed by the firing of interneurons that release the inhibitory neurotransmitter, gamma-aminobutyric acid (GABA; Bartos et al., 2007; Buzsáki & Wang, 2012). A “gamma cycle” begins when excitatory inputs trigger an action potential in

pyramidal neurons. Nearby GABAergic interneurons are excited by glutamate released from the pyramidal neurons, causing the interneurons to fire approximately 3 msec after the pyramidal neurons (Csicsvari et al., 2003; Hasenstaub et al., 2005; Salkoff et al., 2015). The resulting GABA release inhibits nearby pyramidal neurons that receive direct somatic connections from these interneurons (Buzsáki & Wang, 2012). Pyramidal neurons cannot fire again until excitatory inputs overcome the decaying GABAergic inhibition. Pyramidal neurons with stronger excitatory inputs are the first to overcome waning GABAergic inhibition and therefore the first to fire. Firing of these pyramidal neurons restarts the gamma cycle by exciting GABAergic interneurons. In this way, the firing of strongly excited pyramidal neurons becomes entrained to a rhythm in the gamma frequency range as determined by GABAergic interneurons (Buzsáki & Wang, 2012). Importantly, only pyramidal neurons receiving sufficient excitation can fire within the narrow time window before rising inhibition from the next gamma cycle. These strongly excited pyramidal neurons form a coherent cell assembly or neural ensemble (Buzsáki, 2010) representing selected sensory information. Sensory processing could therefore be more selective because only the excited neurons corresponding to attended sensory representations form ensembles that can communicate information to higher levels of the visual processing system. In contrast, pyramidal neurons with weaker excitatory inputs are unable to overcome inhibition from the preceding gamma cycle before the next round of inhibition prevents them from firing. In this "winner-take-all" scenario, weakly excited neurons (such as those representing unattended or ignored sensory information) are functionally selected against and prevented from communicating information to higher processing levels (Fries et al., 2007; Lumer, 2000).

Attended sensory information could also be communicated more effectively due to gamma synchronization *between* sending neurons and receiving neurons that become entrained

in a corresponding gamma rhythm across levels of the visual processing system (Besserve et al., 2015; Buehlmann & Deco, 2010; Roelfsema et al., 1997; Womelsdorf et al., 2007). Gamma-synchronized ensembles at one level of the processing system excite pyramidal neurons at higher levels of the processing system. Repetition of this process could entrain neurons across different cortical areas in the same gamma rhythm. Selected information could then be communicated more effectively between gamma synchronized sending and receiving ensembles for two reasons. *First*, gamma-synchronized inputs arrive at a receiving neuron almost simultaneously and can therefore be integrated before excitatory potentials from individual inputs dissipate (Azouz & Gray, 2003; Buzsáki, 2010; Cannon et al., 2014; Salinas & Sejnowski, 2001). *Second*, following the establishment of gamma synchronization between areas, coherent inputs arrive within the narrow window when receiving pyramidal neurons are maximally receptive prior to another round of inhibition from GABAergic interneurons (Börgers & Kopell, 2008; Fries et al., 2007).

Consistent with the ideas described above, oscillatory theories of attention (e.g., Buschman & Kastner, 2015; Clayton et al., 2015; Fiebelkorn & Kastner, 2019; Niebur et al., 1993; Tiesinga et al., 2004) propose a role for gamma synchronization in the bottom-up processing of attended sensory information. The following sections begin with evidence showing the specific involvement of gamma synchronization in the bottom-up processing of sensory information independent of attention. Evidence is then presented for the modulation of endogenous and sensory-driven gamma synchronization *within* parts of the DAN and visual cortices during visuospatial attention. Finally, evidence is presented linking attention with gamma synchronization *between* parts of frontal, parietal, and visual cortices. Together, these

ideas support the thinking that modulation of gamma-synchronization during attention could be involved in selecting the visual sensory information that we are able to process and perceive.

Gamma Synchronization Facilitates the Bottom-Up Processing of Sensory Information

Gamma synchronization appears to support communication in the bottom-up direction (Buschman & Miller, 2007), consistent with its proposed involvement in sensory processing. Support for the involvement of gamma synchronization in bottom-up processing comes from the use of laminar recording electrodes and current source density analysis, a technique that permits better spatial resolution of electrophysiological recordings. Using this approach, sensory-driven gamma oscillations in primary visual cortex were found to begin in cortical layer IV (van Kerkoerle et al., 2014), which predominately receives feedforward connections from the thalamus (Lund, 1988). Current source density analyses also indicated increased gamma synchronization between V1 and V2 originating in superficial layers of V1 during passive visual stimulation (Roberts et al., 2013). Feedforward projections arise predominantly from superficial cortical layers (Barone et al., 2000; Felleman & Van Essen, 1991); therefore, these results support the thinking that gamma synchronization in one area is stronger in the feedforward direction (i.e., facilitating communication of visual sensory information in the bottom-up direction). Accordingly, electrical stimulation in monkey V1 enhanced gamma synchronization in V4 (van Kerkoerle et al., 2014), while optogenetic stimulation of an area corresponding to V4 in cats did not induce gamma synchronization in the area corresponding to V1 (Ni et al., 2016a). These results provide experimental evidence supporting gamma synchronization as a specialized mechanism for the bottom-up processing of sensory information.

Modulation of Endogenous Gamma Synchronization

While gamma synchronization appears to be specialized for bottom-up sensory processing, modulation of gamma synchronization has been demonstrated in monkeys during the purely endogenous orienting of attention (Fries et al., 2001). For example, gamma synchronization was enhanced in monkey LIP neurons with receptive fields overlapping a cued location prior to the presentation of a target at that location (Saalmann et al., 2018). Enhanced gamma synchronization was also reported in V4 neurons with receptive fields overlapping a cued location prior to visual stimulation at that location (Fries et al., 2008). These findings demonstrate the purely endogenous modulation of gamma synchronization in neurons of parietal and visual cortex during visuospatial attention. Modulation of gamma synchronization in the absence of visual stimulation points to top-down control over this potentially important sensory processing mechanism.

Modulation of Sensory-Driven Gamma Synchronization Within Cortical Areas

Top-down modulation of gamma synchronization during attention could prioritize selected neural representations in preparation for bottom-up sensory processing (Engel et al., 2001). Consistent with this thinking, modulation of sensory-driven gamma synchronization has been demonstrated in DAN areas during visuospatial attention tasks. For example, monkeys performed a cued visuospatial attention task in which the cue indicated which portion of a visual stimulus to attend to detect a delayed change in the stimulus. Gamma synchronization was enhanced in monkey FEF (Fiebelkorn et al., 2018; Gregoriou et al., 2009) and LIP (Fiebelkorn et al., 2018) after the cue oriented attention to a portion of the visual stimulus inside the response fields or receptive fields of recorded neurons. Modulation of sensory-driven gamma synchronization is also apparent in EEG potentials recorded from humans performing

visuospatial attention tasks. For example, the power of gamma frequency oscillations was enhanced over frontal and parietal areas following a cue orienting visuospatial attention to the contralateral side of the visual field (Gruber et al., 1999). These reports from monkey and human electrophysiology are consistent with the thinking that attention's effects on sensory processing involve modulation of sensory-driven gamma synchronization in DAN areas.

Sensory-driven gamma synchronization is also modulated in extrastriate visual cortices during attention. For example, gamma synchronization was increased in monkey V2 (Buffalo et al., 2011) or V4 (Buffalo et al., 2011; Chalk et al., 2010; Fries et al., 2008; Fries et al., 2001; Gregoriou et al., 2009; Ni et al., 2016a; Vinck et al., 2013) neurons when attention was cued to a stimulus inside the receptive fields of the recorded neurons. Interestingly, MUA-MUA coherence recorded from nearby electrodes in monkey V4 demonstrated approximately zero phase difference during attention (Fries et al., 2008). This means that gamma synchronized neurons fired action potentials at the same time (i.e., with no delay on average). This finding is particularly important because synchronized spikes within a neural ensemble (as opposed to the mostly dendritic events that contribute to LFPs) facilitate communication of the represented information to postsynaptic neurons (Azouz & Gray, 2003; Salinas & Sejnowski, 2001; Tiesinga et al., 2004). Consistent with the thinking that gamma synchronization in extrastriate cortex facilitates sensory processing, the strength of V4 gamma synchronization was associated with faster RTs in monkeys performing visuospatial attention tasks (Rohenkohl et al., 2018; Womelsdorf et al., 2006). One study that recorded EEG in humans supports these non-human primate studies. In this study, the power of gamma frequency oscillations was enhanced over parieto-occipital areas following a cue that oriented visuospatial attention to the contralateral side of the visual field (Gruber et al., 1999). This gamma synchronization was enhanced more for

moving stimuli versus stationary stimuli, suggesting that parieto-occipital electrodes detected modulation of gamma synchronization in the extrastriate middle temporal area. These cross-species findings suggest that the modulation of sensory-driven gamma synchronization in extrastriate visual cortices during attention could partially explain attention's effects on sensory processing.

Modulation of sensory-driven gamma synchronization in V1 is less consistent. Decreased gamma synchronization (Chalk et al., 2010; Herrero et al., 2013), no modulation (Bosman et al., 2012; Buffalo et al., 2011), or increased gamma synchronization (van Kerkoerle et al., 2014) have all been reported using various metrics when attention was oriented to stimuli within the receptive fields of recorded V1 neurons. Faster RTs in a test of visuospatial attention have also been associated with enhanced gamma power in monkey V1 (Rohenkohl et al., 2018). While the evidence supporting the modulation of V1 gamma synchronization during attention is mixed, the latter finding is consistent with the involvement of early visual cortical gamma synchronization in the selective sensory processing that occurs during attention.

Modulation of Sensory-Driven Gamma Synchronization Between Cortical Areas

The synchronization of neural activity *between* different cortical areas could also be modulated during attention to influence bottom-up sensory processing. Fiebelkorn and colleagues (2018) provided evidence for the bottom-up propagation of gamma synchronization in the DAN when monkeys oriented attention to a visual stimulus within the response fields of recorded FEF neurons and the receptive fields of recorded LIP neurons. Gamma-band synchronization was observed between spikes in LIP and LFPs in FEF, but this spike-field coherence was not observed in the opposite direction. Importantly, spikes reflect the firing of action potentials that are communicated to other areas, while LFPs reflect mostly synaptic (i.e.,

dendritic) activity arriving at the recorded area (Buzsáki et al., 2012). Therefore, increased gamma spike-field coherence between the LIP and FEF is consistent with the bottom-up spread of gamma synchronization. Gamma synchronization between corresponding monkey V1 and V4 areas was also enhanced during attention (Rohenkohl et al., 2018). Furthermore, enhanced spike-field coherence in the gamma frequency band was reported only in the superficial layers of monkey V1, V2, and V4 during covert spatial attention to a visual stimulus in the receptive fields of recorded neurons (Buffalo et al., 2011). Feedforward projections arise from superficial cortical layers (Barone et al., 2000; Felleman & Van Essen, 1991); therefore, enhanced spike-field coherence in superficial visual cortical layers is consistent with the thinking that gamma synchronization propagates to higher-order areas. Additionally, when monkeys oriented attention inside the receptive fields of recorded neurons in both V1 and V4, analyses of LFP phase shifts (i.e., the delay between the gamma cycles in two areas; van Kerkoerle et al., 2014) and Granger causality analyses of gamma synchronization (Bosman et al., 2012; Richter et al., 2017; van Kerkoerle et al., 2014) revealed significantly stronger influences in the bottom-up direction. Consistent with the involvement of gamma synchronization in attention, one study reported a relationship with behavior that could reflect facilitated sensory processing. In this study, monkeys attended to a stimulus to report a subsequent change in its shape. V1-V4 gamma coherence during this task period was negatively correlated with RTs to the occurrence of the stimulus change (Rohenkohl et al., 2018). Together, these findings support the thinking that attention involves gamma synchronization between distant DAN and visual cortical areas which could facilitate the bottom-up processing of selected sensory information.

Summary

According to the *Communication through Coherence* theory, sensory processing could be facilitated by the synchronization of neural activity in the gamma frequency band within and between cortical areas (Fries, 2015). Consistent with this thinking, gamma synchronization has been associated with the bottom-up pathways by which sensory information is processed. The modulation of gamma synchronization during attention could therefore influence sensory processing and perception. Accordingly, the modulation of purely endogenous and sensory-driven gamma synchronization has been demonstrated in neurons *within* parts of the visual, parietal, and frontal cortices representing attended locations. Additional evidence suggests that attention involves the modulation of gamma synchronization *between* cortical areas. These findings support the thinking that the bottom-up processing of attended sensory information is facilitated by gamma synchronization within and between parts of the frontal, parietal, and visual cortices. The modulation of gamma synchronization could partially explain how attention influences perception.

Modulation of Noise Correlations During Attention

During attention, sensory processing could also be affected by the modulation of trial-to-trial variability in the sensory-driven firing of individual neurons and the correlations in this variability across populations of neurons (Cohen & Kohn, 2011; Seriès et al., 2004). Individual neurons demonstrate variable responses to the same sensory stimulation on a trial-by-trial basis (Arieli et al., 1996; Gawne & Richmond, 1993; Lee et al., 1998; Tolhurst et al., 1983; Tomko & Crapper, 1974) due to fluctuations caused by sensory transduction, random cellular processes (e.g., synthesis and degradation of proteins or opening and closing of ion channels), variability in the speed of action potential propagation, or random synaptic events such as the spontaneous

release of neurotransmitter from vesicles (see Faisal et al., 2008 for review). If the firing rate variability of individual neurons is independent from (i.e., not correlated with) the variability of other neurons, the combined effects could be averaged out across many neurons with little effect on information coding in the network. However, adjacent cortical neurons with shared inputs or similar response tuning often demonstrate correlated firing rate variability (Bair et al., 2001; Gawne & Richmond, 1993; Gawne et al., 1996; Kohn & Smith, 2005; Lee et al., 1998; Reich et al., 2001; Zohary et al., 1994). Within a population of neurons, correlations in firing rate variability, referred to as *noise correlations*, could affect the amount of information encoded in network activity (Averbeck et al., 2006; Averbeck & Lee, 2006; Nirenberg & Latham, 2003; Shadlen & Newsome, 1994, 1998; Snippe & Koenderink, 1992; Zohary et al., 1994). In particular, noise correlations between neurons that respond to similar sensory information (e.g., neurons with overlapping receptive fields) could reduce the information carried in the pooled neural activity (Abbott & Dayan, 1999; Poort & Roelfsema, 2009; Shadlen et al., 1996), which could reduce the reliability of stimulus detection. Consistent with this thinking, high network-level noise correlations have been associated with poorer detection performance and could represent a neural correlate of attentional lapses (Astrand et al., 2016). Attention has been shown to reduce the firing rate variability of neurons in primary (Herrero et al., 2013) and extrastriate visual cortices (Cohen & Maunsell, 2009; Mitchell et al., 2007, 2009; Niebergall et al., 2011); however, one study found no effect in FEF neurons (Chang et al., 2012). Furthermore, noise correlations in primary (Herrero et al., 2013), extrastriate (Cohen & Maunsell, 2009; Mitchell et al., 2009), and prefrontal cortical areas including the FEF (Astrand et al., 2016; Buffalo et al., 2011; Ruff & Cohen, 2014; Tremblay et al., 2015) were reduced during attention. This evidence suggests that reduced firing rate variability at the level of individual neurons could prevent the

pooled effects of noise correlations between similarly tuned neurons at the network level, potentially facilitating the detection of attended sensory information.

Summary – Modulation of Neural Activity During Attention

An interconnected network of frontal, parietal, and visual cortical areas supports the selective processing of important sensory information during visuospatial attention. Event-related fMRI during visuospatial attention tasks was used to isolate the modulation of purely endogenous neural activity in these areas from the resulting top-down feedback-mediated effects on sensory-driven neural activity. As a potential explanation for findings from human imaging studies, numerous monkey electrophysiology studies demonstrated modulation of purely endogenous neural firing rates in frontal, parietal, and visual cortical areas as well as modulation of gamma synchronization within and between these areas. The modulation of endogenous neural activity could represent a content filter put in place during visuospatial attention to promote the bottom-up processing of sensory information at attended locations. Consistent with this thinking, modulation of sensory-driven firing rates, gamma synchronization, and noise correlations have all been reported in DAN and visual cortical areas during tests of visuospatial attention. The modulation of top-down feedback and bottom-up processing could respectively increase the likelihood of efficient processing for selected sensory information (top-down) and increase the efficiency of the subsequent processing (bottom-up).

The top-down modulation of endogenous neural activity during attention and the resulting feedback-mediated effects on bottom-up sensory processing likely involve neurotransmitters like glutamate and neuromodulators like norepinephrine (NE). Findings supporting the involvement of these systems are outlined in the following sections.

Attention Is Supported by Glutamate and Norepinephrine-Mediated Effects

During visuospatial attention, endogenous neural activity generated by top-down feedback in DAN and visual cortical areas acts as a *content filter* to influence the bottom-up processing of sensory information (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Maintenance of this content filter could be mediated by the excitatory neurotransmitter, glutamate, acting at *N*-methyl-D-aspartate (NMDA) receptors. Activation of NMDA receptors could also be important for the subsequent modulation of sensory-driven gamma synchronization and noise correlations. In addition to a content filter, selective sensory processing requires a *temporal filter* to ensure that target detection occurs at the appropriate time. A temporal filter could increase the likelihood that selected sensory information is processed efficiently when it appears. Additionally, such a temporal filter could protect against spurious detections or false alarms when the target is not yet present. The neuromodulator, NE, is released into the cortex in response to the presentation of attended sensory information (Aston-Jones et al., 1994; Aston-Jones & Bloom, 1981; Bouret & Sara, 2002; Foote et al., 1980a; Grant et al., 1988; Sara et al., 1994) where it modulates the responsivity of neurons (Servan-Schreiber et al., 1990). Target-evoked NE release could therefore function as a temporal filter for perception (Aston-Jones & Cohen, 2005). The release of NE and subsequent effects on neural firing rates or gamma synchronization could also depend on the activation of NMDA receptors (Mather et al., 2016).

The following sections detail the possible involvement of NMDA receptor activation and target-evoked NE release in the modulation of neural activity that occurs during attention. *First*, evidence is presented to link the activation of NMDA receptors with the top-down feedback that occurs when attention is endogenously oriented in the absence of visual stimulation. *Second*,

evidence is presented for the involvement of NMDA receptors in sensory-driven neural activity, including gamma synchronization and noise correlations. *Finally*, an introduction to the NE system is provided followed by a description of how target-evoked NE release could interact with NMDA receptor activation to modulate neural activity, including firing rates or gamma synchronization.

NMDA Receptors Could Be Involved in the Modulation of Endogenous Neural Activity

During visuospatial attention, sensory processing depends on top-down feedback associated with the modulation of endogenous neural activity (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Accordingly, persistent modulation of endogenous neural activity has been demonstrated in monkey electrophysiology and human imaging studies when subjects oriented visuospatial attention in expectation of a stimulus (as described above). Like visuospatial attention, spatial working memory involves maintaining a location in mind for a short period of time. This has led to the suggestion that spatial attention is engaged to accomplish this function during spatial working memory (Awh & Jonides, 2001). Consistent with this thinking, activity is increased in overlapping frontal and parietal structures in monkeys (e.g., Andersen et al., 1990; Bushnell et al., 1981; Colby et al., 1996; Funahashi et al., 1993; Kodaka et al., 1997) and humans (e.g., Awh et al., 2000; Corbetta et al., 2002; Kastner et al., 2007; LaBar et al., 1999; Todd & Marois, 2004; Xu & Chun, 2007) during spatial working memory and spatial attention. Additionally, Awh and colleagues (1999) reported topographic modulation of fMRI activity in posterior occipital areas during spatial working memory, paralleling the top-down modulation of visual cortical activity that occurs during visuospatial attention. Analogous to facilitated sensory processing at attended locations, spatial working memory reduced RTs to stimuli at remembered locations (Awh et al., 1998). Furthermore,

memory performance was disrupted by shifts of spatial attention (Awh et al., 1998; Smyth, 1996; Smyth & Scholey, 1994), consistent with the notion that spatial attention is deployed to support spatial working memory. Together, these findings support the thinking that spatial working memory involves the maintenance of spatial attention at the to-be-remembered location (Awh & Jonides, 2001).

If spatial working memory does engage spatial attention, then the persistent modulation of endogenous neural activity during attention could involve the same mechanisms that support working memory. In particular, NMDA receptors are known to be critical for the recurrent network activity that supports working memory (Brunel & Wang, 2001; Compte et al., 2000; van Vugt et al., 2020; Wang et al., 2013; Wang & Arnsten, 2015). Consistent with the evidence linking working memory to the maintenance of spatial attention, top-down feedback to visual cortical areas during visuospatial attention is thought to involve NMDA receptor activation (Wagatsuma et al., 2016). Accordingly, systemic administration of the NMDA antagonist, ketamine, attenuated top-down feedback-mediated effects on neural activity as measured by fMRI in human V1 (van Loon et al., 2016). Additionally, blockade of NMDA receptors in monkey V1 disrupted the local modulation of top-down feedback-mediated neural activity (Self et al., 2012). Together, this evidence suggests that NMDA receptor activation could underlie the persistent increases in neural activity seen in frontal, parietal, and visual cortical areas during visuospatial attention. During attention, NMDA receptor-mediated effects on endogenous neural activity and associated top-down feedback could increase the likelihood that selected sensory information is processed efficiently.

NMDA Receptors Could Be Involved in the Modulation of Sensory-Driven Neural Activity

NMDA Receptors and Gamma Synchronization

Facilitated processing of attended sensory information could depend on NMDA receptor-mediated effects on sensory-driven gamma synchronization in frontal, parietal, and visual cortical areas. Schizophrenia research provides strong evidence linking attention, NMDA receptor activation, and gamma synchronization. Schizophrenia is associated with NMDA receptor hypofunction (Olney et al., 1999) that appears to disrupt gamma synchronization. For example, pharmacological NMDA antagonism is a commonly used animal model for schizophrenia (Adell et al., 2012) that has been linked with abnormal baseline and sensory-driven gamma synchronization in many instances (e.g., Anderson et al., 2014, 2017; Ehrlichman et al., 2009; Hakami et al., 2009; Hudson et al., 2016, 2020; Jones et al., 2012, 2014, 2018; Kehrer et al., 2008; Kulikova et al., 2012; Lee et al., 2017; Pinault, 2008; Saunders et al., 2012). Pharmacological NMDA receptor blockade also disrupted normal gamma synchronization in healthy humans (Shaw et al., 2015). Furthermore, patients with schizophrenia display abnormal gamma synchronization (reviewed in Hunt et al., 2017) which has been observed during various cognitive tasks (Basar-Eroglu et al., 2007; Cho et al., 2006; Kwon et al., 1999; Uhlhaas et al., 2008; Uhlhaas & Singer, 2010). Abnormal gamma synchronization could partially explain the impaired attention that is often seen in individuals with schizophrenia (Cornblatt & Malhotra, 2001; Liu et al., 2002; McCleery et al., 2015; Nuechterlein et al., 2004, 2015).

Abnormal gamma synchronization due to NMDA receptor hypofunction could be explained by disruption of GABAergic circuits (Cohen et al., 2015; see Gonzalez-Burgos et al., 2010 for review) that are thought to be involved in the generation of gamma synchronization (Buzsáki & Wang, 2012). Consistent with this thinking, mutant mice lacking NMDA receptors on GABAergic interneurons demonstrated enhanced baseline gamma synchronization and reduced optogenetically or pharmacologically induced gamma synchronization (Carlén et al.,

2012). Additionally, Kocsis (2012) reported abnormal gamma power in the cortical EEG of mice following the administration of either a nonspecific NMDA antagonist or an antagonist for NMDA receptors containing the NR2A subunit, which is expressed preferentially in NMDA receptors on GABA interneurons (Kinney et al., 2006; Xi et al., 2009). NMDA antagonists that are selective for NMDA receptors with other subunits had only minor effects on gamma synchronization. These findings support the thinking that the abnormal gamma synchronization associated with schizophrenia is related to hypofunction of NMDA receptors on GABAergic interneurons. Pharmacological treatments promoting NMDA receptor activation could restore normal modulation of gamma synchronization in the frontal, parietal, and visual cortical areas of the visual processing system to improve attention in individuals with disorders such as schizophrenia.

NMDA Receptors and Noise Correlations

The activation of NMDA receptors could also influence bottom-up processing via the reduction of noise correlations between neurons representing attended sensory information. Consistent with this thinking, Herrero and colleagues (2013) demonstrated that iontophoretic pharmacological blockade of NMDA receptors in monkey V1 prevented the reductions in firing rate variability and noise correlations that occur during attention without affecting the modulation of firing rates. Interestingly, Mitchell and colleagues (2007) demonstrated that firing rates and firing rate variability of putative inhibitory interneurons were modulated more strongly during attention relative to putative pyramidal neurons. Consistent with the involvement of inhibitory interneurons, Carlén and colleagues (2012) reported increased firing rate variability in mutant mice lacking NMDA receptor expression on GABAergic interneurons. Mutant mice were also impaired in various cognitive functions, including working memory. These findings are

consistent with the thinking that the activation of NMDA receptors plays an important part in the modulation of firing rate variability and network-level noise correlations during attention. Correlations in firing rate variability between neurons transmitting attended information could affect the reliability of the information coded in network activity (Averbeck et al., 2006; Shadlen et al., 1996; Shadlen & Newsome, 1994, 1998; Snippe & Koenderink, 1992; Zohary et al., 1994); therefore, activation of NMDA receptors could have important implications for sensory processing and perception via its role in the modulation of noise correlations.

Summary

In addition to the potential involvement of NMDA receptors in modulating endogenous neural activity (described above), the activation of NMDA receptors could support visuospatial attention by promoting the modulation of sensory-driven neural activity in the frontal, parietal, and visual cortical areas. The activation of NMDA receptors could influence the efficiency of sensory processing in several ways. NMDA receptor activation could be important for the modulation of sensory-driven gamma synchronization, thereby rendering the bottom-up processing of selected sensory information more effective (Fries, 2015). Additionally, NMDA receptor activation could be important for the reduction of noise correlations that could influence the processing of attended sensory information. These effects could enhance the reliability of the neural population code representing attended sensory information.

As described in the following section, NMDA receptor activation could also support the selective processing of attended sensory information via effects on target-evoked NE release.

Target-Evoked Norepinephrine Release as a Temporal Filter for Perception

During attention, top-down feedback associated with the modulation of endogenous neural activity is thought to filter the contents of perception via its effects on the bottom-up processing of sensory information (Corbetta & Shulman, 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). Content filtering needs to be supported by temporal filtering to ensure that the detection of selected sensory information only occurs when that information is present. Such a temporal filter could protect against false alarms and increase the likelihood that selected sensory information is processed efficiently when it appears. Sensory processing could be temporally filtered by the neuromodulatory effects of NE (Aston-Jones & Cohen, 2005). The brainstem nucleus referred to as the locus-coeruleus (LC) is the brain's primary source of NE (Jones & Moore, 1977; Jones & Yang, 1985; Morrison et al., 1982; Samuels & Szabadi, 2008; Swanson & Hartman, 1975). The LC sends projections throughout the brain, including to frontal, parietal, and visual cortical areas (Foote et al., 1983; Mitchell et al., 1994; Pascuzzo & Skeen, 1982; Room et al., 1981; Schwarz & Luo, 2015). Via these diffuse projections, the LC-NE system is ideally positioned to modulate the cortical neural activity underlying sensory processing.

Norepinephrine could influence the efficiency of sensory processing by enhancing the synaptic input gain (Servan-Schreiber et al., 1990) of neurons in frontal, parietal, and visual cortical areas of the visual processing system. Synaptic inputs refer to top-down influences or afferents communicating bottom-up sensory information. Increased gain means that neurons show higher responsivity to both excitatory and inhibitory synaptic inputs. Put simply, neurons receiving more excitatory inputs are increasingly excited and therefore more likely to communicate information to higher levels of the processing system. On the other hand, neurons receiving fewer excitatory inputs and a higher proportion of inhibitory inputs are increasingly

inhibited. These neurons are therefore less likely to communicate to neurons in higher-order cortical areas. The enhancement of gain could benefit visual processing by boosting the *signal* representing the bottom-up processing of selected sensory information, while suppressing extraneous *noise* or neural activity that is unrelated to processing the selected sensory information. Consistent with these ideas, LC activity has been shown to influence the gating or tuning of neural responses to sensory information in various modalities (Bouret & Sara, 2004, 2002; Devilbiss & Waterhouse, 2011; Edeline et al., 2011; Harris & Thiele, 2011; Lecas, 2004; Manunta & Edeline, 1997, 1999; Martins & Froemke, 2015; McLean & Waterhouse, 1994; Navarra & Waterhouse, 2018; Polack et al., 2013; Waterhouse et al., 1990, 1998; see Waterhouse & Navarra, 2019 for review). Increased signal-to-noise ratio of neural responses could lower the threshold for stimulus detection as strengthened signals should be more discernible from reduced noise. Importantly, neural population codes provide the most reliable information regarding the presence of a stimulus (Averbeck et al., 2006; Poort & Roelfsema, 2009; Shadlen & Newsome, 1994; Shadlen et al., 1996) due to variability in the responses of single neurons to repeated presentations of the same stimulus (reviewed in Faisal et al., 2008). NE's effects on gain at the level of individual neurons (Aston-Jones & Cohen, 2005) could affect functional connectivity at the network level (Guedj et al., 2017) as selected neurons communicate information to neurons in higher-order areas that also experience NE-mediated gain modulation. This thinking is consistent with a proposed network-level reset function for the LC-NE system (Bouret & Sara, 2005; Sara & Bouret, 2012). These ideas suggest that NE could lower the threshold for stimulus detection by increasing the signal-to-noise ratio of neural responses across large-scale networks in the frontal, parietal, and visual cortices.

The *Adaptive Gain* theory outlines how the LC-NE system could play a general role in optimizing goal-directed behavior via distinct patterns of LC firing and NE release during different behavioral states (Aston-Jones & Cohen, 2005). At times we might explore the environment to find new sources of reward and at others we might exploit learned stimulus-response contingencies that are expected to produce reward (as in attention). These behavioral states are characterized by distinct patterns of tonic and phasic firing in LC noradrenergic neurons which could be influenced via connections from prefrontal cortex (Arnsten & Goldman-Rakic, 1984; Luppi et al., 1995; Sara & Herve-Minvielle, 1995). Tonic firing refers to sustained low-frequency (0-5Hz) firing, while phasic firing refers to transient bursts comprising multiple spikes (Berridge & Waterhouse, 2003). A "tonic mode" of LC firing is thought to support exploration of the environment for sources of reward (Aston-Jones & Cohen, 2005). The tonic mode is characterized by increased tonic LC firing, reduced or absent phasic LC firing, and impaired performance in signal detection tasks (Aston-Jones et al., 1994; Usher et al., 1999). In contrast, when attention is engaged to exploit a known source of reward, optimal performance is associated with a "phasic mode" characterized by reduced tonic LC firing and stronger phasic LC firing (Aston-Jones et al., 1994; Aston-Jones et al., 1999). Stronger phasic firing leads to increased NE release in target areas (Berridge & Abercrombie, 1999; Dugast et al., 2002; Florin-Lechner et al., 1996). Importantly, phasic LC firing and the resulting NE release occur in response to the appearance of attended stimuli (Aston-Jones et al., 1994; Aston-Jones & Bloom, 1981; Bouret & Sara, 2002; Foote et al., 1980; Grant et al., 1988; Sara et al., 1994). Considering the effects of NE on gain in cortical networks (described above), target-evoked phasic LC firing and the resulting NE release could function as a temporal filter for sensory processing to reduce

the threshold for stimulus detection, thereby increasing the likelihood that we can process important sensory information efficiently when it appears.

Norepinephrine-mediated enhancement of gain increases the signal-to-noise ratios of neural responses (Servan-Schreiber et al., 1990), which at the network-level could functionally lower the threshold for stimulus detection. These effects could explain the link between patterns of LC firing and behavioral measures of attention. The high distractibility associated with the LC tonic mode (Aston-Jones et al., 1994; Usher et al., 1999) could be related to enhanced tonic NE release and a lower threshold for stimulus detection. While potentially disruptive to focused attention, a lower threshold for stimulus detection could be beneficial when exploring the environment for alternative sources of reward. On the other hand, lower tonic NE release during attention could reduce gain in the cortex and therefore raise the threshold for stimulus detection. This could prevent spurious detections or false alarms triggered by salient stimuli that appear when the sought-after information is not present. This thinking is consistent with reduced distractibility during the phasic mode of LC firing (Aston-Jones et al., 1994, 1999). When a target stimulus triggers phasic LC firing, NE release could enhance gain in cortical processing networks to facilitate target detection. Evidence from computer modeling supports the effects of target-evoked NE release on gain (Gilzenrat et al., 2002; Servan-Schreiber et al., 1990; Shea-Brown et al., 2008; Usher et al., 1999). For example, Usher and colleagues (1999) demonstrated that simulated phasic LC firing improved signal detection performance in a model network. In other words, more accurate predictions could be made about the presence of a target based on decoding network activity. The model's performance closely paralleled behavioral effects in monkeys including enhanced target discrimination and reduced variability of RT distributions due to target-evoked NE release (also seen in Aston-Jones et al., 1994). NE-mediated effects on

network activity also resembled the enhancement of discrimination in humans performing tests of attention like the CPT (Servan-Schreiber et al., 1990). These studies support the thinking that the ability to detect attended sensory information at appropriate times depends on the characteristics of tonic and phasic LC firing and the effects of target-evoked NE release in cortical processing networks.

In summary, target-evoked NE release and the resulting increase in the gain of neural responses could functionally reduce the threshold for stimulus detection in sensory processing networks. According to the *Adaptive Gain* theory, the LC-NE system could therefore function as a *temporal filter* for sensory processing and perception. During attention, tonic LC firing is reduced to moderate levels, while enhanced phasic LC firing occurs in response to relevant (i.e., attended) stimuli. Target-evoked NE release could increase gain in neurons throughout the frontal, parietal, and visual cortical areas of the visual processing system, raising the likelihood that detection occurs when task-relevant information is present. Simultaneous enhancement of activity in neurons contributing to target-related signals and suppression of activity in neurons contributing to distractor-related noise requires a mechanism by which NE can selectively facilitate the postsynaptic influences of both excitatory and inhibitory inputs. The following sections describe how NE-mediated enhancement of gain could depend on varying levels of extracellular glutamate in cortical processing networks and the effects of NMDA receptor activation on the amount of NE released by LC neurons.

Norepinephrine's Effects on Firing Rates Could Depend on Extracellular Glutamate Levels

Target-evoked NE release could increase gain and thereby promote the processing of attended sensory information by modulating firing rates in the frontal, parietal, and visual cortices. The amount of NE released and therefore subsequent effects on firing rates could

depend on the activation of NMDA receptors (Mather et al., 2016). Specifically, the *Glutamate Amplifies Noradrenergic Effects* (*GANE*) model proposes that the modulation of firing rates depends on (1) varying levels of extracellular glutamate at synapses communicating prioritized versus non-prioritized sensory information, (2) NMDA receptor-mediated effects on NE release leading to high and low NE concentrations in these synapses, and (3) opposing neuromodulatory effects due to the activation of specific NE receptor subtypes at high and low synaptic NE concentrations.

During sustained attention, firing rates increase endogenously in DAN and visual cortical areas corresponding to attended locations. Increased activity in the pyramidal neurons representing attended visual field locations would be expected to increase glutamate release. At the highly active synapses receiving inputs from these pyramidal neurons, increased glutamate could activate NMDA receptors on nearby LC axon terminals to increase target-evoked NE release. In contrast, glutamate levels would be expected to remain relatively low in synapses communicating irrelevant information (i.e., the inactive synapses receiving inputs from neurons with receptive fields overlapping unattended or ignored locations). Low glutamate levels could lead to reduced NMDA receptor-mediated NE release, causing NE levels to remain relatively low in these synapses. Importantly, NE β-1 receptors are only activated at high synaptic NE concentrations, while α-2 receptors are activated at lower levels of NE (Brian P. Ramos & Arnsten, 2007). Typically, β-1 receptors cause excitatory effects via coupling with G_s proteins (Ferry et al., 1999; Ordway et al., 1987; Summers & McMartin, 1993; Zhang et al., 2005), while α-2 receptors cause inhibitory effects due to coupling with G_i proteins (Bylund, 1992; Ramos et al., 2006). Due to these opposing effects NE could simultaneously increase the firing rates of neurons communicating the signal representing attended information (via β-1 receptors) and

suppress firing rates in neurons communicating noise (via α-2 receptors). The activation of NE β-1 and α-2 receptors at different synapses could therefore enhance gain in neurons across frontal, parietal, and visual cortical areas to influence sensory processing and facilitate the perception of attended information.

Synthesizing these points, the *GANE* model suggests that where glutamate levels are high (active synapses), increased NMDA receptor-mediated NE release leads to positive modulation of firing rates in postsynaptic neurons via β-1 receptor activation. In contrast, where glutamate levels are relatively low (inactive synapses), α-2 receptor activation suppresses NE release and negatively modulates firing rates in postsynaptic neurons. These interactions between the glutamatergic and noradrenergic systems are described in greater detail in the following sections.

Norepinephrine's Effects at Active Synapses

The *GANE* model posits that synapses communicating task-relevant information become "hotspots" of activity. NMDA receptors on the terminal membranes of adjacent LC neurons are activated by glutamate spillover, triggering additional NE release (Fink et al., 1990, 1992; Lehmann et al., 1992; Luccini et al., 2007; Pittaluga et al., 1999). See Fig. 1. Consistent with this thinking, NMDA-mediated NE release has been demonstrated *in vitro* in slices from rat parietal cortex (White & Semba, 1997). Importantly, activation of NMDA receptors requires membrane depolarization (Dingledine et al., 1999; Johnson & Ascher, 1987; Kleckner & Dingledine, 1988; Traynelis et al., 2010). Glutamate's effects on NE release are therefore dependent on the membrane depolarization that accompanies phasic LC firing in response to attended stimuli. In this way, phasic LC firing allows glutamate spillover to activate NMDA receptors to selectively increasing target-evoked NE release at the highly active synapses communicating task-relevant information.

Activation of NMDA receptors on LC terminals increases extracellular NE concentration which then raises the affinity of β-1 receptors for NE (Ramos & Arnsten, 2007). β-1 receptor activation occurs at three notable synaptic locations. First, activation of β-1 receptors on presynaptic glutamatergic terminals stimulates additional glutamate release(Ferrero et al., 2013; Gereau & Conn, 1994; Herrero & Sánchez-Prieto, 1996; Ji et al., 2008; Kobayashi et al., 2008; Mobley & Greengard, 1985). See Fig. 1. Additional glutamate enhances NE release as described above. In turn, NE enhances the release of glutamate. This positive feedback loop is thought to create the "hotspot" of excitation at active synapses communicating task-relevant information. Second, high NE levels activate β-1 autoreceptors on LC terminals to further increase NE release (Chang et al., 1986; Misu & Kubo, 1986; Murugaiah & O'Donnell, 1995a, 1995b; Ueda et al., 1985). See Fig. 1. Finally, high levels of NE activate β-1 receptors located on postsynaptic glutamatergic neurons to positively modulate the excitatory effects of increased glutamate binding at postsynaptic NMDA receptors (Madison & Nicoll, 1982; Nicoll, 1988). See Fig. 1.

Increased excitation at active synapses is also supported by reduced inhibitory neuromodulation. Several inhibitory mechanisms are mediated by α-2 NE receptors (described in greater detail below). In the presence of high levels of NE, however, increased membrane depolarization induces conformational changes in α-2 receptors (Rinne et al., 2013) which reduce their affinity for NE. Elevated NE within the synapses communicating task-relevant information should therefore decrease α-2 receptor-mediated inhibitory effects. The reduced affinity of α-2 receptors is reversed at saturating levels of NE (Rinne et al., 2013) which could protect against excessive activity at "hotspots" (Mather et al., 2016).

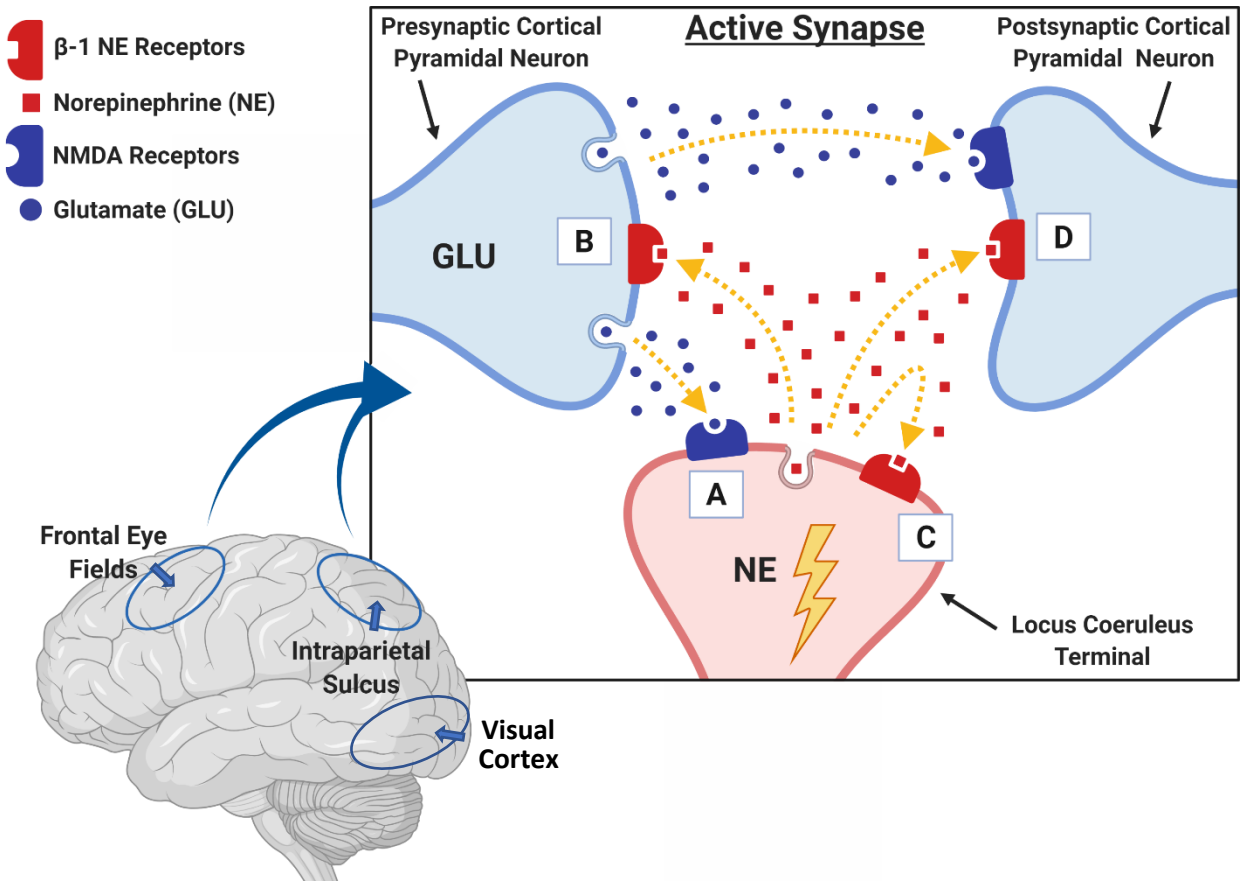

Figure 1. Figure depicting the effects of NE and glutamate at active synapses in human frontal, parietal, and visual cortical areas. A) Spillover glutamate (blue circles) from highly active cortical neurons opens NMDA channels on nearby NE terminals to increase NE release (red squares). Activation of these NMDA receptors requires depolarization of the LC terminal (lightning symbol) as in phasic firing of the LC. B) Increased NE levels activate β-1 receptors on presynaptic glutamatergic neurons to increase glutamate release. C) Increased NE levels activate β-1 receptors on LC terminals to further increase NE release. D) Finally, increased NE levels activate β-1 receptors on postsynaptic glutamatergic neurons to increase excitability.

In summary, NMDA receptor and NE-mediated effects create "hotspots" of excitation at synapses that are highly active. During attention, DAN and visual cortical neurons that transmit task-relevant information demonstrate persistent increases in firing rate; therefore, synapses receiving inputs from these neurons would be expected to show enhanced glutamate levels. Phasic LC firing occurs in response to attended stimuli. The resulting membrane depolarization could then allow excess glutamate to activate NMDA receptors on LC terminals, thereby

enhancing NE release. β-1 receptors are activated by increased NE and could further enhance NE and glutamate release to positively modulate the firing rates of postsynaptic pyramidal neurons. Finally, the affinity of α-2 receptors for NE is reduced due to high NE levels at hotspots, decreasing inhibitory postsynaptic effects at the synapses communicating task-relevant information. Together these effects could boost the *signal* representing sensory information at attended locations.

Norepinephrine's Effects at Inactive Synapses

The *GANE* model provides a possible explanation for how NE can enhance postsynaptic potentials at synapses communicating task-relevant information while simultaneously inhibiting postsynaptic potentials at other synapses in the same brain regions. According to the *Adaptive Gain* model, NE is also released at relatively silent or inactive connections when behaviorally relevant stimuli trigger phasic LC firing. Importantly, neurons with receptive fields overlapping unattended or ignored locations are not highly active and can even be suppressed during attention; therefore, these neurons would be expected to release less glutamate. Lack of glutamate spillover at synapses receiving inputs from these neurons means that NMDA receptors on LC axon terminals are not activated to release additional NE. See Fig. 2. NE levels therefore remain relatively low at the inactive synapses that process unattended information.

Lower levels of NE preferentially activate α-2 receptors (Ramos & Arnsten, 2007). Activation of α-2 receptors occurs at three notable synaptic locations. First, activation of α-2 receptors on presynaptic glutamatergic neurons inhibits glutamate release (Bickler & Hansen, 1996; Egli et al., 2005) to further reduce the firing rates of postsynaptic neurons. See Fig. 2. Second, activation of α-2A autoreceptors on LC terminals inhibits additional NE release (Delaney et al., 2007; Gilsbach & Hein, 2008; Langer, 2008; Starke, 2001). See Fig. 2. Finally,

activation of α-2 receptors on postsynaptic pyramidal neurons negatively modulates postsynaptic glutamatergic effects (Nomura et al., 2014; Wang et al., 2007). See Fig. 2. Together these α-2 receptor-mediated effects increase neuronal response gain in cortical processing networks by inhibiting the communication of sensory information at irrelevant visual field locations (noise).

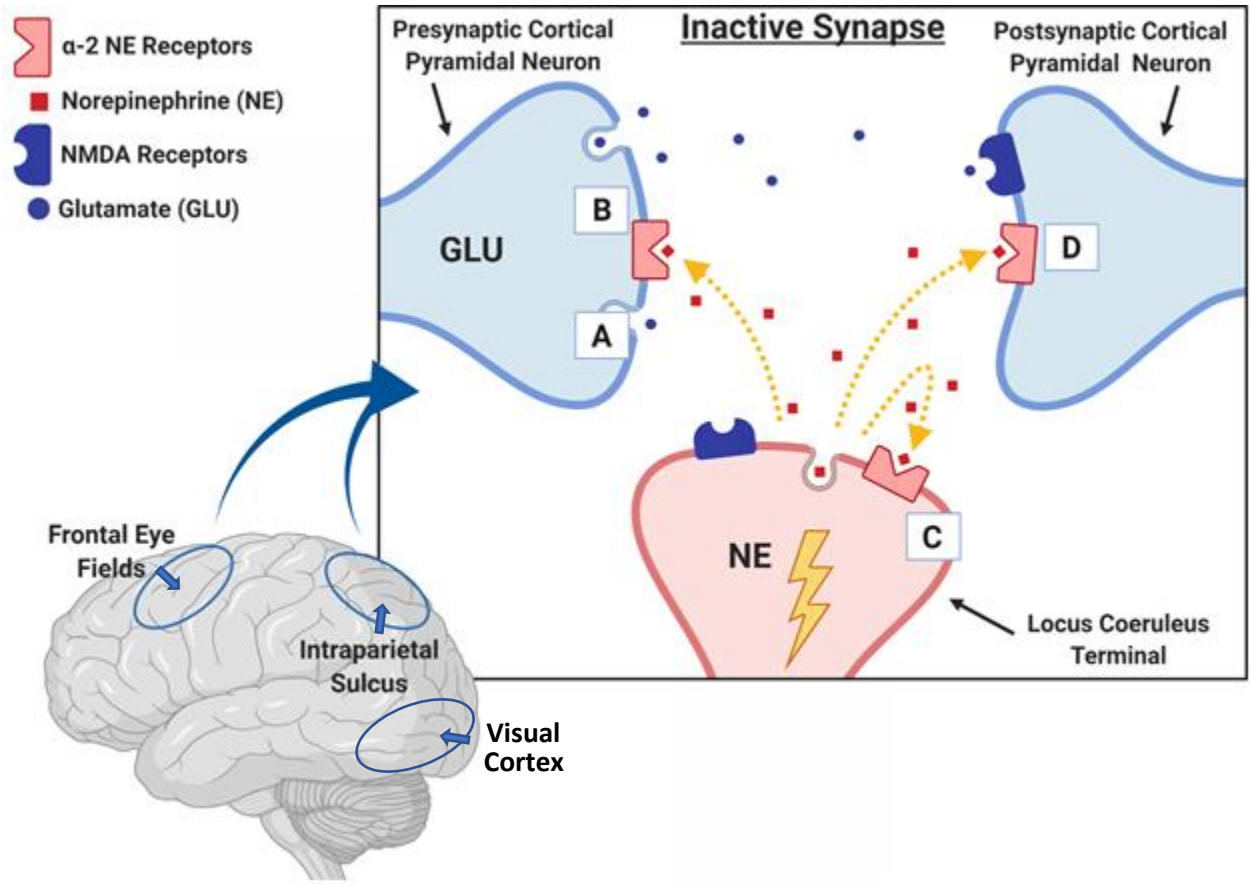

Figure 2. Figure depicting the effects of NE and glutamate at inactive synapses in human frontal, parietal, and visual cortical areas. A) Lack of glutamate overflow (blue circles) at inactive synapses means that NMDA channels on LC terminals are not opened in response to phasic firing. This means that the amount of NE released remains low. B) Low levels of NE activate α-2 receptors on LC terminals to inhibit further NE release. C) Low levels of NE activate presynaptic α-2 receptors on glutamatergic neurons to inhibit glutamate release. D) Low levels of NE activate α-2 receptors on postsynaptic glutamatergic neurons to further inhibit activity at these inactive synapses.

In summary, phasic LC firing releases NE into the cortex, including at the inactive connections receiving inputs from neurons with receptive fields overlapping unattended or ignored locations. Extracellular glutamate levels and NMDA receptor activation remain relatively low; therefore, NE release is not enhanced at these synapses. At relatively low NE levels, α-2 receptors on presynaptic pyramidal neurons and LC terminals are activated, inhibiting the release of glutamate and NE, respectively. Postsynaptic α-2 receptors are also activated to negatively modulate glutamatergic effects on the firing rates of postsynaptic pyramidal neurons. Together, these α-2 receptor-mediated inhibitory effects could facilitate the processing of attended sensory information by reducing the *noise* contributed by neurons with receptive fields overlapping unattended or ignored locations.

Summary

The *GANE* model proposes a mechanism by which attention could selectively facilitate the processing of visual information at attended locations. Endogenous activity in glutamatergic cortical networks (i.e., DAN and visual cortices) and the resulting activation of NMDA receptors could influence the processing of attended sensory information by determining the amount of target-evoked NE release. NMDA receptor activation and increased NE release at active synapses could lead to enhanced firing rates in postsynaptic neurons via β-1 receptor-mediated mechanisms. On the other hand, lack of NMDA receptor activation at inactive synapses could lead to reduced NE release and greater suppression of firing rates via α-2 receptor-mediated mechanisms. In this way, sensory information corresponding to attended locations could be amplified for more effective processing. Importantly, enhanced processing only occurs in response to target stimuli. In other words, the *GANE* model describes a possible integration of

the content filter and temporal filter functions of attention to ensure processing of selected information at appropriate times.

Norepinephrine's Effects on Gamma Synchronization

The facilitated processing of attended sensory information appears to involve target-evoked NE release (Aston-Jones & Cohen, 2005) and the subsequent enhancement of gain (Servan-Schreiber et al., 1990) in cortical areas of the visual processing system. In addition to the potential effects on firing rates described above, NE could enhance gain via effects on gamma synchronization. Ascending neuromodulatory systems including the LC-NE system have long been associated with arousal and the transition from sleep to wakefulness (Berridge, 2008) which is characterized by slow oscillations giving way to fast cortical EEG activity in the gamma frequency range (20-80 Hz; Steriade et al., 1991a, 1991b). Accordingly, NE has been shown to be important for the modulation of high-frequency neural oscillations (Steriade et al., 1993). Consistent with the involvement of NE in the modulation of cortical gamma synchronization, phasic LC firing has been associated with increased gamma synchronization in the prelimbic subregion of the mPFC in anesthetized rats (Marzo et al., 2014; Neves et al., 2018). In these studies, gamma synchronization correlated with the strength of LC phasic firing, supporting the proposed involvement of NE in these effects. Target-evoked NE release in primate DAN and visual cortical areas could similarly explain the modulation of sensory-driven gamma synchronization seen in these areas during tests of visuospatial attention.

The GANE model suggests that the proposed effects of NE on gamma synchronization could be dependent on extracellular glutamate levels and NMDA receptor activation as described above for the modulation of firing rates (Mather et al., 2016). NMDA receptor-mediated facilitation of NE release could selectively enhance gamma synchronization in the neurons

representing attended sensory information. A subset of synapses throughout the frontal, parietal, and visual cortices would be expected to have higher glutamate levels due to enhanced activity in presynaptic neurons that represent attended sensory information. Increased glutamate in these highly active synapses could activate NMDA receptors on adjacent LC terminals to trigger additional target-evoked NE release. High NE levels could then promote gamma synchronization in postsynaptic neurons to facilitate bottom-up processing of the attended sensory information. In contrast, NMDA receptors are not likely to be activated on LC projections adjacent to other less active synapses. These synapses receive inputs from neurons representing unattended or ignored information, which display normal or even suppressed activity. NE release could remain low at these locations due to presynaptic α-2 receptor-mediated autoinhibition. Lower NE could reduce the generation of gamma synchronization in neurons representing irrelevant sensory information, potentially reducing distractibility.

The proposed effects of NE on gamma synchronization in frontal, parietal, and visual cortical neurons could also involve the neuromodulation of inhibitory interneuron activity. Consistent with this thinking, GABAergic neurotransmission is enhanced following iontophoretic application of NE (Waterhouse et al., 1980) in a process that involves β receptor activation (Cheun & Yeh, 1992; Waterhouse et al., 1982). As described above, GABAergic interneurons generate gamma synchronization by rhythmically inhibiting ensembles of pyramidal neurons (Buzsaki & Wang, 2012). Interneuron-mediated gamma synchronization in sending neurons leads to the entrainment of postsynaptic neurons in the same gamma rhythm and repetition of this process could facilitate feedforward communication across large scale networks (Fries, 2015). NE-mediated modulation of gain at the level of individual neurons (Aston-Jones & Cohen, 2005) is similarly thought to bring about functional reorganization at the network level

(Bouret & Sara, 2005; Guedj et al., 2017). These similarities further suggest that NE's effects on gain could involve the modulation of GABA interneuron activity and the resulting effects on gamma synchronization *within* selected neural representations. In turn, network-level effects of NE could be facilitated by gamma synchronization *between* neural ensembles in different areas of frontal, parietal, and visual cortices.

Summary

The LC-NE system could temporally filter sensory processing to ensure that prioritized information is detected at appropriate times (Aston-Jones & Cohen, 2005). Normal functioning of the temporal filter could increase the likelihood that selected sensory information is processed efficiently when it appears. During attention, target-evoked phasic LC firing releases NE into cortical areas of the visual processing system where it enhances gain (Servan-Schreiber et al., 1990), functionally increasing the activity of neurons receiving many excitatory inputs and suppressing the activity of neurons that experience weaker excitation. NE's effects on gain could depend on high and low glutamate levels at synapses receiving prioritized and suppressed inputs, respectively (Mather et al., 2016). High glutamate levels at synapses communicating prioritized sensory information could activate NMDA receptors on LC terminals to trigger additional target-evoked NE release. High NE levels positively modulate neural firing rates via activation of β-1 receptors which could facilitate the processing of attended information. Lower glutamate levels at synapses communicating unattended or ignored information are unlikely to activate NMDA receptors and could therefore fail to trigger additional target-evoked NE release. Lower NE levels could negatively modulate neural firing rates via activation of α-2 receptors to suppress the processing of irrelevant or distracting information. NMDA receptor-mediated effects on NE release could also influence gamma synchronization (Mather et al., 2016) to promote the bottom-

up processing of attended sensory information. These proposed NMDA receptor and NE-mediated effects on sensory-driven neural activity could enhance the efficiency with which selected sensory information is processed.

Overall Summary

Attention biases neural activity in frontal, parietal, and visual cortical networks to promote the processing of selected information (content filtering) at appropriate times (temporal filtering). Consider a possible real-world scenario. You have agreed to meet your friend at a park located between your home and hers. You arrive early and sit down on a bench to wait in a location with a nice view where you can see the entrance by which your friend will enter the park. Your knowledge of where to look for your friend will likely help you notice when she arrives.

As you wait, the modulation of endogenous neural activity in frontal, parietal, and visual cortical areas could prepare the visual processing system for expected sensory information (your friend) at the attended location (the park entrance), acting as a *content filter* for perception (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000). This preparation could involve the modulation of endogenous firing rates or gamma synchronization. Persistent increases in firing rates in particular could be maintained by glutamate release and activation of NMDA receptors as seen in working memory (Brunel & Wang, 2001; Compte et al., 2000; van Vugt et al., 2020; Wang et al., 2013; Wang & Arnsten, 2015). NMDA receptor activation could prepare frontal, parietal, and visual cortical networks to process sensory information corresponding to the arrival of your friend. In other words, NMDA receptor activation could be responsible for maintaining the content filter for perception, thereby preventing attentional lapses characterized by less efficient processing. Your ability to reliably detect your friend's arrival could also be affected by

the amount of NE released into frontal, parietal, and visual cortical areas. As you wait, signals from prefrontal areas could reduce tonic LC firing and NE release. This enhancement of the "phasic mode" could reduce gain in cortical neurons and raise the threshold for stimulus detection, thereby preventing false alarms when your friend has not yet arrived.

Top-down feedback associated with the modulation of endogenous neural activity could affect subsequent sensory-driven neural responses to help you detect your friend *when she arrives* at the park entrance. The modulation of sensory-driven neural activity could involve target-evoked NE release. Phasic firing of LC neurons in response to your friend's appearance could act as a *temporal filter* for sensory processing by releasing NE in frontal, parietal, and visual cortical areas (Aston-Jones & Cohen, 2005) where it enhances the gain of neural activity (Servan-Schreiber et al., 1990). Target-evoked NE release could increase the likelihood that you will efficiently process the arrival of your friend. In other words, increasing the functioning of the temporal filter could also prevent attentional lapses characterized by less efficient sensory processing.

NMDA receptor activation and target-evoked NE release could also increase the efficiency and therefore the speed of processing sensory information corresponding to your friend's arrival. The activation of NMDA receptors could affect bottom-up sensory processing by increasing sensory-driven gamma synchronization or reducing network-level noise correlations. Additionally, the *GANE* model suggests that gain is enhanced via activation of NMDA receptors (or lack thereof) and NE-mediated effects at β-1 (or α-2) receptors in the cortex. High levels of NE could increase firing rates or gamma synchronization in neurons representing attended information due to activation of β-1 receptors. These effects could facilitate the processing of incoming sensory information corresponding to your friend at the

park entrance. On the other hand, NE could decrease firing rates or gamma synchronization in neurons representing unattended or ignored sensory information due to activation of α-2 receptors. These effects could suppress the processing of other salient events going on in the park that might interfere with efficiently processing your friend's arrival. Together, these effects could increase the efficiency with which selected sensory information is processed. In other words, you could potentially process the arrival of your friend faster because of the activation of NMDA receptors and the resulting effects of target-evoked NE release.

The previous sections detailed how neural activity (e.g., firing rates, gamma synchronization, and firing rate variability) is modulated in a series of topographically organized frontal, parietal, and visual cortical areas during attention to determine what we perceive. Theories describing the possible involvement of the glutamate and NE systems in the modulation of various forms of neural activity were then outlined. These ideas illustrate how neurotransmitters (glutamate) and neuromodulators (NE) acting in the frontal, parietal, and visual cortical areas of the visual processing system could allow us to easily meet a friend at the park or perform any of the other goal-directed behaviors required of us each day. The stakes are quite low in the example described here, as a lapse in attention would likely only result in a joke from your friend about your absent-mindedness. On the other hand, failures of attention in other areas could be more problematic. Proposed roles for glutamate and NE in the content and temporal filtering of sensory processing suggest that drugs targeting one or both systems could be effective for the treatment of impaired attention in vulnerable clinical populations. The present research explored these possibilities.

CHAPTER 2 - PRESENT RESEARCH

The theories outlined in the preceding sections suggest several interesting questions, two of which we attempted to address with the present research. *First*, could performance in tests of sustained attention be improved by promoting NMDA receptor-mediated effects at synapses that communicate selected sensory information across cortical areas of the visual processing system? Activation of NMDA receptors requires simultaneous binding of agonists at glutamate-binding and glycine-binding sites (Dingledine et al., 1999; Johnson & Ascher, 1987; Kleckner & Dingledine, 1988; Traynelis et al., 2010). During sustained attention, the synapses receiving inputs from neurons that demonstrate increased endogenous activity would be expected to have higher glutamate levels; therefore, administration of a glycine-binding site agonist could enhance NMDA receptor-mediated effects at these active synapses that communicate selected sensory information. On the other hand, glycine-binding site agonists are likely to have little to no effect at inactive connections due to lower glutamate levels. This approach could improve performance in tests of sustained attention due to enhancing several NMDA receptor-mediated mechanisms. 1) NMDA receptor activation in frontal, parietal, and visual cortical networks could support a content filter for perception by promoting the maintenance of top-down feedback during the endogenous orienting of attention. NMDA receptor-mediated maintenance of this content filter could increase the likelihood that selected sensory information is processed efficiently. 2)

Activation of NMDA receptors could be involved in the modulation of sensory-driven gamma synchronization or noise correlations. These effects could increase the efficiency of processing selected sensory information. 3) Activation of NMDA receptors on the terminal membranes of noradrenergic projections could influence target-evoked NE release, thereby promoting the NE-mediated enhancement of gain. These effects could also increase the efficiency of processing selected sensory information.

We also wanted to address a *second* question with the present research. Could a combination treatment increasing NMDA receptor activation and synaptic NE levels be an effective strategy to improve sustained attention? In past work, we demonstrated that the selective NE reuptake inhibitor, ATX, reduced attentional lapses (Redding et al., 2019). This finding could be related to facilitation of the phasic mode of LC firing and target-evoked NE release (Bari & Aston-Jones, 2013) which could act as a *temporal filter* for perception (Aston-Jones & Cohen, 2005), thereby increasing the likelihood that selected sensory information is detected at the appropriate time. The *GANE* model suggests that both glutamate and NE could support the subsequent processing of selected information (Mather et al., 2016). For an example from another cognitive domain, Liu and colleagues (2009) directly administered glutamate and NE into the bed nucleus of the stria terminalis, an area involved in the formation of memories for emotional stimuli. While neither glutamate nor NE alone affected measures of inhibitory avoidance following the establishment of a tone-shock pairing, co-administration of glutamate and NE increased these conditioned fear responses. The results of this intracranial administration are consistent with the proposals of the *GANE* model, suggesting that an interaction between glutamate and NE supports selective information processing in other cognitive domains, such as emotional memory formation. A combination treatment simultaneously targeting glutamate and

NE-mediated mechanisms could have additive or even synergistic effects on sustained attention. Furthermore, the unique interdependence of NMDA receptor and NE-mediated effects suggests that certain systemically administered pharmaceutical treatments could preferentially affect neurons that demonstrate increased activity during attention. As described above, systemic administration of an NMDA glycine-binding site agonist could be a way to selectively enhance NMDA receptor activation at the highly active synapses processing attended sensory information. The effects of systemic administration of a NE reuptake blocker could also have some degree of selectivity due to the dependence of NE release on extracellular glutamate levels. Blockade of NE reuptake transporters could slow down the normal removal of NE from synapses, promoting the NMDA receptor-mediated buildup of high extracellular NE concentrations needed to activate β-1 receptors at active synapses. On the other hand, NE levels at inactive synapses could remain relatively low due to α-2 receptor-mediated suppression of NE release. These effects could increase the efficiency of processing selected sensory information.

The following sections provide evidence related to the questions laid out above. The first section covers efforts to study the involvement of NMDA receptors in sustained attention using a pharmacological approach, including a description of the mixed effects of targeting glycine-binding sites on NMDA receptors. This section also outlines physiological and behavioral evidence from animal models of other cognitive domains supporting the high-affinity glycine-binding site agonist, D-serine, as a potential candidate for further study. The next section covers the study of NE's effects on sustained attention. This section includes behavioral evidence linking systemic administration of the NE reuptake inhibitor, atomoxetine (ATX), to improved attention in humans and rodents.

Glutamate

Glutamate could support sustained attention through the activation of NMDA receptors and the resulting maintenance of endogenous neural activity in cortical networks, modulation of sensory-driven neural activity, or effects on target-evoked NE release. Consistent with the involvement of NMDA receptors in attention, systemic administration of non-competitive NMDA antagonists in rodents impairs performance on sustained attention tasks. For example, the NMDA antagonist, dizocilpine, reduced accuracy in rats performing choice RT tasks (Barlow et al., 2018; Grottick & Higgins, 2000; Higgins et al., 2003, 2016; Mishima et al., 2002; Paine et al., 2007; Pehrson et al., 2013; Potasiewicz et al., 2017; Smith et al., 2011; Terry et al., 2012). The NMDA antagonist, PCP, reduced accuracy in rats performing 5CSRTTs (Amitai et al., 2007; Auclair et al., 2009; Le Pen et al., 2003; Smith et al., 2011) and impaired accuracy and sensitivity in rats performing the five-choice CPT (Barnes et al., 2016). The NMDA antagonist, memantine, also reduced accuracy in rats performing a 5CSRTT (Smith et al., 2011) and reduced d' in rats performing a rodent CPT (Ding et al., 2018). Finally, the NMDA antagonist, ketamine, impaired accuracy in rats performing a 5CSRTT (Smith et al., 2011) and increased omissions in rats performing another sustained attention task (Nelson et al., 2002). As drugs were administered systemically, these studies do not reveal the specific brain regions in which NMDA-mediated effects support attentional processing. Extensive research indicates that attention is supported by NMDA-mediated effects in higher-order executive control areas in the PFC. For example, NMDA receptor antagonists infused into mPFC (Baviera et al., 2008; Calcagno et al., 2006, 2009; Carli et al., 2006, 2011; Ceglia et al., 2004; Mirjana et al., 2004; Murphy et al., 2005, 2012; Pozzi et al., 2011) and anterior cingulate cortex (Pehrson et al., 2013) impaired performance in sustained attention tasks. However, it remains unclear to what extent NMDA-mediated effects in DAN and visual cortical areas also support information processing

during attention. Future studies using intracranial administration of NMDA antagonists into these areas will be necessary to clarify these points (see Discussion for future directions).

If NMDA receptors in the visual, parietal, and frontal cortices do support selective sensory processing, then they could be potential targets for the treatment of impaired attention. However, several issues are apparent with the direct activation of NMDA receptors. *First*, they are present throughout the nervous system and the neocortex in particular (Conti et al., 1999; Huntley et al., 1994; Monyer et al., 1994); therefore, targeting a specific location using systemic administration initially seems to present quite a challenge. *Second*, direct activation of NMDA receptors with glutamate or NMDA can produce excitotoxic effects (Dohmen et al., 2005; Kihara et al., 2004; Lin et al., 2005; Yu, 2006). Enhancing glutamate-mediated effects on sustained attention requires a way to safely promote NMDA receptor activation at the active synapses communicating task-relevant information without increasing activation of NMDA receptors at inactive connections or NMDA receptors in other brain regions that are not engaged during attention. Importantly, activation of NMDA receptors requires binding at a glutamate-binding site and a glycine-binding site (Johnson & Ascher, 1987; Kleckner & Dingledine, 1988; Traynelis et al., 2010). The requirement of simultaneous binding by two agonists means that enhancing levels of glycine-binding site agonists could be a way to selectively enhance NMDA receptor activation at active synapses without effects at other locations. Increased binding at the glycine-binding site could promote the activation of NMDA receptors at highly active synapses due to the presence of excess glutamate. On the other hand, increased binding at the glycine-binding site could have no effect on NMDA receptor activation at inactive synapses where glutamate levels are expected to be relatively low.

Enhancement of NMDA receptor activation via glycine-binding site activation requires free glycine-binding sites on cortical NMDA receptors. Early attempts were made to determine whether glycine-binding sites are saturated under normal conditions. Some *in vitro* evidence indicated that glycine-binding sites are not saturated (Fossat et al., 2012; Minota et al., 1989; Thomas et al., 1988); however, other reports based on *in vitro* evidence led to proposals that glycine-binding sites are saturated (Crawford & Roberts, 1989; Fletcher & Lodge, 1988; Kemp et al., 1988; Matsui et al., 1995; Ransom & Deschenes, 1989; Taylor et al., 1988). Danysz & Parsons (1998) suggested caution when interpreting these mixed results for several reasons. *First*, traumatic preparation of *in vitro* models can lead to additional release of glycine-binding site agonists and distort measures of extracellular levels. *Second*, estimates of the concentration of a substance in the extracellular space do not necessarily reflect the concentration in the synapse. *Third*, endogenous antagonists, such as kynurenic acid, can compete at the glycine-binding site. *Finally, in vivo* concentrations of important ions (e.g., Zn^{+}) can affect estimates of glycine's affinity when using *in vitro* preparations. Consistent with the thinking that the glycine-binding site is not saturated, many studies have since reported increased NMDA-mediated synaptic transmission following co-agonist administration *in vivo* (for reviews see Danysz & Parsons, 1998; Wolosker, 2007). Driven by this evidence, pharmacological activation of glycine-binding sites has been studied to develop potential treatments for cognitive impairments.

Glycine-binding site activation can be altered using a variety of pharmacological approaches. For example, the site can be activated directly through the administration of agonists, such as glycine (D'Souza et al., 2000). D-serine is another agonist for the glycine-binding site with higher affinity than glycine itself (Berger et al., 1998; Kleckner & Dingledine, 1988; Matsui et al., 1995; Mothet et al., 2000; Schell et al., 1995). Furthermore, D-serine appears

to be an important co-agonist at synaptic NMDA receptors in particular (Papouin et al., 2012). D-cycloserine has affinity for the glycine-binding site; however, it functions as a partial agonist at lower doses and an antagonist at higher doses (Henderson et al., 1990; Monahan et al., 1989). There are also less direct ways to increase activation of glycine-binding sites. For example, extracellular glycine levels are controlled by a glycine reuptake system (Berger et al., 1998; Smith et al., 1992) and inhibitors have been developed for corresponding glycine transporters (Atkinson et al., 2001; Pei et al., 2019; Tsai et al., 2004). D-serine is not known to have a specific reuptake system; however, levels of extracellular D-serine are affected by the actions of D-amino acid oxidase enzymes. Inhibitors of D-amino acid oxidase have also been investigated as potential treatments for cognitive impairments in individuals with schizophrenia (Lane et al., 2013; Smith et al., 2010). Finally, the glycine precursor, milacemide, has been studied as a potential cognitive enhancer due to its effects on glycine levels (Saletu et al., 1986; Saletu & Grünberger, 1984). These pharmacological treatments have been tested for effects on several cognitive abilities, including attention.

Effects of Glycine-Binding Site Agents on Sustained Attention

Human Studies

Glycine-binding site agonists have been shown to improve performance in human sustained attention paradigms. For example, Levin and colleagues (2015) reported that D-serine improved d' in healthy individuals performing a CPT. Similarly, a proprietary glycine formulation improved sustained attention in middle-aged men; however, no effects were seen in healthy college students (File et al., 1999). The glycine precursor, milacemide, improved measures of attention in healthy adults (Saletu & Grünberger, 1984) and elderly subjects (Saletu

et al., 1986). These results support the thinking that increased activation of the glycine-binding sites on NMDA receptors can improve sustained attention in humans.

Other studies have reported no effects on attentional variables following administration of drugs that increase binding at glycine-binding sites. For example, intravenous glycine had no effect on omissions in healthy individuals performing a CPT (D'Souza et al., 2000). Similarly, oral administration of glycine did not affect accuracy in healthy subjects performing a CPT and had no effect on accuracy in a choice RT task (Palmer et al., 2008a). Neumeister and colleagues (2006) also reported no effects of intravenous glycine in healthy subjects performing an attention/vigilance task. D-serine did not affect the number of errors made by older adults performing a computerized attention test (Avellar et al., 2016) and had no effect on d' in patients with schizophrenia performing an AX version of the CPT (D'Souza et al., 2013). Finally, the partial agonist, D-cycloserine, did not affect CPT performance in healthy adults (D'Souza et al., 2000; Duncan et al., 2004).

In summary, the available evidence is limited for effects on behavioral measures of sustained attention following targeting of the glycine-binding site in humans. Several studies reported positive effects following D-serine, glycine, or a glycine precursor; however, other studies have reported no effects of D-serine, glycine, or D-cycloserine. These mixed findings point to a need for further testing of glycine-binding site drugs as treatments for impaired sustained attention.

Rodent Studies

Manipulation of glycine-binding site activation has also revealed effects on attention-related behavior in rodents. For example, Lipina and colleagues (2005) demonstrated that D-

serine (600 mg/kg, s.c.) and a glycine transporter inhibitor each improved latent inhibition in mice. Latent inhibition is thought to reflect the ability to reduce attentional processing of irrelevant stimuli (Chiba et al., 1995). Additionally, a glycine transporter inhibitor improved accuracy in impaired Sp4 hypomorphic mice performing a 5CSRTT without effects in wild-type controls (Young et al., 2015). The Sp4 hypomorphic mouse is a putative model for schizophrenia characterized by reduced NMDA channel expression (Zhou et al., 2010). In sum, the limited available evidence points to a need for further research exploring effects on sustained attention in rodents following pharmacological manipulation of glycine-binding site activation.

Physiological Effects of D-Serine

The limited and mixed evidence described above indicates that more research is needed to clarify the role of NMDA glycine-binding sites in sustained attention. D-serine stands out as a prime candidate for further research with substantial physiological evidence supporting its potential to affect information processing in cortical networks. Numerous studies have reported increased D-serine levels in the cortex following systemic administration. For example, cortical D-serine levels were elevated in rats after subcutaneous doses ranging from 320 – 1280 mg/kg without effects at doses of 160 mg/kg or lower (Smith et al., 2009). Intraperitoneal administration (approximately 1000 mg/kg) also increased D-serine levels in the cortex of rats (Hashimoto & Chiba, 2004; Pernot et al., 2008, 2012; Takahashi et al., 1997). These studies tested high doses which are known to be nephrotoxic in rats (Carone & Ganote, 1975; Ganote et al., 1974; Krug et al., 2007; Maekawa et al., 2005; Orozco-Ibarra et al., 2007). In contrast to the findings of Smith and colleagues (2009) who found no effects on cortical D-serine levels at doses of 160 mg/kg and below, other studies have reported effects at sub-nephrotoxic doses. For example, Fukushima and colleagues (2004) demonstrated increased D-serine levels in the PFC of

rats after exogenous administration of D-serine (50 mg/kg, i.p.). Additionally, Ferraris and colleagues (2008) reported increased D-serine levels in rat PFC after oral D-serine (30 mg/kg). It is notable that both studies using lower doses also reported peak extracellular levels within an hour after exogenous administration (30 minutes in Ferraris et al., 2008; 60 minutes in Fukushima et al., 2004). Therefore, later measurement (at least 1 hr and up to 8 hrs post-administration) of extracellular D-serine concentration could explain the lack of effects reported by Smith and colleagues (2009) at lower doses. Finally, a two-week regimen with daily dosing (approximately 5 mg/kg, oral) did not affect D-serine levels in the cortex of mice (Morikawa et al., 2007). Together, these results suggest that exogenous D-serine at sub-nephrotoxic doses can increase cortical D-serine levels within a window of approximately 30-60 minutes after administration.

Consistent with activation of free glycine-binding sites in the cortex, intravenous D-serine (50 – 100 mg/kg) dose-dependently potentiated NMDA-evoked excitatory responses in the PFC of rats (Chen et al., 2003). On the other hand, D-serine (50 mg/kg, i.p.) did not affect brain activity as measured by fMRI in the cortex of rats (Panizzutti et al., 2005). These divergent findings could be related to the time-dependent effects of D-serine described above. Chen and colleagues (2003) reported increased NMDA-evoked firing a relatively short time (15 minutes) after D-serine administration. On the other hand, Panizzutti and colleagues (2005) imaged the brains of rats two hours after D-serine administration. These findings suggest that D-serine is maximally effective closer to the time of administration (i.e., approximately 30-60 minutes after administration).

In summary, while extremely low doses did not increase cortical D-serine levels (5 mg/kg/day in Morikawa et al., 2007) and changes in cortical activity were not seen in one study

(Panizzutti et al., 2005), most of the available evidence indicates that exogenous D-serine crosses the blood-brain barrier and enhances NMDA receptor activation in the cortex. Furthermore, these effects appear to be dependent on the interval between D-serine administration and the subsequent measurement of extracellular concentration or activity levels. Importantly, physiological effects of D-serine have been reported even at relatively low doses that are not nephrotoxic in rats.

Effects of D-Serine on Other Cognitive Abilities

As described above, the limited reports of D-serine's effects on sustained attention in humans are mixed. D-serine has also been investigated as a treatment for other cognitive impairments in individuals with schizophrenia. For example, Kantrowitz and colleagues (2010) reported improvements in patients with schizophrenia on the MATRICS neurocognitive test battery following D-serine administration (see Nuechterlein et al., 2008 for discussion of MATRICS). D-serine was also shown to improve scores on the PANSS–cognitive subscale and the Wisconsin Card Sorting Test when administered to patients with schizophrenia as an add-on to antipsychotic treatments (Tsai et al., 1998; see Lindenmayer et al., 1994 for discussion of PANSS). On the other hand, no effects were found on these measures when D-serine was administered to patients with schizophrenia as an add-on to the antipsychotic, clozapine (Tsai et al., 1999). Similarly, Weiser and colleagues (2012) reported no effects on MATRICS scores in patients administered D-serine as an add-on treatment to antipsychotics. Finally, D-serine did not affect a global cognitive index created from scores on various behavioral tasks (D'Souza et al., 2013). Mixed effects of D-serine on these cognitive batteries could be related to dosage. Positive effects were reported for higher doses (>30 mg/kg/day; Kantrowitz et al., 2010), mixed effects were reported for moderate doses (30 mg/kg/day; positive finding in Tsai et al., 1998; no effects

in Tsai et al., 1999 and D'Souza et al., 2013), and no effects were reported with low doses (<30 mg/kg/day; Weiser et al., 2012) of D-serine. These findings suggest that doses above 30 mg/kg/day could be required for beneficial effects on cognition. Despite mixed reports, D-serine at sufficient doses could prove to be an effective treatment for cognitive impairments, including impaired attention, in individuals with schizophrenia. Additional research is needed to address the inconsistency of current findings.

Despite a lack of rodent research into D-serine's effects on sustained attention, D-serine has been reported to have positive effects in rodent behavioral models of other cognitive functions. For example, intraperitoneal administration (1000 mg/kg) enhanced retrieval of spatial memories in rats (Zhang et al., 2008). Additionally in rats, intraperitoneal administration (800 mg/kg) increased the speed of extinction learning for fear memories (Bai et al., 2014) and subcutaneous administration (600 mg/kg) enhanced reversal learning (Duffy et al., 2008). Improvements in social memory have been reported after D-serine (800 mg/kg, i.p.) in rats (Shimazaki et al., 2010; Zhou et al., 2016). Additionally, D-serine (1000 mg/kg, i.p.) prevented stress-induced impairments in object recognition and prepulse inhibition of the startle response in mice (Guercio et al., 2014). Finally, intraperitoneal administration (1000 and 2000 mg/kg) decreased immobility in rats performing a forced swim test (Wei et al., 2017). These rodent studies indicate that exogenously administered D-serine can improve cognition; however, each of these studies tested high doses which are known to be nephrotoxic in rats (Carone & Ganote, 1975; Ganote et al., 1974; Krug et al., 2007; Maekawa et al., 2005; Orozco-Ibarra et al., 2007). D-serine has also been found to improve cognitive abilities at lower, safer doses in rodents. For example, D-serine (100 mg/kg, i.p.) improved performance of rats in a delayed-match-to-place task, indicating better spatial working memory (Stouffer et al., 2004). Additionally, D-serine (50

mg/kg, i.p.) improved recognition learning and working memory in mice (Bado et al., 2011). In contrast to the above reports, one study found no effects of D-serine (400 or 800 mg/kg, i.p.) on novel object recognition performance in rats (Karasawa et al., 2008). Additionally, Kawaura and colleagues (2015) reported increased immobility in the forced swim task after D-serine administration (800 mg/kg, i.p.) in contrast to the findings of Wei and colleagues (2017). Despite these latter findings, the available evidence indicates that D-serine can improve various cognitive abilities in rodents even at sub-nephrotoxic doses, supporting its use in the present study.

Summary

While two human studies reported no effects of D-serine on behavioral measures of sustained attention, improvements were reported in one study of healthy subjects. This limited evidence points to the need for a closer look at the effects of D-serine on sustained attention. Most of the available physiological evidence shows that exogenously administered D-serine increases levels in the cortex of rats. More importantly, exogenous D-serine at non-toxic doses affects NMDA-mediated synaptic transmission. These findings support the thinking that D-serine could affect sensory processing in frontal, parietal, and visual cortical areas by increasing NMDA receptor activation. While one study reported no effects, other behavioral evidence indicates that exogenous D-serine affects cognitive abilities in rodents. Although limited evidence is available using lower non-nephrotoxic doses, the existing results are consistent with reported effects at higher doses. Together, this evidence supports the targeting of NMDA glycine-binding sites with D-serine as a potential treatment for impaired attention. The present study begins to address the treatment potential of D-serine using an animal model with measures (IT devmode) that translate well to current RTV measures used in human sustained attention research (Kofler et al., 2013; Tamm et al., 2012).

Norepinephrine

As described above, the NE system is thought to support attention in part by increasing gain in cortical networks (Servan-Schreiber et al., 1990), boosting the signal representing task-relevant sensory information and inhibiting noise from irrelevant inputs. During sustained attention, task-relevant stimuli trigger phasic LC firing (Aston-Jones & Bloom, 1981; Aston-Jones et al., 1994; Bouret & Sara, 2002; Foote et al., 1980; Grant et al., 1988; Sara et al., 1994) to release NE in relevant cortical target areas. NMDA receptor and NE β-1 receptor-mediated effects enhance excitation at active synapses communicating task-relevant information. In contrast, α-2 receptor-mediated effects in the absence of glutamate overflow increase inhibition at inactive synapses that communicate irrelevant information. This increased gain could facilitate the processing of attended sensory information to promote target detection (Corbetta & Shulman, 2002).

Consistent with the involvement of the NE system in sustained attention, deficits in individuals with ADHD (Kofler et al., 2013) are commonly treated using drugs that target the NE system. Stimulant-type medications increase NE levels, but also affect the dopaminergic system (Faraone et al., 2006; Gibson et al., 2006; Peterson et al., 2008; Solanto, 1998). Non-stimulant treatments include drugs with more selective effects on the NE system. In particular the selective NE reuptake inhibitor, ATX, is commonly used to treat attentional impairments (Asherson et al., 2014; Gibson et al., 2006). Inhibition of NE reuptake using drugs like ATX leads to increased synaptic NE levels (Bymaster et al., 2002). Consistent with NE effects on cortical glutamatergic transmission proposed by the *GANE* model, systemic administration of ATX increases NMDA-mediated firing in the PFC of rats (Di Miceli & Gronier, 2015).

Behavioral evidence from human and animal studies of ATX further supports the involvement of the NE system in sustained attention.

Atomoxetine's Effects on Sustained Attention

Human Studies

Pharmacological inhibition of NE reuptake using ATX improves behavioral measures of sustained attention in humans. For example, ATX reduced omissions and increased d' in children with ADHD performing CPTs (Shang & Gau, 2012; Wehmeier et al., 2011, 2012). ATX also reduced measures of RTV in children with ADHD performing CPTs (Kratz et al., 2012; Shang & Gau, 2012; Wehmeier et al., 2011, 2012). Additionally, ATX improved CPT performance in adults with ADHD, increasing d' (Fan et al., 2017; Ni et al., 2013) and hits (Lin & Gau, 2015), and reducing commission errors and the ex-Gaussian measure of RT distribution skew, τ (Ni et al., 2016b). These findings suggest that ATX improves sustained attention in impaired individuals by elevating suboptimal synaptic catecholamine levels. Interestingly, ATX decreased τ in adults with ADHD performing a CPT without affecting RT standard error (Ni et al., 2016b). The latter finding suggests that measures of RT distribution skew are especially sensitive to effects on sustained attention (Tamm et al., 2012).

One study found that ATX did not affect RT standard deviation in healthy adults performing a stop-signal test (Nandam et al., 2011). This finding is consistent with the thinking that synaptic catecholamine levels are near-optimal in healthy individuals prior to treatment. Several studies also reported no effects in impaired individuals performing tests of sustained attention. For example, ATX had no effect on omissions or RT standard deviation in children with ADHD (Bédard et al., 2015) or RT standard error in children with ADHD-like impairments

(Posey et al., 2006a) performing CPTs. Additionally, ATX did not affect the proportion of targets successfully detected by adults with ADHD performing a CPT (Chamberlain et al., 2007b). All these studies reported either traditional measures of sustained attention (e.g., hit rate) or measures of RTV which do not reflect the skew of response distributions; however, measures of RTV that reflect distribution skew could be important for determining the effects of ATX on attentional lapses (Ni et al., 2016b). In summary, the NE reuptake inhibitor, ATX, generally improves sustained attention in humans with some null results possibly relating to baseline catecholamine levels or the use of specific behavioral measures.

Rodent Studies

Pharmacological inhibition of NE reuptake using ATX has also been reported to improve sustained attention in some rodent studies. For example, ATX improved accuracy in rats performing 5CSRTTs (Navarra et al., 2008; Robinson, 2012). ATX also reduced IT devmode (a measure of distribution skew) in rats performing the 2CRTT (Redding et al., 2019). These findings indicate that ATX can improve sustained attention in rats.

In contrast to the many positive findings in humans, most studies reported no effects of ATX in rats. ATX had no effect on accuracy in rats performing 5CSRTTs (Blondeau & Dellu-Hagedorn, 2007; Fernando et al., 2012; Hauser et al., 2017; Koffarnus & Katz, 2011; Liu et al., 2015; Paterson et al., 2011, 2012; Robinson, 2012; Robinson et al., 2008; Sun et al., 2012; Tsutsui-Kimura et al., 2009). ATX also had no effect on d' in rats performing a rodent CPT (Ding et al., 2018).

All of these null reports relied on more traditional measures of sustained attention such as accuracy or d', while only two studies using such measures found positive effects of ATX

(Navarra et al., 2008; Robinson, 2012). On the other hand, the one study that used IT distribution skew found positive effects of ATX (Redding et al., 2019) in agreement with the reports from human studies described above. This pattern of results supports the supplementation of more traditional measures of sustained attention in rodents (e.g., accuracy and d') with analyses of RT (or IT) distribution skew to more closely reflect the analyses of RTV performed in human studies (Tamm et al., 2012).

Null findings could also be related to a moderating effect of baseline performance as suggested by human studies. Consistent with this thinking, ATX improved accuracy in low performing rats in a 5CSRTT without effects in high performing rats (Robinson, 2012). ATX also improved target discrimination in low performing mice in a rodent CPT (Caballero-Puntiverio et al., 2019). Finally, ATX improved accuracy and target sensitivity in low-performing rats and impaired sensitivity in high-performing animals in a five choice-CPT (Tomlinson et al., 2014). Improvements in low-performing animals combined with impairments in high-performing animals could explain the lack of effects in other rodent studies.

Summary

Despite some negative findings, ATX improved sustained attention in most of the studies conducted on children and adults with ADHD. In contrast, rodent studies reported no effects in most cases when traditional measures of sustained attention (e.g., accuracy and d') were used. These traditional measures were affected by ATX in low-performing animals in some cases. Reported improvement in RT distribution skew, but not RT standard error, suggests that measures of distribution skew are particularly important for studying attentional lapses in humans. This finding is supported by reduced IT devmode following ATX administration in rats. Future work using rodent models of sustained attention would be strengthened by similar

analyses of IT distribution skew. Together, the available evidence supports the manipulation of synaptic NE levels with ATX as a treatment for impaired attention. Considering this supporting evidence, the present study addressed the potential of a combination treatment comprising the NMDA receptor co-agonist, D-serine, and the NE reuptake inhibitor, ATX.

CHAPTER 3 - EXPERIMENTAL DESIGN

Experiment 1: D-Serine Dose-Response

The activation of NMDA receptors could support the processing of selected information in a variety of ways (described above). The effects of D-serine on behavioral measures of attention are mixed in human studies; however, improvements have been reported in healthy adults. In contrast, there is currently no behavioral data for D-serine from rodent models of sustained attention. Physiological studies in rats indicate that systemically administered D-serine reaches the cortex and increases NMDA receptor activation at relatively low, non-toxic doses. Additionally, systemic administration of D-serine affects performance in other rodent models of cognition even at lower doses. Together, this evidence encourages further investigation of D-serine's effects in rodent models of sustained attention.

Design and Hypothesis

We used the rat model of sustained attention developed by Sabol and colleagues (2003) to conduct a dose-response determination for the effects of D-serine. The primary measure of sustained attention was initiation time (IT) devmode, a measure of distribution skew that is thought to reflect attentional lapses (Redding et al., 2019; Sabol et al., 2003) in a manner that parallels current human techniques (Kofler et al., 2013; Tamm et al., 2012). Five of six doses (saline, 10, 50, 100, and 150 mg/kg) were below nephrotoxic levels (Hasegawa et al., 2019) and administration of the highest dose (300 mg/kg) was followed by additional recovery time without

drug administration. Based on behavioral and physiological evidence, it was hypothesized that D-serine would improve the performance of rats in the 2CRTT by reducing attentional lapses (IT devmode). As predicted, D-serine reduced IT devmode at the highest dose (300 mg/kg). These results suggest that the activation of NMDA receptors increases the likelihood that expected sensory information will be processed efficiently during attention.

Experiments 2 and 3: Tests of Combination Treatments

The proposed roles for NMDA receptor activation and target-evoked NE release described above suggest that a combination therapy with effects on both systems could be an effective treatment for attentional impairments. Such a combination treatment could allow for the use of lower doses of either drug, reducing the risk of negative side-effects such as nephrotoxicity or anxiogenic effects for D-serine (Hasegawa et al., 2019; Labrie et al., 2009) and headaches or effects related to movement speed, motivation, or sedation for ATX (Heil et al., 2002; Quintana et al., 2007; Redding et al., 2019). Systemic administration of a combination treatment could reduce attentional lapses (IT devmode) by increasing the likelihood that selected sensory information is processed efficiently at the appropriate time. The proposed cooperation between glutamate and NE-mediated effects during sensory processing (Mather et al., 2016) also suggests that the combined effects of targeting both mechanisms could enhance the efficiency with which selected sensory information is processed.

Design and Hypotheses

We used the same rat model of sustained attention (Sabol et al., 2003) to test the effects of either D-serine (100 mg/kg) in combination with saline, ATX (0.5 mg/kg) in combination with saline, or the same doses of D-serine and ATX administered in combination. Performance

following these treatments was compared with performance following the administration of saline only. This test was first performed in the same group of rats from the D-serine dose-response determination (Experiment 1). The dose of ATX was selected based on past research (Redding et al., 2019) and was expected to have no effect on its own. Likewise, a dose of D-serine that was expected to be ineffective was selected based on dose-response data from this study (Experiment 1). We predicted that neither drug would affect IT devmode when administered alone; however, the combination of both drugs was expected to reduce IT devmode. Evidence from this group of rats supported these hypotheses, as IT devmode was significantly reduced only by the combination of D-serine and ATX.

These results informed the development of a follow-up experiment (Experiment 3) using a drug-naïve group of rats. Considering the results of the first test of combination treatments (Experiment 2), we raised the dose of D-serine to 125 mg/kg and reduced the dose of ATX to 0.3 mg/kg for the final test. We tested the effects of D-serine (125 mg/kg) in combination with saline, ATX (0.3 mg/kg) in combination with saline, or these doses of D-serine and ATX administered in combination. Performance following the administration of each of these drug conditions was compared with performance following the administration of saline alone. The collection of additional data in this experiment afforded us sufficient statistical power to test for differences in selected dependent variables between other treatment levels (see Methods for details). We hypothesized that neither drug would affect IT devmode on its own at the doses selected; however, we expected the combination treatment to reduce IT devmode. Furthermore, we predicted that the combination treatment would reduce IT devmode more than either drug on its own. Contrary to our initial prediction, IT devmode was reduced by ATX alone; however,

consistent with our final hypothesis, the combination treatment reduced IT devmode more than either drug alone.

Summary of Study Design

Behavioral evidence supports the involvement of the NE system in sustained attention; however, further work is needed to determine whether sustained attention is promoted by activation of the NMDA receptors. We addressed this need by testing the NMDA co-agonist, D-serine, in a rat model of attentional lapses (Experiment 1). Findings of reduced IT devmode are consistent with improved sustained attention. Building off the effects of D-serine, we asked whether attention could be improved using a combination treatment composed of drugs simultaneously increasing extracellular NE levels and increasing binding at glycine-binding sites on NMDA receptors. The combination therapy could prove to be safer due to the use of lower doses, reducing the risk of side-effects that could occur with higher doses of either drug. Such a combination treatment could also produce additive or synergistic effects on sensory processing due the proposed cooperation between the NE and glutamate systems (Mather et al., 2016). We conducted a test of this proposed combination treatment in a rat model of attentional lapses using the same group of rats that was used to test the effects of D-serine (Experiment 2). The combination treatment significantly reduced attentional lapses (IT devmode), while no significant effects were seen for either drug alone. We then followed up on these findings by adjusting the doses of both drugs and replicating the experiment in a naïve group of rats with the collection of a larger amount of data (Experiment 3). Attentional lapses were unexpectedly reduced by ATX alone; however, the effect of the combination treatment was significantly stronger than that of ATX alone. These findings suggest that a combination of D-serine and ATX could be effective for treating impaired attention in humans.

CHAPTER 4 - METHODS

Subjects

Male Sprague-Dawley rats (n=36) were acquired from Envigo (Indianapolis, USA). The required number of animals for each experimental group (n=16) was determined using effect sizes from previous research with this rat model (Redding et al., 2019) with $\alpha = 0.05$ and desired power of at least 80%. The same group of rats (n=16) was used to test the effects of D-serine (Experiment 1) and a combination treatment of D-serine and ATX (Experiment 2). A second group of drug-naïve rats (n=16) was used to replicate the test of the combination treatment (Experiment 3). Two control rats were also kept with each experimental group. These rats were allowed free access to water and served as references to compare against the body weights of water restricted experimental animals (see below).

Rats were weighed upon arrival and pair housed in filter-top plastic cages with environmental enrichment in the form of a cardboard tube. Lights were on in the colony room from 0700 to 1900 hours. Training and testing sessions were conducted in the lights-on phase. Food was available *ad libitum* to all animals in their home cages. Experimental animals had access to water for 20 min/day during training with a single continuous 24-hr access period once per week (as in Redding et al., 2019). Daily water access was adjusted to 30 min/day for D-serine dose-response determination, while water access remained at 20 min/day throughout testing of the combination treatments (described in Procedures below). The daily average body weight of free-drinking control rats was compared to the weights of experimental rats on

scheduled access to water. All experimental rat weights remained above 75% of the average weight of control rats throughout the study. All procedures were reviewed and approved by the Institutional Animal Care and Use Committee at the University of Mississippi.

Testing Apparatus

Rats were tested in four custom-built operant boxes within chambers that reduced external light and sound. Testing boxes had aluminum front and rear panels, plexiglass side and top panels, and wire floors. Three nose poke apertures were recessed into the front panel. Left and right apertures were centered 1.5 cm above floor level and the middle aperture was centered 4.5 cm above floor level. 5.5 cm separated the center of each lateral aperture from the center of the middle aperture. All nose poke apertures contained photobeams to record entries and exits. Left and right apertures also contained water dispensers calibrated to deliver 50 µl water droplets into a cup shaped reservoir. Stimulus lights were mounted above each aperture. A house light at the top of the rear panel was connected to a potentiometer for calibration of ambient light levels. A small computer fan in the wall of each chamber provided ventilation and ambient noise. Boxes were connected to a 486 computer with an interface by MED Associates Inc. (Fairfax, VA, USA) and experimental contingencies were programmed in the MED-PC programming language.

Training

Experimental rats were placed on scheduled access to water for one week, after which training began under conditions of enhanced stimulus salience (house light off). Each trial started when the rat entered the central nose poke aperture. The rat was then required to hold its nose in the central aperture for a “foreperiod” that was initially set to 0.1 sec. After the foreperiod, the left or right stimulus light (selected at random) was illuminated. Water was dispensed when the

rat interrupted the photobeam in the aperture under the illuminated light. The next trial began when the rat returned to the central aperture. Hand-shaping with a water dropper was required in some cases to orient rats toward the response apertures. Training continued until all rats completed 100 trials within 30 minutes with at least 70% accuracy. Both groups of rats required one week to complete this phase of training.

The maximum foreperiod was then increased from 0.1 to 1.0 sec. Foreperiods for individual trials were selected at random from 30 equally spaced intervals up to the maximum duration. Rats that exited the central nosepoke aperture prematurely were able to complete a foreperiod in multiple trips. The maximum foreperiod length was increased by 1.0 sec each day to the final maximum of 6.0 sec. Foreperiods from this point onward were randomly selected in 0.3 sec intervals (i.e., 0.3, 0.6, 0.9, …, 6.0 sec). A performance-based time limit for responses was implemented the following day. The limit increased after every incorrect or slow response and decreased after two consecutive, correct, and timely responses (see Sabol et al., 2003). These conditions continued until all rats completed 100 trials with greater than 70% accuracy (each group required six days to complete this phase). House lights were illuminated on the following training day to reduce stimulus salience. Training was continued under these final parameters until all rats achieved greater than 70% accuracy and daily average IT and session length were stable (stability metric based on Speaker, unpublished). Training for the first experimental group was completed after seven weeks, while training for the second experimental group required eight weeks.

Drugs

Atomoxetine hydrochloride and D-serine were obtained from Sigma-Aldrich, Inc. (St. Louis, Missouri, USA) in solid form. Drugs were dissolved in physiological saline on test days

and stored in sterile containers prior to use. Doses of ATX (0.3 and 0.5 mg/kg) were selected based on past work (Chawla, unpublished; Redding et al., 2019) and were obtained using freebase calculations. Doses for D-serine (10, 50, 100, 125, 150, and 300 mg/kg) were selected based on physiological and behavioral studies in rats (Bado et al., 2011; Chen et al., 2003; Ferraris et al., 2008; Fukushima et al., 2004; Stouffer et al., 2004) as well as the present results of the D-serine dose-response determination (Experiment 1) and the first test of the combination treatment (Experiment 2). Special attention was paid to avoid potential anxiogenic (Labrie et al., 2009) and nephrotoxic (Carone & Ganote, 1975; Ganote et al., 1974; Hasegawa et al., 2019; Krug et al., 2007; Maekawa et al., 2005; Orozco-Ibarra et al., 2007) effects that have been associated with high doses of D-serine in rats. Drugs were administered via intraperitoneal injection 30 minutes prior to testing. ATX was injected at a volume of 1 ml/kg (as in Redding et al., 2019). D-serine was injected at a volume of 2 ml/kg in the dose-response determination (Experiment 1) due to solubility limitations at higher doses (see Karasawa et al., 2008; Kawaura et al., 2015); however, an injection volume of 1 ml/kg was used in the tests of combination treatments (Experiments 2 and 3) as solubility was not an issue at the lower doses (100 and 125 mg/kg) used in these experiments.

Procedure

Experiment 1: D-serine Dose-Response Determination

Male Sprague-Dawley rats (n = 16) trained in the 2CRTT as described above were administered each D-serine dose (saline, 10, 50, 100, 150, and 300 mg/kg) two times in a repeated measures design. We planned to administer the first five sub-nephrotoxic doses (saline, 10, 50, 100, and 150 mg/kg) twice a week (Tuesday and Friday) on a counterbalanced schedule; however, diuretic effects became apparent during the first week of testing. Beginning on the

second week of the first dose-response series, administrations were conducted once per week (Friday). The highest dose of D-serine (300 mg/kg) was then administered on the Friday after the first dose-response series of five lower doses was complete. All rats received the 300 mg/kg dose on the same day and were not administered drug the following Friday. The 300 mg/kg administration was repeated for all rats the following Friday and again there was no drug administration on the subsequent Friday. The second dose-response series of five lower doses was started the following week. Throughout this second dose-response series, doses were administered once per week (Fridays). Two complete dose-response determinations (all six doses) required 13 weeks (see Table 1 for timeline).

Experiment 2: Test of Combination Treatments

We then tested the effects of a combination treatment involving D-serine and ATX using the same rats (n = 16) from the D-serine dose-response determination in Experiment 1. Each drug combination was experienced twice in a repeated measures design. All rats received each of the following dose combinations: saline + saline, D-serine + saline, ATX + saline, and D-serine + ATX. The dose of ATX (0.5 mg/kg) was expected to have no effect on its own based on past research (Chawla, unpublished; Redding et al., 2019). The dose of D-serine (100 mg/kg) was similarly chosen based on the results of the dose-response determination (Experiment 1). Although we also found no effect on IT devmode following 150 mg/kg of D-serine, a dose of 100 mg/kg was selected to reduce other possible side-effects of D-serine (e.g., diuresis). Drugs were administered twice a week (Tuesday and Friday) on a counterbalanced schedule. This schedule did not result in notable weight loss due to diuresis. Two complete sets of repeated measures required four weeks of testing.

Experiment 3: Final Test of Combination Treatments

A new group of male Sprague-Dawley rats (n = 16) was used to follow-up on the finding of a combination treatment effect found in Experiment 2. The second group of rats was trained in the 2CRTT as described above. As before, all rats were administered each of the dose combinations: saline + saline, D-serine + saline, ATX + saline, and D-serine + ATX. All rats experienced each treatment level three times (as opposed to two times in Experiment 2). The dose of ATX (0.3 mg/kg) was adjusted down from the dose used in Experiment 2. This lower dose was expected to be ineffective on its own. The dose of D-serine (125 mg/kg) was adjusted up from the dose used in Experiment 2. This higher dose was selected to potentiate the effect of the combination treatment but was expected to be ineffective on its own. Based on the lack of harmful effects following drug administration twice a week in the first test of the combination treatments, drugs were again administered twice a week (Tuesday and Friday) on a counterbalanced schedule. Three complete sets of repeated measures (all drug combinations) were completed in six weeks.

Dependent Variables

Response Time Variables

Response time (RT) is the time elapsed from stimulus light onset until the rat enters the correct nosepoke aperture. Each RT was split into initiation time (IT) and movement time (MT) for further analysis. IT is the elapsed time from stimulus light onset until the rat exits the central aperture. MT is the elapsed time from the end of IT until the rat enters the correct aperture. Distributions do not include data from incorrect trials or trials with an IT or MT longer than 2 sec (see omissions below). Mode and deviation from mode (devmode) were calculated from the IT distributions of each rat using the methods detailed in Sabol et al. (2003). IT mode represents sensorimotor processing speed when rats are attentive (i.e., when attention facilitates selective

processing). IT mode was calculated by grouping ITs into overlapping 50 ms bins and computing a running frequency for bins (0 – 50, 10 – 60, 20 – 70, etc). Mode is the midpoint of the bin with the highest frequency of ITs. IT devmode measures distribution skew and was calculated by subtracting IT mode from the IT mean. IT devmode reflects attentional lapses and is therefore the primary measure of sustained attention in this paradigm. MT mode is calculated in the same manner as IT mode and is thought to reflect factors related to movement speed, motivation, or sedation.

Other Dependent Variables

Omissions were recorded when rats required longer than 2 sec to initiate a response following stimulus presentation. Omission percentage was then calculated by dividing the count of omissions by the total number of trials in a session. Premature initiations were counted when rats exited the central aperture before the stimulus light came on but made no response. Premature responses were counted when rats exited the central aperture before the stimulus light came on and completed a response. The counts of premature initiations and responses were divided by the sum of all foreperiods (in seconds) in the testing session to calculate rates for these variables. Finally, the number of trials completed in each testing session was also recorded.

Data Analysis

During the D-serine dose-response determination (Experiment 1), performance data were collected following each of six dose levels of D-serine (saline, 10, 50, 100, 150, and 300 mg/kg). For the tests of combination treatment (Experiments 2 and 3), performance data were collected for each of the four levels of combination drug treatments (saline + saline, D-serine + saline, ATX + saline, and D-serine + ATX). For initial analyses, both the D-serine dose-response

determination (Experiment 1) and the first test of the combination treatment (Experiment 2) included two complete series of repeated measures that yielded a combined total of up to 200 trials for each rat under each level of drug condition (as in Redding et al., 2019). We then adjusted our approach, keeping data from different series of repeated measures separated for all further analyses. This was done to search for an effect of time on attentional lapses (described below). The new approach resulted in two separate distributions of up to 100 trials each per drug condition for each rat rather than a single distribution of up to 200 trials per drug condition for each rat. This approach also provides additional degrees of freedom for statistical tests due to effective doubling of the sample size. Both sets of analyses are reported (see Results) for the D-serine dose-response experiment (Experiment 1) and the first test of the combination treatment (Experiment 2). Only the latter approach with separate distributions for each series of repeated measures was used for the final test of the combination treatments (Experiment 3). In the latter experiment, three full series of repeated measures were completed, resulting in three separate distributions (one more than Experiment 2) of up to 100 trials each per combination treatment for each rat.

All statistical analyses were performed in SPSS (SPSS Inc., Chicago, IL). For the D-serine dose-response determination (Experiment 1) and the initial test of the combination treatment (Experiment 2), linear mixed models were created to account for missing data in some animals without dropping existing data for these animals. For the D-serine dose-response determination, the D-serine dose factor (saline, 10, 50, 100, 150, and 300 mg/kg) was modeled as a fixed effect, while subject ID was included as a random effect. For the first test of combination treatments, combination treatment level was modeled as a fixed effect (saline + saline, D-serine + saline, ATX + saline, and D-serine + ATX), while subject ID was included as a random effect.

During data collection, we suspected an effect of time on our primary attentional variable, IT devmode; therefore, dose-response series (first or second) was included as an additional fixed effect in these linear mixed models. Satterthwaite's method was used to estimate denominator degrees of freedom for tests of significance. Fixed effects were assessed by F-test ($\alpha = .05$). Post-hoc tests were conducted where appropriate to compare each dose with the saline condition using Bonferroni adjustments for multiple comparisons (D-serine dose-response determination: corrected $\alpha = .05/5 = .01$; Initial test of combination treatments: corrected $\alpha = .05/3 = .0167$). A linear mixed model was also used to test for a possible interaction between the effects of D-serine and ATX on IT devmode in the initial test of combination treatments (Experiment 2). D-serine dose (saline or 100 mg/kg) and ATX dose (saline or 0.5 mg/kg) were included as fixed effects and subject ID was included as a random effect.

No data were missing for the final test of combination treatments (Experiment 3); therefore, repeated measures ANOVA was used with combination treatment level as the repeated measures factor. The Greenhouse-Geisser correction was used if data did not meet the assumption of sphericity. All pairwise comparisons were conducted for dependent variables of relevance to clinical attentional outcomes (IT devmode), potential side-effects (MT mode and trials completed), and impulsivity (premature response rate). The threshold for significance was adjusted to account for these additional tests (corrected $\alpha = .05/6 = 0.0083$). A possible interaction between the effects of D-serine and ATX on IT devmode was also tested using repeated measures ANOVA. D-serine dose (saline or 125 mg/kg) and ATX dose (saline or 0.3 mg/kg) were included as repeated measures factors.

CHAPTER 5 - RESULTS

Experiment 1: D-serine Dose-Response Determination

Effects of Dose-Response Series

There was a significant effect of dose-response series on IT devmode $F(1, 163.015) = 28.332$, $p < .001$, reflecting a lower IT devmode in the second dose-response series. There was no evidence for an effect of dose-response series on any of the other dependent variables measured in this experiment. Additionally, there was no evidence for an interaction between dose-response series and drug dose for IT devmode nor any other dependent variables measured in this experiment.

Effects of D-serine Dose

Initiation Time and Omission Percentage

There was no evidence for an effect of D-serine dose on IT mode $F(5, 73.068) = 0.969$, $p = .443$ when data from both dose-response series were combined into one distribution representing performance under each D-serine dose. Likewise, there was no evidence for an effect of D-serine dose on IT mode $F(5, 163.028) = 0.785$, $p = .562$ (see Fig. 3A) when distributions were kept separate to account for the influence of time.

There was a significant effect of D-serine dose on IT devmode $F(5, 73.024) = 4.063$, $p =$

.003. There was also a significant effect of D-serine dose on IT devmode F(5, 163.016) = 4.451, $p < .001$ when distributions were kept separate to account for the influence of time. Post-hoc analyses indicated that IT devmode was reduced at the 300 mg/kg dose relative to saline (see Fig. 3B; see Table 2 for mean differences and associated confidence intervals. Note that all *p* values are uncorrected. Refer to Methods section for corrected α levels for these tests).

There was no evidence for an effect of D-serine dose on omission percentage F(5, 73.234) = 1.016, $p = .414$. Likewise, there was no evidence for an effect of D-serine dose on omission percentage F(5, 163.003) = 0.579, $p = .716$ (see Fig. 3C) when distributions were kept separate to account for the influence of time.

Movement Time and Completed Trials

There was no evidence for effects of D-serine dose on MT mode F(5, 73.044) = 1.482, $p = .206$ or the number of trials completed F(5, 73.127) = 1.5, $p = .2$. There was also no evidence for effects of D-serine dose on MT mode F(5, 163.015) = 0.884, $p = .493$ (see Fig. 3D) or the number of trials completed F(5, 163.078) = 1.405, $p = .225$ (see Fig. 3E) when distributions were kept separate to account for the influence of time.

Premature Initiation and Premature Response Rates

There was no evidence for effects of D-serine dose on premature initiation rate F(5, 73.006) = 0.71, $p = .618$ or premature response rate F(5, 72.937) = 0.9, $p = .486$. There was also no evidence for effects of D-serine dose on premature initiation rate F(5, 163.003) = 0.579, $p = .716$ (see Fig. 3F) or premature response rate F(5, 163.092) = 1.067, $p = .381$ (see Fig. 3G) when distributions were kept separate to account for the influence of time.

Experiment 2: Test of Combination Treatments

Effects of Dose-Response Series

There was no evidence for an effect of dose-response series on IT devmode $F(1, 101.819) = 0.153$, $p = .697$ nor any of the other variables measured in this experiment. There was also no evidence for an interaction between dose-response series and drug dose for IT devmode nor any other dependent variables measured in this study.

Effects of Drug Treatment

Initiation Time and Omission Percentage

Two IT mode scores were dropped for a single rat. These erroneous IT mode scores were dropped from analyses as they were faster than rats can reasonably be expected to respond to a visual stimulus. Initial responses in rat primary visual cortex take place approximately 85 msec following stimulus onset (e.g., Meliza & Dan, 2006). While this is already longer than these erroneous IT mode scores, initiation in the present study would require additional time to execute the planned response after processing of sensory information. Consistent with the thinking that these low IT mode scores are erroneous, each was more than two standard deviations below the mean for this animal. These fast IT mode scores likely resulted from the chance occurrence of premature initiations immediately after stimulus onset. The effect of these premature initiations on IT mode was then inflated due to the low number of trials completed on these test days. As IT devmode is calculated from the difference between distribution mean and mode, the two corresponding IT devmode scores were also dropped.

There was no evidence for an effect of drug treatment on IT mode $F(3, 44.029) = 0.858$, $p = .47$. Likewise, there was no evidence for an effect of drug treatment on IT mode $F(3, 102.046)$

= 0.53, p = .663 (see Fig. 4A) when distributions were kept separate to account for the influence of time.

There was a borderline effect of drug treatment on IT devmode F(3, 44.059) = 2.816, p = .05. In contrast, there was a significant effect of drug treatment on IT devmode F(3, 101.785) = 4.161, p = .008 when distributions were kept separate to account for the influence of time. Post-hoc analyses indicated that IT devmode was reduced by the combination treatment of D-serine and ATX relative to saline only. No other drug treatments were different from saline only (see Fig. 4B; see Table 3 for mean differences and associated confidence intervals). A separate linear mixed model with D-serine dose (saline or 100 mg/kg) and ATX dose (saline or 0.5 mg/kg) modeled as separate fixed effects revealed no evidence for an interaction between the effects of these two drugs on IT devmode F(1, 105.78) = 0.881, p = .35.

There was no evidence for an effect of drug treatment on omission percentage F(3, 44.429) = 1.867, p = .149. Likewise, there was no evidence for an effect of drug treatment on omission percentage F(3, 104.12) = 1.961, p = .124 when distributions were kept separate to account for the influence of time (see Fig. 4C).

Movement Time and Completed Trials

There was a significant effect of drug treatment on MT mode F(3, 44.066) = 9.043, p < .001. Likewise, there was a significant effect of drug treatment on MT mode F(3, 104.016) = 19.755, p < .001 when distributions were kept separate to account for the influence of time. Post-hoc analyses indicated that MT mode was increased by D-serine + saline treatment, ATX + saline treatment, and the combination treatment of D-serine and ATX relative to the saline + saline condition (see Fig. 4D; see Table 3 for mean differences and confidence intervals).

There was a significant effect of drug treatment on trials completed $F(3, 44.074) = 16.702$, $p < .001$. Likewise, there was a significant effect of drug treatment on trials completed $F(3, 104.032) = 22.514$, $p < .001$ when distributions were kept separate to account for the influence of time. Post-hoc analyses indicated that the number of trials completed was reduced by ATX + saline treatment and the combination treatment of D-serine and ATX relative to the saline + saline condition (see Fig. 4E; see Table 3 for mean differences and confidence intervals).

Premature Initiation and Premature Response Rates

There was no evidence for an effect of drug treatment on premature initiation rate $F(3, 44.023) = 0.138$, $p = .936$. Likewise, there was no evidence for an effect of drug treatment on premature initiation rate $F(3, 104.011) = 0.125$, $p = .945$ when distributions were kept separate to account for the influence of time (see Fig. 4F).

There was a significant effect of drug treatment on premature response rate $F(3, 44.348) = 6.612$, $p < .001$. Likewise, there was a significant effect of drug treatment on premature response rate $F(3, 104.036) = 4.693$, $p = .004$ when distributions were kept separate to account for the influence of time. Post-hoc analyses indicated that premature response rate was reduced by the ATX + saline treatment and the combination treatment of D-serine and ATX relative to saline alone (see Fig. 4G; see Table 3 for mean differences and confidence intervals).

Experiment 3: Final Test of Combination Treatments

Effects of Dose-Response Series

There was a significant effect of dose-response series on IT devmode $F(2, 30) = 5.97$, $p = .012$. Post-hoc tests indicated that IT devmode was significantly lower for the third series of

repeated measures relative to the first series of repeated measures (p = .016). There was no evidence for an effect of dose-response series on any of the other dependent variables measured in this experiment. There was no evidence for an interaction between dose-response series and drug treatment for IT devmode nor any other dependent variables measured in this study.

Effects of Drug Treatment

Initiation Time and Omission Percentage

Unlike Experiments 1 and 2 (described above), analyses were only performed on performance variables derived from separate testing sessions in Experiment 3. In other words, the following results only reflect data derived from three separate testing sessions of up to 100 trials each for each level of drug treatment.

Repeated measures ANOVA revealed no evidence for an effect of drug treatment on IT mode $F(3, 45) = 1.159$, $p = .336$ (see Fig. 5A). On the other hand, the effect of drug treatment on IT devmode was significant $F(3, 45) = 30.633$, $p < .001$. Post-hoc analyses indicated that IT devmode was reduced by both ATX + saline and the combination treatment of ATX + D-serine relative to the saline + saline condition. The D-serine + saline condition did not reduce IT devmode relative to the saline + saline condition. Additionally, the combination treatment of ATX + D-serine significantly reduced IT devmode relative to either the ATX + saline condition or the D-serine + saline condition (see Fig. 5B; see Table 4 for mean differences and associated confidence intervals). A separate repeated measures ANOVA was performed to test for a possible interaction between the effects of D-serine and ATX on IT devmode. There was no evidence for an interaction $F(1, 15) = 0.479$, $p = .499$. Finally, there was no evidence for an effect of drug treatment on omission percentage $F(3, 45) = 2.575$, $p = .106$ (see Fig. 5C).

Movement Time and Completed Trials

There was a significant effect of drug treatment on MT mode $F(3, 45) = 8.302$, $p < .001$. Post-hoc analyses indicated that MT mode was increased by the ATX + saline treatment and the combination treatment of ATX + D-serine relative to the saline + saline condition. There was no difference in MT mode between the combination treatment of ATX + D-serine and the ATX + saline condition (see Fig. 5D; see Table 4 for mean differences and confidence intervals).

There was a significant effect of drug treatment on trials completed $F(3, 45) = 9.052$, $p = .001$. Post-hoc analyses indicated that the number of trials completed was reduced by the ATX + saline treatment and the combination treatment of ATX + D-serine relative to the saline + saline condition. There was no difference in the number of trials completed between the combination treatment of ATX + D-serine and the ATX + saline condition (see Fig. 5E; see Table 4 for mean differences and confidence intervals).

Premature Initiation and Premature Response Rates

There was no evidence for an effect of drug treatment on premature initiation rate $F(3, 45) = 1.691$, $p = .182$ (see Fig. 5F). On the other hand, the effect of drug treatment on premature response rate was significant $F(3, 45) = 7.038$, $p < .001$. Post-hoc analyses indicated that the number of trials completed was reduced by the combination treatment of D-serine and ATX relative to the saline + saline condition (see Fig. 5G; see Table 4 for mean differences and confidence intervals).

CHAPTER 6 - DISCUSSION

Effects on Initiation Time Mode and Initiation Time Devmode

During visuospatial attention, endogenous neural activity is enhanced in topographic areas of frontal, parietal, and visual cortices corresponding to attended locations (Corbetta & Shulman, 2002; Kastner & Ungerleider, 2000). This signature of visuospatial attention resembles the recurrent activity that occurs during spatial working memory and could similarly depend on the activation of *N*-methyl-D-aspartate (NMDA) receptors (Compte et al., 2000; Wang et al., 2013; Wang & Arnsten, 2015). Top-down feedback generated during the modulation of endogenous neural activity is thought to act as a *content filter* for perception by preparing frontal, parietal, and visual cortical areas for the processing of selected sensory information. Target-evoked release of the neuromodulator, norepinephrine (NE), could act as a *temporal filter* for perception to increase the likelihood that selected sensory information is detected when it appears.

Subsequent effects on sensory-driven neural activity reflect the facilitated bottom-up processing of attended sensory information (target stimuli). The effects on sensory-driven neural activity, including gamma synchronization or noise correlations, could depend on the activation of NMDA receptors. Additionally, target-evoked NE release could increase gain in cortical neurons (Aston-Jones & Cohen, 2005; Servan-Schreiber et al., 1990) and adjust network-level functional connectivity (Bouret & Sara, 2005; Guedj et al., 2017) to facilitate the processing of

attended sensory information when it appears. Activation of NMDA receptors could play an additional role in determining the amount of NE release, providing a potential explanation for NE's effects on gain (Mather et al., 2016). Together, these ideas describe how NMDA receptor activation and target-evoked NE release could participate in the modulation of sensory-driven neural activity during attention to help us perceive selected sensory information.

These ideas present many interesting hypotheses and we tested two of these in the present study. *First*, by facilitating the processing of attended sensory information, pharmacological activation of NMDA receptors could improve performance in tests of visuospatial attention. Activation of NMDA receptors could affect performance by 1) promoting endogenous neural activity in frontal, parietal, and visual cortical areas and the associated top-down feedback to increase the likelihood that selected sensory information is processed efficiently, 2) modulating the sensory-driven gamma synchronization or noise correlations in these cortical areas to influence the efficiency of bottom-up processing, and 3) determining the effects of NE on sensory-driven neural activity, including firing rates or gamma synchronization. We therefore tested the effects of the NMDA receptor co-agonist, D-serine, on the performance of rats in the two-choice response time (RT) task (2CRTT).

The *second* hypothesis we tested was that pharmacological activation of NMDA receptors in combination with blocking NE reuptake could improve attention without enhancing unwanted side-effects associated with either approach. Positive effects from the present test of D-serine (Experiment 1) and past data demonstrating beneficial effects of the NE reuptake inhibitor, atomoxetine (ATX; Redding et al., 2019) suggest that attention could be improved by enhancing either NMDA receptor activation or synaptic NE levels. To determine whether measures of attention could be enhanced more effectively by enhancing NMDA receptor

activation and synaptic NE levels, we investigated the effects of D-serine in combination with ATX on the performance of rats in the 2CRTT.

Effects on Initiation Time Mode

Data analyses were performed using techniques developed by Sabol and colleagues (2003) to separate components of intraindividual initiation time (IT) and movement time (MT) distributions. IT was first separated from the full-body response (MT) required in the 2CRTT (see below for discussion of effects on MT mode). In this way, IT more closely resembled the overt responses required in sustained attention tasks for non-human primates (e.g., releasing a lever) and humans (e.g., pressing a key). Analyses of IT distributions were used to determine effects on distinct processes, including sensorimotor processing speed and attentional lapses (Sabol et al., 2003). This approach was conceptually based on early work by Hohle (1967) who proposed that RT distributions reflect multiple cognitive processes. According to Hohle, these processes can be measured independently by decomposing RT distributions into Gaussian and exponential components. In this *ex-Gaussian* model, the Gaussian component represents sensorimotor processing speed. Analogous to the ex-Gaussian approach, the method of Sabol et al. (2003) uses the mode of IT distributions as a measure of sensorimotor processing speed when animals are attentive.

There was no evidence for an effect of D-serine on IT mode in the present study, suggesting that increased levels of the NMDA glycine-binding site agonist and therefore increased activation of NMDA receptors do not affect sensorimotor processing speed when rats are attentive in the 2CRTT. There was also no evidence for an effect of ATX on IT mode, suggesting that increasing synaptic NE levels does not affect sensorimotor processing speed when rats are attentive. This finding is consistent with past research that found no evidence for

effects of ATX on IT mode in rats performing the 2CRTT (Redding et al., 2019). Finally, there was no evidence for an effect of the combination of D-serine and ATX on IT mode, suggesting that the combined effects of targeting the glutamate and NE systems did not affect sensorimotor processing speed when rats were attentive.

Sensorimotor processing is less efficient when targets are more difficult to discriminate due to reduced salience. For example, sensorimotor processing speed was slowed in the 2CRTT when the illumination of house lights reduced the salience of target stimuli (Sabol et al., 2003). Reduced stimulus salience has also been shown to increase the mode of RT distributions in rats performing the 2CRTT (Hausknecht et al., 2005). As Sabol and colleagues (2003) reported no effect of stimulus salience on the mode of MT distributions, increased RT mode reported by Hausknecht and colleagues (2005) also appears to reflect effects on sensorimotor processing speed rather than movement speed, motivation, or sedation. These studies both support the thinking that lower stimulus salience slows down sensorimotor processing speed. The salience of target stimuli was reduced in the present study; therefore, sensorimotor processing speeds should have been slower than expected for more salient sensory information. Indeed, the average sensorimotor processing speeds in the present study (224.68 ± 3.89 msec in Experiment 1; 220.81 ± 4.28 msec in Experiment 2; 219.9 ± 3.95 msec in Experiment 3) were slower than those seen in past research conducted under salient conditions (191.56 ± 2.22 msec in Redding et al., 2019, 164 msec in Sabol et al., 2003). If pharmacological manipulation of NMDA receptor activation or synaptic NE levels affected sensorimotor processing speed, these effects would have been expected in the present study. The present findings could therefore be interpreted to suggest that targeting NMDA receptor activation or synaptic NE levels does not prevent the reduced processing efficiency caused by lower stimulus salience.

On the other hand, benefits of NMDA receptor activation and target-evoked NE release on sensorimotor processing speed could become apparent when task conditions other than target salience are manipulated. The proposed effects on sensory-driven neural activity, including firing rates, gamma synchronization, and noise correlations, could enhance the efficiency of processing selected sensory information when the selected information competes with other salient information. In other words, sensorimotor processing speed could be increased by targeting NMDA receptor activation and target-evoked NE release when salient distractors must be suppressed for selected information to be processed efficiently. In past research, we found no effects of ATX on sensorimotor processing speed (IT mode) when flashing light distractors were presented prior to target stimuli (Redding et al., 2019); however, these distractors did not compete for processing resources at the same time as the target stimuli. It is possible that either D-serine or ATX could affect sensorimotor processing speed when selected sensory information is processed less efficiently due to the simultaneous presentation of competing sensory information (see below for discussion of possible improvements to the present research).

While we found no evidence for effects on sensorimotor processing speed in the present study, the findings of reduced IT distribution skew in rats performing the 2CRTT (described below) suggest that increasing NMDA receptor activation or synaptic NE levels could be more important for determining how often rats experience lapses of attention characterized by less efficient processing.

Effects on Initiation Time Devmode

The exponentially distributed component of Hohle's *ex-Gaussian* model represents the characteristic positive skew of RT distributions (Hohle, 1967). This component was originally proposed to reflect decisional processes required to produce the prescribed response to a target

stimulus. More recently, the skew of RT distributions has been proposed to reflect attentional lapses (Leth-Steensen et al., 2000). In the present study we used the skew of IT distributions (IT devmode) to measure the intraindividual variability due to infrequent, abnormally slow ITs (Sabol et al., 2003). These slower ITs are thought to reflect lapses in attention; therefore, IT devmode was used as an overall measure of the attentional lapses occurring with a testing session.

We found that D-serine reduced IT devmode at the highest dose tested (300 mg/kg) in rats performing the 2CRTT. This finding suggests that increasing D-serine levels and therefore increasing NMDA receptor activation can improve performance by reducing attentional lapses in rats performing the 2CRTT. We also found that a combination treatment consisting of D-serine (100 mg/kg) and ATX (0.5 mg/kg) reduced IT devmode, while neither D-serine nor ATX at these doses reduced IT devmode when administered alone. These findings suggest that the combination treatment could be a more effective treatment for impaired attention than either drug alone. In a follow-up experiment, we found that ATX (0.3 mg/kg) reduced IT devmode when administered alone; however, the combination of D-serine (125 mg/kg) and ATX (0.3 mg/kg) reduced IT devmode even more than ATX alone. This finding provides further support for the thinking that the combination treatment could be an especially effective approach for treating impaired attention.

This approach could potentially be used to enhance attention while reducing the risk of side-effects that could occur at higher doses of either drug. For example, ATX has been associated with subjective reports of sedation (Heil et al., 2002) that are consistent with effects on MT mode and trials completed seen in past rodent work (Redding et al., 2019) and in the present study (see below). D-serine has been associated with anxiety in mice (Labrie et al.,

2009). High doses of D-serine have also been associated with nephrotoxicity in rats (Carone & Ganote, 1975; Ganote et al., 1974; Krug et al., 2007; Maekawa et al., 2005; Orozco-Ibarra et al., 2007); however, further research will be required to comprehend the potential nephrotoxic effects of D-serine in humans. Current evidence indicates that even if D-serine had the same level of nephrotoxicity seen in rats, it would need to be administered at doses of more than 450 mg/kg for nephrotoxic effects to appear in humans (Hasegawa et al., 2019). This is already greater than an order of magnitude more than the doses of D-serine (approximately 30 mg/kg) that have been shown to affect cognition in humans (Kantrowitz et al., 2010; Tsai et al., 1998). The administration of D-serine with ATX could produce the same or greater effects on attention with lower doses of D-serine, further reducing the risk of nephrotoxicity.

Consistency of D-Serine's Effects with Other Reports

D-Serine's Effects in Humans

The present effects of D-serine on attentional lapses are consistent with the reported effects of other pharmacological agents targeting NMDA receptor glycine-binding sites in humans (File et al., 1999; Saletu & Grünberger, 1984; Saletu et al., 1986). D-serine itself improved d' in healthy subjects performing a continuous performance task (CPT; Levin et al., 2015). On the other hand, the present findings contrast with other reports. For example, intravenous glycine did not affect omissions in healthy subjects performing a CPT (D'Souza et al., 2000) nor did it affect performance in a vigilance task (Neumeister et al., 2006). Additionally, Palmer and colleagues (2008) reported no effects of oral glycine in healthy subjects performing a CPT or a choice RT task. Finally, D-serine itself had no effect on the number of errors made by older adults performing a computerized attention test (Avellar et al., 2016) and had no effect on d' in patients with schizophrenia performing a CPT (D'Souza et al., 2013).

These contrasting reports could be related to the measures used in these studies. Specifically, null reports relied on more traditional measures of accuracy and omissions (e.g., D'Souza et al., 2000; Neumeister et al., 2006; Palmer et al., 2008). D'Souza and colleagues (2013) also found no effects of D-serine on d'. Importantly, past work suggests that measures of intraindividual RT variability (RTV), especially those reflecting distribution skew, could be especially sensitive to the effects of pharmacological manipulations targeting attention performance (see below for discussion of the use of RTV to measure the effects of ATX). Additionally, contrasting results of targeting NMDA receptor glycine-binding sites could be related to the lower affinity of glycine for these sites relative to D-serine (Matsui et al., 1995); however, two studies also reported no effects of D-serine (Avellar et al., 2016; D'Souza et al., 2013), seemingly contradicting this thinking. The mixed reports of D-serine's effects could also be related to dose. The dose of approximately 30 mg/kg used in studies reporting no effects of D-serine on attention (Avellar et al., 2016; D'Souza et al., 2013) appears to be borderline effective based on the results of studies using cognitive test batteries in patients with schizophrenia. D-serine at this dose had mixed effects on cognitive performance (D'Souza et al., 2013; Tsai et al., 1998, 1999), while higher doses improved performance (Kantrowitz et al., 2010) and lower doses had no effect (Weiser et al., 2012). Further work will be needed to clarify the potential efficacy of D-serine at various doses using measures of RTV to supplement more traditional measures of attention.

D-Serine's Effects in Rodents

The present findings are to our knowledge the first reported effects of D-serine in a rodent behavioral model of attentional lapses. Consistent with the present findings, a glycine transporter inhibitor improved accuracy in impaired Sp4 hypomorphic mice performing a five-

choice serial RT task (5CSRTT); however, no effects were seen in wild-type controls (Young et al., 2015). Beneficial effects of increasing synaptic glycine levels in Sp4 hypomorphic mice, a putative model for schizophrenia (Zhou et al., 2010), suggest that the NMDA receptor glycine-binding site could be an important target for improving sustained attention in individuals with schizophrenia. The reported lack of effects in healthy controls could be related to the sensitivity of behavioral measures as described above for human studies (see below for discussion of the use of RTV to measure the effects of ATX).

Consistency of Atomoxetine's Effects with Other Reports

Atomoxetine's Effects in Humans

The finding of reduced attentional lapses following ATX administration in the present study (Experiment 3) is consistent with various reports from human studies. For example, ATX reduced omissions, increased d' (Shang & Gau, 2012; Wehmeier et al., 2012; Wehmeier et al., 2011), and reduced measures of RTV in children with attention-deficit/hyperactivity disorder (ADHD) performing CPTs (Kratz et al., 2012; Shang & Gau, 2012; Wehmeier et al., 2011, 2012). ATX also improved measures of d' (Fan et al., 2017; Ni et al., 2013), hit rate (Lin & Gau, 2015), commission errors, and the *ex-Gaussian* measure of RT distribution skew, τ (Ni et al., 2016b), in adults with ADHD performing CPTs.

In contrast to the positive effects of ATX described above, several studies reported no effects in impaired individuals. For example, ATX did not affect omissions or RT standard deviation in children with ADHD (Bédard et al., 2015) or RT standard error in children with ADHD-like impairments (Posey et al., 2006a) performing CPTs. ATX did not affect the proportion of targets successfully detected by adults with ADHD performing a CPT

(Chamberlain et al., 2007b). Additionally, ATX did not affect RT standard deviation in healthy adults performing a stop-signal test (Nandam et al., 2011). Similarly, Ni and colleagues (2016) reported no effects of ATX on RT standard error in adults with ADHD performing a CPT.

Discrepancies in ATX's effects on attention could be related to the choice of behavioral measures. Null reports used either traditional measures (e.g., hit rate in Chamberlain et al., 2007) or measures of RTV that do not reflect distribution skew (RT standard deviation in Bédard et al., 2015; RT standard error in Posey et al., 2006). Interestingly, Ni and colleagues (2016) reported reduced τ, a measure that reflects RT distribution skew, without effects on RT standard error. These findings support the thinking that measures of RT distribution skew, like τ or IT devmode, could be especially sensitive to effects on sustained attention as suggested previously (Redding et al., 2019). Despite null effects in some reports that could be related to the use of specific behavioral measures, most reports of ATX's effects on attention agree with the present findings of reduced attentional lapses in a visuospatial discrimination task.

Atomoxetine's Effects in Rodents

Mixed effects of ATX have been reported in rodent studies of attention. The current findings of reduced attentional lapses following ATX administration are consistent with a minority of reports showing improved attention in rodents. For example, ATX improved accuracy in rats performing 5CSRTTs (Navarra et al., 2008; Robinson, 2012). Additionally, we previously found that ATX reduced IT devmode in rats performing a 2CRTT (Redding et al., 2019). In contrast to these few positive reports and the present findings, many studies reported no effects of ATX on accuracy in rats performing 5CSRTTs (Blondeau & Dellu-Hagedorn, 2007; Fernando et al., 2012; Hauser et al., 2017; Koffarnus & Katz, 2011; Liu et al., 2015; Paterson et al., 2011, 2012; Robinson, 2012; Robinson et al., 2008; Sun et al., 2012; Tsutsui-

Kimura et al., 2009). ATX also had no effect on d' in rats performing a rodent CPT (Ding et al., 2018).

The effects of ATX could depend on baseline performance, potentially explaining the lack of effects found in many rodent studies. Robinson (2012) performed a median split to separate rats based on low and high baseline performance in the 5CSRTT. ATX improved accuracy in low performing rats without effects in high performing rats. ATX similarly improved target discrimination in low performing mice in a rodent CPT with no effects in high performers (Caballero-Puntiverio et al., 2019). Finally, ATX improved accuracy and target sensitivity in low-performing rats and impaired sensitivity in high-performing rats in a five choice-CPT (Tomlinson et al., 2014). The lack of effects or even impairments seen in high performing animals could obscure beneficial effects in low-performing animals, potentially explaining the numerous studies that reported no effects of ATX on attention.

The inconsistency in ATX's effects on attention in rodents could also be related to the choice of behavioral measures (as described above for human studies). Studies using more traditional measures (e.g., accuracy and d') reported null findings in 12 out of 14 instances. In contrast, the only other study using a measure of RT distribution skew (IT devmode in Redding et al., 2019) found positive effects of ATX in agreement with the present findings. This pattern of results suggests that analyses of RT (or IT) distribution skew should be used in rodent research alongside more traditional measures of sustained attention. This approach would more closely parallel the current techniques for measuring attentional lapses using RTV in clinical research (Tamm et al., 2012; Kofler et al., 2013).

Consistency of Combination Treatment Effects with Other Reports

To our knowledge the present findings are the first reports of reduced attentional lapses following the simultaneous administration of pharmacological agents targeting NMDA receptor activation and synaptic NE levels in rats. Only one other study has investigated the possible cooperation between the glutamate and NE systems in other cognitive domains. In this study, Liu and colleagues (2009) demonstrated that injections of glutamate or NE into the rat bed nucleus of the stria terminalis, an area involved in the formation of affective memories, had no effect on the conditioning of fear responses to a tone paired with an aversive shock. In contrast, the infusion of glutamate and NE into this area increased later fear responses to the conditioned tone, suggesting that the cooperative effects of glutamate and NE established a stronger memory for the conditioned pairing. Furthermore, pharmacological blockade of NMDA receptors attenuated the effects of glutamate, suggesting that the interaction between the glutamate and NE systems during affective memory formation involves NMDA receptor activation. Additional work will be required to determine if a similar interaction between NMDA receptor activation and NE release could affect sensory processing during visuospatial attention.

How Do NMDA Receptors Support Attention?

The activation of NMDA receptors could support attention in several different ways. The *first* possible role for NMDA receptors involves the maintenance of endogenous neural activity during attention. Endogenous activity and the associated top-down feedback in frontal, parietal, and visual cortical areas of the visual processing system are thought to act as a *content filter* to determine what we perceive (Corbetta et al., 2002; Desimone & Duncan, 1995; Kastner & Ungerleider, 2000). The persistent endogenous activity in frontal, parietal, and visual cortices during the voluntary orienting of attention could be dependent on activation of NMDA receptors.

In support of this thinking, spatial attention is thought to be deployed during spatial working memory (Awh & Jonides, 2001) and spatial working memory is known to depend on NMDA receptor activation (Brunel and Wang, 2001; Compte et al., 2000; van Vugt et al., 2020; Wang, 2001). NMDA receptor activation could therefore reduce attentional lapses by increasing endogenous activity in the neurons representing attended portions of the visual field. These effects could prepare frontal, parietal, and visual cortical neurons for selected sensory information, increasing the likelihood that it is processed efficiently. This thinking is supported by the present findings of reduced attentional lapses (IT devmode) in the 2CRTT following D-serine administration (Experiment 1).

The *second* way that NMDA receptor activation could influence sensory processing and perception during attention involves effects on sensory-driven neural activity, including gamma synchronization, in frontal, parietal, and visual cortices. Gamma synchronization could facilitate bottom-up sensory processing (Fries, 2015) and has been shown to be enhanced in the neurons representing attended sensory information (Buffalo et al., 2011; Chalk et al., 2010; Fiebelkorn et al., 2018; Fries et al., 2001, 2008; Gregoriou et al., 2009; Ni et al., 2016a; van Kerkoerle et al., 2014; Vinck et al., 2013). Consistent with the involvement of NMDA receptors in gamma synchronization, NMDA antagonism disrupts normal gamma synchronization in rodents (reviewed in Hunt & Kasicki, 2013) and humans (Shaw et al., 2015). Furthermore, disrupted gamma synchronization has been linked to hypofunction of NMDA receptors located on gamma-aminobutyric acid (GABA) interneurons (Carlén et al., 2012; Kocsis, 2012) that are critical for the generation of gamma synchronization (Buzsáki & Wang, 2012). Together, these findings suggest that NMDA receptor activation could enhance the efficiency of processing for attended sensory information due to effects on gamma synchronization. This thinking is not supported by

the present findings, as D-serine did not affect sensorimotor processing speed (IT mode) in rats performing the 2CRTT.

The *third* way that NMDA receptors could support attention is via a role in reducing the correlations in firing rate variability between frontal, parietal, and visual cortical neurons processing attended sensory information. The reliability of stimulus detection could be impaired when firing rate variability is correlated in a group of neurons representing the stimulus (Shadlen et al. 1996; Abbott & Dayan 1999); however, these noise correlations are reduced in populations of neurons processing attended sensory information (Astrand et al., 2016; Buffalo et al., 2011; Cohen & Maunsell, 2009; Herrero et al., 2013; Mitchell et al., 2009; Ruff & Cohen, 2014; Tremblay et al., 2015). Blockade of NMDA receptors has been shown to prevent the reduction of noise correlations during attention, leading to increased RTs that could reflect impaired sensory processing (Herrero et al., 2013). These findings suggest that the activation of NMDA receptors could enhance the efficiency of bottom-up processing by reducing noise correlations in the population of neurons representing attended sensory information. This thinking is also not supported by the present findings, as D-serine did not affect sensorimotor processing speed (IT mode) in rats performing the 2CRTT.

The proposed NMDA receptor-mediated effects take place in specific frontal, parietal, and visual cortical areas of the visual processing system; however, D-serine was administered systemically in the present study. Despite this route of administration, there is reason to expect some degree of spatial selectivity in the effects of D-serine. NMDA receptor activation requires binding of both a glycine-binding site and a glutamate-binding site (Dingledine et al., 1999; Traynelis et al., 2010); therefore, systemic administration of a glycine-binding site agonist like D-serine could increase NMDA receptor-mediated effects only at synapses with elevated

glutamate levels. Due to the modulation of neural activity during attention, glutamate would be expected to be released in higher amounts at synapses that communicate task-relevant information (i.e., those receiving inputs from neurons with receptive fields overlapping attended locations). This line of reasoning suggests that D-serine could enhance the activation of a subset of NMDA receptors located near highly active synapses in the frontal, parietal, and visual cortices despite a systemic route of administration.

To summarize, the present effects of systemic D-serine administration could be related to the modulation of endogenous neural activity in frontal, parietal, and visual cortices which could act as a content filter to increase the likelihood that selected sensory information is processed efficiently. D-serine could also affect the processing of attended sensory processing due to the modulation of sensory-driven gamma synchronization or noise correlations. The present findings of reduced attentional lapses (IT devmode) following D-serine administration are consistent with the first proposition outlining the role of NMDA receptors in maintaining a content filter for perception. On the other hand, the lack of effects on sensorimotor processing speed (IT mode) suggests that the proposed beneficial effects of NMDA receptor activation on sensory-driven neural activity did not take place under the task conditions used in the present research. Further research will be required to determine the extent to which the activation of NMDA receptors supports attention via each of these proposed mechanisms.

NMDA Receptor Activation Could Determine NE-Mediated Effects on Sensory Processing

Norepinephrine could take part in the modulation of neural activity to influence what we perceive. During attention, noradrenergic neurons in the locus coeruleus (LC) fire phasic bursts in response to target stimuli (Aston-Jones & Bloom, 1981; Aston-Jones et al., 1994; Bouret & Sara, 2002; Foote et al., 1980; Grant et al., 1988; Sara et al., 1994), releasing NE into the cortex

(Berridge & Abercrombie, 1999). NE increases synaptic input gain, thereby enhancing signal-to-noise ratios (Servan-Schreiber et al., 1990). In frontal, parietal, and visual cortical areas of the visual processing system, target-evoked NE release could function as a *temporal filter* to facilitate the processing of attended sensory information at appropriate times (i.e., when the target appears). Reduced attentional lapses (IT devmode) following administration of ATX in the present study (Experiment 3) could be related to enhanced functioning of this temporal filter (as in Bari & Aston-Jones, 2013), ensuring that selected sensory information is more likely to be processed efficiently when it appears.

The efficiency of processing for selected sensory information could be determined by the effects of NMDA receptor activation on target-evoked NE release (Mather et al., 2016). As described in the *Glutamate Amplifies Noradrenergic Effects (GANE)* model, glutamate activating NMDA receptors could determine the release of NE and therefore mediate subsequent effects on gain. Gain could be enhanced via modulation of neural firing rates or gamma synchronization, both of which could increase the efficiency of sensory processing. In contrast with this thinking, we found no effects of D-serine, ATX, or the combination treatment on sensorimotor processing speed (IT mode) in the present research. These findings indicate that if D-serine or ATX affected sensory-driven firing rates or gamma synchronization in rats performing the 2CRTT, these effects did not influence sensorimotor processing speed under the task conditions used in the present research. Future work will be required to search for specific effects of NMDA receptor activation and target-evoked NE release on the modulation of sensory-driven firing rates and gamma synchronization in frontal, parietal, and visual cortical areas during attention.

Several important questions remain unanswered for now; however, the present findings support the idea that a combination treatment enhancing NMDA receptor activation and synaptic

NE levels could effectively reduce attentional lapses without increasing unwanted side-effects of ATX that could be related to movement speed, motivation, or sedation. These potential side-effects are discussed in the following section.

Effects on MT Mode and Trials Completed

Separation of IT and MT allowed us to measure effects on sensorimotor processing (IT mode) and attentional lapses (IT devmode) relatively free from confounding effects related to movement speed, motivation, or sedation (MT mode). We found no effect of D-serine on MT mode in the dose-response determination (Experiment 1); however, D-serine (100 mg/kg) unexpectedly increased MT mode in the test of the combination treatment in the same group of rats (Experiment 2). The final test of the combination treatment using a new group of rats and an increased amount of data (three complete sets of repeated measures) revealed no effect of D-serine on MT mode even at a higher dose (125 mg/kg; Experiment 3). In contrast to the unexpected slowing of MT mode in Experiment 2, null results from Experiments 1 and 3 support the thinking that D-serine's effects on movement speed, motivation, or sedation-related factors are small or negligible. Supporting this thinking, D-serine did not affect the number of trials completed at any dose in the dose-response determination (Experiment 1) or in either of the two tests of the combination treatment (Experiments 2 and 3). The number of trials completed could be affected by similar factors related to movement speed, motivation, or sedation; therefore, the present lack of effects on trials completed following D-serine administration further suggests that D-serine does not influence these factors. It is unclear why D-serine (100 mg/kg) increased MT mode in the initial test of the combination treatment in (Experiment 2); however, carry-over effects due to extended D-serine exposure in this group of rats (during Experiment 1) cannot be ruled out. Overall, the lack of additional effects on MT mode (Experiments 1 and 3) and

consistent lack of effect on trials completed suggest that D-serine does not have strong effects on movement speed, motivation, or sedation.

In the present study, ATX increased MT mode in both tests of combination treatments (0.5 mg/kg in Experiment 2; 0.3 mg/kg in Experiment 3). These findings are consistent with ATX-induced increases in MT mode seen in past work (Redding et al., 2019) and numerous reports of increased RT in rats (Baarendse & Vanderschuren, 2012; Benn & Robinson, 2017; Blondeau & Dellu-Hagedorn, 2007; Caballero-Puntiverio et al., 2019; Ding et al., 2018; Fernando et al., 2012; Jentsch et al., 2008; Robinson, 2012; Sun et al., 2012). The combination treatment also increased MT mode relative to saline; however, the lack of a difference between the combination treatment and ATX alone in the final test of combination treatments (Experiment 3) suggests that increased MT mode was driven primarily by ATX. On the other hand, the unexpected slowing of MT mode following D-serine administration in Experiment 2 (described above) indicates that a weak effect of D-serine on MT mode cannot be rule out entirely. A similar pattern was seen for effects on trials completed. Both ATX alone and the combination treatment reduced trials completed relative to saline, but the number of trials completed did not differ between the combination treatment and ATX alone. The present findings of increased MT mode and reduced trials completed due to ATX are consistent with subjective reports of sedation in patients taking ATX (Heil et al., 2002) and past findings using the present model that could be related to movement speed, motivation, or sedation (Redding et al., 2019). The fact that the combination treatment did not increase MT mode or reduce trials completed more than ATX alone in the present study supports the original hypothesis that the combination treatment of D-serine and ATX could improve attention without increasing unwanted side-effects of ATX.

Effects on Premature Response Rate

Premature response rate in the 2CRTT reflects impulsivity by measuring the occurrence of nosepoke responses prior to target presentation. We found no effect of D-serine in any experiment; however, ATX reduced premature response rates in the initial test of the combination treatment (Experiment 2). Premature response rates were reduced by ATX alone and the combination treatment relative to saline. In the final test of the combination treatment (Experiment 3), premature response rates in the combination treatment condition were reduced relative to saline alone.

Reduced impulsivity in the present study is consistent with reported effects of ATX in humans. For example, ATX reduced commission errors in children (Shang & Gau 2012; Wehmeier et al. 2011; Wehmeier et al. 2012) and adults (Chamberlain et al. 2007; Ni et al. 2016b) with ADHD performing CPTs. On the other hand, ATX did not affect commission errors in children with ADHD performing Conners' CPT (Bédard et al. 2015; Posey et al. 2006).

Reduced impulsivity in the present study is consistent with reported effects of ATX in most rodent studies. For example, ATX reduced premature responding in numerous studies (Baarendse & Vanderschuren 2012; Benn & Robinson 2017; Blondeau & Dellu-Hagedorn 2007; Ding et al. 2018; Jentsch et al. 2008; Liu et al. 2015; Paterson et al. 2011; Paterson et al. 2012; Robinson et al. 2008; Robinson 2012; Sun et al. 2012; Tsutsui-Kimura et al. 2009). On the other hand, we found no effects of ATX on premature response rate in a previous study using the 2CRTT (Redding et al., 2019).

It is unclear why ATX reduced premature response rates in the present study without affecting premature response rates in past work using the same task and parameters. In

Experiment 2, rats had been exposed to D-serine during Experiment 1, suggesting that carry-over effects from D-serine administration could explain the discrepancy with past findings. However, this thinking appears to be weakened by the fact that the combination treatment reduced premature response rates in Experiment 3 in rats that were naïve to drug exposure as in our past research (Redding et al., 2019). The discrepancy in results between Experiment 3 and past work could be related to the collection of additional data (three complete dose-response series versus two in past research). It is possible that a combination of factors related to carry-over effects from D-serine exposure and the collection of additional data could explain the discrepancies seen between past work and the present findings of reduced premature response rates following ATX administration. The present results together with most findings from cross-species behavioral research suggest that ATX can reduce impulsivity during attention; however, additional work will be required to explore this possibility.

Intriguingly, Usher and colleagues (1999) reported reduced false alarms in monkeys during periods of high engagement in an attentional task. These periods of increased attention and reduced impulsivity were characterized by reduced tonic and enhanced phasic firing of the LC as described by the *Adaptive Gain* theory (Aston-Jones & Cohen, 2005). Reduced tonic LC firing and NE release decreases the responsivity of neurons in cortical processing networks. ATX has been shown to reduce tonic LC firing, while preserving phasic firing (Bari & Aston-Jones, 2013). Reduced tonic LC firing could be mediated by the activation of α-2 autoreceptors located on noradrenergic neurons in the LC itself (Mateo et al., 1998; Miguelez et al., 2009; Starke & Montel, 1973; Svensson et al., 1975; Svensson & Usdin, 1978). Together, these findings suggest that the present reductions in impulsivity could reflect an increase in the threshold for stimulus

detection in cortical processing networks due to reduced tonic LC firing and NE release following the administration of ATX.

Possible Improvements

Investigations Using Food-Restricted Animals

During the dose-response determination for D-serine's effects on IT devmode (Experiment 1), drug administrations were reduced to a single dose per week after the onset of diuresis-induced weight loss. This change was made to protect rats from potentially harmful effects of scheduled access to water in combination with drug-induced urination. Following this change, repeated measures of drug administration required twice as much time, extending the duration of long-term exposure to D-serine. Subsequent tests of combination treatments involving D-serine and ATX (Experiment 2 and 3) indicated that twice weekly D-serine administration is well-tolerated at lower doses (100 and 125 mg/kg in Experiments 2 and 3, respectively) for short periods of time (i.e., the four to six weeks required for two or three complete dose response series). Nevertheless, future studies of D-serine in rodents could benefit from using food restriction procedures to motivate task performance as this could reduce the risk of harmful fluid level reduction.

Investigations of Effects on Initiation Time Mode

While not part of our original hypotheses, increasing NMDA receptor activation or inhibiting NE reuptake could also be expected to increase sensorimotor processing speed. NMDA receptor activation is thought to be involved in the modulation of sensory-driven gamma synchronization or noise correlations during attention. Additionally, NMDA receptor activation and the resulting effects on target-evoked NE release could increase the efficiency with which

selected sensory information is processed. Specifically, NMDA receptor-mediated variance in NE release could be involved in the modulation of sensory-drive firing rates or gamma synchronization. All these proposed effects could increase the efficiency with which selected sensory information is processed.

In contrast with the proposed effects of NMDA receptor activation and NE reuptake blockade, we did not find effects of D-serine, ATX, or the combination treatment on sensorimotor processing speed (IT mode) in the present study. Baseline sensorimotor processing speeds (saline administration only) were slower in the present study in comparison to conditions with higher target salience (Redding et al., 2019; Sabol et al., 2003); therefore, it should have been possible to increase sensorimotor processing speeds. In other words, there should not have been a floor effect. We conclude that increasing NMDA receptor activation and blocking NE reuptake do not affect sensorimotor processing speed when processing efficiency is limited only by stimulus salience as in the current research.

While the present results suggest that NMDA receptor activation and NE reuptake blockade do not increase sensorimotor processing speeds that are limited only by target salience, it is unclear whether targeting these mechanisms could produce beneficial effects on sensorimotor processing speed under different task conditions. It is possible that sensorimotor processing speeds could be increased when they are limited by the competing influences of extraneous sensory information. For example, the *GANE* model proposed that NMDA receptor activation could influence the release of NE and resulting effects on firing rates or gamma synchronization, two mechanisms thought to promote the processing of selected information while suppressing the processing of irrelevant information. Under the conditions used in the present research, there were no competing sources of sensory information that needed to be

suppressed. Future research should address the impact of NMDA receptor activation, NE reuptake blockade, or both treatments on sensorimotor processing speed when target stimuli are presented alongside competing sources of sensory stimulation.

Investigations of Possible Synergy Between D-serine and Atomoxetine

The present study explored the potential beneficial effects of a combination treatment increasing NMDA receptor activation and synaptic NE levels relative to either treatment on its own. Future studies should address possible synergy between drugs targeting NMDA receptors and synaptic NE levels. This could be accomplished on a basic level by testing the interaction between the effects of D-serine and ATX. There was no such interaction between the effects of D-serine and ATX in the present experiments; however, these experiments were not designed to test for this interaction. Caution should therefore be applied to judging the lack of an interaction in the present study. Additional subjects would be required to attain sufficient power for this test. Importantly, the effects of a combination treatment (i.e., additivity vs. synergy) can depend on the ratio of the two drugs (e.g., Tallarida & Raffa, 1995). In the present study, we only tested combination treatments at two ratios (ATX:D-serine at 0.5 mg/kg:100 mg/kg and 0.3 mg/kg:125 mg/kg in Experiments 2 and 3, respectively) and only one ratio was tested in drug-naïve animals (Experiment 3). Future studies could systematically investigate the effects of these drugs at different ratios to determine if synergistic effects on attention could be attained alongside reduced side-effects.

Perhaps the best approach to address the question of additivity versus synergy between D-serine and ATX would be to perform an isobolographic analysis (Tallarida, 2000, 2011). Dose-response analyses could be performed for both drugs individually to determine the doses required to produce a specified change (e.g., ED_{50}) in the dependent variable of interest (e.g., IT

mode or IT devmode). These data could then be used to construct a function referred to as an isobol that predicts the doses of a combination treatment required to produce the predetermined additive effect on IT devmode (i.e., equivalent to ED_{50}) at a given ratio of the two drugs. Experimental dose-response determinations could be performed for the combination treatment itself at different ratios of the two drugs (i.e., 1:2, 1:1, 2:1). The data for each ratio could then be subjected to dose-response analyses to determine ED_{50} for that ratio. The doses at a particular ratio predicted by the isobol function to have the predetermined additive effect (ED_{50}) would be compared to the doses determined to have this effect by experimental dose-response analysis of the combination treatment at that same ratio. Ratios that produce the predetermined effect at the doses predicted by the isobol function are considered additive. Ratios that produce the predetermined effect at lower doses than predicted are considered to have synergistic or super-additive effects. On the other hand, ratios that produce the predetermined effect at higher doses are considered to have sub-additive effects. Importantly, it is possible for some ratios to be synergistic while others are merely additive or even sub-additive.

An isobolographic analysis was originally proposed for the present research; however, after the collection of dose-response data for D-serine, it became clear that this approach would require the collection of additional data due to high variability in the measure of attentional lapses (IT devmode). Increased variability in IT devmode reduces the precision of ED_{50} estimates that are critical for the final tests of additivity. The aim of the present research was shifted to address whether the addition of D-serine to ATX could enhance beneficial effects on attentional lapses without enhancing unwanted side-effects related to movement speed, motivation, or sedation. This line of research could be improved by conducting a systematic

isobolographic analysis for the effects of D-serine and ATX on attentional lapses using additional rats and/or additional data.

Investigations in Rat Models of Neurological Disorders

We conducted the present research to explore the potential of targeting specific neurotransmitter and neuromodulator systems to improve behavioral measures of attentional lapses. Our primary aim is to translate our findings into knowledge that benefits people experiencing impaired attention due to neurological disorders, such as attention-deficit/hyperactivity disorder (ADHD) or schizophrenia. However, we used healthy rats in the present research to study the effects of potential treatments on attentional lapses. Building on the foundation provided by the present work, the translational value of this line of research could be improved by studying behavior in rat models of relevant neurological disorders.

Spontaneously hypertensive rats are commonly used as a model of ADHD as they demonstrate the hallmark behavioral pattern of the ADHD-combined subtype, including hyperactivity, impulsivity, and impaired attention (Johansen et al., 2005, 2005; Li et al., 2007; Sagvolden, 2000; Sagvolden et al., 1998, 2005). These rats can also be used to model the predominately inattentive subtype of ADHD (Sagvolden et al., 2009). Alterations in genes related to the expression of NMDA receptor subunits (DasBanerjee et al., 2008) could be related to impaired NMDA receptor function reported in the prefrontal cortex of spontaneously hypertensive rats (Lehohla et al., 2004). Interestingly, glutamate-stimulated NE release *in vitro* involved NMDA receptors in slices from spontaneously hypertensive rats but not in slices from healthy controls (Howells & Russell, 2008), suggesting that NMDA receptors could be especially important for NE release in spontaneously hypertensive rats. Blunted NMDA receptor function in spontaneously hypertensive rats could reduce the ability of target-evoked NE release

to facilitate the processing of behaviorally relevant sensory information, thereby leading to impaired attention. This thinking could be tested further using D-serine or a combination of D-serine and ATX in spontaneously hypertensive rats performing the 2CRTT. The discovery of beneficial effects in this rat model of ADHD could enhance the translational value of the present approach.

Future Directions

The present research was based on theories outlining possible roles for NMDA receptor activation and subsequent effects on target-evoked NE release during attention. Some of these propositions require additional support, providing opportunities for future research. Several notable questions remain unanswered. During attention, does NMDA receptor activation support the modulation of endogenous and sensory-driven neural activity in frontal, parietal, and visual cortical areas of the visual processing system? Does NMDA receptor activation determine target-evoked NE release? Does target-evoked NE release support attention via the modulation of firing rates and gamma synchronization? What specific roles do NE receptor subtypes (e.g., β-1 and α-2) play in the modulation of sensory-driven firing rates and gamma synchronization in these areas? Finally, how do these proposed NMDA receptor and NE-mediated effects relate to behavioral measures of attention? Future research could address these questions in behaving animal models by taking advantage of electrophysiology to simultaneously record neural activity in the LC and cortex, electrical stimulation or optogenetics to manipulate neural activity in the LC, microscopy and fluorescent biosensors to image cortical NE release, and intracortical pharmacology to probe the involvement of specific receptors.

Linking Behavior to LC Activity in Monkeys

Future work could begin by *recording* or *manipulating* LC activity to determine effects on behavioral measures of attention. Multi-unit activity (MUA) and local field potentials (LFP) could be recorded from the LC in non-human primate or rodent models; however, physical limitations make this approach more difficult in awake rodent models using current electrode technologies. As described by the *Adaptive Gain* theory (Aston-Jones & Cohen, 2005), recordings from the LC of monkeys would be expected to show reduced tonic firing and enhanced phasic responses to target stimuli when animals are attentive. Periods of enhanced tonic firing during attention would likely be reflected in impaired performance (Aston-Jones et al., 1994; Usher et al., 1999), while reduced tonic firing would likely translate to enhanced performance (Aston-Jones et al., 1994, 1999). Phasic LC firing in response to target stimuli would be expected to promote target detection and therefore be associated with enhanced performance (Aston-Jones et al., 1994, 1999).

Direct electrical microstimulation could then be used to manipulate LC activity and NE release. This technique is somewhat imprecise due to excitation of many neurons surrounding the stimulation site. Precision could be especially important considering recent evidence pointing to heterogeneity of noradrenergic projections from the LC (Chandler et al., 2014, 2019; Totah et al., 2019). Despite a lack of selectivity, electrical stimulation of the monkey LC preceding target presentation would be expected to impair performance by inducing false alarms. In contrast, electrical stimulation following target presentation would be expected to enhance performance by triggering additional NE release and facilitating target detection.

Linking Behavior to LC Activity and NE Release Using Rats

Many powerful tools are currently available for rodent research, including optogenetics for manipulating LC activity and fluorescent biosensors for imaging NE release. Different

colored retroactive fluorescent tracers could first be injected into relevant parts of the rat cortex (e.g., posterior parietal and visual cortex). Microscopy could then be used to image the expression of the fluorescent tracers in the LC, revealing the degree of overlap between LC ensembles projecting to different cortical areas (as in Uematsu et al., 2017). As suggested by this study, LC ensembles projecting to different cortical areas would be expected to have relatively little overlap. Optogenetic tools could then be used to directly excite or inhibit selected ensembles of neurons in the LC of behaving rats. The effects of LC activity on cortical NE release could then be confirmed with millisecond precision using fluorescent biosensors (Feng et al., 2019) in combination with two-photon microscopy in rats performing head-fixed attention tasks.

Cortical NE release would be expected to reflect the manipulation of LC activity with predictable effects on behavior. Tonic optogenetic stimulation of LC activity would be expected to increase cortical NE release prior to target presentations. These epochs would be expected to correspond with poorer performance due to increased distractibility. In contrast, phasic optogenetic excitation following target presentation could enhance the release of NE and improve performance by facilitating the processing of targets. Optogenetic inhibition of LC firing would be expected to impair performance by attenuating target-evoked NE release in the cortex.

Linking Behavior to the Effects of LC Firing on Cortical Neural Activity

The effects of LC activity on cortical neural activity could then be determined using recordings of MUA and LFPs in cortical areas and the synchronization between these areas. Activity could be recorded simultaneously in the LC and regions of visual, parietal, and frontal cortices in monkeys or rodents performing attention tasks. Periods of reduced tonic firing during

attention (monkeys) would be expected to correspond with reduced firing rates or gamma synchronization in the cortex. We predict this pattern would be associated with improved performance due to reduced distractibility. On the other hand, increased tonic firing (monkeys) or tonic optogenetic excitation of the LC (rodents) would be expected to enhance cortical firing rates or gamma synchronization prior to target presentation. This enhanced baseline cortical activity would be expected to correspond with increased distractibility and would therefore be expected to impair performance. The effects of increased tonic LC activity could be especially strong in the presence of distractors. Phasic LC firing in response to target stimuli (monkeys) or optogenetic excitation of the LC following target presentation (rodents) would be expected to enhance sensory-driven firing rates or gamma synchronization in cortical areas. Furthermore, increased NE release following phasic LC firing could enhance gamma synchronization between cortical areas to facilitate communication of sensory information across the visual processing system. These predicted effects on cortical activity would be expected to improve target detection and therefore improve performance measures in tests of attention. In contrast, optogenetic inhibition of cortically projecting LC ensembles (rodents) would be expected to reduce NE release, thereby preventing NE-mediated modulation of neural activity. This manipulation would be expected to impair performance by disrupting target detection.

Linking Behavior to the Effects of NMDA and NE Receptors on Cortical Neural Activity

Intracortical administration of selected antagonists could be used to test the involvement of NMDA receptors and NE receptor subtypes in modulating firing rates or gamma synchronization recorded in the cortex. Direct administration of an NMDA antagonist into selected areas of cortex in monkeys or rats performing visuospatial attention tasks would be predicted to attenuate the endogenous activity that precedes visual stimulation. Antagonism of

NMDA receptors could also prevent the enhancement of sensory-driven gamma synchronization or the reduction of noise correlations that would be expected to occur during attention. Finally, the blockade of NMDA receptors could also prevent the modulation of gain by blunting target-evoked NE release and therefore reducing its effects on sensory-driven firing rates or gamma synchronization. Administration of an NMDA receptor antagonist could be used in combination with fluorescent biosensors to further probe the involvement of NMDA receptors in cortical NE release. Due to disruption of one or a combination of the proposed roles for NMDA receptors (maintenance of endogenous activity, modulation of sensory-driven activity, or mediating target-evoked NE release), NMDA receptor antagonism would be expected to impair performance.

Selective antagonists could also be used to test the involvement of specific NE receptor subtypes in the enhancement of gain via modulation of firing rates or gamma synchronization. Administration of a NE β-1 receptor antagonist into the cortex would be predicted to attenuate the positive modulatory effects of NE release. Specifically, blockade of β-1 receptors in the cortex could prevent the enhancement of sensory-driven firing rates or gamma synchronization in neurons communicating task-relevant information. This manipulation would be expected to impair performance by preventing the facilitated processing of attended sensory information. Application of an α-2 antagonist into the cortex would be predicted to attenuate the negative modulatory effects of NE release. In other words, blockade of α-2 receptors could prevent the suppression of sensory-driven firing rates or gamma synchronization in neurons that communicate irrelevant sensory information. This manipulation could impair performance by preventing the suppression of unattended sensory information, especially if salient distractors are presented in tandem with the target stimulus.

Summary of Future Directions

Current theories describing potential roles for NMDA receptor activation and NE-mediated neuromodulation in attention point to several unanswered questions. Researchers currently have a vast toolbox comprising non-human primate and rodent models, behavioral paradigms, and electrophysiological, optogenetic, and pharmacological techniques that could be used to address these questions. This research will undoubtedly be important for understanding not only how attention functions to help us perceive the world around us, but also how the complex systems that support attention could be disrupted in certain neurological disorders.

Conclusion

Attention shapes our perception of the world by selecting the most relevant information from the complex array that we are often presented with in naturalistic scenes. During attention, modulation of endogenous neural activity occurs in the frontal, parietal, and visual cortical areas that are specialized for processing selected sensory information. The top-down feedback that is associated with the modulation of endogenous neural activity could function as a *content filter* for perception that facilitates the bottom-up processing of expected sensory information. The modulation of endogenous neural activity and therefore the maintenance of the content filter could be mediated by the activation of NMDA receptors. Consistent with this thinking, we report reduced attentional lapses as measured by IT devmode following administration of the NMDA glycine-binding site agonist, D-serine, in rats performing a 2CRTT. This finding supports the notion that NMDA receptor activation supports the functioning of the content filter, thereby increasing the likelihood that selected sensory information is processed efficiently.

During attention, noradrenergic neurons in the LC fire phasic bursts in response to target stimuli. This target-evoked NE release and its effects on gain (Servan-Schreiber et al., 1990) could function as a *temporal filter* for perception to ensure that expected sensory information is

detected only when present (Aston-Jones & Cohen, 2005). Such effects could protect against false alarms and increase the likelihood that selected sensory information is processed efficiently when it appears. Consistent with this thinking, we found reduced attentional lapses following the administration of the NE reuptake inhibitor, ATX. Increasing synaptic NE levels could promote the target-evoked release of NE (Bari & Aston-Jones, 2013), thereby reducing the number of lapses during which sensory information is processed with lower efficiency. Furthermore, we report reduced premature response rates following ATX administration, consistent with the thinking that false alarms are reduced by the target-dependence of NE release.

In the present study, we also tested a combination treatment targeting both NMDA receptor activation (D-serine) and synaptic NE levels (ATX). The combination treatment was found to reduce attentional lapses with greater efficacy than either treatment alone. These findings are consistent with the proposed roles of NMDA receptor activation and target-evoked NE release in supporting the content and temporal filtering of sensory processing during attention.

In addition to ensuring that selected sensory information is processed efficiently at appropriate times, NMDA receptor activation or target-evoked NE release could enhance the maximum efficiency at which attended sensory information can be processed. For example, sensory processing could be promoted by effects on sensory-driven gamma synchronization or noise correlations which could involve NMDA receptor activation. NMDA receptor activation could also play a role in determining the effects of target-evoked NE release (Mather et al., 2016). Activation of NMDA receptors on LC projections could boost NE release to enhance neural activity (firing rates or gamma synchronization) related to the processing of attended sensory information. On the other hand, lack of NMDA receptor activation could inhibit NE

release to suppress neural activity related to the processing of unattended or ignored sensory information. These effects could lead to more efficient and therefore faster processing of attended sensory information. In contrast with these ideas, we found no effects of D-serine, ATX, or the combination treatment on IT mode, a measure of sensorimotor processing speed.

The effects of D-serine and ATX on IT devmode suggest that NMDA receptors and target-evoked NE release enhance the likelihood that sensory information will be processed efficiently by rats performing the 2CRTT. On the other hand, the complete lack of effects on IT mode suggests that NMDA receptor activation and target-evoked NE release do not strongly influence the peak efficiency at which attended sensory information can be processed under the conditions tested in the present study. Future work will be required to determine whether targeting these mechanisms could increase the speed of sensorimotor processing under different task conditions (e.g., in the presence of distracting sensory information).

In conclusion, the present findings provide further support for the distribution analysis developed by Sabol and colleagues (2003). This approach can be used to simultaneously test for effects on attentional lapses and sensorimotor processing speed in rodents in a manner that reflects current clinical techniques (Tamm et al., 2012). In support of our hypotheses, the present results suggest that D-serine could be an effective treatment for impaired sustained attention. The present results also suggest that a combination treatment composed of D-serine and ATX at relatively low doses could effectively reduce attentional lapses without increasing unwanted side-effects related to nephrotoxicity (D-serine) or movement speed, motivation, and sedation (ATX). These results could be important first steps toward the development of safer and more effective treatments for people experiencing impairments in sustained attention due to various neurological disorders.

REFERENCES

Abbott, L. F., & Dayan, P. (1999). The Effect of Correlated Variability on the Accuracy of a Population Code. *Neural Computation*, *11*(1), 91–101. https://doi.org/10.1162/089976699300016827

Adell, A., Jiménez-Sánchez, L., López-Gil, X., & Romón, T. (2012). Is the Acute NMDA Receptor Hypofunction a Valid Model of Schizophrenia? *Schizophrenia Bulletin*, *38*(1), 9–14. https://doi.org/10.1093/schbul/sbr133

Ainsworth, M., Lee, S., Cunningham, M. O., Traub, R. D., Kopell, N. J., & Whittington, M. A. (2012). Rates and Rhythms: A Synergistic View of Frequency and Temporal Coding in Neuronal Networks. *Neuron*, *75*(4), 572–583. https://doi.org/10.1016/j.neuron.2012.08.004

Albares, M., Criaud, M., Wardak, C., Nguyen, S. C. T., Ben Hamed, S., & Boulinguez, P. (2011). Attention to baseline: Does orienting visuospatial attention really facilitate target detection? *Journal of Neurophysiology*, *106*(2), 809–816. https://doi.org/10.1152/jn.00206.2011

Amitai, N., Semenova, S., & Markou, A. (2007). Cognitive-disruptive effects of the psychotomimetic phencyclidine and attenuation by atypical antipsychotic medications in rats. *Psychopharmacology*, *193*(4), 521–537. https://doi.org/10.1007/s00213-007-0808-x

Andersen, R., Bracewell, R., Barash, S., Gnadt, J., & Fogassi, L. (1990). Eye position effects on visual, memory, and saccade-related activity in areas LIP and 7a of macaque. *The Journal of Neuroscience*, *10*(4), 1176–1196. https://doi.org/10.1523/JNEUROSCI.10-04-01176.1990

Anderson, P. M., Jones, N. C., O'Brien, T. J., & Pinault, D. (2017). The N-Methyl d-Aspartate Glutamate Receptor Antagonist Ketamine Disrupts the Functional State of the Corticothalamic Pathway. *Cerebral Cortex*, *27*, 3172–3185. https://doi.org/10.1093/cercor/bhw168

Anderson, P. M., Pinault, D., O'Brien, T. J., & Jones, N. C. (2014). Chronic administration of antipsychotics attenuates ongoing and ketamine-induced increases in cortical γ oscillations. *International Journal of Neuropsychopharmacology*, *17*(11), 1895–1904. https://doi.org/10.1017/S1461145714000959

Anton-Erxleben, K., & Carrasco, M. (2013). Attentional enhancement of spatial resolution: Linking behavioural and neurophysiological evidence. *Nature Reviews. Neuroscience*, *14*(3), 188–200. https://doi.org/10.1038/nrn3443

Arieli, A., Sterkin, A., Grinvald, A., & Aertsen, A. D. (1996). Dynamics of Ongoing Activity: Explanation of the Large Variability in Evoked Cortical Responses. *Science*, *273*(5283), 1868–1871.

Armstrong, K. M., Chang, M. H., & Moore, T. (2009). Selection and Maintenance of Spatial Information by Frontal Eye Field Neurons. *Journal of Neuroscience*, *29*(50), 15621–15629. https://doi.org/10.1523/JNEUROSCI.4465-09.2009

Armstrong, K. M., & Moore, T. (2007). Rapid enhancement of visual cortical response discriminability by microstimulation of the frontal eye field. *Proceedings of the National Academy of Sciences*, *104*(22), 9499–9504. https://doi.org/10.1073/pnas.0701104104

Armstrong, Katherine M., Fitzgerald, J. K., & Moore, T. (2006). Changes in Visual Receptive Fields with Microstimulation of Frontal Cortex. *Neuron*, *50*(5), 791–798. https://doi.org/10.1016/j.neuron.2006.05.010

Arnsten, A. F. T., & Goldman-Rakic, P. S. (1984). Selective prefrontal cortical projections to the region of the locus coeruleus and raphe nuclei in the rhesus monkey. *Brain Research*, *306*(1), 9–18. https://doi.org/10.1016/0006-8993(84)90351-2

Asherson, P., Bushe, C., Saylor, K., Tanaka, Y., Deberdt, W., & Upadhyaya, H. (2014). Efficacy of atomoxetine in adults with attention deficit hyperactivity disorder: An integrated analysis of the complete database of multicenter placebo-controlled trials. *Journal of Psychopharmacology*, *28*(9), 837–846. https://doi.org/10.1177/0269881114542453

Astafiev, S. V., Shulman, G. L., Stanley, C. M., Snyder, A. Z., Van Essen, D. C., & Corbetta, M. (2003). Functional Organization of Human Intraparietal and Frontal Cortex for Attending, Looking, and Pointing. *The Journal of Neuroscience*, *23*(11), 4689–4699. https://doi.org/10.1523/JNEUROSCI.23-11-04689.2003

Aston-Jones, G, & Bloom, F. E. (1981). Norepinephrine-containing locus coeruleus neurons in behaving rats exhibit pronounced responses to non-noxious environmental stimuli. *The Journal of Neuroscience*, *1*(8), 887–900.

Aston-Jones, G, Rajkowski, J., Kubiak, P., & Alexinsky, T. (1994a). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *The Journal of Neuroscience*, *14*(7), 4467–4480. https://doi.org/10.1523/JNEUROSCI.14-07-04467.1994

Aston-Jones, G, Rajkowski, J., Kubiak, P., & Alexinsky, T. (1994b). Locus coeruleus neurons in monkey are selectively activated by attended cues in a vigilance task. *The Journal of Neuroscience*, *14*(7), 4467–4480.

Aston-Jones, Gary, & Cohen, J. D. (2005). An integrative theory of locus coeruleus-norepinephrine function: Adaptive gain and optimal performance. *Annual Review of Neuroscience*, *28*, 403–450.

Aston-Jones, Gary, Rajkowski, J., & Cohen, J. (1999). Role of locus coeruleus in attention and behavioral flexibility. *Biological Psychiatry*, *46*(9), 1309–1320.

Astrand, E., Wardak, C., Baraduc, P., & Ben Hamed, S. (2016). Direct Two-Dimensional Access to the Spatial Location of Covert Attention in Macaque Prefrontal Cortex. *Current Biology*, *26*(13), 1699–1704. https://doi.org/10.1016/j.cub.2016.04.054

Atkinson, B. N., Bell, S. C., De Vivo, M., Kowalski, L. R., Lechner, S. M., Ognyanov, V. I., Tham, C. S., Tsai, C., Jia, J., Ashton, D., & Klitenick, M. A. (2001). ALX 5407: A potent, selective inhibitor of the hGlyT1 glycine transporter. *Molecular Pharmacology*, *60*(6), 1414–1420.

Auclair, A. L., Besnard, J., Newman-Tancredi, A., & Depoortère, R. (2009). The five choice serial reaction time task: Comparison between Sprague–Dawley and Long–Evans rats on acquisition of task, and sensitivity to phencyclidine. *Pharmacology Biochemistry and Behavior*, *92*(2), 363–369. https://doi.org/10.1016/j.pbb.2009.01.005

Avellar, M., Scoriels, L., Madeira, C., Vargas-Lopes, C., Marques, P., Dantas, C., Manhães, A. C., Leite, H., & Panizzutti, R. (2016). The effect of D-serine administration on cognition and mood in older adults. *Oncotarget*, *7*(11), 11881–11888.

Averbeck, B. B., Latham, P. E., & Pouget, A. (2006). Neural correlations, population coding and computation. *Nature Reviews Neuroscience*, *7*(5), 358–366. https://doi.org/10.1038/nrn1888

Averbeck, B. B., & Lee, D. (2006). Effects of Noise Correlations on Information Encoding and Decoding. *Journal of Neurophysiology*, *95*(6), 3633–3644. https://doi.org/10.1152/jn.00919.2005

Awh, E., Jonides, J., & Reuter-Lorenz, P. (1998). Rehearsal in spatial working memory. *Journal of Experimental Psychology. Human Perception and Performance*, *24*(3), 780. https://doi.org/10.1037/0096-1523.24.3.780

Awh, E., Vogel, E. K., & Oh, S.-H. (2006). Interactions between attention and working memory. *Neuroscience*, *139*(1), 201–208. https://doi.org/10.1016/j.neuroscience.2005.08.023

Awh, Edward, Anllo-Vento, L., & Hillyard, S. A. (2000). The Role of Spatial Selective Attention in Working Memory for Locations: Evidence from Event-Related Potentials. *Journal of Cognitive Neuroscience*, *12*(5), 840–847. https://doi.org/10.1162/089892900562444

Awh, Edward, & Jonides, J. (2001). Overlapping mechanisms of attention and spatial working memory. *Trends in Cognitive Sciences*, *5*(3), 119–126.

Awh, Edward, Jonides, J., Smith, E. E., Buxton, R. B., Frank, L. R., Love, T., Wong, E. C., & Gmeindl, L. (1999). Rehearsal in Spatial Working Memory: Evidence From Neuroimaging. *Psychological Science*, *10*(5), 433–437.

Azouz, R., & Gray, C. M. (2003). Adaptive Coincidence Detection and Dynamic Gain Control in Visual Cortical Neurons In Vivo. *Neuron*, *37*(3), 513–523. https://doi.org/10.1016/S0896-6273(02)01186-8

Bado, P., Madeira, C., Vargas-Lopes, C., Moulin, T. C., Wasilewska-Sampaio, A. P., Maretti, L., de Oliveira, R. V., Amaral, O. B., & Panizzutti, R. (2011). Effects of low-dose D-serine on recognition and working memory in mice. *Psychopharmacology*, *218*(3), 461–470.

Bai, Y., Zhou, L., Wu, X., & Dong, Z. (2014). D-serine enhances fear extinction by increasing GluA2-containing AMPA receptor endocytosis. *Behavioural Brain Research*, *270*, 223–227.

Bair, W., Zohary, E., & Newsome, W. T. (2001). Correlated Firing in Macaque Visual Area MT: Time Scales and Relationship to Behavior. *The Journal of Neuroscience*, *21*(5), 1676–1697. https://doi.org/10.1523/JNEUROSCI.21-05-01676.2001

Bari, A., & Aston-Jones, G. (2013). Atomoxetine modulates spontaneous and sensory-evoked discharge of locus coeruleus noradrenergic neurons. *Neuropharmacology*, *64*(1), 53–64. https://doi.org/10.1016/j.neuropharm.2012.07.020

Bari, A., Dalley, J. W., & Robbins, T. W. (2008). The application of the 5-choice serial reaction time task for the assessment of visual attentional processes and impulse control in rats. *Nature Protocols*, *3*(5), 759–767.

Barlow, R. L., Dalley, J. W., & Pekcec, A. (2018). Differences in trait impulsivity do not bias the response to pharmacological drug challenge in the rat five-choice serial reaction time task. *Psychopharmacology*, *235*(4), 1199–1209. https://doi.org/10.1007/s00213-018-4836-5

Barnes, S. A., Young, J. W., Bate, S. T., & Neill, J. C. (2016). Dopamine D1 receptor activation improves PCP-induced performance disruption in the 5C-CPT by reducing inappropriate responding. *Behavioural Brain Research*, *300*, 45–55. https://doi.org/10.1016/j.bbr.2015.11.035

Barone, P., Batardiere, A., Knoblauch, K., & Kennedy, H. (2000). Laminar Distribution of Neurons in Extrastriate Areas Projecting to Visual Areas V1 and V4 Correlates with the Hierarchical Rank and Indicates the Operation of a Distance Rule. *The Journal of Neuroscience*, *20*(9), 3263–3281. https://doi.org/10.1523/JNEUROSCI.20-09-03263.2000

Bartos, M., Vida, I., & Jonas, P. (2007). Synaptic mechanisms of synchronized gamma oscillations in inhibitory interneuron networks. *Nature Reviews Neuroscience*, *8*, 45–56.

Basar-Eroglu, C., Brand, A., Hildebrandt, H., Karolina Kedzior, K., Mathes, B., & Schmiedt, C. (2007). Working memory related gamma oscillations in schizophrenia patients. *International Journal of Psychophysiology*, *64*(1), 39–45. https://doi.org/10.1016/j.ijpsycho.2006.07.007

Bashinski, H. S., & Bacharach, V. R. (1980). Enhancement of perceptual sensitivity as the result of selectively attending to spatial locations. *Perception & Psychophysics*, *28*(3), 241–248. https://doi.org/10.3758/BF03204380

Baviera, M., Invernizzi, R. W., & Carli, M. (2008). Haloperidol and clozapine have dissociable effects in a model of attentional performance deficits induced by blockade of NMDA receptors in the mPFC. *Psychopharmacology*, *196*(2), 269–280. https://doi.org/10.1007/s00213-007-0959-9

Beauchamp, M. S., Cox, R. W., & Deyoe, E. A. (1997). Graded Effects of Spatial and Featural Attention on Human Area MT and Associated Motion Processing Areas. *Journal of Neurophysiology*, *78*(1), 516–520. https://doi.org/10.1152/jn.1997.78.1.516

Beauchamp, M. S., Petit, L., Ellmore, T. M., Ingeholm, J., & Haxby, J. V. (2001). A Parametric fMRI Study of Overt and Covert Shifts of Visuospatial Attention. *NeuroImage*, *14*(2), 310–321. https://doi.org/10.1006/nimg.2001.0788

Bédard, A.-C. V., Stein, M. A., Halperin, J. M., Krone, B., Rajwan, E., & Newcorn, J. H. (2015). Differential impact of methylphenidate and atomoxetine on sustained attention in youth with attention-deficit/hyperactivity disorder. *Journal of Child Psychology and Psychiatry, and Allied Disciplines*, *56*(1), 40–48.

Berger, A. J., Dieudonné, S., & Ascher, P. (1998). Glycine uptake governs glycine site occupancy at NMDA receptors of excitatory synapses. *Journal of Neurophysiology*, *80*(6), 3336–3340.

Berridge, C. W, & Abercrombie, E. D. (1999). Relationship between locus coeruleus discharge rates and rates of norepinephrine release within neocortex as assessed by in vivo microdialysis. *Neuroscience*, *93*(4), 1263–1270. https://doi.org/10.1016/S0306-4522(99)00276-6

Berridge, Craig W. (2008). Noradrenergic Modulation of Arousal. *Brain Research Reviews*, *58*(1), 1–17. https://doi.org/10.1016/j.brainresrev.2007.10.013

Berridge, Craig W, & Waterhouse, B. D. (2003). The locus coeruleus–noradrenergic system: Modulation of behavioral state and state-dependent cognitive processes. *Brain Research Reviews*, *42*(1), 33–84. https://doi.org/10.1016/S0165-0173(03)00143-7

Besserve, M., Lowe, S. C., Logothetis, N. K., Schölkopf, B., & Panzeri, S. (2015). Shifts of Gamma Phase across Primary Visual Cortical Sites Reflect Dynamic Stimulus-Modulated Information Transfer. *PLOS Biology*, *13*(9), e1002257. https://doi.org/10.1371/journal.pbio.1002257

Bhakta, S. G., & Young, J. W. (2017). The 5 choice continuous performance test (5C-CPT): A novel tool to assess cognitive control across species. *Journal of Neuroscience Methods*, *292*, 53–60.

Bickler, P. E., & Hansen, B. M. (1996). Alpha 2-adrenergic agonists reduce glutamate release and glutamate receptor-mediated calcium changes in hippocampal slices during hypoxia. *Neuropharmacology*, *35*(6), 679–687.

Blatt, G. J., Andersen, R. A., & Stoner, G. R. (1990). Visual receptive field organization and cortico-cortical connections of the lateral intraparietal area (area LIP) in the macaque. *The Journal of Comparative Neurology*, *299*, 421–445.

Blondeau, C., & Dellu-Hagedorn, F. (2007). Dimensional analysis of ADHD subtypes in rats. *Biological Psychiatry*, *61*(12), 1340–1350. https://doi.org/10.1016/j.biopsych.2006.06.030

Börgers, C., & Kopell, N. (2003). Synchronization in Networks of Excitatory and Inhibitory Neurons with Sparse, Random Connectivity. *Neural Computation*, *15*(3), 509–538. https://doi.org/10.1162/089976603321192059

Börgers, C., & Kopell, N. J. (2008). Gamma Oscillations and Stimulus Selection. *Neural Computation*, *20*(2), 383–414. https://doi.org/10.1162/neco.2007.07-06-289

Bosman, C. A., Schoffelen, J.-M., Brunet, N., Oostenveld, R., Bastos, A. M., Womelsdorf, T., Rubehn, B., Stieglitz, T., De Weerd, P., & Fries, P. (2012). Attentional Stimulus Selection through Selective Synchronization between Monkey Visual Areas. *Neuron*, *75*(5), 875–888. https://doi.org/10.1016/j.neuron.2012.06.037

Bouret, S., & Sara, S. (2004). Reward expectation, orientation of attention and locus coeruleus-medial frontal cortex interplay during learning. *The European Journal of Neuroscience*, *20*, 791–802. https://doi.org/10.1111/j.1460-9568.2004.03526.x

Bouret, S., & Sara, S. J. (2002). Locus coeruleus activation modulates firing rate and temporal organization of odour-induced single-cell responses in rat piriform cortex. *European Journal of Neuroscience*, *16*(12), 2371–2382. https://doi.org/10.1046/j.1460-9568.2002.02413.x

Bouret, S., & Sara, S. J. (2005). Network reset: A simplified overarching theory of locus coeruleus noradrenaline function. *Trends in Neurosciences*, *28*(11), 574–582. https://doi.org/10.1016/j.tins.2005.09.002

Brefczynski, J. A., & DeYoe, E. A. (1999). A physiological correlate of the "spotlight" of visual attention. *Nature Neuroscience*, *2*(4), 370–374. https://doi.org/10.1038/7280

Bressler, S. L., Tang, W., Sylvester, C. M., Shulman, G. L., & Corbetta, M. (2008). Top-Down Control of Human Visual Cortex by Frontal and Parietal Cortex in Anticipatory Visual Spatial Attention. *Journal of Neuroscience*, *28*(40), 10056–10061. https://doi.org/10.1523/JNEUROSCI.1776-08.2008

Broadbent, D. E. (1958). The effects of noise on behaviour. In *Perception and communication* (pp. 81–107). Pergamon Press. https://doi.org/10.1037/10037-005

Brunel, N., & Wang, X.-J. (2001). Effects of Neuromodulation in a Cortical Network Model of Object Working Memory Dominated by Recurrent Inhibition. *Journal of Computational Neuroscience*, *11*(1), 63–85.

Brunel, N., & Wang, X.-J. (2003). What Determines the Frequency of Fast Network Oscillations With Irregular Neural Discharges? I. Synaptic Dynamics and Excitation-Inhibition Balance. *Journal of Neurophysiology*, *90*(1), 415–430. https://doi.org/10.1152/jn.01095.2002

Brunet, N., Bosman, C. A., Roberts, M., Oostenveld, R., Womelsdorf, T., De Weerd, P., & Fries, P. (2015). Visual Cortical Gamma-Band Activity During Free Viewing of Natural Images. *Cerebral Cortex*, *25*(4), 918–926. https://doi.org/10.1093/cercor/bht280

Brunet, N. M., & Fries, P. (2019). Human visual cortical gamma reflects natural image structure. *NeuroImage*, *200*, 635–643. https://doi.org/10.1016/j.neuroimage.2019.06.051

Buckner, R. L., Bandettini, P. A., O'Craven, K. M., Savoy, R. L., Petersen, S. E., Raichle, M. E., & Rosen, B. R. (1996). Detection of cortical activation during averaged single trials of a cognitive task using functional magnetic resonance imaging. *Proceedings of the National Academy of Sciences*, *93*(25), 14878–14883. https://doi.org/10.1073/pnas.93.25.14878

Buckner, Randy L. (1998). Event-related fMRI and the hemodynamic response. *Human Brain Mapping*, *6*(5–6), 373–377. https://doi.org/10.1002/(SICI)1097-0193(1998)6:5/6<373::AID-HBM8>3.0.CO;2-P

Buehlmann, A., & Deco, G. (2008). The Neuronal Basis of Attention: Rate versus Synchronization Modulation. *Journal of Neuroscience*, *28*(30), 7679–7686. https://doi.org/10.1523/JNEUROSCI.5640-07.2008

Buehlmann, Andres, & Deco, G. (2010). Optimal Information Transfer in the Cortex through Synchronization. *PLOS Computational Biology*, *6*(9), e1000934. https://doi.org/10.1371/journal.pcbi.1000934

Buffalo, E. A., Fries, P., Landman, R., Buschman, T. J., & Desimone, R. (2011). Laminar differences in gamma and alpha coherence in the ventral stream. *Proceedings of the National Academy of Sciences*, *108*(27), 11262–11267. https://doi.org/10.1073/pnas.1011284108

Buffalo, E. A., Fries, P., Landman, R., Liang, H., & Desimone, R. (2010). A backward progression of attentional effects in the ventral stream. *Proceedings of the National Academy of Sciences*, *107*(1), 361–365. https://doi.org/10.1073/pnas.0907658106

Buschman, T. J., & Miller, E. K. (2007). Top-Down Versus Bottom-Up Control of Attention in the Prefrontal and Posterior Parietal Cortices. *Science*, *315*(5820), 1860–1862. https://doi.org/10.1126/science.1138071

Buschman, Timothy J., & Kastner, S. (2015). From Behavior to Neural Dynamics: An Integrated Theory of Attention. *Neuron*, *88*(1), 127–144. https://doi.org/10.1016/j.neuron.2015.09.017

Bushnell, M. C., Goldberg, M. E., & Robinson, D. L. (1981). Behavioral enhancement of visual responses in monkey cerebral cortex. I. Modulation in posterior parietal cortex related to selective visual attention. *Journal of Neurophysiology*, *46*(4), 755–772. https://doi.org/10.1152/jn.1981.46.4.755

Buzsáki, G. (2010). Neural Syntax: Cell Assemblies, Synapsembles, and Readers. *Neuron*, *68*(3), 362–385. https://doi.org/10.1016/j.neuron.2010.09.023

Buzsáki, G., Anastassiou, C. A., & Koch, C. (2012). The origin of extracellular fields and currents—EEG, ECoG, LFP and spikes. *Nature Reviews. Neuroscience*, *13*(6), 407–420. https://doi.org/10.1038/nrn3241

Buzsáki, G., & Wang, X.-J. (2012). Mechanisms of Gamma Oscillations. *Annual Review of Neuroscience*, *35*, 203–225. https://doi.org/10.1146/annurev-neuro-062111-150444

Bylund, D. B. (1992). Subtypes of α1- and α2-adrenergic receptors. *The FASEB Journal*, *6*(3), 832–839. https://doi.org/10.1096/fasebj.6.3.1346768

Bymaster, F. P., Katner, J. S., Nelson, D. L., Hemrick-Luecke, S. K., Threkeld, S. M., Heiligenstein, J. H., Gehlert, D., R., & Perry, K. W. (2002). Atomoxetine increases

extracellular level of norepinephrine and dopamine in prefrontal cortex of rat: A potential mechanism for efficacy in attention deficit/hyperactivity disorder. *Neuropsychopharmacology*, *27*(5), 699–711.

Caballero-Puntiverio, M., Lerdrup, L. S., Grupe, M., Larsen, C. W., Dietz, A. G., & Andreasen, J. T. (2019). Effect of ADHD medication in male C57BL/6J mice performing the rodent Continuous Performance Test. *Psychopharmacology*. https://doi.org/10.1007/s00213-019-5167-x

Calcagno, E, Carli, M., Baviera, M., & Invernizzi, R. W. (2009). Endogenous serotonin and serotonin2C receptors are involved in the ability of M100907 to suppress cortical glutamate release induced by NMDA receptor blockade. *Journal of Neurochemistry*, *108*(2), 521–532. https://doi.org/10.1111/j.1471-4159.2008.05789.x

Calcagno, E, Carli, M., & Invernizzi, R. W. (2006). The 5-HT1A receptor agonist 8-OH-DPAT prevents prefrontocortical glutamate and serotonin release in response to blockade of cortical NMDA receptors. *Journal of Neurochemistry*, *96*(3), 853–860. https://doi.org/10.1111/j.1471-4159.2005.03600.x

Cannon, J., McCarthy, M. M., Lee, S., Lee, J., Börgers, C., Whittington, M. A., & Kopell, N. (2014). Neurosystems: Brain rhythms and cognitive processing. *European Journal of Neuroscience*, *39*(5), 705–719. https://doi.org/10.1111/ejn.12453

Carlén, M., Meletis, K., Siegle, J. H., Cardin, J. A., Futai, K., Vierling-Claassen, D., Rühlmann, C., Jones, S. R., Deisseroth, K., Sheng, M., Moore, C. I., & Tsai, L.-H. (2012). A critical role for NMDA receptors in parvalbumin interneurons for gamma rhythm induction and behavior. *Molecular Psychiatry*, *17*(5), 537–548. https://doi.org/10.1038/mp.2011.31

Carli, M., Robbins, T. W., Evenden, J. L., & Everitt, B. J. (1983). Effects of lesions to ascending noradrenergic neurones on performance of a 5-choice serial reaction task in rats: Implications for theories of dorsal noradrenergic bundle function based on selective attention and arousal. *Behavioural Brain Research*, *9*(3), 361–380. https://doi.org/10.1016/0166-4328(83)90138-9

Carli, Mirjana, Baviera, M., Invernizzi, R. W., & Balducci, C. (2006). Dissociable Contribution of 5-HT 1A and 5-HT 2A Receptors in the Medial Prefrontal Cortex to Different Aspects of Executive Control such as Impulsivity and Compulsive Perseveration in Rats. *Neuropsychopharmacology*, *31*(4), 757–767. https://doi.org/10.1038/sj.npp.1300893

Carli, Mirjana, Calcagno, E., Mainini, E., Arnt, J., & Invernizzi, R. W. (2011). Sertindole restores attentional performance and suppresses glutamate release induced by the NMDA receptor antagonist CPP. *Psychopharmacology*, *214*(3), 625–637. https://doi.org/10.1007/s00213-010-2066-6

Carone, F. A., & Ganote, C. E. (1975). D-serine nephrotoxicity. The nature of proteinuria, glucosuria, and aminoaciduria in acute tubular necrosis. *Archives of Pathology*, *99*(12), 658–662.

Carrasco, M., Ling, S., & Read, S. (2004). Attention alters appearance. *Nature Neuroscience*, *7*(3), 308–313. https://doi.org/10.1038/nn1194

Cavada, C., & Goldman-Rakic, P. S. (1989). Posterior parietal cortex in rhesus monkey: I. Parcellation of areas based on distinctive limbic and sensory corticocortical connections. *The Journal of Comparative Neurology*, *287*(4), 393–421. https://doi.org/10.1002/cne.902870402

Ceglia, I., Carli, M., Baviera, M., Renoldi, G., Calcagno, E., & Invernizzi, R. W. (2004). The 5-HT2A receptor antagonist M100,907 prevents extracellular glutamate rising in response

to NMDA receptor blockade in the mPFC. *Journal of Neurochemistry*, *91*(1), 189–199. https://doi.org/10.1111/j.1471-4159.2004.02704.x
Chalk, M., Herrero, J. L., Gieselmann, M. A., Delicato, L. S., Gotthardt, S., & Thiele, A. (2010). Attention Reduces Stimulus-Driven Gamma Frequency Oscillations and Spike Field Coherence in V1. *Neuron*, *66*(1), 114–125. https://doi.org/10.1016/j.neuron.2010.03.013
Chamberlain, S. R., del Campo, N., Dowson, J., Müller, U., Clark, L., Robbins, T. W., & Sahakian, B. J. (2007a). Atomoxetine Improved Response Inhibition in Adults with Attention Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *62*(9), 977–984. https://doi.org/10.1016/j.biopsych.2007.03.003
Chamberlain, S. R., del Campo, N., Dowson, J., Müller, U., Clark, L., Robbins, T. W., & Sahakian, B. J. (2007b). Atomoxetine Improved Response Inhibition in Adults with Attention Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *62*(9), 977–984. https://doi.org/10.1016/j.biopsych.2007.03.003
Chandler, D., Gao, W.-J., & Waterhouse, B. D. (2014). Heterogeneous organization of the locus coeruleus projections to prefrontal and motor cortices. *Proceedings of the National Academy of Sciences*, *111*(18), 6816–6821. https://doi.org/10.1073/pnas.1320827111
Chandler, D., Jensen, P., McCall, J. G., Pickering, A. E., Schwarz, L. A., & Totah, N. K. (2019). Redefining Noradrenergic Neuromodulation of Behavior: Impacts of a Modular Locus Coeruleus Architecture. *The Journal of Neuroscience*, *39*(42), 8239–8249. https://doi.org/10.1523/JNEUROSCI.1164-19.2019
Chang, C. C., Goshima, Y., & Misu, Y. (1986). Evidence for the Existence of Stereoselective Presynaptic β1-Adrenoceptors on Noradrenergic and Dopaminergic Neurons in the Rat Hypothalamus. *The Japanese Journal of Pharmacology*, *42*(3), 447–449. https://doi.org/10.1254/jjp.42.447
Chang, M. H., Armstrong, K. M., & Moore, T. (2012). Dissociation of Response Variability from Firing Rate Effects in Frontal Eye Field Neurons during Visual Stimulation, Working Memory, and Attention. *Journal of Neuroscience*, *32*(6), 2204–2216. https://doi.org/10.1523/JNEUROSCI.2967-11.2012
Chen, L., Muhlhauser, M., & Yang, C. R. (2003). Glycine tranporter-1 blockade potentiates NMDA-mediated responses in rat prefrontal cortical neurons in vitro and in vivo. *Journal of Neurophysiology*, *89*(2), 691–703.
Cheun, J. E., & Yeh, H. H. (1992). Modulation of GABAA receptor-activated current by norepinephrine in cerebellar purkinje cells. *Neuroscience*, *51*(4), 951–960. https://doi.org/10.1016/0306-4522(92)90532-7
Chiba, A. A., Bucci, D. J., Holland, P. C., & Gallagher, M. (1995). Basal forebrain cholinergic lesions disrupt increments but not decrements in conditioned stimulus processing. *The Journal of Neuroscience*, *15*(11), 7315–7322.
Cho, R. Y., Konecky, R. O., & Carter, C. S. (2006). Impairments in frontal cortical synchrony and cognitive control in schizophrenia. *Proceedings of the National Academy of Sciences*, *103*(52), 19878–19883. https://doi.org/10.1073/pnas.0609440103
Clayton, M. S., Yeung, N., & Cohen Kadosh, R. (2015). The roles of cortical oscillations in sustained attention. *Trends in Cognitive Sciences*, *19*(4), 188–195. https://doi.org/10.1016/j.tics.2015.02.004
Cohen, M. R., & Kohn, A. (2011). Measuring and interpreting neuronal correlations. *Nature Neuroscience*, *14*(7), 811–819. https://doi.org/10.1038/nn.2842

Cohen, M. R., & Maunsell, J. H. (2009). Attention improves performance primarily by reducing interneuronal correlations. *Nature Neuroscience*, *12*(12), 1594–1600. https://doi.org/10.1038/nn.2439

Cohen, S. M., Tsien, R. W., Goff, D. C., & Halassa, M. M. (2015). The impact of NMDA Receptor hypofunction on GABAergic interneurons in the pathophysiology of schizophrenia. *Schizophrenia Research*, *167*(0), 98–107. https://doi.org/10.1016/j.schres.2014.12.026

Colby, C. L., Duhamel, J. R., & Goldberg, M. E. (1996). Visual, presaccadic, and cognitive activation of single neurons in monkey lateral intraparietal area. *Journal of Neurophysiology*, *76*(5), 2841–2852. https://doi.org/10.1152/jn.1996.76.5.2841

Colby, Carol L., & Goldberg, M. E. (1999). Space and attention in parietal cortex. *Annual Review of Neuroscience*, *22*(1), 319–349. https://doi.org/10.1146/annurev.neuro.22.1.319

Compte, A, Brunel, N., Goldman-Rakic, P. S., & Wang, X. J. (2000). Synaptic mechanisms and network dynamics underlying spatial working memory in a cortical network model. *Cerebral Cortex (New York, N.Y.: 1991)*, *10*(9), 910–923.

Compte, Albert, Brunel, N., Goldman-Rakic, P. S., & Wang, X.-J. (2000). Synaptic Mechanisms and Network Dynamics Underlying Spatial Working Memory in a Cortical Network Model. *Cerebral Cortex*, *10*(9), 910–923. https://doi.org/10.1093/cercor/10.9.910

Conti, F., Barbaresi, P., Melone, M., & Ducati, A. (1999). Neuronal and Glial Localization of NR1 and NR2A/B Subunits of the NMDA Receptor in the Human Cerebral Cortex. *Cerebral Cortex*, *9*(2), 110–120. https://doi.org/10.1093/cercor/9.2.110

Corbetta, M., Kincade, J. M., & Shulman, G. L. (2002). Neural Systems for Visual Orienting and Their Relationships to Spatial Working Memory. *Journal of Cognitive Neuroscience*, *14*(3), 508–523. https://doi.org/10.1162/089892902317362029

Corbetta, M, Miezin, F., Shulman, G., & Petersen, S. (1993). A PET study of visuospatial attention. *The Journal of Neuroscience*, *13*(3), 1202–1226. https://doi.org/10.1523/JNEUROSCI.13-03-01202.1993

Corbetta, Maurizio, Akbudak, E., Conturo, T. E., Snyder, A. Z., Ollinger, J. M., Drury, H. A., Linenweber, M. R., Petersen, S. E., Raichle, M. E., Van Essen, D. C., & Shulman, G. L. (1998). A Common Network of Functional Areas for Attention and Eye Movements. *Neuron*, *21*(4), 761–773. https://doi.org/10.1016/S0896-6273(00)80593-0

Corbetta, Maurizio, Kincade, J. M., Ollinger, J. M., McAvoy, M. P., & Shulman, G. L. (2000). Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neuroscience*, *3*(3), 292–297. https://doi.org/10.1038/73009

Corbetta, Maurizio, & Shulman, G. L. (2002). Control of goal-directed and stimulus-driven attention in the brain. *Nature Reviews Neuroscience*, *3*(3), 201–215. https://doi.org/10.1038/nrn755

Cornblatt, B. A., & Malhotra, A. K. (2001a). Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. *American Journal of Medical Genetics*, *105*(1), 11–15.

Cornblatt, B. A., & Malhotra, A. K. (2001b). Impaired attention as an endophenotype for molecular genetic studies of schizophrenia. *American Journal of Medical Genetics*, *105*(1), 11–15. https://doi.org/10.1002/1096-8628(20010108)105:1<11::AID-AJMG1045>3.0.CO;2-G

Coull, J. T., & Nobre, A. C. (1998). Where and When to Pay Attention: The Neural Systems for Directing Attention to Spatial Locations and to Time Intervals as Revealed by Both PET

and fMRI. *The Journal of Neuroscience*, *18*(18), 7426–7435. https://doi.org/10.1523/JNEUROSCI.18-18-07426.1998
Crawford, M., & Roberts, P. J. (1989). 1-Hydroxy-3-aminopyrrolid-2-one (HA-966) and kynurenate antagonize N-methyl-D-aspartate induced enhancement of [3H]dopamine release from rat striatal slices. *Biochemical Pharmacology*, *38*(23), 4165–4168.
Crick, F., & Koch, C. (1990). Towards a neurobiological theory of consciousness. *Seminars in the Neurosciences*, *2*, 263–275.
Csicsvari, J., Jamieson, B., Wise, K. D., & Buzsáki, G. (2003). Mechanisms of Gamma Oscillations in the Hippocampus of the Behaving Rat. *Neuron*, *37*(2), 311–322. https://doi.org/10.1016/S0896-6273(02)01169-8
Danysz, W, & Parsons, C. G. (1998). Glycine and N-methyl-D-aspartate receptors: Physiological significance and possible therapeutic applications. *Pharmacological Reviews*, *50*(4), 597–664.
Danysz, Wojciech, & Parsons, C. (1998). Glycine and N-Methyl-D-Aspartate Receptors: Physiological Significance and Possible Therapeutic Applications. *Pharmacological Reviews*, *50*, 597–664.
DasBanerjee, T., Middleton, F. A., Berger, D. F., Lombardo, J. P., Sagvolden, T., & Faraone, S. V. (2008). A Comparison of Molecular Alterations in Environmental and Genetic Rat Models of ADHD: A pilot study. *American Journal of Medical Genetics. Part B, Neuropsychiatric Genetics : The Official Publication of the International Society of Psychiatric Genetics*, *147B*(8), 1554–1563. https://doi.org/10.1002/ajmg.b.30877
Delaney, A. J., Crane, J. W., & Sah, P. (2007). Noradrenaline modulates transmission at a central synapse by a presynaptic mechanism. *Neuron*, *56*(5), 880–892.
Desimone, R., & Duncan, J. (1995). Neural Mechanisms of Selective Visual Attention. *Annual Review of Neuroscience*, *18*(1), 193–222. https://doi.org/10.1146/annurev.ne.18.030195.001205
Devilbiss, D. M., & Waterhouse, B. D. (2011). Phasic and Tonic Patterns of Locus Coeruleus Output Differentially Modulate Sensory Network Function in the Awake Rat. *Journal of Neurophysiology*, *105*(1), 69–87. https://doi.org/10.1152/jn.00445.2010
Di Miceli, M., & Gronier, B. (2015). Psychostimulants and atomoxetine alter the electrophysiological activity of prefrontal cortex neurons, interaction with catecholamine and glutamate NMDA receptors. *Psychopharmacology*, *232*(12), 2191–2205.
Ding, Z., Brown, J. W., Rueter, L. E., & Mohler, E. G. (2018). Profiling attention and cognition enhancing drugs in a rat touchscreen-based continuous performance test. *Psychopharmacology*, *235*(4), 1093–1105.
Dingledine, R., Borges, K., Bowie, D., & Traynelis, S. (1999). The Glutamate Receptor Ion Channels. *Pharmacological Reviews*, *51*, 7–61.
Dohmen, C., Kumura, E., Rosner, G., Heiss, W.-D., & Graf, R. (2005). Extracellular correlates of glutamate toxicity in short-term cerebral ischemia and reperfusion: A direct in vivo comparison between white and gray matter. *Brain Research*, *1037*(1), 43–51. https://doi.org/10.1016/j.brainres.2004.12.046
D'Souza, D C, Gil, R., Cassello, K., Morrissey, K., Abi-Saab, D., White, J., Sturwold, R., Bennett, A., Karper, L. P., Zuzarte, E., Charney, D. S., & Krystal, J. H. (2000). IV glycine and oral D-cycloserine effects on plasma and CSF amino acids in healthy humans. *Biological Psychiatry*, *47*(5), 450–462.

D'Souza, Deepak C, Radhakrishnan, R., Perry, E., Bhakta, S., Singh, N. M., Yadav, R., Abi-Saab, D., Pittman, B., Chaturvedi, S. K., Sharma, M. P., Bell, M., & Andrade, C. (2013). Feasibility, safety, and efficacy of the combination of D-serine and computerized cognitive retraining in schizophrenia: An international collaborative pilot study. *Neuropsychopharmacology*, *38*(3), 492–503.

Duffy, S., Labrie, V., & Roder, J. C. (2008). D-serine augments NMDA-NR2B receptor-dependent hippocampal long-term depression and spatial reversal learning. *Neuropsychopharmacology: Official Publication Of The American College Of Neuropsychopharmacology*, *33*(5), 1004–1018.

Dugast, C., Cespuglio, R., & Suaud-Chagny, M. F. (2002). In vivo monitoring of evoked noradrenaline release in the rat anteroventral thalamic nucleus by continuous amperometry. *Journal of Neurochemistry*, *82*(3), 529–537. https://doi.org/10.1046/j.1471-4159.2002.00991.x

Dugué, L., Merriam, E. P., Heeger, D. J., & Carrasco, M. (2020). Differential impact of endogenous and exogenous attention on activity in human visual cortex. *Scientific Reports*, *10*(1), 21274. https://doi.org/10.1038/s41598-020-78172-x

Duncan, E. J., Szilagyi, S., Schwartz, M. P., Bugarski-Kirola, D., Kunzova, A., Negi, S., Stephanides, M., Efferen, T. R., Angrist, B., Peselow, E., Corwin, J., Gonzenbach, S., & Rotrosen, J. P. (2004). Effects of d-cycloserine on negative symptoms in schizophrenia. *Schizophrenia Research*, *71*(2), 239–248. https://doi.org/10.1016/j.schres.2004.03.013

Edeline, J.-M., Manunta, Y., & Hennevin, E. (2011). Induction of selective plasticity in the frequency tuning of auditory cortex and auditory thalamus neurons by locus coeruleus stimulation. *Hearing Research*, *274*(1–2), 75–84. https://doi.org/10.1016/j.heares.2010.08.005

Egli, R. E., Kash, T. L., Choo, K., Savchenko, V., Matthews, R. T., Blakely, R. D., & Winder, D. G. (2005). Norepinephrine modulates glutamatergic transmission in the bed nucleus of the stria terminalis. *Neuropsychopharmacology*, *30*(4), 657–668.

Egner, T., Monti, J. M. P., Trittschuh, E. H., Wieneke, C. A., Hirsch, J., & Mesulam, M.-M. (2008). Neural Integration of Top-Down Spatial and Feature-Based Information in Visual Search. *Journal of Neuroscience*, *28*(24), 6141–6151. https://doi.org/10.1523/JNEUROSCI.1262-08.2008

Ehrlichman, R. S., Gandal, M. J., Maxwell, C. R., Lazarewicz, M. T., Finkel, L. H., Contreras, D., Turetsky, B. I., & Siegel, S. J. (2009). N-methyl-d-aspartic acid receptor antagonist–induced frequency oscillations in mice recreate pattern of electrophysiological deficits in schizophrenia. *Neuroscience*, *158*(2), 705–712. https://doi.org/10.1016/j.neuroscience.2008.10.031

Ekstrom, L. B., Roelfsema, P. R., Arsenault, J. T., Bonmassar, G., & Vanduffel, W. (2008). Bottom-Up Dependent Gating of Frontal Signals in Early Visual Cortex. *Science*, *321*(5887), 414–417. https://doi.org/10.1126/science.1153276

Engel, A. K., Fries, P., & Singer, W. (2001). Dynamic predictions: Oscillations and synchrony in top–down processing. *Nature Reviews Neuroscience*, *2*(10), 704–716. https://doi.org/10.1038/35094565

Engel, A. K., König, P., Kreiter, A. K., Schillen, T. B., & Singer, W. (1992). Temporal coding in the visual cortex: New vistas on integration in the nervous system. *Trends in Neurosciences*, *15*(6), 218–226. https://doi.org/10.1016/0166-2236(92)90039-B

Eriksen, C. W., & Hoffman, J. E. (1973). The extent of processing of noise elements during selective encoding from visual displays. *Perception & Psychophysics*, *14*(1), 155–160. https://doi.org/10.3758/BF03198630

Faisal, A. A., Selen, L. P. J., & Wolpert, D. M. (2008). Noise in the nervous system. *Nature Reviews. Neuroscience*, *9*(4), 292–303. https://doi.org/10.1038/nrn2258

Fan, L.-Y., Chou, T.-L., & Gau, S. S.-F. (2017). Neural correlates of atomoxetine improving inhibitory control and visual processing in Drug-naïve adults with attention-deficit/hyperactivity disorder. *Human Brain Mapping*, *38*(10), 4850–4864. https://doi.org/10.1002/hbm.23683

Faraone, S. V., Biederman, J., Spencer, T. J., & Aleardi, M. (2006). Comparing the Efficacy of Medications for ADHD Using Meta-analysis. *Medscape General Medicine*, *8*(4), 4.

Felleman, D. J., & Van Essen, D. C. (1991). Distributed Hierarchical Processing in the Primate Cerebral Cortex. *Cerebral Cortex*, *1*(1), 1–47. https://doi.org/10.1093/cercor/1.1.1

Feng, J., Zhang, C., Lischinsky, J. E., Jing, M., Zhou, J., Wang, H., Zhang, Y., Dong, A., Wu, Z., Wu, H., Chen, W., Zhang, P., Zou, J., Hires, S. A., Zhu, J. J., Cui, G., Lin, D., Du, J., & Li, Y. (2019). A Genetically Encoded Fluorescent Sensor for Rapid and Specific In Vivo Detection of Norepinephrine. *Neuron*, *102*(4), 745-761.e8. https://doi.org/10.1016/j.neuron.2019.02.037

Fernando, A. B. P., Economidou, D., Theobald, D. E., Zou, M.-F., Newman, A. H., Spoelder, M., Caprioli, D., Moreno, M., Hipólito, L., Aspinall, A. T., Robbins, T. W., & Dalley, J. W. (2012). Modulation of high impulsivity and attentional performance in rats by selective direct and indirect dopaminergic and noradrenergic receptor agonists. *Psychopharmacology*, *219*(2), 341–352. https://doi.org/10.1007/s00213-011-2408-z

Ferraris, D., Duvall, B., Ko, Y.-S., Thomas, A. G., Rojas, C., Majer, P., Hashimoto, K., & Tsukamoto, T. (2008). Synthesis and biological evaluation of D-amino acid oxidase inhibitors. *Journal Of Medicinal Chemistry*, *51*(12), 3357–3359.

Ferrero, J. J., Alvarez, A. M., Ramírez-Franco, J., Godino, M. C., Bartolomé-Martín, D., Aguado, C., Torres, M., Luján, R., Ciruela, F., & Sánchez-Prieto, J. (2013). β-Adrenergic Receptors Activate Exchange Protein Directly Activated by cAMP (Epac), Translocate Munc13-1, and Enhance the Rab3A-RIM1α Interaction to Potentiate Glutamate Release at Cerebrocortical Nerve Terminals. *Journal of Biological Chemistry*, *288*(43), 31370–31385. https://doi.org/10.1074/jbc.M113.463877

Ferry, B., Roozendaal, B., & McGaugh, J. L. (1999). Basolateral Amygdala Noradrenergic Influences on Memory Storage Are Mediated by an Interaction between β- and α-1 Adrenoceptors. *The Journal of Neuroscience*, *19*(12), 5119–5123. https://doi.org/10.1523/JNEUROSCI.19-12-05119.1999

Fiebelkorn, I. C., & Kastner, S. (2019). A Rhythmic Theory of Attention. *Trends in Cognitive Sciences*, *23*(2), 87–101. https://doi.org/10.1016/j.tics.2018.11.009

Fiebelkorn, I. C., Pinsk, M. A., & Kastner, S. (2018). A Dynamic Interplay within the Frontoparietal Network Underlies Rhythmic Spatial Attention. *Neuron*, *99*(4), 842-853.e8. https://doi.org/10.1016/j.neuron.2018.07.038

File, S. E., Fluck, E., & Fernandes, C. (1999). Beneficial effects of glycine (bioglycin) on memory and attention in young and middle-aged adults. *Journal Of Clinical Psychopharmacology*, *19*(6), 506–512.

Fink, K., Bönisch, H., & Göthert, M. (1990). Presynaptic NMDA receptors stimulate noradrenaline release in the cerebral cortex. *European Journal of Pharmacology*, *185*(1), 115–117. https://doi.org/10.1016/0014-2999(90)90219-V

Fink, K., Schultheiß, R., & Göthert, M. (1992). Stimulation of noradrenaline release in human cerebral cortex mediated by N-methyl-d-aspartate (NMDA) and non-NMDA receptors. *British Journal of Pharmacology*, *106*(1), 67–72.

Fletcher, E. J., & Lodge, D. (1988). Glycine reverses antagonism of N-methyl-D-aspartate (NMDA) by 1-hydroxy-3-aminopyrrolidone-2 (HA-966) but not by D-2-amino-5-phosphonovalerate (D-AP5) on rat cortical slices. *European Journal of Pharmacology*, *151*(1), 161–162.

Florin-Lechner, S. M., Druhan, J. P., Aston-Jones, G., & Valentino, R. J. (1996). Enhanced norepinephrine release in prefrontal cortex with burst stimulation of the locus coeruleus. *Brain Research*, *742*(1), 89–97. https://doi.org/10.1016/S0006-8993(96)00967-5

Foote, S. L., Aston-Jones, G., & Bloom, F. E. (1980a). Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proceedings of the National Academy of Sciences*, *77*(5), 3033–3037.

Foote, S. L., Aston-Jones, G., & Bloom, F. E. (1980b). Impulse activity of locus coeruleus neurons in awake rats and monkeys is a function of sensory stimulation and arousal. *Proceedings of the National Academy of Sciences*, *77*(5), 3033–3037. https://doi.org/10.1073/pnas.77.5.3033

Foote, S. L., Bloom, F. E., & Aston-Jones, G. (1983). Nucleus locus ceruleus: New evidence of anatomical and physiological specificity. *Physiological Reviews*, *63*(3), 844–914. https://doi.org/10.1152/physrev.1983.63.3.844

Fossat, P., Turpin, F. R., Sacchi, S., Dulong, J., Shi, T., Rivet, J.-M., Sweedler, J. V., Pollegioni, L., Millan, M. J., Oliet, S. H. R., & Mothet, J.-P. (2012). Glial D-Serine Gates NMDA Receptors at Excitatory Synapses in Prefrontal Cortex. *Cerebral Cortex*, *22*(3), 595–606. https://doi.org/10.1093/cercor/bhr130

Fries, P., Womelsdorf, T., Oostenveld, R., & Desimone, R. (2008). The Effects of Visual Stimulation and Selective Visual Attention on Rhythmic Neuronal Synchronization in Macaque Area V4. *Journal of Neuroscience*, *28*(18), 4823–4835. https://doi.org/10.1523/JNEUROSCI.4499-07.2008

Fries, Pascal. (2015). Rhythms for Cognition: Communication through Coherence. *Neuron*, *88*(1), 220–235. https://doi.org/10.1016/j.neuron.2015.09.034

Fries, Pascal, Nikolić, D., & Singer, W. (2007). The gamma cycle. *Trends in Neurosciences*, *30*(7), 309–316. https://doi.org/10.1016/j.tins.2007.05.005

Fries, Pascal, Reynolds, J., Rorie, A. E., & Desimone, R. (2001). Modulation of Oscillatory Neuronal Synchronization by Selective Visual Attention. *Science*, *291*, 1560–1563. https://doi.org/10.1126/science.291.5508.1560

Fukushima, T., Kawai, J., Imai, K., & Toyo'oka, T. (2004). Simultaneous determination of D- and L-serine in rat brain microdialysis sample using a column-switching HPLC with fluorimetric detection. *Biomedical Chromatography: BMC*, *18*(10), 813–819.

Funahashi, S., Chafee, M. V., & Goldman-Rakic, P. S. (1993). Prefrontal neuronal activity in rhesus monkeys performing a delayed anti-saccade task. *Nature*, *365*(6448), 753–756.

Gaillard, C., & Ben Hamed, S. (2020). The neural bases of spatial attention and perceptual rhythms. *European Journal of Neuroscience*. https://doi.org/10.1111/ejn.15044

Gandhi, S. P., Heeger, D. J., & Boynton, G. M. (1999). Spatial attention affects brain activity in human primary visual cortex. *Proceedings of the National Academy of Sciences*, *96*(6), 3314–3319. https://doi.org/10.1073/pnas.96.6.3314

Ganote, C E, Peterson, D. R., & Carone, F. A. (1974). The nature of D-serine-induced nephrotoxicity. *The American Journal Of Pathology*, *77*(2), 269–282.

Ganote, Charles E., Peterson, D. R., & Carone, F. A. (1974). The Nature of D-Serine-Induced Nephrotoxicity. *The American Journal of Pathology*, *77*(2), 269–282.

Gawne, T. J., & Richmond, B. J. (1993). How independent are the messages carried by adjacent inferior temporal cortical neurons? *Journal of Neuroscience*, *13*(7), 2758–2771.

Gawne, Timothy J., Kjaer, T. W., Hertz, J. A., & Richmond, B. J. (1996). Adjacent Visual Cortical Complex Cells Share About 20% of Their Stimulus-Related Information. *Cerebral Cortex*, *6*(3), 482–489. https://doi.org/10.1093/cercor/6.3.482

Geisler, C., Brunel, N., & Wang, X.-J. (2005). Contributions of Intrinsic Membrane Dynamics to Fast Network Oscillations With Irregular Neuronal Discharges. *Journal of Neurophysiology*, *94*(6), 4344–4361. https://doi.org/10.1152/jn.00510.2004

Georgopoulos, A. P., Schwartz, A. B., & Kettner, R., E. (1986). Neuronal population coding of movement direction. *Science*, *233*(4771), 1416.

Gereau, R. W., & Conn, P. J. (1994). A cyclic AMP-dependent form of associative synaptic plasticity induced by coactivation of beta-adrenergic receptors and metabotropic glutamate receptors in rat hippocampus. *Journal of Neuroscience*, *14*(5), 3310–3318. https://doi.org/10.1523/JNEUROSCI.14-05-03310.1994

Gibson, A. P., Bettinger, T. L., Patel, N. C., & Crismon, M. L. (2006). Atomoxetine versus stimulants for treatment of attention deficit/hyperactivity disorder. *The Annals of Pharmacotherapy*, *40*(6), 1134–1142.

Gilsbach, R., & Hein, L. (2008). Presynaptic Metabotropic Receptors for Acetylcholine and Adrenaline/Noradrenaline. In K. Starke (Ed.), *Pharmacology of Neurotransmitter Release* (Vol. 184, pp. 261–288). Springer.

Gilzenrat, M. S., Holmes, B. D., Rajkowski, J., Aston-Jones, G., & Cohen, J. D. (2002). Simplified dynamics in a model of noradrenergic modulation of cognitive performance. *Neural Networks*, *15*(4), 647–663. https://doi.org/10.1016/S0893-6080(02)00055-2

Gitelman, D. R., Nobre, A. C., Parrish, T. B., LaBar, K. S., Kim, Y.-H., Meyer, J. R., & Mesulam, M.-M. (1999). A large-scale distributed network for covert spatial attention. *Brain*, *122*(6), 1093–1106. https://doi.org/10.1093/brain/122.6.1093

Gonzalez-Burgos, G., Hashimoto, T., & Lewis, D. A. (2010). Alterations of Cortical GABA Neurons and Network Oscillations in Schizophrenia. *Current Psychiatry Reports*, *12*(4), 335–344. https://doi.org/10.1007/s11920-010-0124-8

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

Grant, S. J., Aston-Jones, G., & Redmond, D. E. (1988a). Responses of primate locus coeruleus neurons to simple and complex sensory stimuli. *Brain Research Bulletin*, *21*(3), 401–410.

Grant, S. J., Aston-Jones, G., & Redmond, D. E. (1988b). Responses of primate locus coeruleus neurons to simple and complex sensory stimuli. *Brain Research Bulletin*, *21*(3), 401–410. https://doi.org/10.1016/0361-9230(88)90152-9

Gray, C. M., & Singer, W. (1989). Stimulus-specific neuronal oscillations in orientation columns of cat visual cortex. *Proceedings of the National Academy of Sciences*, *86*(5), 1698–1702. https://doi.org/10.1073/pnas.86.5.1698

Gray, Charles M., König, P., Engel, A. K., & Singer, W. (1989). Oscillatory responses in cat visual cortex exhibit inter-columnar synchronization which reflects global stimulus properties. *Nature*, *338*(6213), 334–337.

Gregoriou, G. G., Gotts, S. J., Zhou, H., & Desimone, R. (2009). High-frequency, long-range coupling between prefrontal and visual cortex during attention. *Science (New York, N.Y.)*, *324*(5931), 1207–1210. https://doi.org/10.1126/science.1171402

Gregoriou, G. G., Rossi, A. F., Ungerleider, L. G., & Desimone, R. (2014). Lesions of prefrontal cortex reduce attentional modulation of neuronal responses and synchrony in V4. *Nature Neuroscience*, *17*(7), 1003–1011. https://doi.org/10.1038/nn.3742

Grosbras, M.-H., & Paus, T. (2002). Transcranial Magnetic Stimulation of the Human Frontal Eye Field: Effects on Visual Perception and Attention. *Journal of Cognitive Neuroscience*, *14*(7), 1109–1120. https://doi.org/10.1162/089892902320474553

Grottick, A. J., & Higgins, G. A. (2000). Effect of subtype selective nicotinic compounds on attention as assessed by the five-choice serial reaction time task. *Behavioural Brain Research*, *117*(1–2), 197–208. https://doi.org/10.1016/S0166-4328(00)00305-3

Gruber, T., Müller, M. M., Keil, A., & Elbert, T. (1999). Selective visual-spatial attention alters induced gamma band responses in the human EEG. *Clinical Neurophysiology*, *110*(12), 2074–2085. https://doi.org/10.1016/S1388-2457(99)00176-5

Guedj, C., Monfardini, E., Reynaud, A. J., Farnè, A., Meunier, M., & Hadj-Bouziane, F. (2017). Boosting Norepinephrine Transmission Triggers Flexible Reconfiguration of Brain Networks at Rest. *Cerebral Cortex*, *27*(10), 4691–4700. https://doi.org/10.1093/cercor/bhw262

Guercio, G. D., Bevictori, L., Vargas-Lopes, C., Madeira, C., Oliveira, A., Carvalho, V. F., d'Avila, J. C., & Panizzutti, R. (2014). D-serine prevents cognitive deficits induced by acute stress. *Neuropharmacology*, *86*, 1–8.

Hakami, T., Jones, N. C., Tolmacheva, E. A., Gaudias, J., Chaumont, J., Salzberg, M., O'Brien, T. J., & Pinault, D. (2009). NMDA Receptor Hypofunction Leads to Generalized and Persistent Aberrant γ Oscillations Independent of Hyperlocomotion and the State of Consciousness. *PLoS ONE*, *4*(8), e6755. https://doi.org/10.1371/journal.pone.0006755

Harris, K. D., & Thiele, A. (2011). Cortical State and Attention. *Nature Reviews. Neuroscience*, *12*(9), 509–523. https://doi.org/10.1038/nrn3084

Hasegawa, H., Masuda, N., Natori, H., Shinohara, Y., & Ichida, K. (2019). Pharmacokinetics and toxicokinetics of d-serine in rats. *Journal of Pharmaceutical and Biomedical Analysis*, *162*, 264–271.

Hasenstaub, A., Shu, Y., Haider, B., Kraushaar, U., Duque, A., & McCormick, D. A. (2005). Inhibitory Postsynaptic Potentials Carry Synchronized Frequency Information in Active Cortical Networks. *Neuron*, *47*(3), 423–435. https://doi.org/10.1016/j.neuron.2005.06.016

Hashimoto, A., & Chiba, S. (2004). Effect of systemic administration of D-serine on the levels of D- and L-serine in several brain areas and periphery of rat. *European Journal Of Pharmacology*, *495*(2–3), 153–158.

Hauser, J., Reissmann, A., Sontag, T.-A., Tucha, O., & Lange, K. W. (2017). Effects of atomoxetine on attention in Wistar rats treated with the neurotoxin N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP4). *ADHD Attention Deficit and Hyperactivity Disorders*, *9*(4), 253–262. https://doi.org/10.1007/s12402-017-0225-x

Hausknecht, K. A., Acheson, A., Farrar, A. M., Kieres, A. K., Shen, R.-Y., Richards, J. B., & Sabol, K. E. (2005a). Prenatal alcohol exposure causes attention deficits in male rats. *Behavioral Neuroscience*, *119*(1), 302–310. https://doi.org/10.1037/0735-7044.119.1.302

Hausknecht, K. A., Acheson, A., Farrar, A. M., Kieres, A. K., Shen, R.-Y., Richards, J. B., & Sabol, K. E. (2005b). Prenatal Alcohol Exposure Causes Attention Deficits in Male Rats. *Behavioral Neuroscience*, *119*(1), 302–310. https://doi.org/10.1037/0735-7044.119.1.302

Heil, S. H., Holmes, H. W., Bickel, W. K., Higgins, S. T., Badger, G. J., Laws, H. F., & Faries, D. E. (2002a). Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users. *Drug and Alcohol Dependence*, *67*(2), 149–156.

Heil, S. H., Holmes, H. W., Bickel, W. K., Higgins, S. T., Badger, G. J., Laws, H. F., & Faries, D. E. (2002b). Comparison of the subjective, physiological, and psychomotor effects of atomoxetine and methylphenidate in light drug users. *Drug and Alcohol Dependence*, *67*(2), 149–156. https://doi.org/10.1016/S0376-8716(02)00053-4

Henderson, G., Johnson, J. W., & Ascher, P. (1990). Competitive antagonists and partial agonists at the glycine modulatory site of the mouse N-methyl-D-aspartate receptor. *The Journal of Physiology*, *430*, 189–212.

Herrero, I., & Sánchez-Prieto, J. (1996). CAMP-dependent Facilitation of Glutamate Release by β-Adrenergic Receptors in Cerebrocortical Nerve Terminals*. *Journal of Biological Chemistry*, *271*(48), 30554–30560. https://doi.org/10.1074/jbc.271.48.30554

Herrero, J. L., Gieselmann, M. A., Sanayei, M., & Thiele, A. (2013). Attention-Induced Variance and Noise Correlation Reduction in Macaque V1 Is Mediated by NMDA Receptors. *Neuron*, *78*(4), 729–739. https://doi.org/10.1016/j.neuron.2013.03.029

Herrero, J. L., Roberts, M. J., Delicato, L. S., Gieselmann, M. A., Dayan, P., & Thiele, A. (2008). Acetylcholine contributes through muscarinic receptors to attentional modulation in V1. *Nature*, *454*(7208), 1110–1114. https://doi.org/10.1038/nature07141

Higgins, G. A., Enderlin, M., Haman, M., & Fletcher, P. J. (2003). The 5-HT2A receptor antagonist M100,907 attenuates motor and "impulsive-type" behaviours produced by NMDA receptor antagonism. *Psychopharmacology*, *170*(3), 309–319. https://doi.org/10.1007/s00213-003-1549-0

Higgins, G. A., Silenieks, L. B., MacMillan, C., Sevo, J., Zeeb, F. D., & Thevarkunnel, S. (2016). Enhanced attention and impulsive action following NMDA receptor GluN2B-selective antagonist pretreatment. *Behavioural Brain Research*, *311*, 1–14. https://doi.org/10.1016/j.bbr.2016.05.025

Hopfinger, J. B., Buonocore, M. H., & Mangun, G. R. (2000). The neural mechanisms of top-down attentional control. *Nature Neuroscience*, *3*(3), 284–291. https://doi.org/10.1038/72999

Howells, F. M., & Russell, V. A. (2008). Glutamate-stimulated release of norepinephrine in hippocampal slices of animal models of attention-deficit/hyperactivity disorder (spontaneously hypertensive rat) and depression/anxiety-like behaviours (Wistar–Kyoto rat). *Brain Research*, *1200*, 107–115. https://doi.org/10.1016/j.brainres.2008.01.033

Huang-Pollock, C. L., Karalunas, S. L., Tam, H., & Moore, A. N. (2012). Evaluating vigilance deficits in ADHD: A meta-analysis of CPT performance. *Journal of Abnormal Psychology*, *121*(2), 360–371.

Huddleston, W. E., & DeYoe, E. A. (2008). The Representation of Spatial Attention in Human Parietal Cortex Dynamically Modulates with Performance. *Cerebral Cortex*, *18*(6), 1272–1280. https://doi.org/10.1093/cercor/bhm158

Hudson, M. R., Rind, G., O'Brien, T. J., & Jones, N. C. (2016). Reversal of evoked gamma oscillation deficits is predictive of antipsychotic activity with a unique profile for clozapine. *Translational Psychiatry*, *6*(4), e784–e784. https://doi.org/10.1038/tp.2016.51

Hudson, M. R., Sokolenko, E., O'Brien, T. J., & Jones, N. C. (2020). NMDA receptors on parvalbumin-positive interneurons and pyramidal neurons both contribute to MK-801 induced gamma oscillatory disturbances: Complex relationships with behaviour. *Neurobiology of Disease*, *134*, 104625. https://doi.org/10.1016/j.nbd.2019.104625

Huerta, M. F., Krubitzer, L. A., & Kaas, J. H. (1986). Frontal eye field as defined by intracortical microstimulation in squirrel monkeys, owl monkeys, and macaque monkeys: I. Subcortical connections. *The Journal of Comparative Neurology*, *253*(4), 415–439. https://doi.org/10.1002/cne.902530402

Hunt, M. J., Kopell, N. J., Traub, R. D., & Whittington, M. A. (2017). Aberrant Network Activity in Schizophrenia. *Trends in Neurosciences*, *40*(6), 371–382. https://doi.org/10.1016/j.tins.2017.04.003

Huntley, G. W., Vickers, J. C., & Morrison, J. H. (1994). Cellular and synaptic localization of NMDA and non-NMDA receptor subunits in neocortex: Organizational features related to cortical circuitry, function and disease. *Trends in Neurosciences*, *17*(12), 536–543. https://doi.org/10.1016/0166-2236(94)90158-9

Ji, X.-H., Cao, X.-H., Zhang, C.-L., Feng, Z.-J., Zhang, X.-H., Ma, L., & Li, B.-M. (2008b). Pre- and Postsynaptic β-Adrenergic Activation Enhances Excitatory Synaptic Transmission in Layer V/VI Pyramidal Neurons of the Medial Prefrontal Cortex of Rats. *Cerebral Cortex*, *18*(7), 1506–1520. https://doi.org/10.1093/cercor/bhm177

Johansen, E., Sagvolden, T., Aase, H., & Russell, V. A. (2005). The Dynamic Developmental Theory of Attention-Deficit/Hyperactivity Disorder (ADHD): Present Status and Future Perspectives. *Behavioral and Brain Sciences*, *28*(3), 451–454. https://doi.org/10.1017/S0140525X05430071

Johansen, E., Sagvolden, T., & Kvande, G. (2005). Effects of delayed reinforcers on the behavior of an animal model of attention-deficit/hyperactivity disorder (ADHD). *Behavioural Brain Research*, *162*(1), 47–61. https://doi.org/10.1016/j.bbr.2005.02.034

Johnson, J. W., & Ascher, P. (1987a). Glycine potentiates the NMDA response in cultured mouse brain neurons. *Nature*, *325*(6104), 529–531. https://doi.org/10.1038/325529a0

Johnson, J. W., & Ascher, P. (1987b). Glycine potentiates the NMDA response in cultured mouse brain neurons. *Nature*, *325*(6104), 529–531.

Jones, B., & Moore, R. (1977). Ascending projections of the locus coeruleus in the rat. II. Autoradiographic study. *Brain Research*, *127*, 25–53. https://doi.org/10.1016/0006-8993(77)90378-X

Jones, B., & Yang, T.-Z. (1985). The Efferent Projections From the Reticular Formation and the Locus Coeruleus Studied by Anterograde and Retrograde Axonal Transport in the Rat. *The Journal of Comparative Neurology*, *242*, 56–92. https://doi.org/10.1002/cne.902420105

Jones, E. G. (2001). The thalamic matrix and thalamocortical synchrony. *Trends in Neurosciences*, *24*(10), 595–601. https://doi.org/10.1016/S0166-2236(00)01922-6

Jones, N. C., Anderson, P., Rind, G., Sullivan, C., van den Buuse, M., & O'Brien, T. J. (2014). Effects of aberrant gamma frequency oscillations on prepulse inhibition. *International Journal of Neuropsychopharmacology*, *17*(10), 1671–1681. https://doi.org/10.1017/S1461145714000492

Jones, N. C., Hudson, M., Foreman, J., Rind, G., Hill, R., Manning, E. E., & Buuse, M. van den. (2018). Brain-derived neurotrophic factor haploinsufficiency impairs high-frequency cortical oscillations in mice. *European Journal of Neuroscience*, *48*(8), 2816–2825. https://doi.org/10.1111/ejn.13722

Jones, N. C., Reddy, M., Anderson, P., Salzberg, M. R., O'Brien, T. J., & Pinault, D. (2012). Acute administration of typical and atypical antipsychotics reduces EEG gamma power, but only the preclinical compound LY379268 reduces the ketamine-induced rise in gamma power. *International Journal of Neuropsychopharmacology*, *15*(5), 657–668. https://doi.org/10.1017/S1461145711000848

Kantrowitz, J. T., Malhotra, A. K., Cornblatt, B., Silipo, G., Balla, A., Suckow, R. F., D'Souza, C., Saksa, J., Woods, S. W., & Javitt, D. C. (2010a). High dose D-serine in the treatment of schizophrenia. *Schizophrenia Research*, *121*(1–3), 125–130.

Kantrowitz, J. T., Malhotra, A. K., Cornblatt, B., Silipo, G., Balla, A., Suckow, R. F., D'Souza, C., Saksa, J., Woods, S. W., & Javitt, D. C. (2010b). High dose D-serine in the treatment of schizophrenia. *Schizophrenia Research*, *121*(1–3), 125–130. https://doi.org/10.1016/j.schres.2010.05.012

Kanwisher, N., & Wojciulik, E. (2000). Visual attention: Insights from brain imaging. *Nature Reviews Neuroscience*, *1*(2), 91–100. https://doi.org/10.1038/35039043

Karasawa, J.-I., Hashimoto, K., & Chaki, S. (2008). D-Serine and a glycine transporter inhibitor improve MK-801-induced cognitive deficits in a novel object recognition test in rats. *Behavioural Brain Research*, *186*(1), 78–83.

Kastner, S., De Weerd, P., Desimone, R., & Ungerleider, L. G. (1998). Mechanisms of Directed Attention in the Human Extrastriate Cortex as Revealed by Functional MRI. *Science*, *282*(5386), 108–111.

Kastner, S., & Pinsk, M. A. (2004). Visual attention as a multilevel selection process. *Cognitive, Affective, & Behavioral Neuroscience*, *4*(4), 483–500. https://doi.org/10.3758/CABN.4.4.483

Kastner, Sabine, DeSimone, K., Konen, C. S., Szczepanski, S. M., Weiner, K. S., & Schneider, K. A. (2007). Topographic Maps in Human Frontal Cortex Revealed in Memory-Guided Saccade and Spatial Working-Memory Tasks. *Journal of Neurophysiology*, *97*(5), 3494–3507. https://doi.org/10.1152/jn.00010.2007

Kastner, Sabine, Pinsk, M. A., De Weerd, P., Desimone, R., & Ungerleider, L. G. (1999). Increased Activity in Human Visual Cortex during Directed Attention in the Absence of Visual Stimulation. *Neuron*, *22*(4), 751–761. https://doi.org/10.1016/S0896-6273(00)80734-5

Kastner, Sabine, & Ungerleider, L. (2000). Mechanisms of visual attention in the human cortex. *Annual Review of Neuroscience*, *23*(1), 315–341.

Kawaura, K., Koike, H., Kinoshita, K., Kambe, D., Kaku, A., Karasawa, J., Chaki, S., & Hikichi, H. (2015). Effects of a glycine transporter-1 inhibitor and D-serine on MK-801-induced immobility in the forced swimming test in rats. *Behavioural Brain Research*, *278*, 186–192.

Kehrer, C., Maziashvili, N., Dugladze, T., & Gloveli, T. (2008). Altered excitatory-inhibitory balance in the NMDA-hypofunction model of schizophrenia. *Frontiers in Molecular Neuroscience*, *1*, 6.

Kemp, J. A., Foster, A. C., Leeson, P. D., Priestley, T., Tridgett, R., Iversen, L. L., & Woodruff, G. N. (1988). 7-Chlorokynurenic acid is a selective antagonist at the glycine modulatory site of the N-methyl-D-aspartate receptor complex. *Proceedings of The National Academy of Sciences*, *85*(17), 6547–6550.

Kihara, T., Sawada, H., Nakamizo, T., Kanki, R., Yamashita, H., Maelicke, A., & Shimohama, S. (2004). Galantamine modulates nicotinic receptor and blocks Aβ-enhanced glutamate toxicity. *Biochemical and Biophysical Research Communications*, *325*(3), 976–982. https://doi.org/10.1016/j.bbrc.2004.10.132

Kincade, J. M., Abrams, R. A., Astafiev, S. V., Shulman, G. L., & Corbetta, M. (2005). An Event-Related Functional Magnetic Resonance Imaging Study of Voluntary and Stimulus-Driven Orienting of Attention. *Journal of Neuroscience*, *25*(18), 4593–4604. https://doi.org/10.1523/JNEUROSCI.0236-05.2005

Kinney, J. W., Davis, C. N., Tabarean, I., Conti, B., Bartfai, T., & Behrens, M. M. (2006). A Specific Role for NR2A-Containing NMDA Receptors in the Maintenance of Parvalbumin and GAD67 Immunoreactivity in Cultured Interneurons. *Journal of Neuroscience*, *26*(5), 1604–1615. https://doi.org/10.1523/JNEUROSCI.4722-05.2006

Kleckner, N. W., & Dingledine, R. (1988a). Requirement for glycine in activation of NMDA-receptors expressed in Xenopus oocytes. *Science*, *241*(4867), 835–837. https://doi.org/10.1126/science.2841759

Kleckner, N. W., & Dingledine, R. (1988b). Requirement for glycine in activation of NMDA-receptors expressed in Xenopus oocytes. *Science (New York, N.Y.)*, *241*(4867), 835–837.

Kobayashi, M., Kojima, M., Koyanagi, Y., Adachi, K., Imamura, K., & Koshikawa, N. (2008). Presynaptic and postsynaptic modulation of glutamatergic synaptic transmission by activation of α1- and β-adrenoceptors in layer V pyramidal neurons of rat cerebral cortex. *Synapse*, *63*(4), 269–281.

Kocsis, B. (2012). Differential role of NR2A and NR2B subunits in NMDA receptor antagonist-induced aberrant cortical gamma oscillations. *Biological Psychiatry*, *71*(11), 987–995. https://doi.org/10.1016/j.biopsych.2011.10.002

Kodaka, Y., Mikami, A., & Kubota, K. (1997). Neuronal activity in the frontal eye field of the monkey is modulated while attention is focused on to a stimulus in the peripheral visual field, irrespective of eye movement. *Neuroscience Research*, *28*(4), 291–298. https://doi.org/10.1016/S0168-0102(97)00055-2

Koffarnus, M. N., & Katz, J. L. (2011). Response requirement and increases in accuracy produced by stimulant drugs in a 5-choice serial reaction-time task in rats. *Psychopharmacology*, *213*(4), 723–733. https://doi.org/10.1007/s00213-010-2027-0

Kofler, M. J., Rapport, M. D., Sarver, D. E., Raiker, J. S., Orban, S. A., Friedman, L. M., & Kolomeyer, E. G. (2013). Reaction time variability in ADHD: A meta-analytic review of 319 studies. *Clinical Psychology Review*, *33*(6), 795–811. https://doi.org/10.1016/j.cpr.2013.06.001

Kohn, A., & Smith, M. A. (2005). Stimulus Dependence of Neuronal Correlation in Primary Visual Cortex of the Macaque. *Journal of Neuroscience*, *25*(14), 3661–3673. https://doi.org/10.1523/JNEUROSCI.5106-04.2005

Kratz, O., Studer, P., Baack, J., Malcherek, S., Erbe, K., Moll, G. H., & Heinrich, H. (2012). Differential effects of methylphenidate and atomoxetine on attentional processes in children with ADHD: An event-related potential study using the Attention Network Test. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *37*(1), 81–89. https://doi.org/10.1016/j.pnpbp.2011.12.008

Krug, A. W., Völker, K., Dantzler, W. H., & Silbernagl, S. (2007). Why is D-serine nephrotoxic and α-aminoisobutyric acid protective? *American Journal of Physiology-Renal Physiology*, *293*(1), F382–F390. https://doi.org/10.1152/ajprenal.00441.2006

Kulikova, S. P., Tolmacheva, E. A., Anderson, P., Gaudias, J., Adams, B. E., Zheng, T., & Pinault, D. (2012). Opposite effects of ketamine and deep brain stimulation on rat thalamocortical information processing: Ketamine and deep brain stimulation actions in TC systems. *European Journal of Neuroscience*, *36*(10), 3407–3419. https://doi.org/10.1111/j.1460-9568.2012.08263.x

Kwon, J. S., O'Donnell, B. F., Wallenstein, G. V., Greene, R. W., Hirayasu, Y., Nestor, P. G., Hasselmo, M. E., Potts, G. F., Shenton, M. E., & McCarley, R. W. (1999). Gamma Frequency–Range Abnormalities to Auditory Stimulation in Schizophrenia. *Archives of General Psychiatry*, *56*(11), 1001–1005.

LaBar, K. S., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (1999). Neuroanatomic Overlap of Working Memory and Spatial Attention Networks: A Functional MRI Comparison within Subjects. *NeuroImage*, *10*, 695–704.

Labrie, V., Clapcote, S. J., & Roder, J. C. (2009). Mutant mice with reduced NMDA-NR1 glycine affinity or lack of D-amino acid oxidase function exhibit altered anxiety-like behaviors. *Pharmacology, Biochemistry, and Behavior*, *91*(4), 610–620.

Lane, H.-Y., Lin, C.-H., Green, M. F., Hellemann, G., Huang, C.-C., Chen, P.-W., Tun, R., Chang, Y.-C., & Tsai, G. E. (2013). Add-on treatment of benzoate for schizophrenia: A randomized, double-blind, placebo-controlled trial of D-amino acid oxidase inhibitor. *JAMA Psychiatry*, *70*(12), 1267–1275.

Langer, S. Z. (2008). Presynaptic autoreceptors regulating transmitter release. *Neurochemistry International*, *52*(1–2), 26–30.

Langner, R., & Eickhoff, S. B. (2013). Sustaining Attention to Simple Tasks: A Meta-Analytic Review of the Neural Mechanisms of Vigilant Attention. *Psychological Bulletin*, *139*(4), 870–900. https://doi.org/10.1037/a0030694

Le Pen, G., Kew, J., Alberati, D., Borroni, E., Heitz, M.-P., & Moreau, J.-L. (2003). Prepulse inhibition deficits of the startle reflex in neonatal ventral hippocampal–lesioned rats: Reversal by glycine and a glycine transporter inhibitor. *Biological Psychiatry*, *54*(11), 1162–1170. https://doi.org/10.1016/S0006-3223(03)00374-3

Lecas, J.-C. (2004). Locus coeruleus activation shortens synaptic drive while decreasing spike latency and jitter in sensorimotor cortex. Implications for neuronal integration. *European Journal of Neuroscience*, *19*(9), 2519–2530. https://doi.org/10.1111/j.0953-816X.2004.03341.x

Lee, D. K., Koch, C., & Braun, J. (1997). Spatial vision thresholds in the near absence of attention. *Vision Research*, *37*(17), 2409–2418. https://doi.org/10.1016/S0042-6989(97)00055-2

Lee, D., Port, N. L., Kruse, W., & Georgopoulos, A. P. (1998). Variability and Correlated Noise in the Discharge of Neurons in Motor and Parietal Areas of the Primate Cortex. *The*

Journal of Neuroscience, *18*(3), 1161–1170. https://doi.org/10.1523/JNEUROSCI.18-03-01161.1998

Lee, J., Hudson, M., O'Brien, T., Nithianantharajah, J., & Jones, N. (2017). Local NMDA receptor hypofunction evokes generalized effects on gamma and high-frequency oscillations and behavior. *Neuroscience*, *358*, 124–136. https://doi.org/10.1016/j.neuroscience.2017.06.039

Lehmann, J., Valentino, R., & Robine, V. (1992). Cortical norepinephrine release elicited in situ by N-methyl-d-aspartate (NMDA) receptor stimulation: A microdialysis study. *Brain Research*, *599*(1), 171–174. https://doi.org/10.1016/0006-8993(92)90868-A

Lehohla, M., Russell, V. A., & Kellaway, L. (2004). Effect of Enriched Environment on Ca $^{2+}$ Uptake via NMDA Receptors into Barrel Cortex Slices of Spontaneously Hypertensive Rats. *Metabolic Brain Disease*, *19*(1/2), 25–33. https://doi.org/10.1023/B:MEBR.0000027414.01463.f4

Leth-Steensen, C., King Elbaz, Z., & Douglas, V. I. (2000a). Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. *Acta Psychologica*, *104*(2), 167–190. https://doi.org/10.1016/S0001-6918(00)00019-6

Leth-Steensen, C., King Elbaz, Z., & Douglas, V. I. (2000b). Mean response times, variability, and skew in the responding of ADHD children: A response time distributional approach. *Acta Psychologica*, *104*(2), 167–190.

Levin, R., Dor-Abarbanel, A. E., Edelman, S., Durrant, A. R., Hashimoto, K., Javitt, D. C., & Heresco-Levy, U. (2015). Behavioral and cognitive effects of the N-methyl-D-aspartate receptor co-agonist D-serine in healthy humans: Initial findings. *Journal of Psychiatric Research*, *61*, 188–195.

Lewis, J. W., & Van Essen, D. C. (2000). Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. *Journal of Comparative Neurology*, *428*(1), 112–137. https://doi.org/10.1002/1096-9861(20001204)428:1<112::AID-CNE8>3.0.CO;2-9

Li, Q., Lu, G., Antonio, G. E., Mak, Y. T., Rudd, J. A., Fan, M., & Yew, D. T. (2007). The usefulness of the spontaneously hypertensive rat to model attention-deficit/hyperactivity disorder (ADHD) may be explained by the differential expression of dopamine-related genes in the brain. *Neurochemistry International*, *50*(6), 848–857. https://doi.org/10.1016/j.neuint.2007.02.005

Lin, H.-Y., & Gau, S. S.-F. (2015). Atomoxetine Treatment Strengthens an Anti-Correlated Relationship between Functional Brain Networks in Medication-Naïve Adults with Attention-Deficit Hyperactivity Disorder: A Randomized Double-Blind Placebo-Controlled Clinical Trial. *The International Journal Of Neuropsychopharmacology*, *19*(3), pyv094–pyv094. https://doi.org/10.1093/ijnp/pyv094

Lin, Y., Desbois, A., Jiang, S., & Hou, S. T. (2005). P2 receptor antagonist PPADS confers neuroprotection against glutamate/NMDA toxicity. *Neuroscience Letters*, *377*(2), 97–100. https://doi.org/10.1016/j.neulet.2004.11.075

Lindenmayer, J.-P., Bernstein-Hyman, R., & Grochowski, S. (1994). A new five factor model of schizophrenia. *Psychiatric Quarterly*, *65*(4), 299–322. https://doi.org/10.1007/BF02354306

Lipina, T., Labrie, V., Weiner, I., & Roder, J. (2005). Modulators of the glycine site on NMDA receptors, D-serine and ALX 5407, display similar beneficial effects to clozapine in mouse models of schizophrenia. *Psychopharmacology*, *179*(1), 54–67.

Liu, S K, Chiu, C.-H., Chang, C.-J., Hwang, T.-J., Hwu, H.-G., & Chen, W. J. (2002). Deficits in Sustained Attention in Schizophrenia and Affective Disorders: Stable Versus State-Dependent Markers. *American Journal of Psychiatry*, *159*(6), 975–982. https://doi.org/10.1176/appi.ajp.159.6.975

Liu, Shi K., Chiu, C.-H., Chang, C.-J., Hwang, T.-J., Hwu, H.-G., & Chen, W. J. (2002). Deficits in Sustained Attention in Schizophrenia and Affective Disorders: Stable Versus State-Dependent Markers. *American Journal of Psychiatry*, *159*(6), 975–982.

Liu, T.-L., Chen, D.-Y., & Liang, K. C. (2009). Post-training infusion of glutamate into the bed nucleus of the stria terminalis enhanced inhibitory avoidance memory: An effect involving norepinephrine. *Neurobiology of Learning and Memory*, *91*(4), 456–465. https://doi.org/10.1016/j.nlm.2009.01.003

Liu, Y.-P., Huang, T.-S., Tung, C.-S., & Lin, C.-C. (2015). Effects of atomoxetine on attention and impulsivity in the five-choice serial reaction time task in rats with lesions of dorsal noradrenergic ascending bundle. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *56*, 81–90.

Luccini, E., Musante, V., Neri, E., Bas, M. B., Severi, P., Raiteri, M., & Pittaluga, A. (2007). Functional interactions between presynaptic NMDA receptors and metabotropic glutamate receptors co-expressed on rat and human noradrenergic terminals. *British Journal of Pharmacology*, *151*(7), 1087–1094. https://doi.org/10.1038/sj.bjp.0707280

Luck, S. J., Chelazzi, L., Hillyard, S. A., & Desimone, R. (1997). Neural Mechanisms of Spatial Selective Attention in Areas V1, V2, and V4 of Macaque Visual Cortex. *Journal of Neurophysiology*, *77*(1), 24–42. https://doi.org/10.1152/jn.1997.77.1.24

Lumer, E. D. (2000). Effects of Spike Timing on Winner-Take-All Competition in Model Cortical Circuits. *Neural Computation*, *12*(1), 181–194. https://doi.org/10.1162/089976600300015943

Lund, J. S. (1988). Anatomical Organization of Macaque Monkey Striate Visual Cortex. *Annual Review of Neuroscience*, *11*(1), 253–288. https://doi.org/10.1146/annurev.ne.11.030188.001345

Luppi, P.-H., Aston-Jones, G., Akaoka, H., Chouvet, G., & Jouvet, M. (1995). Afferent projections to the rat locus coeruleus demonstrated by retrograde and anterograde tracing with cholera-toxin B subunit and Phaseolus vulgaris leucoagglutinin. *Neuroscience*, *65*(1), 119–160. https://doi.org/10.1016/0306-4522(94)00481-J

Madison, D. V., & Nicoll, R. A. (1982). Noradrenaline blocks accommodation of pyramidal cell discharge in the hippocampus. *Nature*, *299*(5884), 636–638.

Maekawa, M., Okamura, T., Kasai, N., Hori, Y., Summer, K. H., & Konno, R. (2005). D-amino-acid oxidase is involved in D-serine-induced nephrotoxicity. *Chemical Research in Toxicology*, *18*(11), 1678–1682.

Maldonado, P. E., Friedman-Hill, S., & Gray, C. M. (2000). Dynamics of Striate Cortical Activity in the Alert Macaque: II. Fast Time Scale Synchronization. *Cerebral Cortex*, *10*(11), 1117–1131. https://doi.org/10.1093/cercor/10.11.1117

Manunta, Y., & Edeline, J.-M. (1997). Effects of Noradrenaline on Frequency Tuning of Rat Auditory Cortex Neurons. *The European Journal of Neuroscience*, *9*, 833–847. https://doi.org/10.1111/j.1460-9568.1997.tb01433.x

Manunta, Y., & Edeline, J.-M. (1999). Effects of noradrenaline on frequency tuning of auditory cortex neurons during wakefulness and slow-wave sleep. *European Journal of Neuroscience*, *11*(6), 2134–2150. https://doi.org/10.1046/j.1460-9568.1999.00633.x

Martin, A. B., Yang, X., Saalmann, Y. B., Wang, L., Shestyuk, A., Lin, J. J., Parvizi, J., Knight, R. T., & Kastner, S. (2019). Temporal Dynamics and Response Modulation across the Human Visual System in a Spatial Attention Task: An ECoG Study. *The Journal of Neuroscience*, *39*(2), 333–352. https://doi.org/10.1523/JNEUROSCI.1889-18.2018

Martins, A. R. O., & Froemke, R. C. (2015). Coordinated forms of noradrenergic plasticity in the locus coeruleus and primary auditory cortex. *Nature Neuroscience*, *18*(10), 1483–1492. https://doi.org/10.1038/nn.4090

Marzo, A., Totah, N. K., Neves, R. M., Logothetis, N. K., & Eschenko, O. (2014). Unilateral electrical stimulation of rat locus coeruleus elicits bilateral response of norepinephrine neurons and sustained activation of medial prefrontal cortex. *Journal of Neurophysiology*, *111*(12), 2570–2588.

Mateo, Y., Pineda, J., & Meana, J. J. (1998). Somatodendritic α2-Adrenoceptors in the Locus Coeruleus Are Involved in the In Vivo Modulation of Cortical Noradrenaline Release by the Antidepressant Desipramine. *Journal of Neurochemistry*, *71*(2), 790–798. https://doi.org/10.1046/j.1471-4159.1998.71020790.x

Mather, M., Clewett, D., Sakaki, M., & Harley, C. W. (2016). Norepinephrine ignites local hot spots of neuronal excitation: How arousal amplifies selectivity in perception and memory. *The Behavioral and Brain Sciences*, *39*, e200. https://doi.org/10.1017/S0140525X15000667

Matsui, T., Sekiguchi, M., Hashimoto, A., Tomita, U., Nishikawa, T., & Wada, K. (1995). Functional comparison of D-serine and glycine in rodents: The effect on cloned NMDA receptors and the extracellular concentration. *Journal of Neurochemistry*, *65*(1), 454–458.

McAdams, C. J., & Maunsell, J. H. R. (1999). Effects of Attention on Orientation-Tuning Functions of Single Neurons in Macaque Cortical Area V4. *The Journal of Neuroscience*, *19*(1), 431–441. https://doi.org/10.1523/JNEUROSCI.19-01-00431.1999

McCleery, A., Green, M. F., Hellemann, G. S., Baade, L. E., Gold, J. M., Keefe, R. S. E., Kern, R. S., Mesholam-Gately, R. I., Seidman, L. J., Subotnik, K. L., Ventura, J., & Nuechterlein, K. H. (2015). Latent structure of cognition in schizophrenia: A confirmatory factor analysis of the MATRICS Consensus Cognitive Battery (MCCB). *Psychological Medicine*, *45*(12), 2657–2666. https://doi.org/10.1017/S0033291715000641

McCleery, Amanda, Green, M. F., Hellemann, G. S., Baade, L. E., Gold, J. M., Keefe, R. S. E., Kern, R. S., Mesholam-Gately, R. I., Seidman, L. J., Subotnik, K. L., Ventura, J., & Nuechterlein, K. H. (2015). Latent structure of cognition in schizophrenia: A confirmatory factor analysis of the MATRICS Consensus Cognitive Battery (MCCB). *Psychological Medicine*, *45*(12), 2657–2666.

McLean, J., & Waterhouse, B. D. (1994). Noradrenergic modulation of cat area 17 neuronal responses to moving visual stimuli. *Brain Research*, *667*(1), 83–97. https://doi.org/10.1016/0006-8993(94)91716-7

Meliza, C. D., & Dan, Y. (2006). Receptive-Field Modification in Rat Visual Cortex Induced by Paired Visual Stimulation and Single-Cell Spiking. *Neuron*, *49*(2), 183–189. https://doi.org/10.1016/j.neuron.2005.12.009

Miguelez, C., Fernandez-Aedo, I., Torrecilla, M., Grandoso, L., & Ugedo, L. (2009). A2-Adrenoceptors mediate the acute inhibitory effect of fluoxetine on locus coeruleus noradrenergic neurons. *Neuropharmacology*, *56*(6), 1068–1073. https://doi.org/10.1016/j.neuropharm.2009.03.004

Minota, S., Miyazaki, T., Wang, M. Y., Read, H. L., & Dun, N. J. (1989). Glycine potentiates NMDA responses in rat hippocampal CA1 neurons. *Neuroscience Letters*, *100*(1), 237–242. https://doi.org/10.1016/0304-3940(89)90691-5

Mirjana, C., Baviera, M., Invernizzi, R. W., & Balducci, C. (2004). The Serotonin 5-HT 2A Receptors Antagonist M100907 Prevents Impairment in Attentional Performance by NMDA Receptor Blockade in the Rat Prefrontal Cortex. *Neuropsychopharmacology*, *29*(9), 1637–1647. https://doi.org/10.1038/sj.npp.1300479

Mishima, K., Fujii, M., Aoo, N., Yoshikawa, T., Fukue, Y., Honda, Y., Egashira, N., Iwasaki, K., Shoyama, Y., & Fujiwara, M. (2002). The Pharmacological Characterization of Attentional Processes Using a Two-lever Choice Reaction Time Task in Rats. *Biological and Pharmaceutical Bulletin*, *25*(12), 1570–1576. https://doi.org/10.1248/bpb.25.1570

Misu, Y., & Kubo, T. (1986). Presynaptic beta-adrenoceptors. *Medicinal Research Reviews*, *6*(2), 197–225. https://doi.org/10.1002/med.2610060204

Mitchell, J. F., Sundberg, K. A., & Reynolds, J. H. (2007). Differential Attention-Dependent Response Modulation across Cell Classes in Macaque Visual Area V4. *Neuron*, *55*(1), 131–141. https://doi.org/10.1016/j.neuron.2007.06.018

Mitchell, J. F., Sundberg, K. A., & Reynolds, J. H. (2009). Spatial Attention Decorrelates Intrinsic Activity Fluctuations in Macaque Area V4. *Neuron*, *63*(6), 879–888. https://doi.org/10.1016/j.neuron.2009.09.013

Mitchell, K., Oke, A. F., & Adams, R. N. (1994). In Vivo Dynamics of Norepinephrine Release-Reuptake in Multiple Terminal Field Regions of Rat Brain. *Journal of Neurochemistry*, *63*(3), 917–926. https://doi.org/10.1046/j.1471-4159.1994.63030917.x

Mobley, P., & Greengard, P. (1985a). Evidence for widespread effects of noradrenaline on axon terminals in the rat frontal cortex. *Proceedings of the National Academy of Sciences*, *82*(3), 945–947. https://doi.org/10.1073/pnas.82.3.945

Monahan, J. B., Handelmann, G. E., Hood, W. F., & Cordi, A. A. (1989). D-cycloserine, a positive modulator of the N-methyl-D-aspartate receptor, enhances performance of learning tasks in rats. *Pharmacology, Biochemistry, and Behavior*, *34*(3), 649–653.

Monosov, I. E., & Thompson, K. G. (2009). Frontal Eye Field Activity Enhances Object Identification During Covert Visual Search. *Journal of Neurophysiology*, *102*(6), 3656–3672. https://doi.org/10.1152/jn.00750.2009

Monyer, H., Burnashev, N., Laurie, D. J., Sakmann, B., & Seeburg, P. H. (1994). Developmental and regional expression in the rat brain and functional properties of four NMDA receptors. *Neuron*, *12*(3), 529–540. https://doi.org/10.1016/0896-6273(94)90210-0

Moore, T., & Armstrong, K. M. (2003). Selective gating of visual signals by microstimulation of frontal cortex. *Nature*, *421*(6921), 370–373. https://doi.org/10.1038/nature01341

Moore, T., & Fallah, M. (2001). Control of eye movements and spatial attention. *Proceedings of the National Academy of Sciences*, *98*(3), 1273–1276.

Moore, T., & Fallah, M. (2004). Microstimulation of the Frontal Eye Field and Its Effects on Covert Spatial Attention. *Journal of Neurophysiology*, *91*(1), 152–162.

Morikawa, A., Hamase, K., Inoue, T., Konno, R., & Zaitsu, K. (2007). Alterations in D-amino acid levels in the brains of mice and rats after the administration of D-amino acids. *Amino Acids*, *32*(1), 13–20.

Morishima, Y., Akaishi, R., Yamada, Y., Okuda, J., Toma, K., & Sakai, K. (2009). Task-specific signal transmission from prefrontal cortex in visual selective attention. *Nature Neuroscience*, *12*, 85–91. https://doi.org/10.1038/nn.2237

Morrison, J. H., Foote, S. L., O'Connor, D., & Bloom, F. E. (1982). Laminar, tangential and regional organization of the noradrenergic innervation of monkey cortex: Dopamine-β-hydroxylase immunohistochemistry. *Brain Research Bulletin*, *9*(1), 309–319. https://doi.org/10.1016/0361-9230(82)90144-7

Mothet, J. P., Parent, A. T., Wolosker, H., Brady, R. O., Jr, Linden, D. J., Ferris, C. D., Rogawski, M. A., & Snyder, S. H. (2000). D-serine is an endogenous ligand for the glycine site of the N-methyl-D-aspartate receptor. *Proceedings of The National Academy of Sciences*, *97*(9), 4926–4931.

Murphy, E. R., Dalley, J. W., & Robbins, T. W. (2005). Local glutamate receptor antagonism in the rat prefrontal cortex disrupts response inhibition in a visuospatial attentional task. *Psychopharmacology*, *179*(1), 99–107. https://doi.org/10.1007/s00213-004-2068-3

Murphy, E. R., Fernando, A. B. P., Urcelay, G. P., Robinson, E. S. J., Mar, A. C., Theobald, D. E. H., Dalley, J. W., & Robbins, T. W. (2012). Impulsive behaviour induced by both NMDA receptor antagonism and GABAA receptor activation in rat ventromedial prefrontal cortex. *Psychopharmacology*, *219*(2), 401–410. https://doi.org/10.1007/s00213-011-2572-1

Murugaiah, K D, & O'Donnell, J. M. (1995). Facilitation of norepinephrine release from cerebral cortex is mediated by β2-adrenergic receptors. *Life Sciences*, *57*(20), PL327–PL332. https://doi.org/10.1016/0024-3205(95)02173-G

Murugaiah, K D, & O'Donnell, J. M. (1995). Beta adrenergic receptors facilitate norepinephrine release from rat hypothalamic and hippocampal slices. *Research Communications in Molecular Pathology and Pharmacology*, *90*(2), 179–190.

Nandam, L. S., Hester, R., Wagner, J., Cummins, T. D. R., Garner, K., Dean, A. J., Kim, B. N., Nathan, P. J., Mattingley, J. B., & Bellgrove, M. A. (2011). Methylphenidate But Not Atomoxetine or Citalopram Modulates Inhibitory Control and Response Time Variability. *Biological Psychiatry*, *69*(9), 902–904. https://doi.org/10.1016/j.biopsych.2010.11.014

Navarra, R., Graf, R., Huang, Y., Logue, S., Comery, T., Hughes, Z., & Day, M. (2008). Effects of atomoxetine and methylphenidate on attention and impulsivity in the 5-choice serial reaction time test. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*, *32*(1), 34–41.

Navarra, R., & Waterhouse, B. (2018). Considering noradrenergically mediated facilitation of sensory signal processing as a component of psychostimulant-induced performance enhancement. *Brain Research*, *1709*. https://doi.org/10.1016/j.brainres.2018.06.027

Nelson, C., Burk, J., Bruno, J., & Sarter, M. (2002). Effects of acute and repeated systemic administration of ketamine on prefrontal acetylcholine release and sustained attention performance in rats. *Psychopharmacology*, *161*(2), 168–179. https://doi.org/10.1007/s00213-002-1004-7

Neumeister, A., Carson, R., Henry, S., Planeta-Wilson, B., Binneman, B., Maguire, R. P., Luckenbaugh, D. A., D'Souza, C., Krystal, J. H., & Frost, J. J. (2006a). Cerebral metabolic effects of intravenous glycine in healthy human subjects. *Journal Of Clinical Psychopharmacology*, *26*(6), 595–599.

Neumeister, A., Carson, R., Henry, S., Planeta-Wilson, B., Binneman, B., Maguire, R. P., Luckenbaugh, D. A., D'Souza, C., Krystal, J. H., & Frost, J. J. (2006b). Cerebral Metabolic Effects of Intravenous Glycine in Healthy Human Subjects. *Journal of Clinical*

Psychopharmacology, *26*(6), 595–599. https://doi.org/10.1097/01.jcp.0000245558.14284.aa

Neves, R. M., van Keulen, S., Yang, M., Logothetis, N. K., & Eschenko, O. (2018). Locus coeruleus phasic discharge is essential for stimulus-induced gamma oscillations in the prefrontal cortex. *Journal of Neurophysiology*, *119*(3), 904–920. https://doi.org/10.1152/jn.00552.2017

Ni, H.-C., Hwang Gu, S.-L., Lin, H.-Y., Lin, Y.-J., Yang, L.-K., Huang, H.-C., & Gau, S. S.-F. (2016). Atomoxetine could improve intra-individual variability in drug-naïve adults with attention-deficit/hyperactivity disorder comparably with methylphenidate: A head-to-head randomized clinical trial. *Journal of Psychopharmacology*, *30*(5), 459–467.

Ni, H.-C., Shang, C.-Y., Gau, S. S.-F., Lin, Y.-J., Huang, H.-C., & Yang, L.-K. (2013). A head-to-head randomized clinical trial of methylphenidate and atomoxetine treatment for executive function in adults with attention-deficit hyperactivity disorder. *The International Journal of Neuropsychopharmacology*, *16*(09), 1959–1973. https://doi.org/10.1017/S1461145713000357

Ni, J., Wunderle, T., Lewis, C. M., Desimone, R., Diester, I., & Fries, P. (2016). Gamma-Rhythmic Gain Modulation. *Neuron*, *92*(1), 240–251. https://doi.org/10.1016/j.neuron.2016.09.003

Nicoll, R. A. (1988). The coupling of neurotransmitter receptors to ion channels in the brain. *Science (New York, N.Y.)*, *241*(4865), 545–551.

Niebergall, R., Khayat, P. S., Treue, S., & Martinez-Trujillo, J. C. (2011). Expansion of MT Neurons Excitatory Receptive Fields during Covert Attentive Tracking. *Journal of Neuroscience*, *31*(43), 15499–15510. https://doi.org/10.1523/JNEUROSCI.2822-11.2011

Niebur, E., Koch, C., & Rosin, C. (1993). An oscillation-based model for the neuronal basis of attention. *Vision Research*, *33*(18), 2789–2802. https://doi.org/10.1016/0042-6989(93)90236-P

Nirenberg, S., & Latham, P. E. (2003). Decoding neuronal spike trains: How important are correlations? *Proceedings of the National Academy of Sciences*, *100*(12), 7348–7353. https://doi.org/10.1073/pnas.1131895100

Nobre, A. C., Sebestyen, G. N., Gitelman, D. R., Mesulam, M. M., Frackowiak, R. S., & Frith, C. D. (1997). Functional localization of the system for visuospatial attention using positron emission tomography. *Brain: A Journal of Neurology*, *120*(3), 515–533.

Nomura, S., Bouhadana, M., Morel, C., Faure, P., Cauli, B., Lambolez, B., & Hepp, R. (2014). Noradrenalin and dopamine receptors both control cAMP-PKA signaling throughout the cerebral cortex. *Frontiers In Cellular Neuroscience*, *8*, 247–247.

Nuechterlein, K H, Barch, D. M., Gold, J. M., Goldberg, T. E., Green, M. F., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, *72*(1), 29–39. https://doi.org/10.1016/j.schres.2004.09.007

Nuechterlein, Keith H., Green, M. F., Calkins, M. E., Greenwood, T. A., Gur, R. E., Gur, R. C., Lazzeroni, L. C., Light, G. A., Radant, A. D., Seidman, L. J., Siever, L. J., Silverman, J. M., Sprock, J., Stone, W. S., Sugar, C. A., Swerdlow, N. R., Tsuang, D. W., Tsuang, M. T., Turetsky, B. I., & Braff, D. L. (2015a). Attention/Vigilance in Schizophrenia: Performance Results from a Large Multi-Site Study of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophrenia Research*, *163*(0), 38–46.

Nuechterlein, K H, Green, M. F., Calkins, M. E., Greenwood, T. A., Gur, R. E., Gur, R. C., Lazzeroni, L. C., Light, G. A., Radant, A. D., Seidman, L. J., Siever, L. J., Silverman, J.

M., Sprock, J., Stone, W. S., Sugar, C. A., Swerdlow, N. R., Tsuang, D. W., Tsuang, M. T., Turetsky, B. I., & Braff, D. L. (2015b). Attention/Vigilance in Schizophrenia: Performance Results from a Large Multi-Site Study of the Consortium on the Genetics of Schizophrenia (COGS). *Schizophrenia Research*, *163*(0), 38–46. https://doi.org/10.1016/j.schres.2015.01.017

Nuechterlein, Keith H., Barch, D. M., Gold, J. M., Goldberg, T. E., & Heaton, R. K. (2004). Identification of separable cognitive factors in schizophrenia. *Schizophrenia Research*, *72*, 29–39.

Nuechterlein, Keith H, Green, M. F., Kern, R. S., Baade, L. E., Barch, D. M., Cohen, J. D., Essock, S., Fenton, W. S., Frese, F. J., 3rd, Gold, J. M., Goldberg, T., Heaton, R. K., Keefe, R. S. E., Kraemer, H., Mesholam-Gately, R., Seidman, L. J., Stover, E., Weinberger, D. R., Young, A. S., … Marder, S. R. (2008). The MATRICS Consensus Cognitive Battery, part 1: Test selection, reliability, and validity. *The American Journal Of Psychiatry*, *165*(2), 203–213.

Olney, J. W., Newcomer, J. W., & Farber, N. B. (1999). NMDA receptor hypofunction model of schizophrenia. *Journal of Psychiatric Research*, *33*(6), 523–533. https://doi.org/10.1016/S0022-3956(99)00029-1

Ordway, G., O'Donnell, J., & Frazer, A. (1987). Effects of clenbuterol on central β1 and β2 adrenergic receptors of the rat. *The Journal of Pharmacology and Experimental Therapeutics*, *241*, 187–195.

Orozco-Ibarra, M., Medina-Campos, O. N., Sánchez-González, D. J., Martínez-Martínez, C. M., Floriano-Sánchez, E., Santamaría, A., Ramirez, V., Bobadilla, N. A., & Pedraza-Chaverri, J. (2007a). Evaluation of oxidative stress in d-serine induced nephrotoxicity. *Toxicology*, *229*(1), 123–135. https://doi.org/10.1016/j.tox.2006.10.008

Orozco-Ibarra, M., Medina-Campos, O. N., Sánchez-González, D. J., Martínez-Martínez, C. M., Floriano-Sánchez, E., Santamaría, A., Ramirez, V., Bobadilla, N. A., & Pedraza-Chaverri, J. (2007b). Evaluation of oxidative stress in D-serine induced nephrotoxicity. *Toxicology*, *229*(1–2), 123–135.

Paine, T. A., Tomasiewicz, H. C., Zhang, K., & Carlezon, W. A. (2007). Sensitivity of the Five-Choice Serial Reaction Time Task to the Effects of Various Psychotropic Drugs in Sprague-Dawley Rats. *Biological Psychiatry*, *62*(6), 687–693. https://doi.org/10.1016/j.biopsych.2006.11.017

Palmer, C., Ellis, K. A., O'Neill, B. V., Croft, R. J., Leung, S., Oliver, C., Wesnes, K. A., & Nathan, P. J. (2008a). The cognitive effects of modulating the glycine site of the NMDA receptor with high-dose glycine in healthy controls. *Human Psychopharmacology*, *23*(2), 151–159.

Palmer, C., Ellis, K., O'Neill, B., Croft, R., Leung, S., Oliver, C., Wesnes, K., & Nathan, P. (2008b). The cognitive effects of modulating the glycine site of the NMDA receptor with high-dose glycine in healthy controls. *Human Psychopharmacology: Clinical and Experimental*, *23*(2), 151–159. https://doi.org/10.1002/hup.904

Panizzutti, R., Rausch, M., Zurbrügg, S., Baumann, D., Beckmann, N., & Rudin, M. (2005). The pharmacological stimulation of NMDA receptors via co-agonist site: An fMRI study in the rat brain. *Neuroscience Letters*, *380*(1–2), 111–115.

Papouin, T., Ladépêche, L., Ruel, J., Sacchi, S., Labasque, M., Hanini, M., Groc, L., Pollegioni, L., Mothet, J.-P., & Oliet, S. H. R. (2012). Synaptic and extrasynaptic NMDA receptors are gated by different endogenous coagonists. *Cell*, *150*(3), 633–646.

Paradiso, M. (1988). A theory for the use of visual orientation information which exploits the columnar structure of striate cortex. *Biological Cybernetics*, *58*, 35–49. https://doi.org/10.1007/BF00363954

Parasuraman, R., Warm, J. S., & See, J. E. (1998). Brain systems of vigilance. In *The attentive brain* (pp. 221–256). The MIT Press.

Pascuzzo, G. J., & Skeen, L. C. (1982). Brainstem projections to the frontal eye field in cat. *Brain Research*, *241*(2), 341–346. https://doi.org/10.1016/0006-8993(82)91074-5

Paterson, N. E., Ricciardi, J., Wetzler, C., & Hanania, T. (2011). Sub-optimal performance in the 5-choice serial reaction time task in rats was sensitive to methylphenidate, atomoxetine and d-amphetamine, but unaffected by the COMT inhibitor tolcapone. *Neuroscience Research*, *69*(1), 41–50. https://doi.org/10.1016/j.neures.2010.10.001

Paterson, N. E., Wetzler, C., Hackett, A., & Hanania, T. (2012). Impulsive action and impulsive choice are mediated by distinct neuropharmacological substrates in rat. *The International Journal of Neuropsychopharmacology*, *15*(10), 1473–1487.

Pattij, T., Schetters, D., Schoffelmeer, A. N. M., & van Gaalen, M. M. (2012). On the improvement of inhibitory response control and visuospatial attention by indirect and direct adrenoceptor agonists. *Psychopharmacology*, *219*(2), 327–340.

Paus, T. (1996). Location and function of the human frontal eye-field: A selective review. *Neuropsychologia*, *34*(6), 475–483. https://doi.org/10.1016/0028-3932(95)00134-4

Paus, T., Jech, R., Thompson, C. J., Comeau, R., Peters, T., & Evans, A. C. (1997). Transcranial Magnetic Stimulation during Positron Emission Tomography: A New Method for Studying Connectivity of the Human Cerebral Cortex. *The Journal of Neuroscience*, *17*(9), 3178–3184. https://doi.org/10.1523/JNEUROSCI.17-09-03178.1997

Pehrson, A. L., Bondi, C. O., Totah, N. K. B., & Moghaddam, B. (2013). The influence of NMDA and GABAA receptors and glutamic acid decarboxylase (GAD) activity on attention. *Psychopharmacology*, *225*(1), 31–39. https://doi.org/10.1007/s00213-012-2792-z

Pei, J.-C., Hung, W.-L., Lin, B.-X., Shih, M.-H., Lu, L.-Y., Luo, D.-Z., Tai, H.-C., Studer, V., Min, M.-Y., & Lai, W.-S. (2019). Therapeutic potential and underlying mechanism of sarcosine (N-methylglycine) in N-methyl-D-aspartate (NMDA) receptor hypofunction models of schizophrenia. *Journal Of Psychopharmacology (Oxford, England)*, *33*(10), 1288–1302.

Pernot, P., Maucler, C., Tholance, Y., Vasylieva, N., Debilly, G., Pollegioni, L., Cespuglio, R., & Marinesco, S. (2012). d-Serine diffusion through the blood-brain barrier: Effect on d-serine compartmentalization and storage. *Neurochemistry International*, *60*(8), 837–845.

Pernot, P., Mothet, J.-P., Schuvailo, O., Soldatkin, A., Pollegioni, L., Pilone, M., Adeline, M.-T., Cespuglio, R., & Marinesco, S. (2008). Characterization of a yeast D-amino acid oxidase microbiosensor for D-serine detection in the central nervous system. *Analytical Chemistry*, *80*(5), 1589–1597.

Perry, R. J., & Zeki, S. (2000). The neurology of saccades and covert shifts in spatial attention. *Brain*, *123*(11), 2273–2288. https://doi.org/10.1093/brain/123.11.2273

Petersen, S. E., & Posner, M. I. (2012). The Attention System of the Human Brain: 20 Years After. *Annual Review of Neuroscience*, *35*(1), 73–89. https://doi.org/10.1146/annurev-neuro-062111-150525

Peterson, K., McDonagh, M. S., & Fu, R. (2008). Comparative benefits and harms of competing medications for adults with attention-deficit hyperactivity disorder: A systematic review and indirect comparison meta-analysis. *Psychopharmacology*, *197*(1), 1–11.

Pinault, D. (2008). N-Methyl d-Aspartate Receptor Antagonists Ketamine and MK-801 Induce Wake-Related Aberrant γ Oscillations in the Rat Neocortex. *Biological Psychiatry*, *63*(8), 730–735. https://doi.org/10.1016/j.biopsych.2007.10.006

Pittaluga, A., Pattarini, R., Andrioli, G. C., Viola, C., Munari, C., & Raiteri, M. (1999). Activity of Putative Cognition Enhancers in Kynurenate Test Performed with Human Neocortex Slices. *The Journal of Pharmacology and Experimental Therapeutics*, *290*(1), 423–428.

Polack, P.-O., Friedman, J., & Golshani, P. (2013). Cellular mechanisms of brain-state-dependent gain modulation in visual cortex. *Nature Neuroscience*, *16*(9), 1331–1339. https://doi.org/10.1038/nn.3464

Poort, J., & Roelfsema, P. R. (2009). Noise correlations have little influence on the coding of selective attention in area V1. *Cerebral Cortex*, *19*(3), 543–553.

Posey, D. J., Wiegand, R. E., Wilkerson, J., Maynard, M., Stigler, K. A., & McDougle, C. J. (2006a). Open-label atomoxetine for attention-deficit/ hyperactivity disorder symptoms associated with high-functioning pervasive developmental disorders. *Journal of Child and Adolescent Psychopharmacology*, *16*(5), 599–610.

Posey, D. J., Wiegand, R. E., Wilkerson, J., Maynard, M., Stigler, K. A., & McDougle, C. J. (2006b). Open-Label Atomoxetine for Attention-Deficit/ Hyperactivity Disorder Symptoms Associated with High-Functioning Pervasive Developmental Disorders. *Journal of Child and Adolescent Psychopharmacology*, *16*(5), 599–610. https://doi.org/10.1089/cap.2006.16.599

Posner, M. (1980). Orienting of Attention. *The Quarterly Journal of Experimental Psychology*, *32*, 3–25. https://doi.org/10.1080/00335558008248231

Potasiewicz, A., Nikiforuk, A., Holuj, M., & Popik, P. (2017). Stimulation of nicotinic acetylcholine alpha7 receptors rescue schizophrenia-like cognitive impairments in rats. *Journal of Psychopharmacology*, *31*(2), 260–271.

Pozzi, L., Baviera, M., Sacchetti, G., Calcagno, E., Balducci, C., Invernizzi, R. W., & Carli, M. (2011). Attention deficit induced by blockade of N-methyl d-aspartate receptors in the prefrontal cortex is associated with enhanced glutamate release and cAMP response element binding protein phosphorylation: Role of metabotropic glutamate receptors 2/3. *Neuroscience*, *176*, 336–348. https://doi.org/10.1016/j.neuroscience.2010.11.060

Quintana, H., Cherlin, E. A., Duesenberg, D. A., Bangs, M. E., Ramsey, J. L., Feldman, P. D., Allen, A. J., & Kelsey, D. K. (2007). Transition from methylphenidate or amphetamine to atomoxetine in children and adolescents with attention-deficit/hyperactivity disorder—A preliminary tolerability and efficacy study. *Clinical Therapeutics*, *29*(6), 1168–1177. https://doi.org/10.1016/j.clinthera.2007.06.017

Ramos, B. P., Stark, D., Verduzco, L., van Dyck, C. H., & Arnsten, A. F. T. (2006). 2A-adrenoceptor stimulation improves prefrontal cortical regulation of behavior through inhibition of cAMP signaling in aging animals. *Learning & Memory*, *13*(6), 770–776. https://doi.org/10.1101/lm.298006

Ramos, Brian P., & Arnsten, A. F. T. (2007). Adrenergic Pharmacology and Cognition: Focus on the Prefrontal Cortex. *Pharmacology & Therapeutics*, *113*(3), 523–536.

Ransom, R. W., & Deschenes, N. L. (1989). Glycine modulation of NMDA-evoked release of [3H]acetylcholine and [3H]dopamine from rat striatal slices. *Neuroscience Letters*, *96*(3), 323–328.
Redding, Z. V., Chawla, P., & Sabol, K. E. (2019a). The use of reaction time distributions to study attention in male rats: The effects of atomoxetine and guanfacine. *Psychopharmacology*. https://doi.org/10.1007/s00213-019-05329-6
Redding, Z. V., Chawla, P., & Sabol, K. E. (2019b). The use of reaction time distributions to study attention in male rats: The effects of atomoxetine and guanfacine. *Psychopharmacology*, *236*(12), 3579–3592. https://doi.org/10.1007/s00213-019-05329-6
Reich, D. S., Mechler, F., & Victor, J. D. (2001). Independent and Redundant Information in Nearby Cortical Neurons. *Science*, *294*(5551), 2566–2568.
Ress, D., Backus, B. T., & Heeger, D. J. (2000). Activity in primary visual cortex predicts performance in a visual detection task. *Nature Neuroscience*, *3*(9), 940–945. https://doi.org/10.1038/78856
Reynolds, J. H., & Heeger, D. J. (2009). The Normalization Model of Attention. *Neuron*, *61*(2), 168–185. https://doi.org/10.1016/j.neuron.2009.01.002
Riccio, C. A., Reynolds, C. R., Lowe, P., & Moore, J. J. (2002). The continuous performance test: A window on the neural substrates for attention? *Archives of Clinical Neuropsychology*, 38.
Richter, C. G., Thompson, W. H., Bosman, C. A., & Fries, P. (2017). Top-Down Beta Enhances Bottom-Up Gamma. *The Journal of Neuroscience*, *37*(28), 6698–6711. https://doi.org/10.1523/JNEUROSCI.3771-16.2017
Rinne, A., Birk, A., & Bünemann, M. (2013). Voltage regulates adrenergic receptor function. *Proceedings of The National Academy of Sciences*, *110*(4), 1536–1541.
Robbins, T. (2002). The 5-choice serial reaction time task: Behavioural pharmacology and functional neurochemistry. *Psychopharmacology*, *163*(3–4), 362–380.
Roberts, M. J., Lowet, E., Brunet, N. M., Ter Wal, M., Tiesinga, P., Fries, P., & De Weerd, P. (2013). Robust Gamma Coherence between Macaque V1 and V2 by Dynamic Frequency Matching. *Neuron*, *78*(3), 523–536. https://doi.org/10.1016/j.neuron.2013.03.003
Robinson, D. A., & Fuchs, A. F. (1969). Eye movements evoked by stimulation of frontal eye fields. *Journal of Neurophysiology*, *32*(5), 637–648. https://doi.org/10.1152/jn.1969.32.5.637
Robinson, E. S. J. (2012). Blockade of noradrenaline re-uptake sites improves accuracy and impulse control in rats performing a five-choice serial reaction time tasks. *Psychopharmacology*, *219*(2), 303–312.
Robinson, E. S. J., Eagle, D. M., Mar, A. C., Bari, A., Banerjee, G., Jiang, X., Dalley, J. W., & Robbins, T. W. (2008). Similar effects of the selective noradrenaline reuptake inhibitor atomoxetine on three distinct forms of impulsivity in the rat. *Neuropsychopharmacology*, *33*(5), 1028–1037.
Roelfsema, P. R., Engel, A. K., König, P., & Singer, W. (1997). Visuomotor integration is associated with zero time-lag synchronization among cortical areas. *Nature*, *385*(6612), 157–161. https://doi.org/10.1038/385157a0
Rohenkohl, G., Bosman, C. A., & Fries, P. (2018). Gamma Synchronization between V1 and V4 Improves Behavioral Performance. *Neuron*, *100*(4), 953-963.e3. https://doi.org/10.1016/j.neuron.2018.09.019

Room, P., Postema, F., & Korf, J. (1981). Divergent axon collaterals of rat locus coeruleus neurons: Demonstration by a fluorescent double labeling technique. *Brain Research*, *221*, 219–230.

Rosvold, H. E., Mirsky, A. F., Sarason, I., Bransome, E. D., & Beck, L. H. (1956). A continuous performance test of brain damage. *Journal of Consulting Psychology*, *20*(5), 343–350. https://doi.org/10.1037/h0043220

Ruff, C. C., Bestmann, S., Blankenburg, F., Bjoertomt, O., Josephs, O., Weiskopf, N., Deichmann, R., & Driver, J. (2008). Distinct Causal Influences of Parietal Versus Frontal Areas on Human Visual Cortex: Evidence from Concurrent TMS–fMRI. *Cerebral Cortex*, *18*(4), 817–827. https://doi.org/10.1093/cercor/bhm128

Ruff, C. C., Blankenburg, F., Bjoertomt, O., Bestmann, S., Freeman, E., Haynes, J.-D., Rees, G., Josephs, O., Deichmann, R., & Driver, J. (2006). Concurrent TMS-fMRI and Psychophysics Reveal Frontal Influences on Human Retinotopic Visual Cortex. *Current Biology*, *16*(15), 1479–1488. https://doi.org/10.1016/j.cub.2006.06.057

Ruff, D. A., & Cohen, M. R. (2014). Attention can either increase or decrease spike count correlations in visual cortex. *Nature Neuroscience*, *17*(11), 1591–1597.

Saalmann, Y. B., Ly, R., Pinsk, M. A., & Kastner, S. (2018). Pulvinar influences parietal delay activity and information transmission between dorsal and ventral visual cortex in macaques. *BioRxiv*. https://doi.org/10.1101/405381

Sabol, K. E., Richards, J. B., Broom, S. L., Roach, J. T., & Hausknecht, K. (2003). Effects of stimulus salience and methamphetamine on choice reaction time in the rat: Central tendency versus distribution skew. *Behavioural Pharmacology*, *14*(7), 489.

Sagvolden, T. (2000). Behavioral validation of the spontaneously hypertensive rat (SHR) as an animal model of attention-deficit/hyperactivity disorder (AD/HD). *Neuroscience & Biobehavioral Reviews*, *24*(1), 31–39. https://doi.org/10.1016/S0149-7634(99)00058-5

Sagvolden, T., Aase, H., Zeiner, P., & Berger, D. (1998). Altered reinforcement mechanisms in attention-deficit/hyperactivity disorder. *Behavioural Brain Research*, *94*(1), 61–71. https://doi.org/10.1016/S0166-4328(97)00170-8

Sagvolden, T., Johansen, E. B., Wøien, G., Walaas, S. I., Storm-Mathisen, J., Bergersen, L. H., Hvalby, Ø., Jensen, V., Aase, H., Russell, V. A., Killeen, P. R., DasBanerjee, T., Middleton, F. A., & Faraone, S. V. (2009). The spontaneously hypertensive rat model of ADHD – The importance of selecting the appropriate reference strain. *Neuropharmacology*, *57*(7), 619–626. https://doi.org/10.1016/j.neuropharm.2009.08.004

Sagvolden, T., Russell, V. A., Aase, H., Johansen, E. B., & Farshbaf, M. (2005). Rodent Models of Attention-Deficit/Hyperactivity Disorder. *Biological Psychiatry*, *57*(11), 1239–1247. https://doi.org/10.1016/j.biopsych.2005.02.002

Saletu, B., & Grünberger, J. (1984). Early clinical pharmacological trials with a new anti-epileptic, milacemide, using pharmaco-EEG and psychometry. *Methods and Findings in Experimental and Clinical Pharmacology*, *6*(6), 317–330.

Saletu, B., Grünberger, J., & Linzmayer, L. (1986). Acute and subacute CNS effects of milacemide in elderly people: Double-blind, placebo-controlled quantitative EEG and psychometric investigations. *Archives Of Gerontology And Geriatrics*, *5*(3), 165–181.

Salinas, E., & Sejnowski, T. J. (2001). Correlated neuronal activity and the flow of neural information. *Nature Reviews Neuroscience*, *2*(8), 539–550. https://doi.org/10.1038/35086012

Salkoff, D. B., Zagha, E., Yuzgec, O., & McCormick, D. A. (2015). Synaptic Mechanisms of Tight Spike Synchrony at Gamma Frequency in Cerebral Cortex. *Journal of Neuroscience*, *35*(28), 10236–10251. https://doi.org/10.1523/JNEUROSCI.0828-15.2015

Samuels, E. R., & Szabadi, E. (2008). Functional Neuroanatomy of the Noradrenergic Locus Coeruleus: Its Roles in the Regulation of Arousal and Autonomic Function Part I: Principles of Functional Organisation. *Current Neuropharmacology*, *6*(3), 235–253. https://doi.org/10.2174/157015908785777229

Sapir, A., d'Avossa, G., McAvoy, M., Shulman, G. L., & Corbetta, M. (2005). Brain signals for spatial attention predict performance in a motion discrimination task. *Proceedings of the National Academy of Sciences*, *102*(49), 17810–17815. https://doi.org/10.1073/pnas.0504678102

Sara, S. J., & Herve-Minvielle, A. (1995). Inhibitory influence of frontal cortex on locus coeruleus neurons. *Proceedings of the National Academy of Sciences*, *92*(13), 6032–6036. https://doi.org/10.1073/pnas.92.13.6032

Sara, S J, Vankov, A., & Hervé, A. (1994). Locus coeruleus-evoked responses in behaving rats: A clue to the role of noradrenaline in memory. *Brain Research Bulletin*, *35*(5–6), 457–465.

Sara, Susan J., Vankov, A., & Hervé, A. (1994). Locus coeruleus-evoked responses in behaving rats: A clue to the role of noradrenaline in memory. *Brain Research Bulletin*, *35*(5), 457–465. https://doi.org/10.1016/0361-9230(94)90159-7

Sara, Susan J., & Bouret, S. (2012). Orienting and Reorienting: The Locus Coeruleus Mediates Cognition through Arousal. *Neuron*, *76*(1), 130–141. https://doi.org/10.1016/j.neuron.2012.09.011

Saunders, J., Gandal, M., & Siegel, S. (2012). NMDA Antagonists Recreate Signal-to-Noise Ratio and Timing Perturbations Present in Schizophrenia. *Neurobiology of Disease*, *46*(1), 93–100. https://doi.org/10.1016/j.nbd.2011.12.049

Saygin, A. P., & Sereno, M. I. (2008). Retinotopy and Attention in Human Occipital, Temporal, Parietal, and Frontal Cortex. *Cerebral Cortex*, *18*(9), 2158–2168. https://doi.org/10.1093/cercor/bhm242

Schafer, R. J., & Moore, T. (2011). Selective Attention from Voluntary Control of Neurons in Prefrontal Cortex. *Science (New York, N.y.)*, *332*(6037), 1568–1571. https://doi.org/10.1126/science.1199892

Schell, M. J., Molliver, M. E., & Snyder, S. H. (1995). D-serine, an endogenous synaptic modulator: Localization to astrocytes and glutamate-stimulated release. *Proceedings of The National Academy of Sciences*, *92*(9), 3948–3952.

Schneider, W., & Shiffrin, R. M. (1977). Controlled and automatic human information processing: I. Detection, search, and attention. *Psychological Review*, *84*(1), 1–66. https://doi.org/10.1037/0033-295X.84.1.1

Schwarz, L. A., & Luo, L. (2015). Organization of the Locus Coeruleus-Norepinephrine System. *Current Biology*, *25*(21), R1051–R1056. https://doi.org/10.1016/j.cub.2015.09.039

Selemon, L., & Goldman-Rakic, P. (1988). Common cortical and subcortical targets of the dorsolateral prefrontal and posterior parietal cortices in the rhesus monkey: Evidence for a distributed neural network subserving spatially guided behavior. *The Journal of Neuroscience*, *8*(11), 4049–4068. https://doi.org/10.1523/JNEUROSCI.08-11-04049.1988

Self, M. W., Kooijmans, R. N., Super, H., Lamme, V. A., & Roelfsema, P. R. (2012). Different glutamate receptors convey feedforward and recurrent processing in macaque V1. *Proceedings of the National Academy of Sciences*, *109*(27), 11031–11036. https://doi.org/10.1073/pnas.1119527109

Serences, J. T., & Yantis, S. (2007). Spatially Selective Representations of Voluntary and Stimulus-Driven Attentional Priority in Human Occipital, Parietal, and Frontal Cortex. *Cerebral Cortex*, *17*(2), 284–293. https://doi.org/10.1093/cercor/bhj146

Sereno, M., Pitzalis, S., & Martinez, A. (2001). Mapping of Contralateral Space in Retinotopic Coordinates by a Parietal Cortical Area in Humans. *Science (New York, N.Y.)*, *294*, 1350–1354. https://doi.org/10.1126/science.1063695

Seriès, P., Latham, P., & Pouget, A. (2004). Tuning curve sharpening for orientation selectivity: Coding efficiency and the impact of correlations. *Nature Neuroscience*, *7*(10), 1129–1135. https://doi.org/10.1038/nn1321

Servan-Schreiber, D., Printz, H., & Cohen, J. (1990). A Network Model of Catecholamiine Effects: Gain, Signal-to-Noise Ratio, and Behavior. *Science*, *249*(4971), 892–895.

Shadlen, M. N., Britten, K. H., Newsome, W. T., & Movshon, J. A. (1996). A computational analysis of the relationship between neuronal and behavioral responses to visual motion. *The Journal of Neuroscience*, *16*(4), 1486–1510. https://doi.org/10.1523/JNEUROSCI.16-04-01486.1996

Shadlen, Michael N., & Newsome, W. T. (1994). Noise, neural codes and cortical organization. *Current Opinion in Neurobiology*, *4*(4), 569–579. https://doi.org/10.1016/0959-4388(94)90059-0

Shadlen, Michael N., & Newsome, W. T. (1998). The Variable Discharge of Cortical Neurons: Implications for Connectivity, Computation, and Information Coding. *The Journal of Neuroscience*, *18*(10), 3870–3896. https://doi.org/10.1523/JNEUROSCI.18-10-03870.1998

Shang, C.-Y., & Gau, S. S.-F. (2012). Improving visual memory, attention, and school function with atomoxetine in boys with attention-deficit/hyperactivity disorder. *Journal of Child and Adolescent Psychopharmacology*, *22*(5), 353–363. https://doi.org/10.1089/cap.2011.0149

Shaw, A. D., Saxena, N., E. Jackson, L., Hall, J. E., Singh, K. D., & Muthukumaraswamy, S. D. (2015). Ketamine amplifies induced gamma frequency oscillations in the human cerebral cortex. *European Neuropsychopharmacology*, *25*(8), 1136–1146. https://doi.org/10.1016/j.euroneuro.2015.04.012

Shea-Brown, E., Gilzenrat, M. S., & Cohen, J. D. (2008). Optimization of Decision Making in Multilayer Networks: The Role of Locus Coeruleus. *Neural Computation*, *20*(12), 2863–2894. https://doi.org/10.1162/neco.2008.03-07-487

Shimazaki, T., Kaku, A., & Chaki, S. (2010). D-Serine and a glycine transporter-1 inhibitor enhance social memory in rats. *Psychopharmacology*, *209*(3), 263–270.

Shipp, S. (2003). The functional logic of cortico–pulvinar connections. *Philosophical Transactions of the Royal Society of London. Series B: Biological Sciences*, *358*(1438), 1605–1624. https://doi.org/10.1098/rstb.2002.1213

Silvanto, J., Lavie, N., & Walsh, V. (2006). Stimulation of the Human Frontal Eye Fields Modulates Sensitivity of Extrastriate Visual Cortex. *Journal of Neurophysiology*, *96*(2), 941–945. https://doi.org/10.1152/jn.00015.2006

Silver, M. A., Ress, D., & Heeger, D. J. (2005). Topographic Maps of Visual Spatial Attention in Human Parietal Cortex. *Journal of Neurophysiology*, *94*(2), 1358–1371. https://doi.org/10.1152/jn.01316.2004

Silver, M. A., Ress, D., & Heeger, D. J. (2007). Neural Correlates of Sustained Spatial Attention in Human Early Visual Cortex. *Journal of Neurophysiology*, *97*(1), 229–237. https://doi.org/10.1152/jn.00677.2006

Singer, W., & Gray, C. M. (1995). Visual Feature Integration and the Temporal Correlation Hypothesis. *Annual Review of Neuroscience*, *18*, 555–586.

Smith, J. W., Gastambide, F., Gilmour, G., Dix, S., Foss, J., Lloyd, K., Malik, N., & Tricklebank, M. (2011). A comparison of the effects of ketamine and phencyclidine with other antagonists of the NMDA receptor in rodent assays of attention and working memory. *Psychopharmacology*, *217*(2), 255–269. https://doi.org/10.1007/s00213-011-2277-5

Smith, K. E., Borden, L. A., Hartig, P. R., Branchek, T., & Weinshank, R. L. (1992). Cloning and expression of a glycine transporter reveal colocalization with NMDA receptors. *Neuron*, *8*(5), 927–935.

Smith, S. M., Uslaner, J. M., & Hutson, P. H. (2010). The Therapeutic Potential of D-Amino Acid Oxidase (DAAO) Inhibitors. *The Open Medicinal Chemistry Journal*, *4*, 3–9.

Smith, S. M., Uslaner, J. M., Yao, L., Mullins, C. M., Surles, N. O., Huszar, S. L., McNaughton, C. H., Pascarella, D. M., Kandebo, M., Hinchliffe, R. M., Sparey, T., Brandon, N. J., Jones, B., Venkatraman, S., Young, M. B., Sachs, N., Jacobson, M. A., & Hutson, P. H. (2009). The behavioral and neurochemical effects of a novel D-amino acid oxidase inhibitor compound 8 [4H-thieno [3,2-b]pyrrole-5-carboxylic acid] and D-serine. *The Journal Of Pharmacology And Experimental Therapeutics*, *328*(3), 921–930.

Smyth, M. M. (1996). Interference with Rehearsal in Spatial Working Memory in the Absence of Eye Movements. *The Quarterly Journal of Experimental Psychology*, *49*(4), 940–949. https://doi.org/10.1080/713755669

Smyth, M. M., & Scholey, K. A. (1994). Interference in immediate spatial memory. *Memory & Cognition*, *22*(1), 1–13. https://doi.org/10.3758/BF03202756

Snippe, H. P., & Koenderink, J. J. (1992). Information in channel-coded systems: Correlated receivers. *Biological Cybernetics*, *67*(2), 183–190. https://doi.org/10.1007/BF00201025

Solanto, M. V. (1998). Neuropsychopharmacological mechanisms of stimulant drug action in attention-deficit hyperactivity disorder: A review and integration. *Behavioural Brain Research*, *94*(1), 127–152.

Spitzer, H., Desimone, R., & Moran, J. (1988). Increased attention enhances both behavioral and neuronal performance. *Science*, *240*(4850), 338–340. https://doi.org/10.1126/science.3353728

Stanton, G. B., Bruce, C. J., & Goldberg, M. E. (1995). Topography of projections to posterior cortical areas from the macaque frontal eye fields. *The Journal of Comparative Neurology*, *353*(2), 291–305. https://doi.org/10.1002/cne.903530210

Starke, K. (2001). Presynaptic autoreceptors in the third decade: Focus on alpha2-adrenoceptors. *Journal Of Neurochemistry*, *78*(4), 685–693.

Starke, K., & Montel, H. (1973). Sympathomimetic inhibition of noradrenaline release: Mediated by prostaglandins? *Naunyn-Schmiedeberg's Archives of Pharmacology*, *278*(1), 111–116. https://doi.org/10.1007/BF00501869

Steriade, M., Amzica, F., & Nunez, A. (1993). Cholinergic and noradrenergic modulation of the slow (approximately 0.3 Hz) oscillation in neocortical cells. *Journal of Neurophysiology*, *70*(4), 1385–1400. https://doi.org/10.1152/jn.1993.70.4.1385

Steriade, M., Dossi, R. C., & Nunez, A. (1991). Network modulation of a slow intrinsic oscillation of cat thalamocortical neurons implicated in sleep delta waves: Cortically induced synchronization and brainstem cholinergic suppression. *The Journal of Neuroscience*, *11*(10), 3200–3217. https://doi.org/10.1523/JNEUROSCI.11-10-03200.1991

Steriade, M., Dossi, R. C., Pare, D., & Oakson, G. (1991). Fast oscillations (20-40 Hz) in thalamocortical systems and their potentiation by mesopontine cholinergic nuclei in the cat. *Proceedings of the National Academy of Sciences*, *88*(10), 4396–4400. https://doi.org/10.1073/pnas.88.10.4396

Stouffer, E. M., Petri, H. L., & Devan, B. D. (2004). Effect of D-serine on a delayed match-to-place task for the water maze. *Behavioural Brain Research*, *152*(2), 447–452.

Summers, R. J., & McMartin, L. R. (1993). Adrenoceptors and Their Second Messenger Systems. *Journal of Neurochemistry*, *60*(1), 10–23. https://doi.org/10.1111/j.1471-4159.1993.tb05817.x

Sun, H., Cocker, P. J., Zeeb, F. D., & Winstanley, C. A. (2012). Chronic atomoxetine treatment during adolescence decreases impulsive choice, but not impulsive action, in adult rats and alters markers of synaptic plasticity in the orbitofrontal cortex. *Psychopharmacology*, *219*(2), 285–301. https://doi.org/10.1007/s00213-011-2419-9

Svensson, T. H., Bunney, B. S., & Aghajanian, G. K. (1975). Inhibition of both noradrenergic and serotonergic neurons in brain by the α-adrenergic agonist clonidine. *Brain Research*, *92*(2), 291–306. https://doi.org/10.1016/0006-8993(75)90276-0

Svensson, T. H., & Usdin, T. (1978). Feedback inhibition of brain noradrenaline neurons by tricyclic antidepressants: Alpha-receptor mediation. *Science*, *202*(4372), 1089–1091. https://doi.org/10.1126/science.213833

Swanson, L. W., & Hartman, B. K. (1975). The central adrenergic system. An immunofluorescence study of the location of cell bodies and their efferent connections in the rat utilizing dopamine-B-hydroxylase as a marker. *Journal of Comparative Neurology*, *163*(4), 467–505.

Sylvester, C. M., Shulman, G. L., Jack, A. I., & Corbetta, M. (2007). Asymmetry of Anticipatory Activity in Visual Cortex Predicts the Locus of Attention and Perception. *Journal of Neuroscience*, *27*(52), 14424–14433. https://doi.org/10.1523/JNEUROSCI.3759-07.2007

Szczepanski, S. M., Konen, C. S., & Kastner, S. (2010). Mechanisms of Spatial Attention Control in Frontal and Parietal Cortex. *Journal of Neuroscience*, *30*(1), 148–160. https://doi.org/10.1523/JNEUROSCI.3862-09.2010

Szczepanski, S. M., Pinsk, M. A., Douglas, M. M., Kastner, S., & Saalmann, Y. B. (2013). Functional and structural architecture of the human dorsal frontoparietal attention network. *Proceedings of the National Academy of Sciences*, *110*(39), 15806–15811. https://doi.org/10.1073/pnas.1313903110

Takahashi, K., Hayashi, F., & Nishikawa, T. (1997). In vivo evidence for the link between L- and D-serine metabolism in rat cerebral cortex. *Journal Of Neurochemistry*, *69*(3), 1286–1290.

Tallarida, R. J. (2000). *Drug Synergism and Dose-Effect Data Analysis*. CRC Press.

Tallarida, R. J. (2011). Quantitative Methods for Assessing Drug Synergism. *Genes & Cancer*, *2*(11), 1003–1008. https://doi.org/10.1177/1947601912440575

Tallarida, R. J., & Raffa, R. B. (1995). Testing for synergism over a range of fixed ratio drug combinations: Replacing the isobologram. *Life Sciences*, *58*(2), PL23–PL28. https://doi.org/10.1016/0024-3205(95)02271-6

Tamm, L., Narad, M. E., Antonini, T. N., O'Brien, K. M., Hawk, L. W., & Epstein, J. N. (2012a). Reaction Time Variability in ADHD: A Review. *Neurotherapeutics*, *9*(3), 500–508. https://doi.org/10.1007/s13311-012-0138-5

Tamm, L., Narad, M. E., Antonini, T. N., O'Brien, K. M., Hawk, L. W., & Epstein, J. N. (2012b). Reaction time variability in ADHD: A review. *Neurotherapeutics*, *9*(3), 500–508.

Taylor, C. A., Tsai, C., & Lehmann, J. (1988). Glycine-evoked release of [3H]acetylcholine from rat striatal slices is independent of the NMDA receptor. *Naunyn-Schmiedeberg's Archives Of Pharmacology*, *337*(5), 552–555.

Taylor, P. C. J., Nobre, A. C., & Rushworth, M. F. S. (2007). FEF TMS Affects Visual Cortical Activity. *Cerebral Cortex*, *17*(2), 391–399. https://doi.org/10.1093/cercor/bhj156

Terry, A. V., Buccafusco, J. J., Schade, R. F., Vandenhuerk, L., Callahan, P. M., Beck, W. D., Hutchings, E. J., Chapman, J. M., Li, P., & Bartlett, M. G. (2012). The nicotine metabolite, cotinine, attenuates glutamate (NMDA) antagonist-related effects on the performance of the five choice serial reaction time task (5C-SRTT) in rats. *Biochemical Pharmacology*, *83*(7), 941–951. https://doi.org/10.1016/j.bcp.2011.12.043

Thomas, J. W., Hood, W. F., Monahan, J. B., Contreras, P. C., & O'Donohue, T. L. (1988). Glycine modulation of the phencyclidine binding site in mammalian brain. *Brain Research*, *442*(2), 396–398. https://doi.org/10.1016/0006-8993(88)91533-8

Thompson, K., & Bichot, N. (2005). A visual salience map in the primate frontal eye field. *Progress in Brain Research*, *147*, 251–262.

Thompson, K. G., Bichot, N. P., & Schall, J. D. (1997). Dissociation of visual discrimination from saccade programming in macaque frontal eye field. *Journal of Neurophysiology*, *77*(2), 1046–1050.

Thompson, K. G., Biscoe, K. L., & Sato, T. R. (2005). Neuronal Basis of Covert Spatial Attention in the Frontal Eye Field. *Journal of Neuroscience*, *25*(41), 9479–9487. https://doi.org/10.1523/JNEUROSCI.0741-05.2005

Tiesinga, P. H., Fellous, J.-M., Salinas, E., José, J. V., & Sejnowski, T. J. (2004). Inhibitory synchrony as a mechanism for attentional gain modulation. *Journal of Physiology, Paris*, *98*(4–6), 296–314. https://doi.org/10.1016/j.jphysparis.2005.09.002

Tiesinga, P., & Sejnowski, T. J. (2009). Cortical Enlightenment: Are Attentional Gamma Oscillations Driven by ING or PING? *Neuron*, *63*(6), 727–732. https://doi.org/10.1016/j.neuron.2009.09.009

Todd, J. J., & Marois, R. (2004). Capacity limit of visual short-term memory in human posterior parietal cortex. *Nature*, *428*(6984), 751–754. https://doi.org/10.1038/nature02466

Tolhurst, D. J., Movshon, J. A., & Dean, A. F. (1983). The statistical reliability of signals in single neurons in cat and monkey visual cortex. *Vision Research*, *23*(8), 775–785. https://doi.org/10.1016/0042-6989(83)90200-6

Tomko, G. J., & Crapper, D. R. (1974). Neuronal variability: Non-stationary responses to identical visual stimuli. *Brain Research*, *79*(3), 405–418. https://doi.org/10.1016/0006-8993(74)90438-7

Tomlinson, A., Grayson, B., Marsh, S., Harte, M. K., Barnes, S. A., Marshall, K. M., & Neill, J. C. (2014). Pay attention to impulsivity: Modelling low attentive and high impulsive subtypes of adult ADHD in the 5-choice continuous performance task (5C-CPT) in female rats. *European Neuropsychopharmacology*, *24*(8), 1371–1380. https://doi.org/10.1016/j.euroneuro.2014.04.008

Totah, N. K. B., Logothetis, N. K., & Eschenko, O. (2019). Noradrenergic ensemble-based modulation of cognition over multiple timescales. *Brain Research*, *1709*, 50–66. https://doi.org/10.1016/j.brainres.2018.12.031

Traynelis, S. F., Wollmuth, L. P., McBain, C. J., Menniti, F. S., Vance, K. M., Ogden, K. K., Hansen, K. B., Yuan, H., Myers, S. J., & Dingledine, R. (2010). Glutamate Receptor Ion Channels: Structure, Regulation, and Function. *Pharmacological Reviews*, *62*(3), 405–496. https://doi.org/10.1124/pr.109.002451

Treisman, A. M., & Gelade, G. (1980). *A Feature-Integration Theory of Attention*. *12*, 97–136.

Tremblay, S., Doucet, G., Pieper, F., Sachs, A., & Martinez-Trujillo, J. (2015). Single-Trial Decoding of Visual Attention from Local Field Potentials in the Primate Lateral Prefrontal Cortex Is Frequency-Dependent. *Journal of Neuroscience*, *35*(24), 9038–9049. https://doi.org/10.1523/JNEUROSCI.1041-15.2015

Tsai, G. E., Yang, P., Chung, L. C., Tsai, I. C., Tsai, C. W., & Coyle, J. T. (1999). D-serine added to clozapine for the treatment of schizophrenia. *The American Journal of Psychiatry*, *156*(11), 1822–1825.

Tsai, G, Yang, P., Chung, L. C., Lange, N., & Coyle, J. T. (1998). D-serine added to antipsychotics for the treatment of schizophrenia. *Biological Psychiatry*, *44*(11), 1081–1089.

Tsai, Guochuan, Lane, H.-Y., Yang, P., Chong, M.-Y., & Lange, N. (2004). Glycine transporter I inhibitor, N-methylglycine (sarcosine), added to antipsychotics for the treatment of schizophrenia. *Biological Psychiatry*, *55*(5), 452–456.

Tsotsos, J. (1990). Analyzing Vision at the Complexity Level. *Behavioral and Brain Sciences*, *13*(3), 423–469. https://doi.org/10.1017/S0140525X00079577

Tsutsui-Kimura, I., Ohmura, Y., Izumi, T., Yamaguchi, T., Yoshida, T., & Yoshioka, M. (2009). The effects of serotionin and/or noradrenaline reuptake inhibitors on impulsive-like action assessed by the three-choice serial reaction time task: A simple and valid model of impulsive action using rats. *Behavioral Pharmacology*, *20*(5–6), 45.

Ueda, H., Goshima, Y., Kubo, T., & Misu, Y. (1985). Involvement of epinephrine in the presynaptic beta adrenoceptor mechanism of norepinephrine release from rat hypothalamic slices. *The Journal of Pharmacology and Experimental Therapeutics*, *232*(2), 507–512.

Uematsu, A., Tan, B. Z., Ycu, E. A., Cuevas, J. S., Koivumaa, J., Junyent, F., Kremer, E. J., Witten, I. B., Deisseroth, K., & Johansen, J. P. (2017). Modular organization of the brainstem noradrenaline system coordinates opposing learning states. *Nature Neuroscience*, *20*(11), 1602–1611. https://doi.org/10.1038/nn.4642

Uhlhaas, P. J., Haenschel, C., Nikolic, D., & Singer, W. (2008). The Role of Oscillations and Synchrony in Cortical Networks and Their Putative Relevance for the Pathophysiology of Schizophrenia. *Schizophrenia Bulletin*, *34*(5), 927–943. https://doi.org/10.1093/schbul/sbn062

Uhlhaas, Peter J., & Singer, W. (2010). Abnormal neural oscillations and synchrony in schizophrenia. *Nature Reviews Neuroscience*, *11*(2), 100–113. https://doi.org/10.1038/nrn2774

Ungerleider, L. G., Galkin, T. W., Desimone, R., & Gattass, R. (2008). Cortical Connections of Area V4 in the Macaque. *Cerebral Cortex*, *18*(3), 477–499. https://doi.org/10.1093/cercor/bhm061

Ungerleider, Leslie G., & Haxby, J. V. (1994). "What" and "where" in the human brain. *Current Opinion in Neurobiology*, *4*(2), 157–165. https://doi.org/10.1016/0959-4388(94)90066-3

Usher, M., Cohen, J. D., Servan-Schreiber, D., Rajkowski, J., & Aston-Jones, G. (1999a). The Role of Locus Coeruleus in the Regulation of Cognitive Performance. *Science*, *283*(5401), 549–554. https://doi.org/10.1126/science.283.5401.549

Usher, M., Cohen, J. D., Servan-Schreiber, D., Rajkowski, J., & Aston-Jones, G. (1999b). The Role of Locus Coeruleus in the Regulation of Cognitive Performance. *Science*, *283*(5401), 549–554.

Van Essen, D. C., Lewis, J. W., Drury, H. A., Hadjikhani, N., Tootell, R. B. H., Bakircioglu, M., & Miller, M. I. (2001). Mapping visual cortex in monkeys and humans using surface-based atlases. *Vision Research*, *41*(10–11), 1359–1378. https://doi.org/10.1016/S0042-6989(01)00045-1

van Kerkoerle, T., Self, M. W., Dagnino, B., Gariel-Mathis, M.-A., Poort, J., van der Togt, C., & Roelfsema, P. R. (2014). Alpha and gamma oscillations characterize feedback and feedforward processing in monkey visual cortex. *Proceedings of the National Academy of Sciences*, *111*(40), 14332–14341. https://doi.org/10.1073/pnas.1402773111

van Loon, A. M., Fahrenfort, J. J., van der Velde, B., Lirk, P. B., Vulink, N. C. C., Hollmann, M. W., Steven Scholte, H., & Lamme, V. A. F. (2016). NMDA Receptor Antagonist Ketamine Distorts Object Recognition by Reducing Feedback to Early Visual Cortex. *Cerebral Cortex*, *26*(5), 1986–1996. https://doi.org/10.1093/cercor/bhv018

van Vugt, B., van Kerkoerle, T., Vartak, D., & Roelfsema, P. R. (2020). The Contribution of AMPA and NMDA Receptors to Persistent Firing in the Dorsolateral Prefrontal Cortex in Working Memory. *The Journal of Neuroscience*, *40*(12), 2458–2470. https://doi.org/10.1523/JNEUROSCI.2121-19.2020

Vandenberghe, R., Gitelman, D. R., Parrish, T. B., & Mesulam, M. M. (2001). Location- or Feature-Based Targeting of Peripheral Attention. *NeuroImage*, *14*(1), 37–47. https://doi.org/10.1006/nimg.2001.0790

Vinck, M., Womelsdorf, T., Buffalo, E. A., Desimone, R., & Fries, P. (2013). Attentional Modulation of Cell-Class-Specific Gamma-Band Synchronization in Awake Monkey Area V4. *Neuron*, *80*(4), 1077–1089. https://doi.org/10.1016/j.neuron.2013.08.019

Wagatsuma, N., von der Heydt, R., & Niebur, E. (2016). Spike synchrony generated by modulatory common input through NMDA-type synapses. *Journal of Neurophysiology*, *116*(3), 1418–1433.

Wang, M., & Arnsten, A. F. T. (2015). Contribution of NMDA receptors to dorsolateral prefrontal cortical networks in primates. *Neuroscience Bulletin*, *31*(2), 191–197. https://doi.org/10.1007/s12264-014-1504-6

Wang, M., Ramos, B. P., Paspalas, C. D., Shu, Y., Simen, A., Duque, A., Vijayraghavan, S., Brennan, A., Dudley, A., Nou, E., Mazer, J. A., McCormick, D. A., & Arnsten, A. F. T. (2007). A2A-adrenoceptors strengthen working memory networks by inhibiting cAMP-HCN channel signaling in prefrontal cortex. *Cell*, *129*(2), 397–410.

Wang, M., Yang, Y., Wang, C.-J., Gamo, N. J., Jin, L. E., Mazer, J. A., Morrison, J. H., Wang, X.-J., & Arnsten, A. F. T. (2013a). NMDA Receptors Subserve Persistent Neuronal Firing during Working Memory in Dorsolateral Prefrontal Cortex. *Neuron*, *77*(4), 736–749. https://doi.org/10.1016/j.neuron.2012.12.032

Wang, M., Yang, Y., Wang, C.-J., Gamo, N. J., Jin, L. E., Mazer, J. A., Morrison, J. H., Wang, X.-J., & Arnsten, A. F. T. (2013b). NMDA receptors subserve persistent neuronal firing during working memory in dorsolateral prefrontal cortex. *Neuron*, *77*(4), 736–749.

Waterhouse, B D, Ausim Azizi, S., Burne, R. A., & Woodward, D. J. (1990). Modulation of rat cortical area 17 neuronal responses to moving visual stimuli during norepinephrine and serotonin microiontophoresis. *Brain Research*, *514*(2), 276–292. https://doi.org/10.1016/0006-8993(90)91422-D

Waterhouse, B D, Moises, H. C., & Woodward, D. J. (1980). Noradrenergic modulation of somatosensory cortical neuronal responses to lontophoretically applied putative neurotransmitters. *Experimental Neurology*, *69*(1), 30–49. https://doi.org/10.1016/0014-4886(80)90141-7

Waterhouse, B D, Moises, H. C., & Woodward, D. J. (1998). Phasic activation of the locus coeruleus enhances responses of primary sensory cortical neurons to peripheral receptive field stimulation. *Brain Research*, *790*(1–2), 33–34.

Waterhouse, B D, Moises, H. C., Yeh, H. H., & Woodward, D. J. (1982). Norepinephrine enhancement of inhibitory synaptic mechanisms in cerebellum and cerebral cortex: Mediation by beta adrenergic receptors. *The Journal of Pharmacology and Experimental Therapeutics*, *221*(2), 495–506.

Waterhouse, Barry D., & Navarra, R. L. (2019). The locus coeruleus-norepinephrine system and sensory signal processing: A historical review and current perspectives. *Brain Research*, *1709*, 1–15. https://doi.org/10.1016/j.brainres.2018.08.032

Wehmeier, P. M., Schacht, A., Ulberstad, F., Lehmann, M., Schneider-Fresenius, C., Lehmkuhl, G., Dittmann, R. W., & Banaschewski, T. (2012). Does Atomoxetine Improve Executive Function, Inhibitory Control, and Hyperactivity?: Results From a Placebo-Controlled Trial Using Quantitative Measurement Technology. *Journal of Clinical Psychopharmacology*, *32*(5), 653. https://doi.org/10.1097/JCP.0b013e318267c304

Wehmeier, P. M., Schacht, A., Wolff, C., Otto, W. R., Dittmann, R. W., & Banaschewski, T. (2011). Neuropsychological outcomes across the day in children with attention-deficit/hyperactivity disorder treated with atomoxetine: Results from a placebo-controlled study using a computer-based continuous performance test combined with an infra-red motion-tracking device. *Journal of Child and Adolescent Psychopharmacology*, *21*(5), 433-. Health Reference Center Academic.

Wei, I.-H., Chen, K.-T., Tsai, M.-H., Wu, C.-H., Lane, H.-Y., & Huang, C.-C. (2017). Acute amino acid d-serine administration, similar to ketamine, produces antidepressant-like effects through identical mechanisms. *Journal of Agricultural and Food Chemistry*, *65*(49), 10792–10803.

Weiser, M., Heresco-Levy, U., Davidson, M., Javitt, D. C., Werbeloff, N., Gershon, A. A., Abramovich, Y., Amital, D., Doron, A., Konas, S., Levkovitz, Y., Liba, D., Teitelbaum, A., Mashiach, M., & Zimmerman, Y. (2012). A multicenter, add-on randomized controlled trial of low-dose d-serine for negative and cognitive symptoms of schizophrenia. *The Journal Of Clinical Psychiatry*, *73*(6), e728–e734.

White, T. D., & Semba, K. (1997). A comparison of (±)epibatidine with NMDA in releasing [3H]noradrenaline and adenosine from slices of rat hippocampus and parietal cortex. *Neuroscience Letters*, *235*(3), 125–128. https://doi.org/10.1016/S0304-3940(97)00734-9

Whittington, M. A., Traub, R. D., Kopell, N., Ermentrout, B., & Buhl, E. H. (2000). Inhibition-based rhythms: Experimental and mathematical observations on network dynamics. *International Journal of Psychophysiology*, *38*(3), 315–336. https://doi.org/10.1016/S0167-8760(00)00173-2

Wojciulik, E., & Kanwisher, N. (1999). The Generality of Parietal Involvement in Visual Attention. *Neuron*, *23*(4), 747–764. https://doi.org/10.1016/S0896-6273(01)80033-7

Wolosker, H. (2007). NMDA receptor regulation by D-serine: New findings and perspectives. *Molecular Neurobiology*, *36*(2), 152–164.

Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A. K., & Fries, P. (2007). Modulation of Neuronal Interactions Through Neuronal Synchronization. *Science*, *316*(5831), 1609–1612. https://doi.org/10.1126/science.1139597

Womelsdorf, Thilo, Fries, P., Mitra, P., & Desimone, R. (2006). Gamma-band synchronization in visual cortex predicts speed of change detection. *Nature*, *439*, 733–736. https://doi.org/10.1038/nature04258

Xi, D., Keeler, B., Zhang, W., Houle, J. D., & Gao, W.-J. (2009). NMDA receptor subunit expression in GABAergic interneurons in the prefrontal cortex: Application of laser microdissection technique. *Journal of Neuroscience Methods*, *176*(2), 172–181. https://doi.org/10.1016/j.jneumeth.2008.09.013

Xu, Y., & Chun, M. M. (2007). Visual grouping in human parietal cortex. *Proceedings of the National Academy of Sciences*, *104*(47), 18766–18771. https://doi.org/10.1073/pnas.0705618104

Yantis, S., Schwarzbach, J., Serences, J. T., Carlson, R. L., Steinmetz, M. A., Pekar, J. J., & Courtney, S. M. (2002). Transient neural activity in human parietal cortex during spatial attention shifts. *Nature Neuroscience*, *5*(10), 995–1002. https://doi.org/10.1038/nn921

Young, J. W., Kamenski, M. E., Higa, K. K., Light, G. A., Geyer, M. A., & Zhou, X. (2015). GlyT-1 inhibition attenuates attentional but not learning or motivational deficits of the Sp4 hypomorphic mouse model relevant to psychiatric disorders. *Neuropsychopharmacology*, *40*(12), 2715–2726.

Young, J. W., Light, G. A., Marston, H. M., Sharp, R., & Geyer, M. A. (2009). The 5-choice continuous performance test: Evidence for a translational test of vigilance for mice. *Plos One*, *4*(1), e4227–e4227. https://doi.org/10.1371/journal.pone.0004227

Yu, X.-M. (2006a). The role of intracellular sodium in the regulation of NMDA-receptor-mediated channel activity and toxicity. *Molecular Neurobiology*, *33*(1), 63–79. https://doi.org/10.1385/MN:33:1:063

Zhang, H.-T., Huang, Y., Mishler, K., Roerig, S. C., & O'Donnell, J. M. (2005). Interaction between the antidepressant-like behavioral effects of beta adrenergic agonists and the cyclic AMP PDE inhibitor rolipram in rats. *Psychopharmacology*, *182*(1), 104–115. https://doi.org/10.1007/s00213-005-0055-y

Zhang, Z., Gong, N., Wang, W., Xu, L., & Xu, T.-L. (2008). Bell-shaped D-serine actions on hippocampal long-term depression and spatial memory retrieval. *Cerebral Cortex*, *18*(10), 2391–2401.

Zhou, H.-H., & Thompson, K. G. (2009). Cognitively directed spatial selection in the frontal eye field in anticipation of visual stimuli to be discriminated. *Vision Research*, *49*(10), 1205–1215. https://doi.org/10.1016/j.visres.2008.03.024

Zhou, Xianjin, Nie, Z., Roberts, A., Zhang, D., Sebat, J., Malhotra, D., Kelsoe, J. R., & Geyer, M. A. (2010). Reduced NMDAR1 expression in the Sp4 hypomorphic mouse may contribute to endophenotypes of human psychiatric disorders. *Human Molecular Genetics*, *19*(19), 3797–3805.

Zhou, Xingqin, Liu, D., Zhang, R., Peng, Y., Qin, X., & Mao, S. (2016). Modulation of glycine sites enhances social memory in rats using PQQ combined with d-serine. *Behavioural Brain Research*, *308*, 217–221.

Zohary, E., Shadlen, M. N., & Newsome, W. T. (1994). Correlated neuronal discharge rate and its implications for psychophysical performance. *Nature*, *370*(6485), 140–143.

APPENDIX

Experiment 1: D-serine Dose-Response Determination

Table 1 – Timeline for D-serine Dose-Response Determination

Week(s)	1	2 – 4	5	6	7	8	9 – 13
Stage	First D-R Series	First D-R Series	300 mg/kg	No Drug	300 mg/kg	No Drug	Second D-R Series
Administration Day	Tuesday & Friday	Fridays	Friday	None	Friday	None	Fridays

Table 1. Timeline for the D-serine dose-response determination.

Figure 3 - Experiment 1 Results

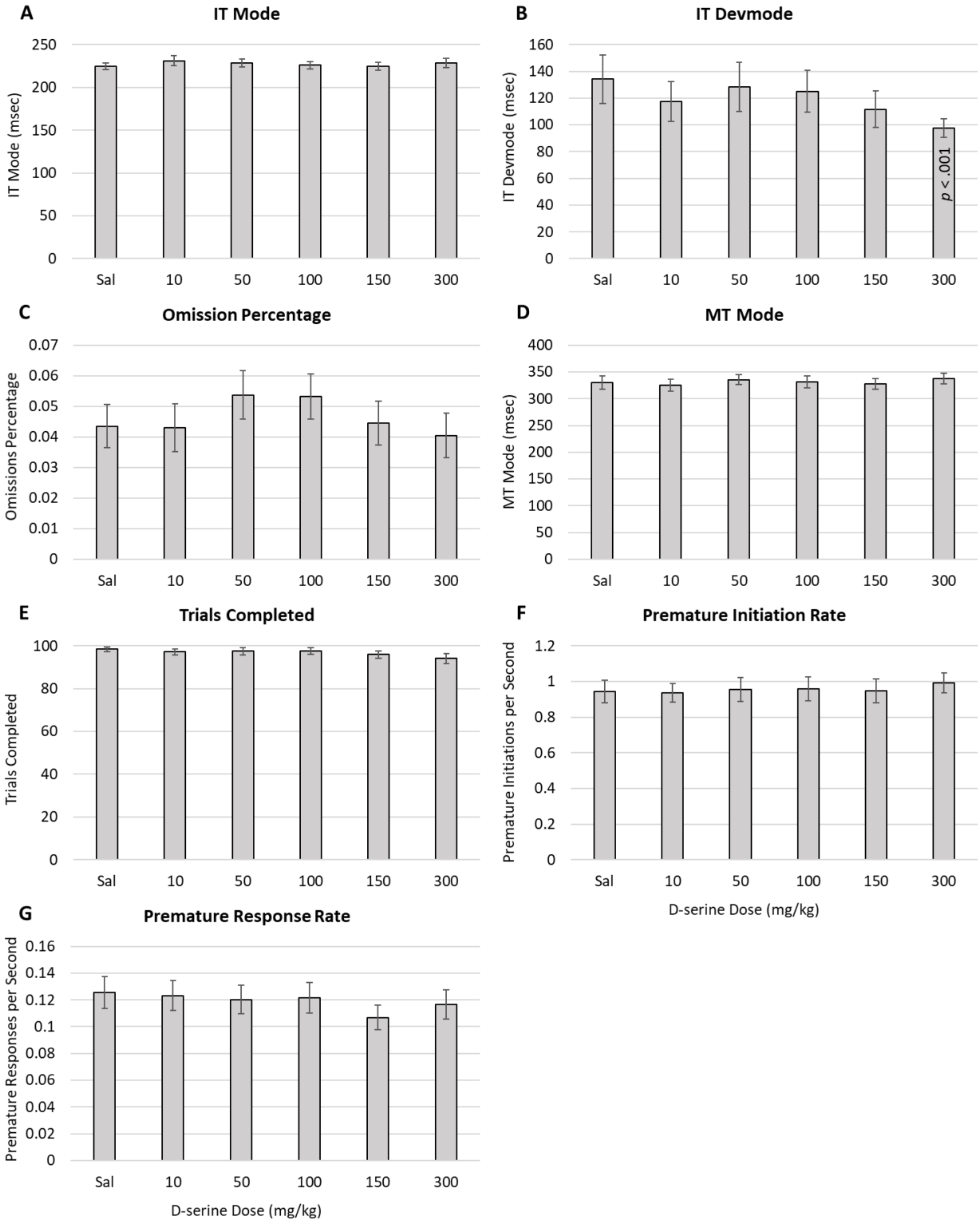

Figure 3. Results of the D-serine dose-response determination (Experiment 1). All *p* values are uncorrected.

Table 2 – Experiment 1 Contrasts

IT Devmode Contrasts

Dose (mg/kg)	Mean Difference (versus saline)	df	95% CI [Low, High]	*p*
10	-15.5	163.023	[-40.24, 9.24]	.218
50	-4.4	163.023	[-29.14, 20.34]	.726
100	-7.77	163.023	[-32.51, 16.97]	.536
150	-21.09	163.023	[-45.83, 3.64]	.094
300	-51.89	163.047	[-76.85, -26.93]	< .001

Table 2. Post-hoc comparisons conducted for the D-serine dose-response determination. All *p* values are uncorrected.

Experiment 2: Test of Combination Treatments

Figure 4 - Experiment 2 Results

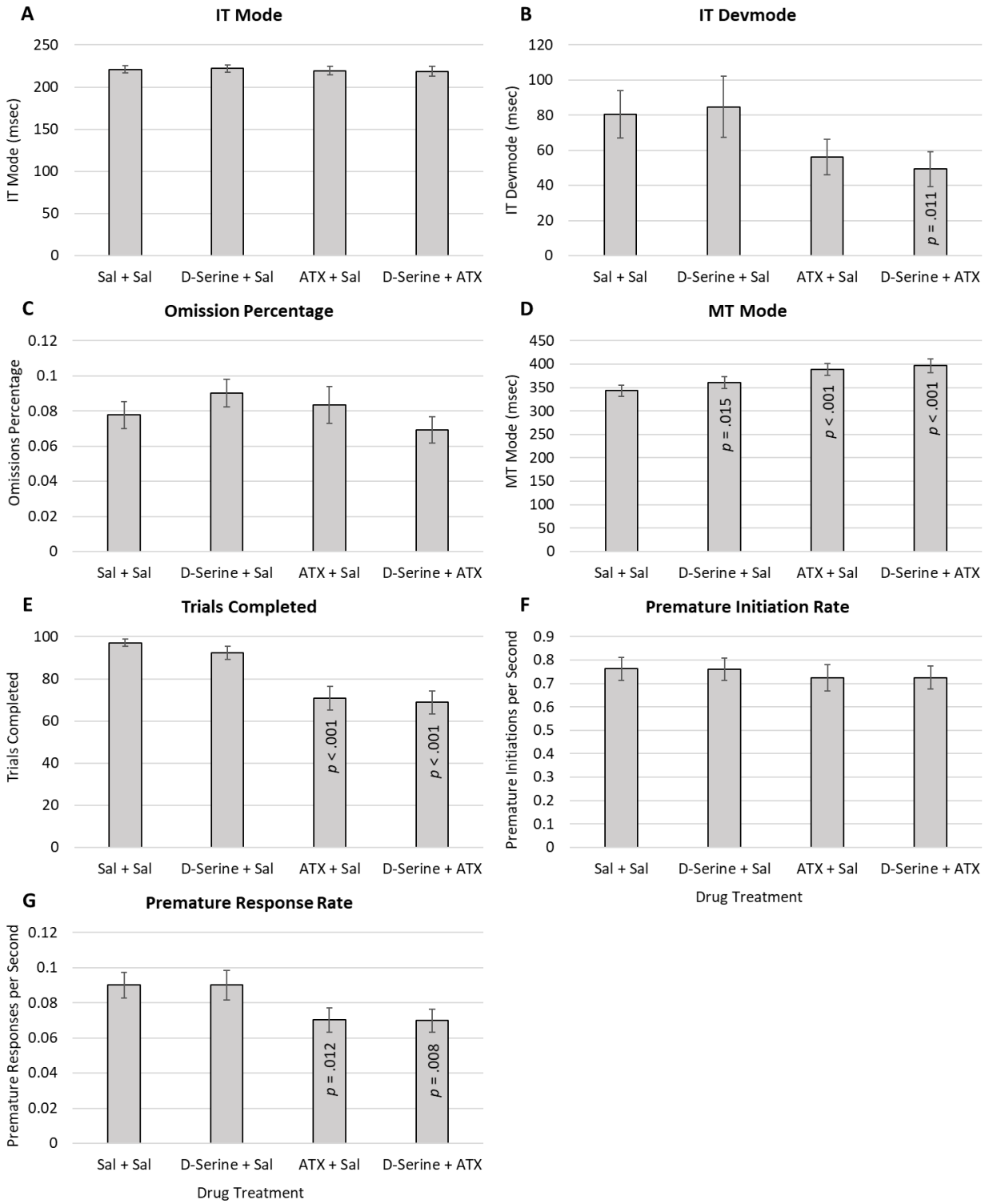

Figure 4. Results from the initial test of the combination treatment (Experiment 2). D-serine at 100 mg/kg and ATX at 0.5 mg/kg. All *p* values are uncorrected.

Table 3 – Experiment 2 Contrasts

IT Devmode Contrasts

Drug Treatment	Mean Difference (vs. saline + saline)	df	95% CI [Low, High]	*p*
D-serine + saline	4.36	101.758	[-14.35, 23.08]	.645
Saline + ATX	-17.0	101.783	[-35.9, 1.9]	.077
D-serine + ATX	-24.97	101.804	[-44.07, -5.87]	.011

MT Mode Contrasts

Drug Treatment	Mean Difference (vs. saline + saline)	df	95% CI [Low, High]	*p*
D-serine + saline	19.06	104.008	[3.82, 34.31]	.015
Saline + ATX	44.38	104.008	[29.13, 59.62]	< .001
D-serine + ATX	53.44	104.023	[38.05, 68.84]	< .001

Trials Completed Contrasts

Drug Treatment	Mean Difference (vs. saline + saline)	df	95% CI [Low, High]	*p*
D-serine + saline	-2.84	104	[-11.56, 5.87]	.519
Saline + ATX	-25.72	104	[-34.43, -17.01]	< .001
D-serine + ATX	-28.2	104.064	[-36.99, -19.4]	< .001

Premature Response Rate Contrasts

Drug Treatment	Mean Difference (vs. saline + saline)	df	95% CI [Low, High]	*p*
D-serine + saline	0	104.014	[-0.013, 0.013]	.985
Saline + ATX	-0.017	104.014	[-0.029, -0.004]	.012
D-serine + ATX	-0.018	104.058	[-0.031, -0.005]	.008

Table 3. Post-hoc comparisons conducted for the initial test of combination treatments (Experiment 2). All *p* values are uncorrected.

Experiment 3: Final Test of Combination Treatments

Figure 5 - Experiment 3 Results

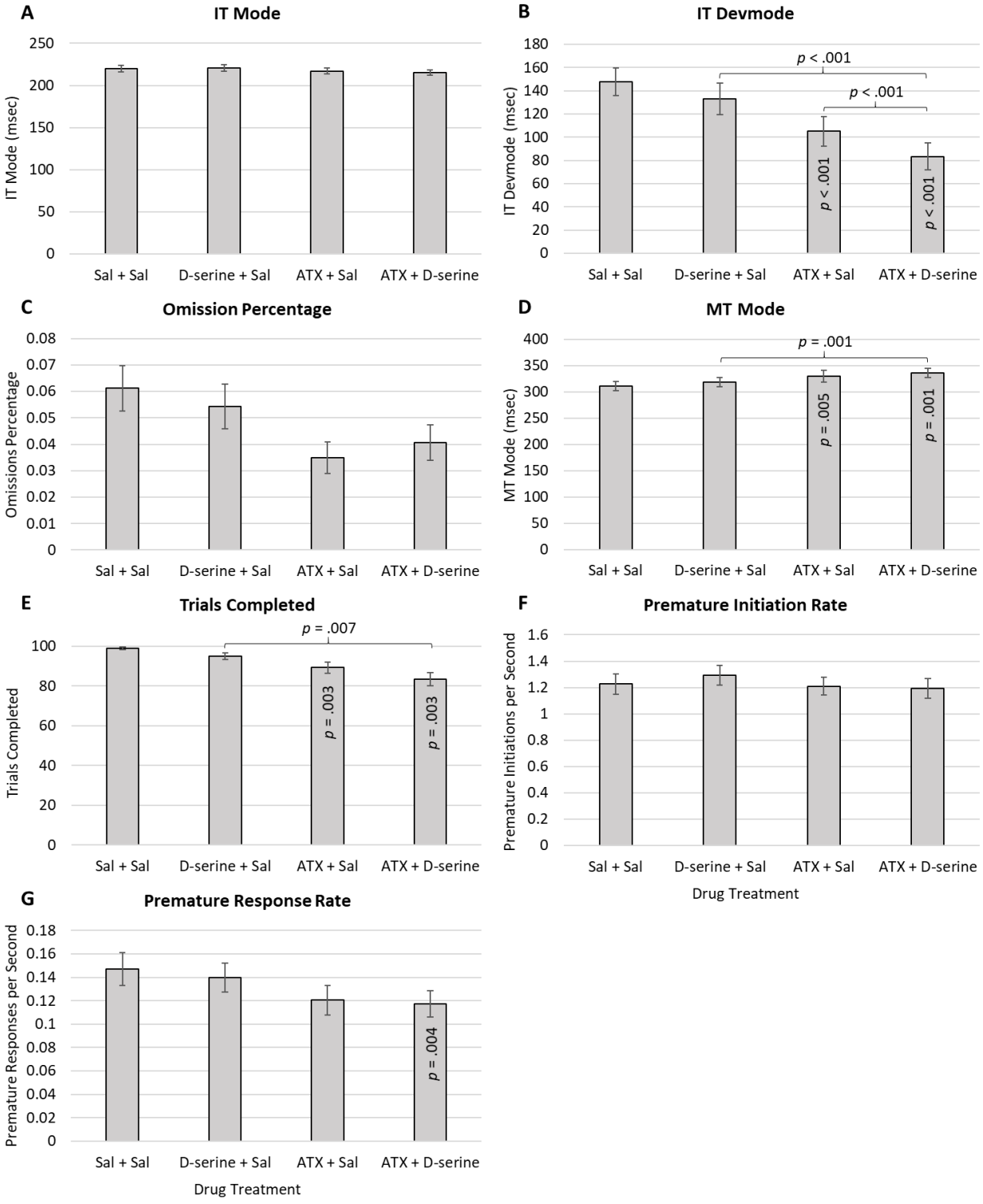

Figure 5. Results from the final test of the combination treatment (Experiment 3). D-serine at 125 mg/kg and ATX at 0.3 mg/kg. All *p* values are uncorrected.

Table 4 – Experiment 3 Contrasts

IT Devmode Contrasts

Contrast	Mean Difference	95% CI [Low, High]	*p*
Sal + Sal vs. D-serine + Sal	14.8	[-1.53, 31.12]	.072
Sal + Sal vs. ATX + Sal	42.43	[23.94, 60.93]	< .001
Sal + Sal vs. ATX + D-serine	64.2	[47.08, 81.32]	< .001
D-serine + Sal vs. ATX + D-serine	49.4	[33.47, 65.34]	< .001
ATX + Sal vs. ATX + D-serine	21.77	[11.96, 31.58]	< .001

MT Mode Contrasts

Contrast	Mean Difference	95% CI [Low, High]	*p*
Sal + Sal vs. D-serine + Sal	-6.98	[3.35, -17.31]	.17
Sal + Sal vs. ATX + Sal	-18.75	[-6.56, -30.94]	.005
Sal + Sal vs. ATX + D-serine	-25.1	[-11.72, -38.49]	.001
D-serine + Sal vs. ATX + D-serine	-18.12	[-8.42, -27.83]	.001
ATX + Sal vs. ATX + D-serine	-6.35	[5.63, -18.34]	.276

Trials Completed Contrasts

Contrast	Mean Difference	95% CI [Low, High]	*p*
Sal + Sal vs. D-serine + Sal	3.81	[0.76, 6.87]	.018
Sal + Sal vs. ATX + Sal	9.6	[3.76, 15.45]	.003
Sal + Sal vs. ATX + D-serine	15.5	[6.25, 24.75]	.003
D-serine + Sal vs. ATX + D-serine	11.69	[3.75, 19.62]	.007
ATX + Sal vs. ATX + D-serine	5.9	[-1.43, 13.23]	.107

Premature Response Rate Contrasts

Contrast	Mean Difference	95% CI [Low, High]	*p*
Sal + Sal vs. D-serine + Sal	0.007	[-0.008, 0.023]	.343
Sal + Sal vs. ATX + Sal	0.026	[0.007, 0.046]	.011
Sal + Sal vs. ATX + D-serine	0.03	[0.011, 0.048]	.004
D-serine + Sal vs. ATX + D-serine	0.023	[0.006, 0.039]	.01
ATX + Sal vs. ATX + D-serine	0.003	[-0.007, 0.014]	.497

Table 4. Post-hoc comparisons conducted for final test of combination treatments (Experiment 3). All *p* values are uncorrected.

VITA

Bachelor of Science, Psychology
University of Tennessee, Knoxville, TN, May 2012
Minor: Biology

Master of Science, Psychology
University of Memphis, Memphis, TN, August 2015
Concentration: Experimental Psychology

Master of Arts, Experimental Psychology
The University of Mississippi, University, MS, August 2018
Concentration: Behavioral Neuroscience
Thesis: Effects of Atomoxetine and Guanfacine on Two-Choice Reaction Time Task Performance in Rats