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Orexin Receptor Antagonism And Schizophrenia: Addressing Attentional Impairment In An NMDA Receptor Hypofunction Model Of Psychosis

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ABSTRACT

Attention is the psychological process by which the external world is actively perceived, interpreted, and navigated, allowing for organisms to selectively focus on relevant stimuli at the exclusion of irrelevant noise and distraction. Schizophrenia is a neuropsychiatric condition that arises from excitatory imbalances throughout the brain and is associated with not only hallucinations and delusions, but treatment-resistant attentional impairments, providing a clinical impetus to explore alternate antipsychotic targets. Receptors of the hypothalamic orexin system represent promising targets, as they are expressed on numerous attention- and schizophrenia-relevant nuclei. The experiments included in this dissertation tested the capacity for orexin receptor antagonists to treat attentional and electrophysiological deficits associated with a commonly-employed rodent model of psychosis. It was found that the dual orexin receptor antagonist filorexant and the selective orexin-1 receptor inhibitor SB-334867 both improved performance in a sustained visual attention task for rats co-administered a low dose of the psychotogenic N-methyl-D-aspartate receptor antagonist dizocilpine. However, for mice given a higher concentration of dizocilpine, filorexant was unable to improve deficient synchronization of neuronal firing at frequencies in the gamma band that coincide with attentional processing. Taken together, these findings are the first to reveal a potential dissociation of the efficacy of anti-orexinergic compounds for the treatment of attentional impairments in animal models of schizophrenia; namely, the behavioral abnormalities which arise from low degrees of psychotomimesis may be more easily reversed than the anomalous neuronal oscillatory activity present in a more potently psychosis-like state.

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PREFACE

Located within the lateral region of the vertebrate hypothalamus is a small nucleus of far-reaching neurons that produce a class of peptide neurotransmitters that possess CNS-wide stimulatory effects stemming from the near ubiquity of their constituent receptors. These neurons, which together comprise the lateral hypothalamic orexinergic system, integrate signals bearing information about internal states with information about the external world and, in doing so, regulate a plethora of survival-promoting autonomic and psychobiological functions according to bodily drives and the demands of the immediate environment. Many of these psychological and behavioral states - including but not limited to wakefulness, alertness, motivation, and cognition - rely on coordinated and prolonged excitation of multiple orexin-recipient brain networks, such as sleep-regulating thalamic neurons, wake-active brainstem monoaminergic systems, reward-associated midbrain structures, and cognition-associated forebrain and cortical circuitry (Harris & Aston-Jones, 2006; Saper et al., 2005). In this regard, orexins can be conceptualized as multitasking neuromodulators, orchestrating the simultaneous activity of numerous neuronal populations for the purpose of producing an animal that is awake, alert, and ready to act in an expansive range of contexts and situations.

The influence of orexins on attentional processing has begun to emerge in recent years following their initial detection in 1998. In brief, the release of orexins enhances exteroception and informs organisms what is worthy of attention in the surrounding environment by bringing physiological signals into

conscious awareness. Augmented orexin efflux upon the perception of salient stimuli and cues - especially in the case of those pertaining to homeostatic maintenance - facilitates the release of a multitude of neurotransmitters that are important for incentivized vigilance, including glutamate, GABA, dopamine, norepinephrine, histamine, serotonin, and acetylcholine (Fadel & Burk, 2010; Korotkova et al., 2003; Mieda et al., 2011; Schöne et al., 2014; Walling et al., 2004). A particularly important anatomical and functional relationship that permits orexin neurons to exert their potent influence on consciousness and vigilance stems from orexinergic outputs to the basal forebrain, a region of magnocellular neurons which sends projections to the entire cortical mantle and incites rapid and lasting cortical activation through cholinergic, fast-spiking GABAergic, and glutamatergic mechanisms (Yang et al., 2017). As such, lateral hypothalamic orexinergic innervations of corticopetal BF neurons comprise a key anatomical substrate of consciousness and attention, with agonism of orexin receptors expressed on ascending cholinergic and non-cholinergic nuclei depolarizing these neurons, enhancing cortical excitation, and boosting attentional capacity (Fadel & Burk, 2010; Villano et al., 2017).

Notwithstanding the abundance of knowledge about the orexinergic system and the numerous neurobiological and psychological roles it serves that has accumulated since their discovery fourteen years ago, the therapeutic potential of orexin receptor-targeting ligands is not fully understood. A common goal of ongoing orexin-centric research involves parsing its involvement in neuropsychiatric conditions for which arousal and cognition are abnormal or

compromised. Thus, the information and experiments presented herein emphasize the potential benefits of using orexin-suppressing compounds for the treatment of the attentional impairments associated with schizophrenia, which are profound and, despite the widespread availability of antipsychotic medications since the mid-20th century, relatively resistant to treatment. This dissertation will begin by describing the neurological correlates of attentional processing and performance, with particular emphasis on the critical importance of ascending basal forebrain projections in enabling normal attentional function. Next, key symptoms of schizophrenia are discussed, primarily detailing the neuropsychology of schizophrenia-associated attentional deficits and why modern neuroleptic medications often fail to adequately treat them. The orexinergic system is then introduced, both generally and in a clinical context, with the case for orexin inhibitors as novel pro-cognitive antipsychotic agents being presented in conjunction with three experiments designed to measure the influence of orexin receptor antagonists on attentional performance and attention-relevant neuronal oscillations in a pharmacological model of psychosis. Ultimately, this dissertation constitutes one piece of emergent evidence suggesting that orexin receptor antagonism has therapeutic promise in the treatment of schizophrenia.

CHAPTER 1. Signal detection, sustained attention, and their neurological correlates

"Without alertness, we are as if asleep, unresponsive to the world around us; without sustained attention, the world fragments; without vigilance, we cannot become aware of anything we do not already know."

- Ian McGilchrist, *The Master and his Emissary*

Attention, defined as the act of concentrating awareness towards discrete elements in one's surroundings, is a word which is derived from the Latin verb "attendere", meaning "to heed". Though its articulation as a concept dates back to at least ancient Rome (Tsotsos et al., 2005), the first documented attempts to explain the psychological state of attentiveness with physiological phenomena emerged in the 17th century, with René Descartes emphasizing a putative function of the pineal gland, which he described as the "seat of rational thought" in his book *The Passions of the Soul*, in enabling an individual to focus on one object at the exclusion of others for a period of time (Abhyankar, 2020). Though its role in the psyche was pondered, delineated, and re-conceptualized over the years, it was not until 1890 that the psychologist William James - who defined the act of paying attention as "the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought" in his seminal text *The Principles of Psychology* - described distinct physiological and intellectual aspects of attentional processing. He elaborates

that the physical level of attention, which necessitates the recruitment of sensory organs, the nervous system, and other bodily functions, creates the foundation for the intellectual level, being the deliberate mental selection of entities in one's surroundings based on the throughput generated by these sensory networks (James, 1890). This emphasis on the contribution of physical phenomena to attentional efficacy in the late 19th century prefaced over one hundred years of significant progress in elucidating and describing attention and its many neurobiological, neuropsychological, and neuropharmacological underpinnings.

In a broad sense, attention can be described as the psychological mechanism through which finite cognitive resources are purposefully harnessed towards distinct components of the environment, often in support of objective-directed behavior (Proulx et al., 2014; Sarter et al., 2001). Attention is likened to both a searchlight mechanism that an individual consciously employs to focus on relevant stimuli and a filter-like mechanism that excludes irrelevant noise from conscious awareness (Crick, 1984). Additionally, attention is a limited-capacity system, not only due to energy expenditure, but also limited brain regions for attentional processing (Broadbent, 1958). Attention can be divided into four major subtypes: selective attention, or the ability to focus on particular things while ignoring irrelevant inputs; divided attention, or the ability to focus on multiple things simultaneously; executive attention, serving a supervisory-like role in activating and inhibiting appropriate and inappropriate behavioral responses, respectively; and, lastly, sustained attention, which is a state of prolonged readiness to identify rare and unpredictable signals in the environment (Koelega,

1996; Sarter et al., 2001). Vigilance and sustained attention are terms which are commonly used interchangeably, as they both refer to the ability to maintain focus for an extended period of time, though the former has more of an emphasis on wakefulness and tonic alertness (Koelega, 1989; Oken et al., 2006). Generalized arousal and sustained attention both comprise the *intensity* axis of attention that allows for the successful execution of the more cognitively-complex divided and selective attention, which together make the *selection* axis (Sturm & Willmes, 2001). Thus, because vigilant attention is critical for attention as a whole, much of this document will focus on describing the neurological and psychological mechanisms which enable an organism to pay attention for an extended period of time.

Regardless of species, the survival of an individual animal relies, in part, on its ability to extract, interpret, and respond to satiety- and safety-relevant signals in an ever-changing and often uncertain world. Deciphering the similarities (and differences) in the neurobiological and psychological apparati across species contributes to our understanding of the common circuitry that controls not only attention in its natural state, but in a plethora of psychiatric illnesses for which attention is deficient. As such, several batteries designed to measure multiple types of attention have been developed for a variety of study species, with most of these tasks measuring the ability of an organism to reliably identify the occurrence of a fleeting signal amongst varying levels of distraction. Signal detection, defined by Posner and colleagues (1980) as “the entry of information concerning the presence of a signal into a system that allows the

subject to report the existence of the signal by an arbitrary response indicated by the experimenter", is the earliest stage of a long chain of perceptual processes during which target inputs are selected among a barrage of unimportant sensory signals and further propelled for higher-order processing (Kwon et al., 2021). Simply put, signal detection tasks necessitate that the observer indicate, with a pre-determined behavioral response, the occurrence of a signal over a number of trials; in this sense, the more reliably the signal is identified, the better the attentional performance of the subject. These tasks often have rigid trial-by-trial temporal constraints, necessitating action in a narrow window of time following the presentation of the target stimulus. In a similar vein, these tasks also commonly measure reaction times alongside performance accuracy, with increased response latencies coinciding with, among other possibilities, failure to maintain attention. Because humans, non-human primates, felines, rodents, and even some non-mammalian vertebrates such as pigeons and lizards are capable of mastering simple signal detection tasks (Dayer et al., 2000; Fleishman & Persons, 2001; McGinley et al., 2015), it can be suggested that the signal detection paradigm has a high degree of cross-species translational validity and can therefore be a useful tool to measure attention and perceptual sensitivity in a variety of contexts and with a variety of manipulations.

An example of a well-validated visual sustained attention task is the psychomotor vigilance test (PVT) and its version for rodents, the rodent PVT (rPVT). The PVT was originally used to measure the sleep deprivation-induced lapses in sustained vigilance in the 19th century (Patrick & Gilbert, 1896). The

rPVT simply measures the amount of time it takes for rats and mice to notice and respond to the illumination of a cue light signaling reward availability as a reflection of attentional capacity (Davis et al., 2016). The five-choice serial reaction time task (5-CSRTT) is another such test of sustained signal detection (Muir et al., 1996). Modeled after the human continuous performance task, the 5-CSRTT and its two- and three-choice variations quantify visuospatial attention in mice and rats by testing their ability to direct focus towards five nose-poke apertures (which are often, but not always, arranged within a nine-aperture arc) over a large number of trials, giving them a short response window to identify and approach whichever of the five nose poke ports was transiently illuminated during any given trial (Robbins, 2002). The 5-CSRTT is similar to the rPVT in that both measure reaction time as a reflection of attentional functioning, but the addition of multiple cue lights increases the demands of the task by introducing the possibility of incorrect responding. A third frequently-used signal detection task which measures prolonged attention, the rodent sustained attention task (SAT), offers two possible operands - most commonly levers - to which a response must be made depending on the presence or absence of a visual signal in any given trial (McGaughy & Sarter, 1995). Animals are trained to press one lever if a centralized signal light temporarily illuminates, and they are similarly trained to press the other lever if the light does not illuminate during the trial. This task is similar in function and purpose to the 5-CSRTT, but it differs in two distinct ways: firstly, whereas the 5-CSRTT only requires signal-driven responding, the SAT necessitates the deliberate acknowledgement of non-signal “events” alongside

signal events and additionally randomizes the presentation of signal and non-signal trials. Also unlike the 5-CSRTT, where the signal appears in one of five possible locations in the testing chamber throughout the session, the SAT provides spatial certainty in that animals must only attend to one central signal light. These and other tasks of signal detection are particularly sensitive to experimental manipulation-induced detriments, and their widespread usage over the last several decades has enabled substantial discoveries regarding the neurobiology and neuropsychology of sustained attentional processing as well as pharmacotherapeutics and other treatments to provide relief for conditions which impair attentional capabilities.

In short, attention is the psychological lens through which the external world is interpreted, navigated, and remembered. What is given our attention shapes the experience and memories of day-to-day life. Because of its absolute necessity for basic cognitive functioning, an important interest is taken not only in the basic neuropsychopharmacology of attention, but also the effects of its impairment in numerous psychiatric and degenerative ailments. It is therefore of the utmost importance to understand the neurological foundations of attention in order to develop pro-cognitive medications and other treatments that provide relief for these illnesses, particularly those for which attentional impairment is a primary symptom. The majority of this chapter will detail how complex interactions between various brain regions - particularly those between the cortex and the subcortex - give rise to the psychological states of sustained focus and attentional flexibility.

Cortical mechanisms of attention

With a constant stream of multimodal information entering the brain at virtually every waking moment, a significant portion of the CNS is dedicated to quickly deciphering incoming sensory signals and guiding behavior based on the perceptions generated by these signals. The cerebral cortex, which is the outermost, largest, and most highly innervated area of the CNS regardless of mammalian species, is one such potent processor of sensory signals. The cortex contains cells that are specialized to receive and respond to inputs from sense- and motor-relevant neurons from the subcortex and is chiefly responsible for the temporal organization and initiation of volitional behaviors in response to the ever-changing environment. 90 percent of all cortical neurons belong to the neocortex, a six-layer-thick region of cortical tissue consisting of approximately 80 percent excitatory neurons and 20 percent inhibitory neurons (Wonders & Anderson, 2006; Xu et al., 2016). The neocortex is further divided into parietal, occipital, temporal, and frontal lobes, all of which communicate extensively with one another via intercortical projections and serve distinct but related purposes in processing incoming perceptual information. Nicknamed the “action cortex”, the frontal cortex contains an abundance of corticopetal, corticofugal, and cortico-cortical projection pathways which together comprise a network devoted to instigating some form of purposeful action relating to salient internal or external signals (Fuster, 2008). Additionally, between the neocortex and diencephalon is the three-layered archicortex, which is the phylogenetically oldest region of the

cerebral cortex and contains such structures as the olfactory bulbs, tracts, and cortex as well as parts of the hippocampus (HPC), a mostly-limbic structure which both facilitates the encoding of memories depending on what is being paid attention to and guides attention based on the recall of previously-experienced events and learned associations (Goldfarb et al., 2016; Hagan et al., 2012; Muzzio et al., 2009). Taken together, the cerebral cortex represents the central information-processing hub of the brain, with the predominant role of the frontal neocortex being to interpret sensory information in order to orchestrate and guide volitional and goal-oriented behaviors.

The neocortex is organized into six anatomically-distinct layers comprised of vertically-organized microcolumns, with each sheet containing glutamatergic and γ-Aminobutyric acid (GABA)-ergic neurons serving unique but significantly overlapping roles in facilitating information processing (Callaway, 1998). Cortical layers I, II, and III are rich with intracortical axons, permitting rapid communication to and from other regions of the cortex. While layers IV, V, and VI also have cortico-cortical projections, they also contain neurons which leave and operate outside of the cortex (Jones, 2000). In the first instances of perception, thalamocortical radiations receive signals from sensory systems and relay them to thalamorecipient cells of cortical layer IV (Miller, 2003). Sensory information is then tuned, amplified, and sent to cortical layers II and III, where it is imbued with contextual information stored in other cortical areas via associational and interhemispheric cortico-cortical inputs (Fuster, 2001; Mrzljak et al., 1991), enabling the initial percept of the stimulus of interest. Once informed of the

percept, layer V communicates with other cortical neurons via intratelencephalic neurons of layer 5a as well as various populations of cells of the striatum - primarily neurons of the basal ganglia which control voluntary movement - via pyramidal tract neurons of layer 5b (Hattox & Nelson, 2007; Naka & Adesnik, 2016). Lastly, neurons in layer VI both exert gain control over all other layers of the cortex via extensive cross-cortical connections and influence the sensitivity of cortex-projecting thalamic neurons to incoming sensory stimuli (Kim et al., 2014; Olsen et al., 2012; Proulx et al., 2014; Sherman, 2007). Though the various laminar functions described above are very likely not this clear-cut and homogeneous (Guy & Staiger, 2017), this well-conserved physical organization of the mammalian neocortex may exist to optimize and improve synchronization of synaptic transmission between various cortical cell populations to best subserve complex, multi-level information processing.

The prefrontal cortex (PFC), which is located at the anterior pole of the mammalian CNS, is a region of the frontal cortex that is anatomically defined by the projections it receives from the medial dorsal thalamic nucleus (Fuster, 2001). Though it is the last brain region to develop, it comprises nearly 30 percent of total cortical volume in humans (Carlén, 2017; Fuster, 2001). It is divided into two functionally distinct areas: the ventromedial PFC, which can be further categorized into ventral and medial subdivisions, and the primate-exclusive lateral PFC, which contains both the dorsolateral and ventrolateral prefrontal cortices (Hathaway & Newton, 2021). As a whole, this extensively-connected area of the brain sends and receives projections to and from

effectively every other sensorimotor cortical network and coordinates what are commonly referred to as “higher” cognitive processes, including executive functioning, planning, emotional regulation, and decision-making (Bloem et al., 2014). Miller and Cohen (2001) describe the primary role of the PFC as “the active maintenance of patterns of activity that represent goals and the means to achieve them”; indeed, in conjunction with outerlying vigilance-related cortical areas, such as parietal and anterior cingulate cortices, the PFC is distinctly involved in the top-down switching of attentional control based on ever-changing attentional demands (Rossi et al., 2009). Moreover, the PFC concerns itself most with novelty, such as unrehearsed behaviors, perceptions, reasonings, etc., with Fuster (2001) further defining the role of the PFC as the representation and execution of *new* forms of organized goal-directed action. The functional integrity of the PFC is critical for attentional processing which is more cognitively tedious and during unfamiliar circumstances and situations that deviate from routine; that is, as opposed to well-learned behaviors stemming from established and relatively inflexible neural pathways, the PFC is most active during the willful coordination of more effortful top-down processing, allowing for greater cognitive control in situations where the connections between sensory, memory, and decision-making systems are less established (see also Fuster, 2008).

The PFC also demonstrates subregion-specific functional and temporal disparities, with dissociable recruitment of these areas depending on the step of attentional processing. The medial PFC (mPFC) acts in the short-term by detecting behaviorally-salient cues which may represent multiple potentially-

conflicting possible responses, and the lateral PFC (lPFC) receives this information via tightly-coupled interactions with the mPFC and acts in the longer-term by retaining information relevant to the task at hand, identifying changes in behavioral requirements, and implementing appropriate behavioral control measures (Alexander & Womelsdorf, 2021; Gehring et al., 2018). Furthermore, the activity of the dorsal-prelimbic and ventral-infralimbic regions of the mPFC promotes and suppresses the execution of conditioned responding, respectively, particularly in the context of behaviors related to the acquisition of highly-motivating rewards (Caballero et al., 2019; Riaz et al., 2019). The right PFC appears to play a more substantial role in the maintenance of attention over long periods of time than the left; as the cognitive load of a task increases, be it from introduction of distracters or from continuous performance, activation of the right dorsolateral PFC, but not the left, tends to increase as a reflection of augmented attentional effort (Lustig & Sarter, 2015; St. Peters et al., 2011).

Overall, the cerebral cortex exists at the crux of a plethora of complex interactions between sensory and behavioral information, constantly updating changing relationships between stimuli and cues and their expected outcomes. It spans the entire mantle of the brain and is composed of multiple interconnected regions which have unique but cooperate effects on signal-driven attention and associated conditioned behavioral response sets. The PFC specifically coordinates attentional functioning by organizing the activity of various other cortical and non-cortical neurological systems and facilitating the temporal organization of purposeful behaviors in response to the demands of the

environment (Fuster, 2009). While undoubtedly powerful in its own regard, the ability for the cortex to generate perception, attention, and action depends heavily on inputs from extracortical nuclei; as such, it can be argued that corticopetal networks play an equally important role in attentional processing as the cortex itself.

The basal forebrain cholinergic system in attention

Signals related to stimuli or cues of interest are often muddled by some degree of noise; as such, sensory-recipient brain regions must employ multiple mechanisms to selectively amplify the pertinent inputs and suppress non-relevant inputs. One such filtration system is the basal forebrain (BF), a region of magnocellular neurons comprising a myriad of heterogeneous and anatomically-complex structures which project throughout the brain. Neurons of the rostral BF, which includes the medial septum and the vertical limb of the diagonal band of Broca, innervate the HPC, and neurons of the caudal BF - which includes the nucleus basalis, horizontal limb of the diagonal band of Broca, preoptic area, substantia innominata, and ventral pallidum project to various brainstem, thalamic, hypothalamic, hippocampal, and neocortical nuclei (Brown & McKenna, 2015). The entire BF consists of three non-overlapping populations of neurons: glutamatergic, GABAergic, and cholinergic neurons, with approximately 90 percent of total BF neurons synthesizing glutamate (Glu), 35 percent synthesizing GABA, and 10 to 20 percent synthesizing acetylcholine (ACh) depending on the subregion (Gritti et al., 2006; Yang et al., 2017). ACh is a

small-molecule neurotransmitter that, in addition to its actions in the CNS, is also active in the autonomic nervous system largely through the adrenal medulla as well as the peripheral nervous systems at the neuromuscular junction. The BF is best known for its extensive rostral cholinergic network, which has a high degree of axonal collateralization with fronto-striatal and fronto-limbic regions and acts as a powerful source of modulatory input throughout the brain, particularly to areas involved in psychological processes which promote cognition, such as the neocortex (Everitt & Robbins, 1997; Olincy et al., 2006; Perry et al., 1999). Though its neurons have ample extracortical targets, the dense innervations from the BF to various cortical nuclei establish it as a major regulator of neuronal activity in the cortex and, by extension, psychological states which are enabled by cortical activation, including attention (*Figure 1*; Yang et al., 2017).

There are two central cholinergic networks in the mammalian brain which together provide the entire CNS with ACh. These cholinergic nuclei are often referenced by cholinergic cell groups 1-6 (Ch1-6) according to Mesulam nomenclature (Mesulam et al., 1983). One such network, the mesopontine cholinergic system, originates in the pedunculopontine and laterodorsal tegmental nuclei (PPT/LDT, Ch5 and Ch6) which together innervate various brainstem, thalamic, and midbrain areas (Mesulam et al., 1983; Wang & Morales, 2009). The other is the BF cholinergic system, a highly-topographic and clustered projection system of ACh-producing neurons that has roughly three major divisions in humans and non-human primates (Baxter & Chiba, 1999; Everitt & Robbins, 1997; Heimer & Alheid, 1991): the medial septum (Ch1), the diagonal

band of Broca (Ch2-3), and the nucleus basalis of Meynert (Ch4). The most substantial projection from the medial septal nucleus is to the hippocampal formation (Senut et al., 1989). The diagonal band of Broca can be further divided into vertical (Ch2) and horizontal limbs (Ch3); the former limb projects to the cingulate cortex and HPC, and the latter limb innervates the entorhinal cortex and olfactory bulb (Liu & Gentleman, 2021). Efferents from the nucleus basalis mostly synapse with neurons of the amygdala, reticular nucleus of the thalamus, and the cerebral cortex, with the entire cortical mantle being innervated by these BF cholinergic neurons (Zaborszky et al., 2015). Though cholinergic projection patterns are greatly preserved across species, the nucleus basalis is less of a discrete structure in the rodent brain than it is in the primate brain (Baxter & Chiba, 1999), with the rat and mouse equivalent being the nucleus basalis magnocellularis and substantia innominata (nBM/SI). Regardless of mammalian vertebrate species studied, around half of the total BF corticopetal projection is cholinergic neurons from the nucleus basalis as well as the diagonal band, magnocellular preoptic nucleus, and substantia innominata, and the other half of the projection is predominantly GABAergic neurons (Proulx et al., 2014; Zaborszky et al., 1999). Despite these cholinergic neurons projecting to numerous brain areas, they themselves receive relatively sparse innervations; however, these innervations come from a broad range of brain structures, suggesting that the various BF cholinergic subsystems receive a wealth of sensation- and perception-relevant inputs (Azimi et al., 2020; Gotti et al., 1997).

Intermediate and caudal corticopetal cholinergic neurons of the BF act as a neuromodulatory circuit that optimizes sensory processing by enhancing salient thalamic inputs and suppressing associational inputs as they enter the cortex (Castro-Alamancos & Gulati, 2014; Goard & Dan, 2009). Cholinergic terminals are found virtually everywhere in the cortex and, as a result, ACh-producing neurons gate the processing of all incoming information in the cortex (Mesulam, 1990; Sarter et al., 2001). These neurons synapse significantly with neurons of cortical layers I, IV, V, and VI and weakly with those of layers II and III (Gotti et al., 1997; Naka & Adesnik, 2016), suggesting that extensive cholinergic modulation is present at cortical cells that project to numerous other cortical and subcortical regions. Described as a “major arm of the brain’s top-down machinery” (Lustig & Sarter, 2015), cholinergic neurons are purposefully recruited during engagement with the outside world, acting to rapidly activate the cortex and allocate attention in short temporal timescales by flexibly tuning cortical activity and modulating the response of pyramidal cells to incoming glutamatergic excitatory signals (Fadel & Burk, 2010; McCormick, 1993). Well-timed cholinergic transients in the PFC, which occur on the sub-seconds- to seconds-scale, mark a transition from a state of passive attentiveness to enacting cue-oriented behaviors, such as pressing a lever following the presentation of a visual signal that results in the receipt of a reward (Howe et al., 2013; Lustig & Sarter, 2015; Sarter et al., 2014). Thus, while these neurons play a multitude of roles and support a variety of psychological functions, they subserve attentional needs by strengthening and enhancing incoming signals

pertaining to the object of interest, allowing the cortex to more effectively communicate relevant information and guide appropriate goal-oriented behavioral responses. Additionally, the PFC contains the only neurons in the cortex that directly project to the cholinergic BF; these corticofugal inputs comprise one of two major glutamatergic afferents to the BF - with the other being from amygdaloid nuclei (Carnes et al., 1990) - and are speculated to generate phasic cholinergic signaling through top-down, cortex-driven mechanisms (Gaykema et al., 1991; Sarter et al., 2014; Zaborszky et al., 1997).

Studies employing non-specific cholinotoxins and antagonists in non-human species suggest that cholinergic modulation of cortical neuron excitability is essential for success in operant tasks which require adequate attention and focus (Everitt & Robbins, 1997; Proulx et al., 2014). Less selective BF lesioning techniques, such as with ibotenic acid, quisqualic acid, or α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), have been shown to induce widespread impairments in attention, learning, and memory in animal studies, including in signal detection tasks (Aigner et al., 1991; Robbins et al., 1989; Voytko, 1996). With the advent of the immunotoxin 192 immunoglobulin G (IgG)-saporin, which is highly selective for BF cholinergic neurons (Wenk et al., 1994), it was soon discovered that many of the learning- and memory-specific deficits induced by previous lesioning techniques failed to replicate (Baxter et al., 1995; Baxter & Gallagher, 1996; McGaughy et al., 2000). Attention, however, remains significantly impaired following 192 IgG saporin-induced cholinergic deafferentation, with various deficits arising in the 5-CSRTT (McGaughy et al.,

2002). SAT (McGaughy & Sarter, 1995), and crossmodal divided attention paradigm (Turchi & Sarter, 1997) in rats. Because attention is robustly impacted by BF cholinergic lesions while learning and memory are less affected, it suggests that, while non-cholinergic projections to cortical neurons appear to be instrumental in cortex-mediated working memory and learning processes, ACh fuels attentional processing by enhancing the response of cortical pyramidal neurons to sense-relevant glutamatergic inputs (Fadel & Burk, 2010; McCormick, 1993; Metherate & Ashe, 1993). Additionally, inactivation of nucleus basalis cholinergic neurons by intrabasalis infusions of muscimol, a GABA receptor agonist, worsens performance outcomes in the 5-CSRTT via a putatively anticholinergic mechanism of action in the PFC (Muir et al., 1994). Thus, the primary role of cortical ACh in supporting cognition appears to be to excite attentional networks which, in turn, facilitate learning and memory (Baxter & Chiba, 1999).

Cortex-innervating BF cholinergic afferents are important for normal attention, but they are of particular importance in attentionally-demanding circumstances. For example, it is both intuitively and empirically understood that the longer an individual must consciously maintain attention, the more prone they are to errors stemming from lapses in attentional capacity (Gomez et al., 2007; Manly, 1999; Nosek & Banaji, 2001). Corticopetal cholinergic neurons are extensively recruited when attention must be paid for an extended period of time, with increased BF neuron activity coinciding with sustained attentional performance across species (Fadel & Burk, 2010; Himmelheber et al., 2000).

This same phenomenon has been observed when distracting stimuli are present; disruptive sensory information muddles signals regarding the percept of interest, requiring a compensatory increase in cortical cholinergic inputs to further enhance relevant signals and stabilize performance. Furthermore, rodent microdialysis studies and human neuroimaging studies have shown that task-dependent increases in cortical ACh are notable in the right, but not the left, mPFC (Callicott et al., 1999; Martinez & Sarter, 2004; Van Snellenberg et al., 2015), with right mPFC ACh levels rising from baseline to task performance and rising further in response to increasing attentional demands, particularly during the presentation of a distracting stimulus. During basal attentional processing, both hemispheres of the frontal cortex are recruited relatively equally, but during attentional challenge, auxiliary rises in cortical ACh are lateralized to the right hemisphere (Berry et al., 2014; Demeter et al., 2011). Genetic polymorphisms which affect cholinergic neurotransmission, deletions of the choline transporter gene, and lesions of frontocortical cholinergic neurons reveal mechanistic failures of the right mPFC in flexibly augmenting ACh efflux in response to distraction or increasing task demands (Lustig & Sarter, 2015; McGaughy et al., 1999). These findings further specify that the predominant function of the BF-PFC cholinergic pathway is to aid in cortical top-down control of attention in the face of increasing bottom-up distractions (Kim et al., 2017).

ACh exerts its neurobiological and psychological effects in the vertebrate brain through its activity at two major types of endogenous cholinergic receptors. Named after their affinity for the stimulant nicotine, rapid-onset and fast-acting

nicotinic ACh (nACh) receptors belong to a family of ligand-gated ion channels which are widely distributed on skeletal muscles at the neuromuscular junction and brain areas associated with reward and cognition, including but not limited to the cortex, ventral tegmental area (VTA), nucleus accumbens (NAcc), HPC, and thalamus (Clarke, 1984; Gotti et al., 1997; Mamede et al., 2004). Neuronal-type nACh receptors are pentameric in their structure and can be further divided into functional arrangements of various combinations of subunits, with high-affinity alpha-4 beta-2 (α4β2) and low-affinity alpha-7 (α7) subunits being the most commonly-found nicotinic complexes in the CNS (Gotti & Clementi, 2004). The α4β2-nACh receptor, which is the most abundant of the two and most commonly found on the postsynaptic neuron, is heteromeric and comprised of various combinations of α4 and β2 subunits surrounding a central pore; the homomeric α7-nACh receptor subtype - which is expressed presynaptically - possesses five α7 subunits. Both receptor subtypes are ligand-gated cation channels, necessitating the binding of ACh or another cholinomimetic compound to open the channel pore, and upon their stimulation, they increase intracellular calcium in the presynaptic terminal and boost the release of the endogenous neurotransmitter of the host neuron. Acute activity of nACh receptors produces rapid excitatory responses on the order of milliseconds and facilitates rapid synaptic transmission, though their continued or repeated stimulation can lead to quick desensitization and loss of functional responding (Akaike & Izumi, 2018; Quick & Lester, 2002).

Much like nACh receptors were named after nicotine, the muscarinic ACh (mACh) receptors - being the second type of cholinergic receptor - were named after their affinity for the nonselective mACh receptor agonist muscarine, which is a compound found in certain species of mushroom. Also similarly to nACh receptors, mACh receptors are found throughout the CNS, autonomic nervous system, and neuromuscular junction. They belong to a superfamily of metabotropic receptors, the various subtypes of which share a significant degree of sequence similarity across a number of mammalian as well as non-mammalian study species. There are five known mACh receptor subtypes, labeled M1 through M5, expressed throughout the body; while only M2- and M3-mACh receptors are found in the periphery and play an important role in physiological regulation, including heart rate, smooth muscle contraction, and glandular secretion (Wess et al., 2007), all five mACh receptor subtypes are represented throughout the CNS and are involved in a plethora of physiological and psychological functions relating to cognition that can be subdivided into two “functional classes” based on the G proteins with which they couple. M1-, M3-, and M5-mACh receptors couple to the Gq/11 family of G proteins and tend to be expressed on the postsynaptic neuron. When stimulated, the Gq/11 protein activates beta-type phospholipase C beta enzymes which stimulate downstream effector molecules that ultimately lead to the depolarization neurons through calcium and protein kinase C signaling pathways (Kruse et al., 2014). Conversely, M2- and M4-mACh receptors, which are located presynaptically in the brain, are Gi/o-linked receptors that inhibit cellular activations via suppression

of the adenylyl cyclase intracellular signaling cascade (Durkee et al., 2019; Migeon et al., 1995).

The diffuse expression of nACh and mACh receptors in vigilance-pertinent regions of the mammalian cortex suggest that their function modulates incoming signals at multiple levels of processing (Arroyo et al., 2014). Both nACh receptor subtypes are expressed on GABAergic interneurons throughout the cortex as well as on pyramidal neurons of layer IV, and α7- and α4β2-nACh receptors are preferentially expressed on pyramidal neurons of layers V and VI, respectively (Poorthuis et al., 2013). Additionally, high-affinity accessory alpha-5 (α5) nACh receptor subunits, whose presence in the CNS is otherwise rare, are co-localized with the β2 subunit throughout layer VI and enhance both local nACh receptor activity and thalamic outputs to the cortex through their expression on dense corticothalamic feedback projections (Proulx et al., 2014). In general, nACh receptors are well-known for their attention-boosting properties, with much of the earlier research using nicotine to study their unique role in paying and sustaining attention. Nicotine and other nACh receptor agonists are broadly known to have nootropic qualities in smokers and non-smokers (Burk et al., 2018; Foulds et al., 1996; Hahn et al., 2003), but because nACh receptor agonists exert quick stimulatory effects which are likely to be most pertinent to the demands of the immediate environment, these drugs fortify learning and memory by enhancing underlying attentional processing (Hahn, 2015). Selective α4β2-nACh receptor-stimulating ligands, including S38232 and ABT-089, which are full and partial agonists, respectively, improve detectability of a visual signal in the rodent SAT

and the 5-CSRTT (Howe et al., 2010). Similarly, the α7-nACh receptor agonist R3487/MEM3454 boosted basal attentional accuracy in the SAT while similar compounds such as AR-R17779, RG3487, PNU-282987, and GTS-21 improve performance following pharmacologically-induced deficits in an attentional set-shifting task and the 5-CSRTT (Hahn et al., 2003; K. M. Jones et al., 2014; Rezvani et al., 2009).

The highest concentration of mACh receptors in the brain is located in the cortex, including throughout all six layers of the neocortex and on hippocampal archicortical neurons (Scarr, 2012). Of the mACh receptors, the M1 receptor subtype, which is found on every neocortical layer with particular emphasis on pyramidal neurons of layers III, V, and VI (Harrison et al., 1991; Mrzljak et al., 1993), is the most important out of this family of receptors for attentional function (Gould et al., 2015). Cholinomimetic drugs which boost M1-mACh receptor function, such as the orthosteric agonist xanomeline and the allosteric agonist N-Desmethylclozapine, increase the levels of ACh in the cortex and enhance attentional performance (Li et al., 2005). On the other hand, mACh receptor antagonists like scopolamine and dicyclomine suppress cortical ACh activity and impair signal detection as evidenced by worsened performance in the SAT - particularly when the house light flashed during a portion of testing - and the 5-CSRTT (Mirza & Stolerman, 2000; Robinson et al., 2012). Conversely, agonism of the M2-mACh receptor, which has opposing actions on cellular activity than does the M1 subtype, inhibits HPC-mediated inputs to the mPFC (Wang & Yuan, 2009), highlighting potential attentional detriment; M2-mACh receptor knockout,

on the other hand, worsens learning and memory-related processes but enhances sustained attention in mice (Romberg et al., 2018). Interestingly, studies in humans and rodents have shown that, while scopolamine-induced mACh receptor blockade reliably worsens sustained attentional performance, nACh receptor antagonism with mecamylamine does not (Mirza & Stolerman, 2000); however, indiscriminate cholinergic receptor antagonism had a more detrimental effect on attention and general cognition than mACh or nACh receptor antagonism alone. Based on these findings, it is possible that mACh receptors play a more critical role in attentional processing while nACh receptors serve an accessory - but still important - function in supporting attention, with the activity of both cholinergic receptor types ultimately cooperating synergistically in order to best serve attentional needs.

ACh supports attention by promoting wakefulness

Another important role of cholinergic neurotransmission that maintains vigilant attention is cortical activation as it relates to wakefulness and arousal. It is both intuitively and empirically understood that the ability to attend requires a generalized state of arousal (Killgore, 2010). Consciousness and attentiveness are mutually-beneficial behavioral states - with attention being referred to as the “gateway to consciousness” due to its close relationship to alertness (Proulx et al., 2014) - that serve tightly-entangled, survival-promoting evolutionary purposes. Daniel Kahneman suggests that the extent to which a stimulus of interest can be processed relies on attentional capacity, and this capacity

depends on the degree of arousal as well as effort required (Kahneman, 1973). The PFC is particularly sensitive to the pressures of elevated homeostatic sleep drive, and nearly all functions reliant on adequate cortical excitation - including not only attention, but emotional regulation, executive functioning, and general cognition as well - suffer when consistent cortical activity cannot be maintained (Drummond, 2001). Doran and colleagues (2001) posit that, rather than causing consistent impairment of attentional performance, lack of adequate sleep induces wake “state instability” which requires the recruitment of compensatory networks to boost cortical activity in order to maintain vigilance (see also Dinges, 2020), meaning that subjects that are sleep deprived are more likely to experience intermittent lapses of attention interspersed with transient periods of attentiveness which are supported by these extracortical mechanisms. Attentional capabilities are also liable to worsen during periods of hyper-arousal, such as when experiencing excessive excitement or fear (Easterbrook, 1959). The Yerkes-Dodson theory (Winton, 1987; Yerkes & Dodson, 1908) states that optimal cognitive performance is attained when arousal levels are within a relatively narrow window, with both too little and excessive activity in attention, learning, and memory networks inducing impairments in these domains. Therefore, a general state of arousal is required to pay attention, and balanced cortical excitation is required to maintain it.

Corticopetal projections from the BF comprise the concluding node of the ventral arm of the ascending reticular activating system (ARAS; Fuller et al., 2011; Kim et al., 2015); therefore, it can be expected that sleep, wakefulness,

and vigilant attention share many overlapping frontoparietal brain regions, and they are all influenced by ACh in some way. In addition to promoting attention and learning, elevations in cortical cholinergic tone mark periods of behavioral activation during active wakefulness as well as the rapid eye movement (REM) state of sleep; conversely, lower cholinergic tone - which occurs during quiet, disengaged wakefulness and non-REM sleep - facilitates memory consolidation (Dias et al., 2021; Hasselmo & McGaughy, 2004). ACh promotes wakefulness and arousal through two parallel activating pathways. Both brainstem and forebrain cholinergic networks comprise major ascending arousal systems, with neurons of the PPT/LDT modulating sleep-relevant thalamic nuclei and neurons of the nucleus basalis projecting to both the thalamic reticular nucleus (TRN) and the cortex (Steriade, 2004). Though the PPT/LDT does not directly innervate the cortex like the nucleus basalis, it stimulates nucleus basalis cholinergic neurons through a primarily glutamatergic mechanism (Lavoie & Parent, 1994; Rasmusson et al., 1994), thereby increasing cortical ACh indirectly. Stimulation of BF cholinergic neurons has been shown to instigate a transition into wakefulness from non-REM, but not from REM, sleep (Han et al., 2014; Irmak & de Lecea, 2014; Xu et al., 2015) as well as abolish spontaneous and evoked slow oscillations indicative of sleep in the cortex (Favero et al., 2012), suggesting that the cortical release of ACh through BF cholinergic neuron activation plays an important role in facilitating consciousness through the suppression of slow-wave sleep.

Selective stimulation of BF cholinergic neurons also promotes wakefulness through their actions at non-cholinergic BF neurons, such as through the depolarization of neighboring corticopetal glutamatergic and GABAergic neurons (Yang et al., 2014; Zant et al., 2016) as well as neurons of other sleep-relevant subcortical regions (Hirata & Castro-Alamancos, 2010). In a similar vein, lesioning BF corticopetal cholinergic and non-cholinergic neurons increases non-REM (NREM) sleep and augments delta power in the cortex, respectively (Buzsaki et al., 1988; Kaur et al., 2008), highlighting a dichotomy in function of the various frontocortical projections. In particular, ACh-producing neurons of the BF instigate wakefulness primarily by stimulating cholinoceptive cortical pyramidal neurons, and non-cholinergic neurons promote arousal by suppressing the slow delta waves generated by the TRN that occur during non-REM sleep. Taken together, through their direct projections to the cortex and through their actions at nearby cortex-innervating glutamatergic and GABAergic neurons, BF cholinergic neurons promote consciousness via their excitation of cortical neurons and suppression of sleep-facilitating systems.

The activity of BF cholinergic and cortical neurons is modulated by several sleep-relevant neurotransmitter systems that have also been found to influence attentional processing. For example, the arousal-inhibiting chemical adenosine accumulates in the brain during periods of prolonged wakefulness and suppresses the waking phenotype through the hyperpolarization of cortical pyramidal neurons, requiring increased attentional effort in order to overcome fatigue and maintain focus (Basheer et al., 2004). The activity of adenosine on

BF-mediated cortical stimulation is both a key mediator of sleep homeostasis and a significant determinant of attentional performance; namely, adenosine works to suppress consciousness through Gi/o protein-linked adenosine-1 receptors expressed on neurons in the BF which synapse with cortical nuclei (Basheer et al., 2004; Satoh et al., 1998; Van Dort et al., 2009). Conversely to adenosine, norepinephrine (NE), which is produced by the locus coeruleus (LC), serves a similar function as ACh in stimulating cortical activity and instigating at state of alertness, and much of its wakefulness-facilitating actions are mediated through the BF. Intrabasalis microinjections of alpha-1 (α1) adrenergic receptor agonists, such as NE itself and methoxamine, inhibit NREM sleep largely, but not exclusively, via their actions at cortex-synapsing BF cholinergic neurons, and destruction of corticopetal cholinergic neurons with 192 IgG-saporin abolished this effect (Lelkes et al., 2013). LC-mediated NE efflux has also been shown to correlate with attentional function, with methoxamine, atomoxetine, and methylphenidate - a NE reuptake inhibitor used to treat attention deficit/hyperactivity disorder (ADHD; Arnsten & Li, 2005) - boosting cortical NE and supporting attentional efforts (Bymaster, 2002). Howells and colleagues (2012) asserted that both tonic and phasic firing of LC NE neurons are necessary for peak attentional performance. Neurons from other wake-supporting neurotransmitter networks, such as serotonergic cells of the raphe nucleus and histaminergic cells of the tuberomammillary nucleus (TMN), send efferents to BF cholinergic neurons and exert notable influence on cortical excitation, in part, via these inputs to the BF and thus serve overlapping roles in the instigation of

alertness and vigilance. The enlistment of these described consciousness-enabling transmitters as well as the suppression of sleep-promoting compounds serve converging and somewhat redundant functions in stimulating the mutually-beneficial psychological states of wakefulness and vigilant attention (Agostinelli et al., 2019; Castro-Alamancos & Gulati, 2014).

ACh supports attention by promoting motivation

In addition to enabling attention through the promotion of wakefulness and alertness, cholinergic activity plays a crucial role in attention tasks which rely heavily on incentive to perform. In a general sense, striatal motivation networks send outputs to frontoparietal attention systems to preserve performance and support top-down modulation of vigilance under challenging contexts (Christakou, 2004; Engelmann & Pessoa, 2007). If the impetus to remain engaged is not proportional to the energy or effort required to maintain attention, performance tends to decline or cease, not necessarily because subjects cannot pay attention, but because they are not adequately motivated to do so. Sarter and colleagues (2006) describe attentional effort as a necessary reflection of motivation (Berridge & Robinson, 2003), and deleterious manipulations, such as time spent on task, distractions, sleepiness, or drug-induced effects, de-incentivize on-task behavior. Thus, while high motivation leads to the willing recruitment of top-down mechanisms to boost attention, low motivation leads to disengagement with the task, thereby establishing incentive as a significantly important predictor of attentional performance.

Incentive-dependent spikes in dopaminergic neurotransmission exert considerable influence over frontocortical excitation and, as a result, attentional functioning. Cortical cholinergic signaling is reliably enhanced throughout engagement in reward-seeking behaviors, such as during prolonged engagement in a task for which access to a reinforcer is contingent upon accurate responding, highlighting the involvement of BF cholinergic activity during inspired on-task behavior (Arias-Carrión & Pŏppel, 2007; Hanson et al., 2021). The mesofrontal projection from the midbrain dopaminergic system to BF ACh neurons is critical for the integration of motivational and attentional functioning. Following the perception of rewarding stimuli such as food, water, or drugs as well as cues which predict such rewards, levels of the reward-relevant neurotransmitter dopamine (DA) by neurons of the VTA rise, leading to increased agonism of dopaminergic receptors on BF corticopetal cholinergic neurons. Additionally, both dopaminergic and GABAergic neurons contact BF-targeting medium spiny neurons of the NAcc, which together comprise another significant modulator of BF corticopetal neuron function (Swanson, 1982). The activation of BF cholinergic system-synapsing dopaminergic efferents from the VTA and GABAergic nuclei from the NAcc together boost the motivational salience of the task at hand; that is, this stimulatory pathway is most active when the motivation to maintain attention and on-task behavior is high based on reinforcement parameters, including the frequency, quality, magnitude, and immediacy of reward (Cooper & Knutson, 2008; Ventura et al., 2007). All in all, a survival-salient outcome of the activity of mesocorticolimbic reward circuitry, which is

largely driven by the activity of various VTA DA projection pathways, is incentivized attentional performance.

In addition to acting on cholinergic neurotransmission to bias attention towards relevant rewarding or reward-signaling stimuli, mesolimbic and mesocortical activity is also modulated by cholinergic inputs to the midbrain. Though ACh-producing neurons of the BF do not themselves project to DA-producing neurons of the VTA, mesopontine cholinergic nuclei do innervate and exert significant influence over dopaminergic neurons in this region (Xiao et al., 2016). NACh and mACh receptors in the midbrain reward circuit facilitate reward-linked behaviors and enhance reinforcement learning upon their agonism with endogenous ACh supplied primarily by pontomesencephalic cholinergic innervations as well as by exogenous cholinomimetic compounds (Oakman et al., 1995). Increased VTA nACh and mACh receptor agonism biases attention towards stimuli and cues that predict reward through a number of different VTA projections, including to the DA receptor-rich cortex, BF, and NAcc (Swanson, 1982). Presynaptic α7-nACh receptors found on VTA Glu neurons are also implicated in DA production by stimulating local mesolimbic Glu circuits (Schilström et al., 2000; Yan et al., 2018). Additionally postsynaptic mACh receptors found on accumbal cholinergic interneurons synapse with GABAergic NAcc neurons and have a similar effect as DA in increasing the firing frequency of NAcc GABAergic efferents that promote the stimulation of the BF (Yee et al., 2011). Taken together, ACh, nicotine, and other cholinergic receptor agonists

subserve attention in the midbrain reward network largely through their stimulation of cholinergic receptors in the VTA.

Interestingly, despite the well-established role of DA as a key neurotransmitter involved in reward-linked behaviors, the activation of cholinergic neurons in response to rewarding stimuli does not wholly depend on inputs from the midbrain DA system. While discharge of BF cholinergic neurons in response to the delivery of previously-reinforced stimuli occurs in around 15 to 20 ms (Hangya et al., 2015), DA-producing neurons can take up to 50 ms longer to demonstrate the same reward-linked depolarization (Cohen et al., 2012). BF cholinergic neurons have sparse descending projections and fail to synapse with DA neurons; however, non-cholinergic glutamatergic and GABAergic fibers send ample projections to the subcortex, including to the VTA (Agostinelli et al., 2019). Hangya and colleagues (2015) postulate that after the BF receives signals regarding the rewarding percept via thalamic and PFC inputs, cholinergic neurons recruit neighboring non-cholinergic neurons by stimulating nACh receptors on VTA-projecting GABAergic neurons in order to rapidly disinhibit mesencephalic dopaminergic nuclei. This, in turn, increases DA efflux and results in further activation of BF-projecting dopaminergic pathways, ultimately enhancing BF and PFC cholinergic neurotransmission and biasing attention towards the reinforcing stimulus.

Lustig and Sarter (2015; see also Raizada, 2008; Sarter et al., 2006) posit that the mesolimbic-cholinergic-cortical network, particularly as it pertains to enhancing excitatory PFC neurotransmission for the purpose of enhancing

cognition, acts to integrate motivational and attentional functioning and plays an indispensable role in “challenge-driven” attention. Indeed, glutamatergic signaling in the shell of the NAcc boosts performance in the SAT with a flashing visual distracter, and cholinotoxic lesioning of BF corticopetal cholinergic neurons using 192 IgG-saporin attenuated this enhancement, suggesting that BF cholinergic neurons act as a gateway through which motivation to perform boosts attentional processing (St. Peters et al., 2011). However, as is the case with many other neurochemical systems, optimal dopaminergic activity is balanced, with too little and too much DA efflux impairing cognitive performance. This idea is supported by the fact that both stimulation and suppression of DA receptors can worsen attention and increase the number of omitted trials, with the latter variable often used as a measure of motivation and on-task behavior - in the 5-CSRTT (Boekhoudt et al., 2017; Winstanley et al., 2010). Therefore, this complex and overlapping network of interconnected regions spanning the brainstem to the cortical mantle form the anatomical correlate of incentivized attention, especially when faced with salient distracters.

Non-cholinergic BF neurons in attention

Until the development of advanced genetic manipulation techniques like chemogenetics and optogenetics, which allowed non-cholinergic neurons of the BF to be selectively manipulated at the exclusion of their cholinergic neighbors, most of the attention-boosting qualities of the BF were attributed predominantly to the activity of cholinergic cells. Over time, it has been revealed that, while

cortical ACh provided by BF cholinergic inputs is undoubtedly important for attentional performance in both normal and challenging contexts, the glutamatergic and GABAergic neurons - which together vastly outnumber cholinergic neurons of the BF - subserve attentional processing through differing mechanisms. Around half of the total corticopetal BF innervation is GABAergic, with cortex-innervating cholinergic and GABAergic efferents being largely co-distributed in the globus pallidus and substantia innominata (Gritti et al., 1993). BF GABAergic neurons can be further demarcated into separate populations as determined by their co-localization with various binding molecules (Brown & McKenna, 2015). One such group of GABAergic neurons contains the calcium-binding protein parvalbumin (PV) and is maximally active during wakefulness and REM sleep (Hassani et al., 2009; Xu et al., 2015; Yang et al., 2017). These BF PV neurons travel to the cortex and exclusively target cortical PV- or somatostatin-expressing GABAergic interneurons, with cortical PV neurons being potent regulators of high-frequency local network oscillatory activity (Buzsaki et al., 1988) and sleep-promoting somatostatin neurons typically operating with resonances in the low-frequency theta range (Gloveli et al., 2005). BF corticopetal PV-positive projections exert their pro-excitatory effects through perisomatic suppression of inhibitory cortical interneurons, effectively disinhibiting pyramidal neurons and, in doing so, acting alongside corticopetal cholinergic neurons to enhance cortical activation (Alitto & Dan, 2013). Lastly, while glutamatergic BF efferents sparsely synapse with cortical neurons, they indirectly stimulate cortical activity through their projections to neighboring corticopetal

cholinergic neurons as well as other cortex-projecting subcortical neurons (Xu et al., 2015).

Earlier research attempting to parse the role of cortex-projecting, PV-expressing GABAergic neurons in attention frequently employed the neurotoxicant ibotenic acid; while technically having moderately deleterious effects at cholinergic and glutamatergic neurons, ibotenic acid preferentially targets PV-expressing GABAergic neurons (Schwarcz et al., 1979). When compared to cholinotoxic 192 IgG-saporin lesions, which worsen signal detection as evidenced by increased responding at the non-signal lever in signal trials as well as increase omissions in the rodent SAT (McGaughy et al., 2000; McGaughy & Sarter, 1995), the destruction of predominantly-GABAergic neurons with ibotenic acid increases how often rats select the signal lever at the conclusion of non-signal trials (Burk & Sarter, 2001), suggesting a deficit in switching from rules which govern responding in signal trials to those which direct non-signal responses. Lesioning with ibotenic acid also reduces response latencies for these incorrectly-answered trials, highlighting an increased propensity towards impulsive responding only for false alarms (Burk & Sarter, 2001). Thus, cholinergic and GABAergic neurons of the BF appear to mediate opposing elements of attentional performance in signal detection tasks, where cholinergic neurotransmission facilitates signal-driven attention and GABAergic activity facilitates more executive components of attentional performance.

Fast-spiking parvalbuminergic projections from the BF to the cortex have recently been shown to influence cortical excitability largely through the

generation of gamma band oscillations (GBOs; Kim et al., 2015). These low-amplitude, high-frequency rhythmic fluctuations of neural activity - ranging from 30 to 100 Hz and centering around 40 Hz - are correlated with widespread, large-scale network activity, and are associated with visual attention and the awareness of stimuli (Crick & Koch, 1990; Fan et al., 2007; Keil et al., 2001). Cortical pyramidal neurons whose action potentials are tuned in the gamma range are found to quickly and efficiently transmit and integrate signals relating to the features and properties of a stimulus to create a composite perception of the immediate environment (Bharti et al., 2020; Fitzgibbon et al., 2004; Fries et al., 1997; McNally & McCarley, 2016). The ability to rapidly form a coherent representation of a perceived object - a phenomenon known as *feature binding* - requires selective attention towards distinct features of a stimulus and, as such, the PFC likely recruits BF corticopetal PV neurons to instantaneously stimulate and synchronize pyramidal neuron activity at a high frequency during observation or intense focus. Therefore, by generating synchronous gamma-frequency activity in the cortex, BF PV neurons allow for the transient amalgamation of sensory inputs to inform top-down control of attentional resources (Desimone & Duncan, 1995; Fell et al., 2003; Schoenfeld et al., 2003).

When considering the unique roles of BF neuronal populations, both cholinergic and GABAergic BF outputs to the cortex support attentional processing in parallel, but dissociable, ways. For example, while ACh generated by the BF cholinergic nucleus directly stimulates attention-pertinent cortical neurons, the facilitation of cortical GBOs appears to be reliant on the integrity of

the BF parvalbuminergic projection. Optogenetic excitation of cortically-projecting BF PV neurons promotes GBO generation in the PFC, and cholinotoxic lesions are insufficient to abate cortical gamma activity (Kaur et al., 2008; Kim et al., 2015), suggesting that, while cholinergic projections may serve an accessory role in support of GBO, BF PV-positive GABA efferents are themselves the primary promotor of cortical gamma oscillatory synchronization and the psychological processes associated with and supported by GBOs. It is also worth mentioning that, despite having distinct effects on cortical activity, much of the influence of cholinergic and GABAergic neurons in the cortex are synergistic, with cholinergic receptors being directly expressed on BF PV neurons, cholinergic neurons themselves innervating local BF PV neurons, and cholinomimetic drugs such as nicotine increasing GBO generation in the mPFC (Aracri et al., 2010; Bueno-Junior et al., 2017; Henny & Jones, 2008; Yang et al., 2014). Ultimately, the ways in which these two neuronal populations exert their excitatory effects differ, but the activity of one coincides with and influences the activity of the other, with both working together to enable an attentive state through adequate cortical stimulation.

The rhythmic inhibition of cortical pyramidal neurons by these BF PV neurons influences brain activity in such a way that promotes alertness, encourages self-directed behaviors, and coincides with improved attentional performance in humans and non-human animals; however, it is not the only frequency range that supports attention. The oscillatory selection hypothesis, described by Schroeder and Lakatos (2015; see also Frey et al., 2015), suggests

that gamma and 10-12 Hz alpha waves in the cortex are associated with different, but complementing, aspects of vigilance. Increased gamma power reflects active stimulus processing as well as the continuous maintenance of sensory representations pertinent to the task at hand, and alpha oscillations - the generation of which increases in anticipation of distraction - are involved in functional inhibition through their suppression of neurons processing unimportant sensory information (Bonnefond & Jensen, 2013). In support of this, heightened power in the gamma *and* alpha bands has been observed when attention must be selectively paid to a distinct stimulus amongst noise, such as when participants are told to attend to a tone being played in one ear while ignoring a separate tone in the other ear (Fell et al., 2003; Tiitinen et al., 1997; Tiitinen et al., 1993; Weisz et al., 2011). Beta waves, which occur between 12.5 and 30 Hz, are also implicated in attention. While elevated low-frequency beta power is commonly accompanied by impaired attentional capacity, such as in the ADHD-affected brain (Clarke et al., 2001), high-frequency beta waves - which are sometimes referred to as the “low gamma” component or beta-gamma oscillations - are associated with increased arousal and are prominent during unexpected, uncertain, and low-probability events (HajiHosseini et al., 2012). In this regard, an important function of GBOs (as well as beta oscillations closer to 30 Hz) is to maintain a state of cortical excitation that facilitates attention while well-timed pulses in the alpha range protect against attentional detriment by inhibiting the processing of irrelevant and distracting inputs.

In the context of signal detection, increases in broadband gamma power in the visual and frontal cortices of human subjects occur within 50 ms of the onset of a salient signal, followed shortly thereafter by suppression of default mode network (DMN) activity, indicating a shift from disengaged wakefulness to focused attention (Kwon et al., 2021). Kim and colleagues (2016) revealed natural increases in spontaneous bouts of cortical GBOs in the 30-40 Hz range just prior to and during correctly-answered trials for rodents in a three-choice modification of the 5-CSRTT. During trials that were either answered incorrectly or omitted altogether, the cortex demonstrated moderate, but not sufficient, gamma activity. Additionally, direct and selective activation of these neurons has been shown to benefit attentional processing. Schiffino et al. (2021) enhanced fast cortical gamma by ontogenetically stimulating corticopetal BF PV-expressing neurons of mice just prior to the presentation of a cue light in a lever-release version of the rPVT; this brief stimulation that was timed closely with stimulus onset improved attentional performance as determined by reduced reaction times. This stimulation also sufficed to improve response latencies which were slowed by loss of sleep for sleep-deprived mice, suggesting that PV-expressing GABAergic neurons of the BF promote vigilance largely by regulating transient fluctuations in cortical alertness and enabling more effortful and sustained attentional processing (Schiffino et al., 2021).

Conclusion

In summary, the ability to pay attention to distinct elements in the environment is an important psychological phenomenon that supports not only survival, but day-to-day life and goal-directed behavior; as such, a variety of behavioral tasks have been created for the purpose of measuring attentional capacity in a number of different species. These tasks have determined that, via its many reciprocal cortical and subcortical projection pathways, the cerebral cortex plays a crucial role in attentional functioning by enhancing and propagating multimodal signals from salient stimuli while suppressing inputs from irrelevant distractions. There is particular emphasis on the importance of the frontal neocortex in attention, with the PFC being distinctly involved in top-down switching of attentional control. By providing the PFC and other cortical areas with ACh, a neurotransmitter which improves attention by amplifying the response of cortical neurons to sensation- and perception-relevant signals and optimizing intercortical communications, corticopetal BF cholinergic innervations comprise a critical anatomical substrate of waking alertness and vigilant attention. Cholinergic neurons also subserve attentional needs by enhancing wakefulness and arousal as a major branch of the ascending arousal system and by incorporating incentivized inputs from reward-sensitive dopaminergic neurons. Lastly, PV-positive GABAergic neurons of the BF support attention alongside cholinergic neurons largely by generating cortical oscillations in the gamma range and regulating millisecond-range synchrony between vigilance-relevant cortical neurons.

CHAPTER 2. Schizophrenia: psychopathology, neurobiology, and relevance to attention

“If the doors of perception were cleansed every thing would appear to man as it is: Infinite.
For man has closed himself up, till he sees all things thro' narrow chinks of his cavern.”

- William Blake, *The Marriage of Heaven and Hell*

Schizophrenia (SZ) is a chronic and enigmatic neurodevelopmental disorder for which, despite being first documented in medical texts over two hundred years ago, treatment outcomes remain poor. Clinical descriptions resembling SZ have been noted since the age of antiquity, and ethnographic studies establish its existence in cultures and civilizations throughout recorded history. The earliest known record of presumed psychosis can be traced to the Vedas of ancient Hindus in 1400 BCE, describing those afflicted as suffering from a condition “brought on by devils” (Adityanjee et al., 1999). Originally coined *dementia præcox* (“precocious madness”) by Emil Kraepelin in the late 1890s, early nosological efforts classified this condition as a form of dementia that, rather than appearing later in life, emerges during youth, most commonly in late adolescence and early adulthood. It was eventually recognized that the disorder was etiologically distinct from dementia in that it lacks the characteristic neurodegenerative brain lesions (Insel, 2010); thus, it was updated to the modern

terminology in 1908 by Swiss psychiatrist Eugen Bleuler in his book *The prognosis of dementia praecox: the group of schizophrenias*. SZ is derived from the greek word “σχιζοφρένεια”, or *schizofréneia*, which translates to “splitting of the mind”; indeed, it was at this time that SZ was reframed as an illness which is defined by an overwhelming sense of *derealization*, or a detachment (split) from reality. Described by Silvano Arieti as “the retreat from reason, from emotion, and from society” (Arieti, 1956), SZ is a psychiatric illness with extensively poor clinical outcomes, highlighting a pervasive need to understand its causes and origins to better treat those who are afflicted.

In general, a diagnosis of SZ is associated with symptoms which most commonly emerge in early adulthood and persist throughout the lifetime, ebbing and flowing in intensity over the years and ultimately becoming less severe in old age. Neurodevelopmental abnormalities linked to SZ have been observed prior to birth, with atypical neuronal migration which results in structural deviations in the brain being apparent in the second trimester of fetal development in predisposed individuals (Murray et al., 2007). According to the National Institute of Mental Health (NIMH), the prevalence of SZ is similar across the world, with anywhere from 0.33 to 0.75 percent of people having a diagnosis at any given point and roughly 20 million people receiving their diagnosis every year. While around half of those with SZ are eventually able to enter a state of enduring remission during the course of their illness, the other half do not recover and experience a severe pathology throughout their lives (Vita & Barlati, 2018). With an average lifespan that is nearly three decades less than their peers, those with SZ are susceptible

to various medical comorbidities which put their health at further risk, such as heart disease, high blood pressure, liver diseases, diabetes, obesity, and dental issues (Olfson et al., 2015). Half of those with SZ also have at least one other co-occurring psychological condition - including major depressive disorder, anxiety disorder, panic disorder, post-traumatic stress disorder, obsessive-compulsive disorder, and substance abuse disorder - and death rate by suicide consistently hovers around five percent (Buckley et al., 2009; Palmer et al., 2005; Tsai & Rosenheck, 2013). Additionally, men and women experience some differences in how the illness manifests, with more men than women qualifying for a diagnosis, symptoms appearing earlier for men, and poorer premorbid functioning for men (Canuso & Pandina, 2007; Ochoa et al., 2012; Schultz et al., 2007; Seeman, 2000).

As detailed by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) as well as the Positive and Negative Syndrome Scale (PANSS), SZ is one of several disorders which are characterized by the presence of *psychosis*, which is a condition comprised of a number of debilitating symptoms related to reality distortion which can greatly impact functioning and quality of life. The initial emergence of psychosis is considered a psychotic break, which is also referred to as the *acute phase* of psychosis, is necessarily preceded by a months- or years-long prodrome during which the individual demonstrates changes in affect, thoughts, perceptions, and behaviors that, while abnormal, could be indicative of a number of psychiatric conditions, making early detection and diagnosis of SZ challenging. To qualify for a diagnosis of SZ, a

person must experience hallucinations, delusions, or disorganized speech - which are collectively considered the *positive* subset of symptoms because they are additions to typical behavior - for at least six months, including one month or longer of active-phase symptoms. Hallucinations are salient “perception-like” experiences during normal waking consciousness that are not present and are not similarly perceived by others. The two most common types of hallucinations are visual and auditory, with the latter being regularly experienced by over 70 percent of people with SZ (Hugdahl, 2008). Auditory hallucinations most commonly take on the form of human-like voices which seem distinct from the individual’s own thoughts. Though less prevalent, hallucinations can also be tactile, olfactory, and gustatory (Lewandowski et al., 2009). Delusions are considered to be fixed beliefs which are strongly held, even in light of contradictory evidence. The most frequently-reported delusions are related to persecution, which is the persistent feeling that one is being watched, followed, or conspired against in some way, as well as related to grandeur, the belief that one has substantially more power, influence, or abilities than they do. The DSM-5 and the American Psychological Association list other positive symptoms, such as disorganized speech, which is characterized by loose associations, neologisms, and repeating words and phrases, and erratic behaviors like inappropriate emotional responses, unpredictable agitation, lack of impulse control, and catatonia. Together, these abnormal psychological and behavioral states indicate a perception and understanding of the world which is, to some, not rooted in reality.

Until the 1980s, most research efforts focused on the neurological correlates of hallucinations, delusions, and other positive symptoms; however, while the positive symptoms are most stereotypically associated with the disorder, SZ is more than just psychosis and derealization. The second subset of schizophrenia symptoms - *negative* symptoms - encompass subtractions from typical behavior. As determined by PANSS and other similar rating scales, such symptoms include but are not limited to flattening of affect, alogia (poverty of speech), avolition-apathy (lack of motivation), asociality (avoidance of social interactions), and anhedonia (diminished ability to experience joy; Javitt, 1987). In 1982, Nancy Andreasen noted a “renaissance of interest” in negative symptoms because they are prominent in 40 percent of individuals with a SZ diagnosis, are important indicators of treatment responses and outcomes, and at the time, little was known about their neurobiological correlates (Andreasen, 1982; Carbon & Correll, 2014). While less common in other psychotic disorders, negative symptoms comprise a significant component of the SZ phenotype, and the severity of negative symptoms more strongly correlates with treatment outcomes than positive symptom severity (Tamminga et al., 1998). For 73 percent of individuals with SZ, the onset of negative symptoms precedes the emergence of positive symptoms (An der Heiden et al., 2016), suggesting that the neurological substrates within which the disease develops may first begin with network aberrations that produce negative symptoms, and as the illness progresses, the positive symptoms emerge, officially qualifying someone for a diagnosis of SZ.

The remainder of this chapter will focus primarily on the *cognitive* subgroup of SZ psychopathology, a collection of symptoms which were originally included in the list of negative symptoms but became their own central and defining feature of SZ over time. Though the emergence of positive symptoms is commonly considered the realization of SZ, there is ample evidence that the cognitive symptoms are present prior to the onset of psychosis and persist in both active and remitted states (Asarnow & MacCrimmon, 1978; Bowie & Harvey, 2006; Davidson et al., 1999; Nuechterlein & Dawson, 1984). In fact, research suggests that around 80 percent of individuals with a diagnosis of SZ demonstrate profound cognitive deficits, many of which report these deficits in the premorbid prodromal phase (Green et al., 2004; Woodberry et al., 2008). While the occurrence and severity of hallucinations and delusions tend to fluctuate throughout the course of the illness, irregularities of mood and cognition remain relatively steady over time, can persist even between psychotic episodes, and, as such, have a higher burden of illness (Cohen et al., 2019; Correll & Schooler, 2020; Eaton, 1995). These impairments are common not only for those with a diagnosis of SZ, but for their non-diagnosed first-degree relatives as well (Chen et al., 1998; Laurent et al., 1999). Despite adequate cognitive functioning underlying virtually every aspect of day-to-day life to some extent, such impairments are not mandatory for a diagnosis of SZ as determined by the DSM-5; despite this, their presence and prevalence are a cornerstone of the disorder.

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative, which was spearheaded by the NIMH in the

early 2000s, has identified seven distinct domains of cognition which are markedly deficient in SZ: attention, processing speed, reasoning and problem solving, working memory, visual learning and memory, verbal learning and memory, and social cognition (see also Bowie & Harvey, 2006; Nuechterlein et al., 2004). The MATRICS consensus cognitive battery was developed by NIMH in 2002 to measure the aforementioned cognitive impairment domains in SZ; namely, it was designed to be an endpoint of clinical trials for antipsychotic agents to measure their efficacy in improving cognitive outcomes (August et al., 2012; Green et al., 2004; Kern et al., 2008; Marder, 2006; Nuechterlein et al., 2008). The Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) project was created shortly thereafter to improve translational research and lead to better treatments through the development of tests that have greater specificity for certain brain functions and easy-to-manipulate measures of cognition for ease of interpretation (Harvey, 2008). These and other similar initiatives were developed as a response to persistently poor treatment outcomes for cognitive impairments despite extant medications significantly improving hallucination and delusion severity; therefore, such a push was deemed necessary to better direct research efforts towards the development of cognition-enhancing pharmacotherapeutics.

Impairments of attention and information processing in SZ were noted alongside the hallucinations and delusions in the earliest attempts to clearly define the disorder. The first clinical articulation of an attentional deficit in SZ was made by Bleuler in 1911, stating that individuals suffering from psychosis have a

“general tendency to fatigue”, indicating a rapid and premature dwindling of attentional reserves (see also Braff, 1993). Five years later, Emil Kraeplin further expanded upon this idea, where he noted that individuals exhibiting signs of psychosis have a “certain unsteadiness of attention” and frequently “lose both inclination and ability on their own initiative to keep their attention fixed for any length of time” (Hahn et al., 2012). Because attention is a multi-faceted and ubiquitous psychological process for which any performance deficit could potentially be blamed on its impairment (Luck & Gold, 2008; Sarter et al., 2014), CNTRICS established that, for research purposes, attentional deficits in the context of SZ stem from a systemic failure of *input selection*, defined as the capacity to choose which inputs among a bombardment of non-important sensory information are worthy of focus based on internal representations which are liable to change, thereby necessitating some degree of cognitive flexibility in the top-down control of task-pertinent behavior (Gold et al., 2007; Lustig & Sarter, 2015). Input selection is a narrow, explicitly-defined, and parsimonious measure of attention which is easier to interpret than attention as a general construct, which is a multi-faceted umbrella concept that encompasses several subtypes. For example, those with SZ have difficulty maintaining attention during the continuous performance task, which is similar to the 5-CSRTT for rodents and measures sustained and selective attention by requiring participants to indicate the appearance of a target stimulus while ignoring competing stimuli (Kurtz et al., 2001; Laurent et al., 1999; Rutschmann, 1977). A second CNTRICS-determined construct of attention as it relates to cognitive impairment

in SZ is *rule selection*, being the deliberate activation of relevant rule sets in a given task; together, signal detection and executive processing work together to enable a subject to maintain adequate signal detection performance, and their mutual impairment leads to widespread and pervasive attentional dysfunction (Luck & Gold, 2008).

Interestingly, some researchers believe that the cognitive impairments observed in SZ and other psychotic disorders, including those important to attention and input selection, may be more significantly impacted by negative emotions and motivational deactivation than previously thought. In fact, impaired motivation in SZ is profound and cannot be overstated (Petrides, 2000); it can also be experimentally difficult to separate the ability to perform in a cognitive task from the overall desire to participate and maintain engagement. In an important study conducted by Moritz and colleagues (2017), individuals with and without a diagnosis of SZ underwent a routine neurocognitive assessment, and prior to and following this assessment, they were given the *Momentary Influences, Attitudes and Motivation Impact* questionnaire, which asks participants to rate their incentive to perform, concerns about the cognitive assessment, fear about testing and performance outcomes, and negative momentary influences such as poor sleep. As was expected, patients with SZ tended to perform worse on measures of cognition than those without a diagnosis; however, it was also found that the incentive to maintain on-task behavior was much lower, and anxieties about testing results were markedly higher, respectively, than what was reported by their disease-free peers (Moritz

et al., 2017). It was therefore concluded that, rather than a widespread failure of core cognitive networks, emotionally-salient confounds such as desire to engage with the task at hand and stress about testing outcomes can, at a minimum, contribute to attentional efficacy. Moritz cautions that clinicians should attempt to measure what are referred to as “secondary impairments” alongside primary indicators of attentional performance. In support of this, Lustig and Sarter (2015) explain that, because circuits which control attention and motivation are inextricably intertwined and rely on each other to achieve maximal functioning, is likely a combination of attentional and motivational lapsing which result in poor performance in a task of sustained attention.

In summary, SZ is a disabling psychiatric illness which comprises a multitude of symptoms which largely affect perception, motivation, and cognition, all of which are involved in virtually every aspect of daily life. While current antipsychotics are effective in alleviating the severity of hallucinations, delusions, and other positive symptoms, they often fail to treat the diminished motivation, attention, learning, and memory that are prevalent in those with the illness. The failure to maintain control of attention over an extended period of time as well as a lack of motivation to do so are significant cognitive rate-limiting factors which suppresses problem solving, acquisition of important skills, and the completion of daily tasks, leading to worse vocational outcomes and poorer quality of life when inadequately treated (Green, 1996; Luck & Gold, 2008). As such, an understanding of the neurological substrates of SZ symptom expression is

fundamental for not only for diagnostic purposes, but for treatment purposes as well.

The dopaminergic system in SZ

At the neurological level, SZ is described as a disorder of impaired integration, characterized by a critical inability to organize and amalgamate local neuronal activity in order to accurately process information about the external world (Andreasen, 2000; Sato, 2006). One reason that treatment outcomes remain poor for those with SZ is that, despite ample progress elucidating key pertinent neurotransmitter systems, its underlying neuropathology is extremely complex. Though 5-HT and NE were the first neurotransmitters identified as being abnormally regulated in SZ (Carlsson et al., 1959; Twarog & Page, 1953), the role of DA in SZ was first conceptualized when, following the discovery of DA as a neurotransmitter in the CNS by Arvid Carlsson and colleagues (1957), it was found that compounds which lessen the severity of psychosis happened to reduce monoaminergic turnover, with particular efficiency in lessening CNS DA levels (Carlsson & Lindqvist, 1963; Delay et al., 1952; van Rossum, 1966). These nearly-simultaneous discoveries, as well as the first evidence that these compounds have the strongest affinity for DA receptors being published in 1974, led to the emergence of the foundational DA hypothesis of SZ (Howes & Kapur, 2009; Seeman, 1987). In a similar vein, excessive psychostimulant exposure can lead to a transient adverse reaction that can be difficult to distinguish from the clinical psychosis phenotype (Ham et al., 2017; Janowsky & Risch, 1979;

Lieberman et al., 2005). The logical assumption stands that, because drugs that lessen or enhance DA neurotransmission provide relief for or induce psychotic symptoms, respectively, dopaminergic network dysfunction is central in the etiology of SZ. This assumption quickly became a well-established tenet of SZ as well as other psychotic disorders, and for over half of a century, it has guided the research and development of medications to provide relief for the psychosis that necessarily accompanies this disorder.

In the CNS, DA receptors are expressed throughout regions associated with not only motivation and cognition, but motor control, sensory processing, and neuroendocrine functioning as well. G protein-coupled DA receptors exist in five types, in numerical order from DA-1 (D1) to DA-5 (D5; Missale et al., 1998). These are further divided into two DA receptor subgroups which have opposing influences on the intracellular signaling molecules of the neurons upon which they are expressed: $G\alpha_s$ protein-linked *D1-like* receptors and Gi_α protein-linked *D2-like* receptors. D1-like receptors, which include D1 and D5 subtypes, facilitate excitatory neurotransmission through the activation of the cyclic adenosine monophosphate (cAMP) secondary messenger pathway, leading to augmented release of cAMP-dependent protein kinase A and increased transcription in the nucleus (PKA; Beninger, 1998; Trantham-Davidson, 2004). The D1 receptor subtype - which is the most highly-expressed DA receptor in the brain - is widely distributed throughout the striatum, such as on neurons of the caudate putamen, substantia nigra, ventral tegmentum, olfactory tubercle, and NAcc, and are additionally found in forebrain and frontocortical tissues (Bergson et al., 1995;

Pei, 2004). Relevant to cognition, their agonism is well-known to modify both striato-cortical and cortico-striatal glutamatergic synapses in response to reward-pertinent increases in DA efflux; in doing so, this DA receptor subtype establishes a positive feedback loop which enhances incentivized cognition-relevant neurotransmission (Beninger, 1998).

Conversely, the D2-like receptors, which are predominantly composed of the D2 receptor isoform but also of D3 and D4 receptor subtypes, downregulate the intracellular cAMP signaling pathway upon their agonism, leading to reduced release of the endogenous transmitter of the constituent cell (Fuziwara et al., 2005). The D2 receptor subtype, being the most prolific D2-like DA receptor subtype as well as the second-most prolific DA receptor in the CNS, is richly expressed on midbrain, striatal, and pituitary cells, therefore regulating not only reward, cognition, and movement-related processes, but endocrine functioning as well (Kapur et al., 2006). Trantham-Davidson and colleagues (2004) posit that, while low levels of extracellular DA preferentially activate D1 receptors and lead to suppressed prefrontal cortical activation, higher DA concentrations - especially as it relates to reward-contingent rises in DA efflux - have greater influence on D2 receptors, ultimately suppressing GABA-mediated inhibition of motivation- and attention-involved cortical pyramidal neurons and temporarily enhancing behaviors surrounding the rewarding event. Thus, the activity of these DA receptors and the disparities in their cellular influences largely rely on synaptic levels of endogenous DA or DA-mimetic compounds where these receptors are found.

In its earliest conceptualization, the DA hypothesis asserted that excessive dopaminergic neurotransmission is the primary phenomenon from which SZ symptoms - particularly the positive symptoms more strongly associated with psychosis - arise. Indeed, histochemistry and neuroimaging studies over the better half of a century have consistently revealed elevated biomarkers of presynaptic DA activity in the striata of subjects with psychosis. Though levels of the DA active transporter (DAT) remain relatively unchanged, increased presence of tyrosine hydroxylase - the rate-limiting enzyme involved in DA synthesis - has been found in nigral dopaminergic cell bodies and their various striatal terminals, revealing an increased capacity for DA production in susceptible individuals (Howes et al., 2015; Howes et al., 2013). Evidence of heightened intrinsic DA activity is present in the prodrome of the illness and increases over time, leading to the onset of a psychotic episode (Howes et al., 2009; Kegeles et al., 2010; Sorg et al., 2013). Levels of aldehyde dehydrogenase, an indicator of DA degradation, are notably reduced in the VTA of schizophrenic subjects compared to non-schizophrenic controls (Galter et al., 2003). D2 receptor-targeting radioligands are also displaced to a greater extent upon the introduction of DA-stimulating amphetamines in subjects with SZ than in healthy controls, suggesting a DA system that is not only overactive, but sensitized in an active disease state (Breier et al., 1997). Taken together, the extant literature establishes hyperdopaminergia as a robust and well-replicated phenomenon that remains a fundamental pillar of research of SZ and psychosis.

There are four major dopaminergic pathways which emerge from various brainstem nuclei and are associated with a diverse array of survival-promoting processes and behaviors. The tuberoinfundibular DA pathway originates in the infundibular nucleus of the hypothalamus and is largely involved in pituitary gland-mediated prolactin release; specifically, activity of these projections tonically inhibits prolactin release, and their suppression increases prolactin levels and results in the production of breastmilk, most commonly during and following pregnancy (Gudelsky, 1981; Moore & Wuerthele, 1979). The nigrostriatal DA projection, which originates in the substantia nigra pars compacta and contains roughly 80 percent of the DA-producing neurons in the brain, innervates the caudate putamen of the basal ganglia and plays a role in controlling motor sequences and generating purposeful movement (Cenci, 2007). The cell bodies of the final two dopaminergic pathways are contained within the VTA, the basic anatomy of which is worth reiterating in greater detail from its brief description in the context of reinforcement-guided attention in the previous chapter. Around two-thirds of the neurons of the ventral tegmentum synthesize DA, while the other third are predominantly GABAergic and, to a lesser extent, glutamatergic (Nair-Roberts et al., 2008; Bourab et al., 2019). The last two major dopaminergic efferent projections, which are the mesocortical and mesolimbic pathways, originate in the VTA and comprise the major reward systems of the CNS (Haber & Knutson, 2010; Lammel et al., 2012). These two efferent pathways - which are collectively called the mesocorticolimbic system - work together to integrate processes involved in hedonic experience and reward-

seeking behavior, with Satoshi Ikemoto suggesting that DA acts through these neurons to energize approach and the generation of conditioned responding (Ikemoto, 2007, 2010; Ikemoto & Panksepp, 1999). In addition to these two major projection pathways, ventral tegmental DA neurons are also known to synapse with other brain nuclei, including the HPC and amygdala, which are especially involved in emotional and spatial learning and memory (Duszkiewicz et al., 2019; Robison et al., 2020), as well with cortex-innervating neurons of the BF, which will be discussed in depth shortly. Ultimately, all dopaminergic activity in the brain is implicated in SZ as well as in its pharmacological treatment; that is, anomalous activity of these pathways is involved in either the psychopathology of the disorder or in the side effects of drugs which are prescribed to treat psychosis.

The mesocortical DA projection consists of neurons in the ventral midbrain which synapse with neurons of the PFC and other neighboring frontocortical regions (Chinta & Andersen, 2005). These outputs from the rostromedial VTA directly influence various PFC-mediated psychological processes, with dorsolateral prefrontal afferents affecting elements of attention, learning, memory, and executive functioning (Hertrich et al., 2021; MacDonald et al., 2000) and ventromedial prefrontal afferents influencing emotional and affective regulation (Hiser & Koenigs, 2018; Winecoff et al., 2013). The VTA pathway to the cortex is also highly glutamatergic in its composition, with a majority of VTA PFC-synapsing neurons in both humans and rats containing the vesicular Glu transporter 2 (VGLUT2), and between 20 and 30 percent of varicosities in the PFC contain both VGLUT2 and the DA rate-limiting enzyme tyrosine

hydroxylase, suggesting that a significant portion of the inputs from the mesocortical pathway co-release both Glu and DA (Gorelova et al., 2012). It is thus believed that in the cortex, glutamatergic inputs from the VTA mediate more immediate and temporally-precise signaling, and DA acts as a slow but sustained modulator of cortical activation (Lapish et al., 2007). While the role of this pathway in SZ is still a matter of debate, it is believed that VTA innervations of the PFC - particularly the DLPFC - are underactive, which would result in suppressed excitatory inputs to cortical regions responsible for attentional processing, particularly as it pertains to cognition-relevant cortical activation (Cohen & Servan-Schreiber, 1992; Patel et al., 2014). It is worth mentioning that people with SZ are particularly prone to both acute and chronic stress, which lead to augmented and attenuated VTA-mediated cortical DA release, respectively, resulting in both higher- and lower-than-average cortical dopaminergic activity and abnormal regulation of DA-dependent long-term potentiation (LTP) and long-term depression (LTD) in the PFC (Otani, 2003). Thus, in general, unstable mesocortical functioning - regardless of whether it is over- or under-activation of these projections - constitutes an important neuroanatomical substrate for deficient attentional and informational processing.

Lastly, the mesolimbic DA pathway, which is also called the mesoaccumbens projection, sends DA to the NAcc in the ventral striatum component of the basal ganglia, a structure which is concerned with the execution of purposeful movement (Lanciego et al., 2012; Nicola, 2007). These VTA-NAcc connections govern the processing of emotions regarding pleasurable

experiences and the behaviors associated with them, and they centrally contribute to the instigation of behaviors related to the attainment of life-supporting or otherwise rewarding stimuli (Ikemoto, 2007). The dopaminoceptive NAcc - particularly the DA receptor-rich accumbal shell - is composed of approximately 95 percent medium spiny GABAergic cells, with cholinergic and GABAergic interneurons comprising the remaining accumbal cell populations (Collins et al., 2019; Pennartz et al., 1994). As a whole, the NAcc is involved in reinforcement learning, and it can be divided into anatomically and functionally separable shell and core regions; while the shell subdivision is part of the extended amygdala and plays an integral role in hedonic experience and the motivation to acquire desired stimuli, the NAcc core facilitates motoric functioning and conditioned responding related to reward acquisition (Chaudhri et al., 2010; Di Chiara, 2002). The vast majority of DA receptors are located in the shell rather than the core (Yager et al., 2015), offering further support that the NAcc shell is particularly sensitive to reward-related increases in VTA DA efflux and excites neurons of the core to instigate goal-oriented behaviors related to the rewarding stimulus. Taken together, these two subregions and the communications between them exist at the junction of subjective motivation and the initiation of motivated behavior.

The NAcc is anatomically considered a structure of the BF and has a number of efferent pathways. The main target of accumbal neurons is the ventral pallidum of the basal ganglia, an output nucleus that predominantly relays signals to the memory-relevant medial dorsal nucleus of the thalamus (McAlonan et al.,

1993). Axon collaterals of NAcc shell neurons also innervate BF cholinergic neurons, exerting a significant modulatory influence over their depolarization (Sarter et al., 2001). Stimulation of dopaminergic receptors in the NAcc inhibits GABAergic outputs to other regions of the BF, leading to the disinhibition of corticopetal cholinergic neuron-facilitated increases in cortical ACh neurotransmission (Arnold et al., 2001; Bourdelais & Kalivas, 1990; Ferré et al., 1994). This NAcc-mediated transsynaptic regulation of putatively cortex-innervating cholinergic nuclei is made further apparent in experiments showing that intra-accumbal infusions of DA increase BF cholinergic output in the cortex, and the pro-cholinergic effects of systemic administration of the benzodiazepine receptor partial inverse agonist FG 7142 are quelled by microinjections of DA receptor antagonists into the NAcc (Moore et al., 1999; Yang & Mogenson, 1989). Therefore, in congruence with direct projections from VTA neurons to the cholinergic BF (Gaykema & Zaborszky, 1996; Zahm & Trimble, 2008), the interactions between the VTA and NAcc play an inextricable role in instigating cortical cholinergic neurotransmission and facilitating reward-guided cognition.

Aberrations of the various DA receptor subtypes were the initial focus of research efforts elucidating the dopaminergic dysfunction upon which the DA hypothesis was built. Though there is evidence that D3, D4, and D5 receptors are abnormal in SZ (Schroeder & Lakatos, 2009; Semba, 2004; Sobell et al., 1995), the vast majority of DA receptor dysfunction in the context of psychosis research has focused on the D1 and D2 receptors and their complementary contributions to the realization of the SZ phenotype. While the D1 receptor is not

a primary target of drugs which treat psychosis, earlier radioligand binding and positron emission studies exploring cortical D1 receptor prevalence have found reduced D1 receptor expression in the prefrontal cortices of SZ patients, ultimately resulting in suppressed frontocortical dopaminergic neurotransmission (Abi-Dargham et al., 2002; Guo et al., 2014; Okubo et al., 1997). Conversely, evidence from early post-mortem analyses implicate conformational alterations of the more highly-studied D2 receptor subtype, with such studies commonly revealing higher-than-average DA content in the striatum accompanied by increased density of presynaptic D2 autoreceptors expressed on mesolimbic DA-producing neurons (Cross et al., 1981). Tissues stained with D2 receptor-targeting ligands, such as [^{3}H]-spiroperidol and [^{3}H]-flupenthixol, have revealed enhanced sensitivity and binding of D2 receptors in the caudate nucleus, putamen and NAcc (Owen et al., 1978; Cross et al., 1981). Abnormalities in this DA receptor subtype appear to be specifically localized to the striatum. There is a particular emphasis on elevated expression of high-affinity, rather than low-affinity, D2 receptors, as individuals with SZ demonstrate a hypersensitivity to endogenous DA efflux as well as DA-mimetic drugs (Seeman, 2011). Additionally, polymorphisms in the DRD2 gene in SZ-affected individuals additionally implies this receptor in the development of the illness (Kukreti et al., 2006). Thus, because of the well-established aberrations of the D2 receptor and its implications for SZ symptom severity, this DA receptor subtype has always been and currently remains the primary target of antipsychotic medications.

Antipsychotics for the treatment of SZ

All extant antipsychotic drugs, which are also referred to as neuroleptics and major tranquilizers, reduce the activity of dopaminergic neurons to varying degrees. First-generation antipsychotics (FGAs), also referred to as typical antipsychotics, were first prescribed in the 1950s and exert their antipsychotic effects by way of D2 receptor antagonism (Creese et al., 1976; Iversen, 1975; Seeman & Lee, 1975). The capacity for DA-attenuating phenothiazines - which were referred to as “vegetative stabilizers” in 1952 by the neurobiologist Henri Laborit - to abate the psychosis phenotype is what ultimately led to the advent and widespread prescription of classical antipsychotics. The drug chlorpromazine, which was the first prescribed medication to treat SZ in the mid-1950s, is categorized as a low-potency neuroleptic because it does not bind as tightly to D2 receptors as do mid-potency FGAs like loxapine and perphenazine and high-potency FGAs such as haloperidol and fluphenazine (Ban, 2007; Gianfrancesco et al., 2002; Leucht et al., 2003). Those medications with lower D2 receptor potency have more off-target effects and produce side effects associated with the blockade of histaminergic, alpha-adrenergic, and cholinergic receptors (Howes & Kapur, 2009; Kaar et al., 2020). Those that have high affinity for D2 receptors have less direct activity outside of the dopaminergic system, but they increase the severity of extrapyramidal side effects (EPS). EPS are a result of disturbances of the nigrostriatal extrapyramidal system and include numerous motoric abnormalities such as pseudoparkinsonism (Parkinson’s disease-like tremors), tardive dyskinesia (involuntary jerking of facial and neck muscles),

akathisia (insatiable urge to move and inability to stay still), and dystonia (uncontrollable twisting and repetitive movements). The extent of D2 receptor binding correlates with clinical efficacy, with 60 to 80 percent of D2 receptor occupancy being most effective in the reduction of psychosis severity (Creese et al., 1976; de Greef et al., 2011; Seeman & Lee, 1975). There is no evidence that above 80 percent D2 receptor occupancy exerts any additional antipsychotic benefits, and the higher affinity for the D2 receptor, the more prevalent and disruptive EPS tend to be. Thus, efforts to reduce DA activity without directly antagonizing D2 receptors became a central focus of novel neuroleptic research.

With the advent of atypical/second-generation antipsychotics (SGAs) two decades later came an alternative pharmacotherapeutic route: rather than D2 receptor antagonism, these medications are partial agonists at the D2 receptor and directly modulate the activity of a variety of other brain systems (Seeman, 2002). Unlike typical antipsychotics, which bind to D2 receptors more tightly than DA itself, atypical antipsychotics bind more loosely with these receptors while still displacing endogenous DA (Seeman, 2002). Clozapine, the first atypical antipsychotic to be prescribed, has substantial extradopaminergic mechanisms of action, with its most notable effect being the blockade of M1-mACh receptors (Miyamoto et al., 2005). Most SGAs, including clozapine as well as the commonly-prescribed olanzapine, quetiapine, risperidone, also target 5-HT receptors, with the most common being the 5-HT2A receptor subtype (Meltzer, 1999). 5-HT neurons synapse with neurons of the substantia nigra as well as the mesolimbic and mesocortical pathways and stimulate DA activity by way of their

midbrain serotonergic receptors; therefore, the suppression of serotonergic inputs to DA neurons by SGAs leads to a reduction in DA neuron activation (Alex & Pehek, 2007; Breier, 1995). Other targets of atypical antipsychotics include histamine (HA) and NE receptors (Aringhieri et al., 2018; Mauri et al., 2014). By emphasizing antiserotonergic and de-emphasizing antidopaminergic mechanisms of action, these medications are known to produce less EPS than FGAs and thus are, more often than not, associated with less unpleasant physiological and psychological side effects than D2 receptor antagonists.

The efficacy of currently-prescribed antipsychotics is moderate, with most relief being reported for the hallucinations, delusions, and other derealization-related symptoms (Lieberman et al., 2005). However, 30 percent of patients prescribed antipsychotic medications do not experience sufficient relief, and 60 percent of those taking these pharmacotherapies still experience disruptive SZ symptoms despite having at least a partial response to these medications (Girgis et al., 2019). Moreover, the physiological side effects of neuroleptics - extrapyramidal or otherwise - range from mildly unpleasant to reportedly unbearable, pervasive, and potentially lethal. In addition to the motoric abnormalities associated with DA suppression in the substantia nigra, prolonged use of antipsychotics can lead to the development of other serious side effects such as obesity, diabetes, heart disease, and neuroleptic malignant syndrome, a reaction with a range of symptoms including fever, hypothermia, autonomic dysregulation, and altered mental status (Berman et al., 2000). Because of the severity of some of these symptoms, medicinal non-compliance is a common

phenomenon for patients prescribed antipsychotics, with between 40 and 50 percent of individuals prescribed these medications not adhering to the recommended dose (Haddad et al., 2014; Oehl et al., 2000).

One potential reason for the significant failure of extant antipsychotic treatments in adequately treating SZ is contention regarding the true nature of dopaminergic abnormalities. For instance, prolonged exposure to neuroleptics and recreational drugs increases D2 receptor prevalence and sensitivity in the midbrain (Seeman & Van Tol, 1994); as such, it can be difficult to parse what is naturally-occurring in an active disease state from what is influenced by DA-modulating compounds. An extensive meta-analysis conducted by Howes and colleagues (2009; see also Howes et al., 2012) revealed modestly increased striatal expression of the D2 receptor when subjects with SZ are grouped with little to no regard to medication status; however, studies which analyzed drug-naive SZ patients separately often fail to discern a notable increase in striatal D2 receptor activity from healthy controls, suggesting that this well-established increase in this DA receptor subtype may be an artifact of drug exposure. It is currently understood that, for the neuroleptic-naive individual with SZ, there is between a 10 to 20 percent elevation in striatal D2/3 receptor density in the striata of unmedicated people with SZ, with little to no change in their density outside of this region, and D1 receptors demonstrate a slight reduction in the cortices when compared to controls (Howes & Kapur, 2009; Stenkrona et al., 2019). If it is the case that levels of DA are elevated in the midbrain in SZ while D2 receptor expression is not significantly changed from what is observed in the

brains of people without the disease, the source of dopaminergic abnormalities may originate in an upstream locus rather than within the DA system itself. Additionally, if current neuroleptic medications, which predominantly antagonize or partially agonize D2 receptors, provide significant relief for only positive symptoms while failing to alleviate or potentially worsening many of the negative and cognitive symptoms in SZ, this beckons the question as to whether pharmacotherapeutics would be more effective if their primary mechanisms of action were outside of the D2 receptor. Taken together, this evidence suggests that the dopaminergic system in SZ is relatively normal but is driven to excess by outlying afferent nuclei, and it is a worthwhile endeavor to discuss the role of outlying influential CNS networks in the realization of SZ symptoms in an effort to more holistically treat the symptoms beyond psychosis.

Glutamatergic and GABAergic systems in SZ

Though the dopaminergic system is undoubtedly dysregulated in SZ, the dysfunction of other neurotransmitter systems has been identified as playing key roles in the etiology of the illness. It was first noted in the 1950s that the administration of N-methyl-D-aspartate (NMDA) receptor antagonists produces a phenotype which strikingly resembles what is seen in SZ, hence their early classification as “schizophrenomimetic” compounds (Luby, 1959). These drugs, which are classified as dissociative anesthetics, are unique in that they can yield not only the positive symptoms in humans and positive symptom-like phenomena in non-human animals, but many of the negative and cognitive symptoms of SZ

that DA receptor agonists like amphetamines and apomorphine frequently fail to evoke (Jentsch, 1999). The propensity for NMDA receptor antagonists to induce behaviors akin to what are commonly observed during an episode of psychosis in otherwise intact subjects (Coyle, 2012) as well as evoke a resurgence of psychotic symptoms in otherwise stable individuals with SZ (Lindsley et al., 2006) implies that NMDA receptors play a significant role in the etiology of the disorder. The NMDA receptor hypofunction hypothesis of SZ, which emerged in the 1980s as a result of failed attempts to adequately treat the disorder with DA suppressants, asserts that reduced NMDA receptor inputs to key neurotransmitter systems drive the endophenotype and behavioral abnormalities of the disease (Jentsch, 1999; Olney et al., 1999). This hypothesis goes a step further by suggesting that the aberrations of dopaminergic signaling observed in SZ are a consequence of anomalous glutamatergic activity stemming from impaired NMDA receptor function, thereby creating a more unified hypothesis of brain-wide disruptions involving multiple neurotransmitter systems.

NMDA receptors are one of three glutamatergic ligand-gated ion channel subtypes in the CNS. All three are named after the compounds, outside of Glu itself, with which they bind: NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionic acid (AMPA), and kainic acid, which have an affinity for NMDA, AMPA, and kainate receptors, respectively. The NMDA receptor is found at the majority of excitatory synapses throughout the brain, especially in the HPC and the cortex, with most being located on the postsynaptic dendritic spines of neurons in these regions (Collingridge, 1987; Conti, 1997; Magnusson, 2010). They are

either di- or tri-heteromeric in their arrangement, consisting of one of eight obligatory NR1 isoforms alongside various constellations of NR2 (NR2-A, -B, -C, and -D) and NR3 (NR3-A and NR3-B) subunits (Mori & Mishina, 1995). They differ from AMPA and kainate receptors in that they require a co-agonist that acts at the NR1 glycine modulatory site, such as D-serine or glycine, to dislodge the extracellular magnesium ion which blocks the channel at resting potential (Balu & Coyle, 2015). Once open, the pore of the NMDA receptor permits the influx of calcium through the membrane, thereby instigating intracellular enzymatic activity that depolarizes and enhances the activity of the cell and, in doing so, plays a critical role in local synaptic plasticity and efficacy (Lau & Zukin, 2007; Paoletti et al., 2013; Ruppersberg et al., 1994).

Pharmacological inhibitors of the NMDA receptor have a variety of effects depending on the dosages used. Ketamine and phencyclidine (PCP), two such NMDA receptor antagonists, non-competitively suppress NMDA receptor-mediated influx of positively-charged ions by binding to a site inside of the ionophore (Willetts et al., 1990). At high doses, ketamine and PCP act as anesthetics and were initially synthesized to be used as sedatives for surgical procedures (Flohr et al., 1998). At lower, sub-anesthetic doses, NMDA receptor antagonists have been explored and used for several different medical conditions; for example, in addition to demonstrating analgesic qualities (Hewitt, 2000), ketamine and its analogs, including methoxetamine, deschloroketamine, and esketamine, have been investigated as fast-acting antidepressants and anxiolytics (Berman et al., 2000; Coppola & Mondola, 2012; Daly et al., 2018;

Jurásek et al., 2018). Additionally, both ketamine and PCP are used recreationally (Morgan et al., 2012), and acute and chronic exposure to NMDA receptor antagonists are capable of producing neurological and behavioral phenotypes which closely resemble psychosis (Lahti, 1995, 2001). In fact, the symptoms of acute PCP-induced psychosis - such as hallucinations, delusions, paranoia, aggression, and confusion - so closely resemble SZ at times that, prior to the discovery that PCP can produce a transient psychosis, many people who regularly used PCP were misdiagnosed with the disorder (Javitt, 1987; Nabeshima et al., 1984; Steinpreis, 1996). Because of this, ketamine, PCP, and other NMDA receptor antagonists are commonly used in lieu of DA receptor-binding ligands to model SZ and psychosis in humans and non-human animals.

In SZ, inhibitory cortical microcircuitry is dysfunctional, with aberrant glutamatergic neurotransmission in the cortico-mesocortical loop originating in the telencephalon inducing many of these abnormalities. Normally, elevated agonism of NMDA receptors which are expressed on GABAergic interneurons in the cortex leads to increased GABA outflow as a compensatory response to restore balanced cortical activity, and these GABAergic neurons rely on inputs from NMDA receptors to exert their inhibitory influence (Olney et al., 1999). However, beginning in early postnatal development, cortical NMDA receptors are underactive in susceptible individuals and those who eventually develop the disorder, and this dysfunction persists during critical maturational changes in cortical development during late adolescence and young adulthood, when symptoms of psychosis are most likely to first emerge (Gogtay et al., 2011).

These NMDA receptor deficiencies are especially localized to cortical fast-spiking, PV-containing GABAergic chandelier cells that synapse with and modulate the activity of neighboring pyramidal neurons, the proper function of which is - as has been previously discussed - necessary for normal informational and attentional processing. When these NMDA receptors are deficient, GABAergic interneurons display a reduction of intrinsic excitability, resulting in unimpinged stimulation of corticofugal pyramidal cells which innervate a variety of excitatory transmitter systems throughout the CNS (Olney et al., 1999; Howes & Kapur, 2009). Ultimately, NMDA receptor hypofunction induces imbalances in the cortical excitatory-inhibitory (E/I) ratio which disrupts numerous cortical and extracortical communications and, as such, has widespread consequences for a wide variety of neurological and behavioral processes.

At the local level, reduced NMDA receptor inputs to cortical PV-positive GABA neurons yield deficient inhibition of cortical pyramidal neurons, an outcome which has a number of widespread consequences, including impaired synchronization of local network activity in the gamma range that begets deficient cortical information processing (Hirano et al., 2015; White & Siegel, 2016; Winterer et al., 2004). In the PFC, these NMDA receptors preferentially drive cortical interneuron activity and are critical for the generation of gamma rhythms, with their inhibition producing a near-immediate decrease in GABAergic neuron activity followed by a delayed increase in the activity of most cortical pyramidal neurons (Hashimoto et al., 2005; Homayoun & Moghaddam, 2007). Cortical GABAergic chandelier cells have extensive axonal arborizations, with each

singular neuron synapsing with and providing inhibitory inputs to over 200 pyramidal neurons (Cobb et al., 1995); therefore, dysfunction of even one of these interneurons can quell perisomatic suppression of potentially hundreds of neurons. Kwon and colleagues (1999) observed that, when participants were exposed to trains of 20, 30, and 40 Hz clicks, EEG recordings reveal significantly decreased power at the 40 Hz frequency for those with a diagnosis of SZ when compared to healthy controls, but the same disparity in evoked oscillations was not observed for 30 and 20 Hz frequencies, highlighting a particular dysfunction of GBO-generating nuclei (see also McNally & McCarley, 2016). Ketamine and other NMDA receptor antagonists similarly weaken activity in the gamma band in response to a 40 Hz auditory stimulus (Gonzalez-Burgos & Lewis, 2012; McNally et al., 2021). When considered alongside research showing that cortical gamma activity in subjects with SZ is elevated in the absence of stimulation when compared to control subjects (Hirano et al., 2015), it can be surmised that sustained disinhibition of cortical GABAergic interneurons increases resting-state and decreases evoked GBOs, respectively, thereby reducing the signal-to-noise ratio in these areas. The asynchrony of pyramidal cell discharge stemming from a functional failure of GABAergic interneurons dampens the response of these neurons to incoming sensory information and is believed to be a key underlying mechanism by which cognitive and attentional processing are disrupted in SZ.

Diminished functioning of cortical NMDA receptors has influence outside of the cortex which, in turn, further exacerbates cortical dysfunction in SZ. Unimpinged, hyperactive corticofugal glutamatergic projections - which would

ordinarily be calmed by adequate GABAergic inputs - travel to the midbrain, including to the dopaminergic VTA network, resulting in increased glutamatergic tone in the DA neuron-rich mesolimbic pathway. Heightened activation of Glu receptors on dopaminergic neurons as well as on non-dopaminergic neurons that modulate DA activity, including VTA GABAergic interneurons, augments the release of DA, stimulates efferents from the VTA to the NAcc, and produces a hyperactive and hypersensitive ventral striatum which significantly contributes to the realization of the psychosis phenotype (Howes & Kapur, 2009; Kegeles et al., 2002). In this regard, cortical NMDA receptor hypofunction directly induces the characteristic mesolimbic hyperdopaminergia and resulting aberrant cortex- and subcortex-innervating outputs from the midbrain that are well-known to underlie the positive, negative, and cognitive aspects of SZ.

The notion that the NMDA receptor hypofunction hypothesis better encompasses the broad range of SZ symptoms than does the DA hypothesis is illustrated by experimental research using ketamine, PCP, and similar drugs in this class to induce a transient state of psychosis in non-human animals. Overall, SZ is a uniquely human disease with genetic and exogenous nuances that are not feasible to reproduce in non-human animals; for example, if the neurological substrates within which the broad range of SZ symptoms develop are highly cortical, it can be impossible to adequately replicate in animals with reduced cortical volume compared to the rest of the brain. Regardless, alongside other methodological techniques such as genetic manipulations and neuronal ablation, pharmacological models attempt to recreate key abnormalities of the neurological

environment from which the human illness arises. Such research endeavors, which began over half a century ago, commonly employed pro-dopaminergic drugs, such as amphetamines, to reproduce a SZ-like drug-induced psychosis (Ellinwood et al., 1973; Snyder, 1973). As the role of NMDA receptors and glutamatergic dysfunction in SZ began to be delineated in the 1980s, administration of drugs like ketamine, PCP, and other NMDA receptor-targeting agents quickly gained popularity as valid psychotogenic techniques (Carlsson & Carlsson, 1990; Javitt, 1987; Olney et al., 1999). While both acute and repeated administration of amphetamines and other DA neuron-stimulating compounds can reliably evoke positive-like symptoms such as psychomotor agitation, stereotypy, and hypersensitivity to other psychotomimetic chemicals, ketamine and PCP are able to produce those same effects as well as the negative and cognitive symptoms that DA receptor agonist models of SZ often fail to adequately replicate (Jentsch, 1999; Powell & Miyakawa, 2006; Sams-Dodd, 1998).

At sub-anesthetic concentrations, NMDA receptor antagonists exert most of their dysregulatory effects through the inhibition of NMDA receptors expressed on parvalbuminergic GABA interneurons in the cortex and HPC. These neurons have higher baseline activity and more readily depolarize than the pyramidal neurons to which they project and, as such, provide a more favorable environment for the dislodgement of the magnesium ion which blocks the NMDA receptor channel at a resting state (Cohen et al., 2015; Gonzalez-Burgos & Lewis, 2012; Lewis & Moghaddam, 2006). This preferential blockade of NMDA

receptor inputs to GABAergic interneurons results in the disinhibition of far-reaching stimulatory efferents and, in doing so, produces a generalized state of brain-wide hyperarousal through the recruitment of multiple cortical and subcortical excitatory networks. This idea is supported by research revealing the robust propensity of both short-term and long-term NMDA receptor antagonism to exert both psychotogenic and attention-impairing effects in humans and non-human animals. Experiments during which monkeys and rodents were systemically administered low doses of PCP reveal disrupted input selection and worsened attentional performance, and these behavioral indices were accompanied by increased amplitude of pre-stimulus GBOs - a phenomenon which is negatively correlated with accuracy in continuous performance paradigms - as well as a suppression of low-frequency alpha and theta waves (Fries et al., 2001; Goonawardena et al., 2016). Importantly, primarily-antidopaminergic FGAs and SGAs are not able to attenuate NMDA receptor blockade-induced hyperfrontality and are unable to consistently improve attentional performance, suggesting that attempting to treat NMDA receptor hypofunction with D2 receptor-targeting drugs does not suffice to normalize alterations of cortical GABAergic activity and, in failing to do so, suggests that the D2 receptor is not the ideal target to treat cognitive impairments.

This dichotomy in the capacity for DA receptor agonists and NMDA receptor antagonists to reproduce the broad range of SZ symptoms is also supported by research with human participants who are either prescribed or recreationally consume drugs in these categories. Studies on chronic drug use

revealed that long-time ketamine and PCP users were more likely than cocaine and amphetamine users to experience symptoms of drug-induced psychosis, which include but are not limited to hallucinations, delusions of grandeur, and thought disorder (Farber, 2003; Newcomer & Krystal, 2001) as well as social withdrawal and cognitive impairment (Linn & Javitt, 2001). These reports coincide with findings showing that profound NMDA receptor hypofunction stemming from overuse of such drugs induces neurobiological changes and a clinical syndrome which are reminiscent of a psychotic state, including a sensitized dopaminergic system and dysfunctional cortical neurotransmission (Jentsch & Roth, 1999; Cahart-Harris et al., 2013). In this sense, while both DA and NMDA receptor-centric models of SZ can encapsulate many of the symptoms seen in humans with the disorder, the use of the latter drug class may better reproduce a broader symptom range and, therefore, have greater relevance for the development of medications which can better treat the negative and cognitive symptoms in addition to the positive symptoms.

The BF cholinergic system in SZ

Despite their success in providing relief for the positive symptoms, neuroleptics are inconsistent in treating the negative and cognitive symptoms of SZ because their antidopaminergic mechanisms of action work primarily downstream from the hyperactive corticofugal efferents which drive an active disease state. This need for more effective treatments encouraged the exploration of outlying neurotransmitter systems as they contribute to certain

aspects of SZ psychopathology (Hyde & Crook, 2001). The cholinergic system, being one such dysregulated network, contributes to not only attention itself, but the motivated recruitment of limited cognitive resources required to pay attention. While the number of BF cholinergic neurons as well as their innervations of other forebrain regions appear normal in the brains of those with SZ (Adams, 2007), Tandon and colleagues (1989) suggested that negative and cognitive symptoms may stem from cholinergic system hyperactivity. In a similar vein, Sarter and Bruno (1998) illustrate the importance of balanced cortical cholinergic tone in normal cognitive functioning by juxtaposing SZ and Lewy Body Dementia, both of which are characterized by hallucinations and significant cognitive impairment; the authors suggest that chronically-disinhibited cholinergic inputs to the cortex in SZ and, on the other end of this spectrum, persistently suppressed cortical cholinergic neurotransmission in Lewy body dementia both result in a profound impairment in cortical information processing (Sarter & Bruno, 1998; see also Perry et al., 1995). In this sense, an inability for the cortex to selectively amplify important information and filter out extraneous sensations produces abnormal perceptions and cognitive deficits, regardless of whether this cortical dysfunction stems from excessive or insufficient ACh neurotransmission in sensory processing-relevant regions.

Anomalous ascending cholinergic signaling may play some role in the experience of positive symptoms, but the notion that it is most relevant to the negative and cognitive symptoms has garnered ample empirical support over the years. In particular, research efforts suggest that abnormal NAcc output to the BF

is largely to blame for the neurobiological origins of frontocortical cholinergic dysfunction in SZ. Increased DA receptor agonism in the NAcc has been shown to disinhibit GABAergic output to the BF and other forebrain nuclei, resulting in lessened BF GABA than what would be seen in the non-SZ-affected CNS. Because BF corticopetal cholinergic neurons receive a majority of their inhibitory inputs from these NAcc GABAergic projections (Salgado & Kaplitt, 2015; Sarter & Bruno, 1998; Záborszky et al., 1999), the hypoactivation of these accumbal afferents in response to elevated mesolimbic DA neurotransmission reduces BF GABA levels and renders subcortical ACh-generating neurons abnormally and unsustainably reactive in the earliest instances of attentional effort (*Figure 2*; Sarter et al., 2005; Kozak et al., 2007; Lustig & Sarter, 2015). Kozak et al. (2007) measured prefrontal cortical ACh efflux as well as attentional performance for rats with sensitized mesolimbic dopaminergic systems resulting from amphetamine challenge and discovered that those animals failed to demonstrate a task-specific increase in cortical ACh levels when juxtaposed with animals were not pre-treated with amphetamine, suggesting that their cholinergic systems were frozen at baseline and unable to flexibly respond to increasing attentional demands (see also Lustig & Sarter, 2015). Additionally, small populations of cholinergic interneurons in the NAcc also influence spontaneous phasic dopaminergic release via nACh receptor stimulation on dopaminergic terminals (Yorgason et al., 2017); as such, these neurons play a supplementary and indirect role in producing an overstimulated BF.

Over the years, both hyperfrontality and hypofrontality have been proposed as potential culprits for the cognitive and attentional deficits in SZ, with ample and at-times opposing evidence existing for both arguments. Manoach (2003) suggests that both are accurate reflections of prefrontal cortical activity in an active disease state depending on a number of variables, including task parameters, attentional demands of the task, and duration of task participation. It was revealed that, when participants were engaged in a working memory task reliant on intact cholinergic and prefrontal cortical functioning, a peak shift in maximal prefrontal cortical activation and deactivation occurred earlier for those with SZ than for control subjects (Manoach, 2003; see also Fletcher et al., 1998; Minzenberg et al., 2009), suggesting that the increased effort necessary to focus during task performance could not be sustained over time. This earlier peak shift resulted in overall worsened performance as well as increased intra-session variability, and these irregularities coincided with inconsistencies in the recruitment of attention-critical brain areas throughout performance when compared to controls (Manoach, 2003). The proposed BF-PFC dysfunction is posited to be the primary pathway through which input selection is disrupted and attentional and motivational functioning is impaired as time progresses, especially during periods of environmental distraction (Demeter et al., 2013; Sarter, 2005). Taken together, the elevated DA efflux in an active disease state leads to reduced GABAergic activity at cholinergic neurons, resulting in a BF that is more active earlier in attentional endeavors and ineffectual in appropriately modulating cortical excitation as attentional demands increase.

Pharmacological models of SZ using NMDA receptor inhibiting drugs modulate BF and cortical cholinergic functioning in ways that are similar to what is seen in the human disorder. In addition to inciting changes in gamma generation that disrupt information processing at the local level, acute ketamine, PCP, and other drugs of this class evoke the release of several excitatory neurochemicals, including 5-HT, NE, DA, and ACh throughout the brain, with increased choline acetyltransferase and acetylcholinesterase being evidence of elevated ACh release and turnover through the cortices of rats (Dazzi et al., 1995; Hsu et al., 1980; Jentsch, 1999). The anticholinergic antipsychotic clozapine, but *not* primarily antidopaminergic SGAs like haloperidol and raclopride, suffices to attenuate transient and sub-chronic PCP-induced overactivation of PFC pyramidal neurons, more effectively reduces PCP-associated neurotoxicity, and reverses performance deficits and impulsive responding in tasks of attention and working memory, such as the 5-CSRTT, SAT, and the novel object recognition task (Baviera et al., 2008; Farber et al., 1993; Jentsch, 1999; Neill et al., 2010; Paine & Carlezon, 2009; White et al., 1995). Taken together, this suggests that, in terms of addressing NMDA receptor hypofunction-linked cortical neuron dysfunction, drugs with anticholinergic-dominant mechanisms of action may be better at addressing symptoms which negatively affect behaviors and psychological states reliant on the integrity of PFC neurotransmission.

Overall, cholinergic receptor functioning appears to be reduced in the brains of those with SZ. This could potentially be a compensatory downregulation

in response to excessive activation of cholinergic neurons. Research on nACh receptors has shown a 40 percent reduction in low-affinity α7-nACh receptor binding and reduced receptor density specific to frontocortical neurons, and similar findings were also demonstrated for high-affinity α4β2-nACh receptors in the cortical tissue (Durany et al., 2000; Guan et al., 1999). There are also deficiencies of both nACh receptor subtypes in the HPC, particularly those which are found on putative GABAergic interneurons of the CA1 region (Breese, 2000; Freedman et al., 1994, 1995). Reduced cholinergic mediation of fast synaptic transmission normally facilitated by these interneurons results in the non-suppression of P50 evoked waveforms, which are stimulus-driven neurophysiological responses that are generated by α7-nACh receptor-dependent hippocampal neurons and play an important role in sensory gating (Alkondon et al., 1998). The P50 response normally lessens in intensity following repeated stimuli presentations - particularly auditory stimuli - and a failure to adjust P50 wave amplitude to these redundancies produces psychological deficits associated with SZ, such as sensory overload, distractibility, and impaired concentration (Moxon et al., 2003; Olincy et al., 2006). Markers for GABAergic interneurons are also deficient in hippocampal tissue of SZ subjects (Reynolds et al., 1990), suggesting that less hippocampal nACh receptors could largely be a consequence of hypofunctional GABAergic cells which would ordinarily highly express these receptors.

There is a very well-documented relationship between psychotic disorders and nicotine use. The SZ clinical population is particularly prone to tobacco

consumption, with over 60 percent engaging in regular cigarette smoking compared to less than 20 percent of the general population (Hartz et al., 2014; Gogos et al., 2019). One potential explanation for this relationship is that nicotine is both rewarding through activity at nACh receptors on sensitized VTA DA neurons and nootropic via stimulation of nACh receptors in cognition-relevant frontocortical regions (Laviolette & van der Kooy, 2003; Yeomans & Baptista, 1997). While nicotine primarily targets α4β2-nACh receptors, high doses can also upregulate SZ-deficient α7-nACh receptors (De Luca et al., 2006). Breese et al. (2000) revealed a significantly increased quantity of nACh receptors in the cortices of nicotine-treated animals, and this increase also persisted for those co-treated with the antipsychotic haloperidol, insinuating that individuals with SZ who take neuroleptic medications may use cigarettes and other forms of nicotine consumption as a way to compensate for nACh receptor loss in areas associated with vigilance and motivation. Substance use disorder is a common comorbidity with psychosis, with an overactive mesolimbic DA system in SZ underlying increased addiction risk and drug cravings for not only nicotine, but virtually all psychoactive drugs, including cannabis, alcohol, and cocaine (Baigent et al., 1995; Dixon et al., 1991; Khokhar et al., 2018; Tsapakis et al., 2003). The hypothesis that nicotine usage is a form of self-medication is supported on multiple levels. Not only does it transiently enhance cholinergic functioning by compensating for reduced cortical nACh receptor expression and function (McKee et al., 2009; Williams & Gandhi, 2008), but it also attenuates some of the sedating side effects of neuroleptic drugs, as many patients report reduced

extrapyramidal side effects and improved energy when they smoked cigarettes (Goff et al., 1992). Nicotine does appear to enhance - but not completely normalize - attention for SZ patients as evidenced by improved performance in rapid visual information-processing tasks and auditory attention paradigms (Harris et al., 2004; Hong et al., 2011; Levin & Rezvani, 2002). Taken together, increased nicotine consumption for those with psychosis may be related to the subjective increase in the rewarding aspect of drug use, a reduction in antipsychotic side effect severity, and the temporary boost in attention and cognition through its agonism of nACh receptors.

There is also ample evidence for regionally-specific decreases in mACh receptor functioning in SZ, including in attention-critical cortical regions. M1-mACh receptor binding potential is reportedly reduced in the dorsolateral prefrontal cortices of medication-naive SZ patients, and this deficit coincides with cognitive deficits, particularly those which relate to the information processing speed (Bakker et al., 2018; Dean et al., 2003). Ellis et al. (2005) found that human subjects without SZ demonstrated impaired sustained attention and memory formation when they were given the mACh receptor antagonist scopolamine, which emulates the consequences of deficient mACh functioning in SZ, but *not* when they were given the nACh receptor antagonist mecamylamine, highlighting the unique necessity of mACh receptors in cognition and the consequences of their detriment. This mACh receptor depletion is particularly evident in a subgroup of people with a diagnosis of SZ. For example, Scarr and colleagues conducted a radioligand study which revealed that over a quarter of

their SZ sample size had markedly reduced [^{3}H]-pirenzepine binding in the DLPFC, and these individuals were defined as having “muscarinic receptor deficient schizophrenia”. It has been suggested that SZ is not necessarily homogeneous from person to person, but rather composed of multiple illnesses which, while together sharing a similar symptom profile, offer slight variations in their neurobiological outcomes (Jablensky, 2006; Scarr et al., 2009). In this sense, profound mACh receptor impairment may underlie one possible manifestation of SZ which correlates with heightened severity of negative and especially cognitive symptoms, making those individuals less likely to experience the same degree of symptom relief through the use of traditional antipsychotic medications as those with less mACh receptor dysfunction.

Sleep and the cholinergic system in SZ

In the previous chapter, it was discussed that balanced cholinergic activity promotes wakefulness as well as REM sleep; in contrast, SZ-linked hypercholinergia elicits a state of hyperarousal that worsens quality of sleep (Sitaram, 1982; Tandon, 1999). Sleep disturbances in SZ are common and pervasive - especially during an acute psychotic episode - with up to 80 percent of patients with SZ experiencing problems falling or staying asleep (Cohrs, 2008); these reports are solidified by ample polysomnographic evidence of reduced REM and NREM latency as well as dysfunctional REM rebound, a phenomenon which occurs as a result of REM sleep deprivation (Keshavan et al., 1990). When given to SZ patients, the anticholinergic compound biperiden increases REM

sleep and reduces the severity of negative symptoms, indicating that drugs which quell the activity of ACh-producing cells are not only beneficial for relatively treatment-resistant aspects of the disorder, but for sleep as well (Tandon et al., 1999). It is difficult to determine whether improved cognition from anticholinergic compounds stems from addressing the primary neurobiological phenomena which yield primary SZ symptoms or as a result of improved sleep; nevertheless, such a finding suggests that an overactive cholinergic system worsens sleep and cholinergic receptor antagonism, or at least the suppression of these neurons, induces a multi-faceted benefit for those with the disorder.

Neuroleptics, which have also been referred to as “major tranquilizers”, are so called because they are highly sedating at clinically-effective doses (Kołaczkowski et al., 2014). Antipsychotic medications increase sleep duration due to their wake-suppressing qualities which largely stem from antihistaminergic mechanisms of action; in fact, while not common, SGAs can be prescribed for people without psychosis solely for the purpose of promoting sleep, with over 12 percent of a multi-thousand-participant survey indicating that the only reason they take antipsychotics is to quell sleep disturbances (Hermes et al., 2013; Miller, 2004). However, D2 receptor antagonism and, to a lesser but still clinically-salient extent, partial agonism are also associated with a litany of side effects which can worsen sleep quality. For example, patients who are particularly susceptible to EPS stemming from depletions of nigrostriatal outputs to brain areas associated with motoric functioning, such as involuntary tremors, tardive dyskinesia, and other such parkinsonisms, indicate an impairment in their

ability to fall and stay asleep (Brotini & Gigli, 2004). Additionally, neuroleptic-induced obesity is linked to breathing disorders such as sleep apnea and, as such, has a similarly negative impact on sleep quality (Winkelman, 2001). Thus, it may be that extant antipsychotics increase the duration, but not the quality, of sleep due to their highly-sedating characteristics.

Motivation and the cholinergic system in SZ

In addition to underlying attentional and general cognitive deficits, abnormal signaling from the NAcc to the BF, and thus from the BF to the PFC, is suspected to underlie demotivation-linked deficits of cue-motivated behavior in SZ (Collins et al., 2016). Reward-contingent discharge of midbrain dopaminergic neurons encourages frontocortical ACh release through the BF-encompassing mesolimbic pathway, the functional integrity of which is critical for the incentivized enhancement of attentional performance (Lustig & Sarter, 2015). With the help of cholinergic inputs, the mPFC and lPFC work together to integrate motivation- and attention-pertinent signals into purposeful actions, with the mPFC receiving and conveying information regarding reward and penalty to the lPFC, resulting in largely lPFC-mediated top-down selection and activation of behavioral sets relevant to the acquisition of said reward in what is referred to by Kouneiher et al. (2009) as “reward-based energization of higher cognitive resources". As was also mentioned previously, this process seems to be largely lateralized to the right PFC. In this regard, ACh neurotransmission acts at the junction of input selection and the motivation to identify reward-predicting signals. It can therefore

be logically deduced that the cholinergic abnormalities observed in SZ would not only worsen attentional capacity, but the desire to expend the increased energy required to adequately pay attention in situations of increasing cognitive load. It is therefore proposed that increases in PFC ACh - particularly in the right hemisphere - reflect the motivated recruitment of mechanisms which enable attentional processing. If cortical ACh levels are already in excess, as is seen in SZ, cognitive systems which ordinarily require balanced BF cholinergic inputs will be dysfunctional, ultimately leading to worsened attentional performance.

Evidence suggests that currently-prescribed antipsychotics, particularly those with a higher degree of D2 receptor antagonism, are not particularly effective at improving amotivation; in fact, they can instead further exacerbate the motivational deactivation that is already problematic for those with SZ in a medication-free state. Animal research employing non-antipsychotic antidopaminergic drugs to measure their effects on task engagement reveal impairments in reinforcement learning and, for animals trained in a task, a progressive within-session decline in responding (Wise, 2004). The same outcome, which is referred to as “neuroleptic-induced anhedonia”, has long been observed for rats administered antipsychotics, with higher doses even precluding learning (McFarland & Ettenberg, 1995; Wise et al., 1978). This suggests that, despite the consequences of hyperdopaminergia on incentivized performance, that the blockade of DA receptors - particularly the D2 receptor subtype - does not suffice to restore motivational processing in the SZ-affected brain. One could posit that, while reducing excessive DA lessens overstimulation of the NAcc and,

as a result, BF corticopetal nuclei to an extent which would lessen cholinergic hyperactivity and restore E/I balance in the cortex, the anti-rewarding quality of such compounds tarnishes such a hypothetical benefit. As such, in terms of addressing the lack of motivation for those with SZ, available neuroleptics fall short in providing relief for this pervasive and treatment-resistant symptom.

Non-cholinergic BF neurons in SZ

Little is known about the exact nature of BF PV-positive corticopetal GABAergic neuron dysfunction in an active disease state, largely because the technology which allows for the selective targeting and manipulation of such neurons is relatively new. As was already detailed, the functional integrity of BF PV neurons is necessary for the generation of cortical GBO, and abnormalities in both spontaneous and evoked gamma oscillations in the cortex are well-established phenomena in SZ and psychosis. Despite lack of clear evidence that BF parvalbuminergic projections are abnormal in the disorder, their critical role in engendering cortical gamma through their actions at cortical GABAergic interneurons implies their dysfunction. McNally et al. (2021) revealed a psychotomimetic quality of long-duration stimulation of this population of BF neurons; in contrast to phasic optogenetic excitation of cortex-innervating PV+ GABAergic projections, which induces transient narrowband oscillations in the cortex (Kim et al., 2015; Schiffino et al., 2021), low-wattage tonic excitation of these neurons augments cortical broadband power in the gamma range and suppresses evoked gamma in response to a 40 Hz auditory stimulus train. These

neurobiological changes were accompanied by behavioral indices which parallel what is observed in SZ, such as worsened performance in a novel object recognition task and hyperlocomotion measured in an open-field arena (McNally et al., 2021). While more research needs to be done to parse the exact role of BF PV-expressing cells in the grand scheme of the illness, this recent evidence does hint at a potentially important role in the expression of the SZ phenotype, particularly as it pertains to cortex-reliant sensory integration and attentional processing.

Issues with cholinergic receptor-targeting ligands for the treatment of SZ

Though there is a plethora of evidence that abnormal cholinergic neurotransmission contributes to attentional impairments in SZ, there has not been much progress in the use of anticholinergic agents for the treatment of psychosis. Conflicting efficacy of primarily cholinergic receptor-binding drugs in a therapeutic context makes it unlikely that this family of receptors will be a primary antipsychotic target. The SGA clozapine has potent anticholinergic properties through its antagonism of M1-mACh receptors and, despite being first prescribed in the 1950s, is still considered one of the most effective medications in treating cognition-related symptoms in treatment-resistant SZ (Goldberg et al., 1993; Hagger et al., 1993); however, the drug is considered a “last-resort antipsychotic” and comes with a litany of unpleasant and potentially dangerous side effects (Miller, 2000), many of which are unique to its antimuscarinic qualities, ultimately limiting its usage due to safety despite its pro-cognitive qualities. Conversely,

cholinomimetic compounds such as nicotine have also been shown to improve cognitive impairments in people with SZ (Freedman, 2014). To further complicate matters, both anticholinergic and pro-cholinergic drugs have demonstrated psychotogenic tendencies at specific doses for individuals with as well as without a SZ diagnosis, revealing a narrow therapeutic window (Das et al., 2020; Eum et al., 2017; Quigley & MacCabe, 2019; Simosky et al., 2002). Additionally, nACh receptors desensitize very quickly with repeated and chronic stimulation, and mACh receptor orthosteric binding sites are highly conserved across the subtypes, making the development and utilization of mACh receptor-specific ligands a challenge (Jakubík et al., 2008; Quick & Lester, 2002). Thus, while it is clear that dysregulated cortical cholinergic neurotransmission impairs attention, drugs which directly target and modulate the activity of endogenous cholinergic receptors may not be effective long-term treatments for the cognitive deficits of the disorder.

Conclusion

To recapitulate, SZ is a psychiatric disorder which, alongside symptoms such as hallucinations, delusions, and disorganized behavior, is characterized by profound and occasionally incapacitating motivational and cognitive impairments that disrupt basic functioning and day-to-day life. The extent of Glu, DA cortical ACh dysfunction predicts the severity of positive, negative, and cognitive symptom subsets of the illness. Structural and functional abnormalities of mesocorticolimbic circuitry, particularly as they relate to hypoactive NMDA

receptors on cortical GABAergic interneurons excessively stimulating VTA and NAcc neurons, produce an abnormally reactive BF cholinergic system that markedly disrupts cortical E/I balance during baseline as well during engaged, on-task behavior. Unlike the positive symptoms, which are adequately treated by commonly-prescribed antidopaminergic medications, the negative and cognitive symptoms often remain unaddressed and can even be exacerbated by antipsychotic treatment. The failure of these pharmacotherapies to treat salient symptoms of the disorder is likely because they do not address the primary loci of attentional and motivational disability. Additionally, the side effects of these medications can be unpleasant and disruptive at best to devastating or potentially lethal at worst, leading to many patients prescribed such drugs to not adhere to their dosing regimens or, if they do, possibly experience life-long disabilities. Thus, drugs that primarily target DA receptors are not able to holistically treat SZ and provide an impetus to explore alternative brain circuitry to identify novel neurobiological systems to target for the treatment of this complex and potentially devastating diagnosis.

CHAPTER 3. The lateral hypothalamic orexin system: functions and therapeutic potential

"The great topmost sheet of the mass, that where hardly a light had twinkled or moved, becomes now a sparkling field of rhythmic flashing points with trains of traveling sparks hurrying hither and thither. The brain is waking and with it the mind is returning. It is as if the Milky Way entered upon some cosmic dance. Swiftly the head mass becomes an enchanted loom where millions of flashing shuttles weave a dissolving pattern, always a meaningful pattern though never an abiding one; a shifting harmony of subpatterns."

- Charles S. Sherrington, *Man on His Nature*

The hypothalamus is a small but prolific structure of the brainstem whose cell bodies are situated inferiorly to the thalamus. Its putative functions have been the topic of intense interest since its first documentation in the 2nd century alongside a similar description of the pineal gland. In the 14th century, Italian physician Mondino de Luzzi described the hypothalamus as "the faculty of reasoning (*virtus cogitativa*) and thought (*merito*)" which "combines imagination and past memories, so as to separate physical sensations (*sensatis*) from abstract feelings (*non sensata*)" in his human anatomy text *Anothomia* (see Toni, 2000). In 1662, René Descartes detailed a speculative anatomical pathway by which chemical information regarding a visual stimulus might traverse the brain, traveling along the optic chiasm from the ocular globe to the third ventricle - that

corresponds to the suprachiasmatic nucleus of the hypothalamus - and terminating at the pineal gland, ultimately stimulating what is referred to as the release of the *animal spirit* (Lechan & Toni, 2000). Despite lacking a clear understanding of the relationships between discrete anatomical structures and their behavioral domains, these early efforts in articulating hypothalamic function suggest that it was understood that this structure exists at a critical junction of sensation and perception, integrating and organizing incoming sensory information into voluntary behaviors and purposeful actions.

It is currently acknowledged that the hypothalamus exists at a major crossroads in the brain and has been referred to as the conduit of homeostatic, nervous, and endocrine functioning. It receives a continuous stream of incoming sensory and physiological information and, through its small but widely-projecting nuclei, influences and subserves many mutually beneficial and survival promoting physiological and psychological states. For example, the hypothalamus acts as the body's thermostat and plays a critical role in thermoregulation by promoting heat generation when core body temperature is too low and increasing sweat production when body temperature becomes too elevated via an efferent heat production pathway that is particularly sensitive to serotonergic and cholinergic inputs (Myers & Yaksh, 1969). Hypothalamic neurons also generate a plethora of regulatory polypeptides that communicate extensively with the pituitary gland largely via a portal system of blood vessels (Daniel, 1976). In doing so, the hypothalamus promotes the release of homeostasis-relevant hormones that regulate homeostasis-relevant physiological

and psychological processes, including stress-induced cortisol via the hypothalamic-pituitary-adrenal axis, the pro-reproductive hormone kisspeptin through the hypothalamic-pituitary-gonadal axis, and metabolism-linked thyroid hormone by way of the hypothalamic-pituitary-thyroid axis (Rivier & Rivest, 1991; Tsigos & Chrousos, 2002; Zoeller et al., 2007).

In addition to its hormonal effects through various pituitary pathways, the hypothalamus comprises several integrative and functionally-distinct subregions which have numerous neurotransmitter targets. It can be divided in multiple ways, including into anterior and posterior regions along a coronal plane and paraventricular, medial, and lateral nuclei along a sagittal plane. The anterior and posterior nuclei of the hypothalamus are involved in sleep- and arousal-relevant processes and are responsible for dissociable steps of a broad array of functions, including thermoregulation, blood pressure, sleep, and social drives (Boulant, 2000; Donaldson & Young, 2008). The paraventricular nucleus (PVN) promotes the release of oxytocin and vasopressin, two pituitary neuropeptides that are involved in social behavior and bonding (Ishunina & Swaab, 1999), and the medial hypothalamus regulates fluid balance, energy homeostasis, growth, the stress response, and reproductive behaviors (Pearson & Placzek, 2013). The lateral hypothalamus (LH) houses the cell bodies of a major category of neuropeptides which, like other hypothalamic peptidergic networks, promotes survival and homeostasis, with these in particular facilitating wakefulness, alertness, and reward-seeking behavior. These lateral hypothalamic neuropeptides and their constituent receptors are a significant focus of this

dissertation, and their roles in attention- and SZ-relevant neuromodulation will be detailed in depth throughout the remainder of this chapter. As a whole, the hypothalamus is a multifaceted structure which, through its many efferent projections, is responsible for a plethora of basic life functions.

Despite their clearly potent effects on numerous neurobiological and behavioral processes, the neuropeptides produced by the LH were only recently discovered at the end of the 20th century. The first articles on the classification and role of this peptidergic system were published almost simultaneously in the same year, with Luis de Lecea et al. (1998) going into depth about various orexinergic projections and establishing the orexins as peptide neurotransmitters using directional tag polymerase chain reaction (PCR) subtraction, and Takeshi Sakurai and colleagues (1998) using complementary-DNA sequencing to explore the role of these previously-orphan orexin receptors in appetitive drive and feeding behaviors. Both groups described the same two neuropeptides produced by the LH by names which are currently interchangeable in the literature: *hypocretins*, a combination of “hypothalamic” and “incretin”, and *orexins*, derived from the Greek word “orexis”, meaning “appetite”, a homage to their pro-appetitive qualities. These works also discussed two previously-orphan G protein-coupled receptors associated with this system which are stimulated by endogenous orexin release. Since their initial discovery, the widespread influence of these newly-discovered neurons has gained significant interest, both in the context of basic systems neuroscience and as a potential therapeutic target for numerous psychiatric conditions.

Cells that produce these neuropeptides, which will be referred to as orexins, are restrictively distributed in the dorsal hypothalamus and LH as well as the adjacent perifornical area (PFA) in the posterior LH. Though there are only 70,000 orexin-releasing neurons in the human brain, they project throughout virtually the entire CNS and, in doing so, exert brain-wide influence through their actions at numerous neurotransmitter systems (Deutch & Bubser, 2006; Nambu et al., 1999; Thannickal et al., 2000). Individual orexin neurons can, and often do, collateralize to project to numerous targets throughout the brain, offering further support for their ubiquitous influence in the CNS (España et al., 2005). Like other peptides active in the CNS, orexins are neuromodulators; though they do not themselves have direct actions at ion channels, they enhance the release of other neurotransmitters by affecting various orexin-receptive cell groups. Because of the ubiquity of these orexin fibers, the effects of changes in orexin activity are widespread, with other hypothalamic nuclei, the medial thalamus, monoaminergic arousal circuitry, and the BF being the four main targets of orexinergic projections (Peyron et al., 1998). Such neurotransmitters stimulated by the presence of orexins include HA via the TMN, DA via the VTA, NE from the LC, and ACh by way of both PPT/LDT and BF cholinergic systems (Eriksson et al., 2001; Hagan et al., 1999; Korotkova et al., 2003; Villano et al., 2017). The activity of orexin neurons is also regulated by inputs from these monoaminergic and cholinergic networks in multiple positive feedback loops, establishing a feedback loop between these regions (Sakurai et al., 2021; Yamanaka et al., 2003). In doing so, the circumstantial activation of orexin neurons recruits and is

recruited by a number of outlying systems responsible for numerous psychological states which coincide with arousal and motivation.

There are two peptide neurotransmitters proliferated by orexinergic neurons of the LH/PFA. Orexin-A (OxA) and orexin-B (OxB), which are separate cleaved halves of the precursor protein prepro-orexin, share approximately 50 percent of their sequence identities and are strongly conserved, with both orexin isoforms found in all studied species of vertebrates (Inutsuka & Yamanaka, 2013; Wong et al., 2011). There are additionally two G protein-coupled orexin receptor subtypes that are notably homogenous at the transcript level (Sakurai et al., 1998). Orexin-1 (Ox1) receptors are coupled with Gq proteins while orexin-2 receptors can be either Gq- Gi/o-coupled, with both receptor subtypes ultimately influencing neuronal activation through the phospholipase C intracellular cascade and the latter receptor having the capability of suppressing cAMP-dependent protein kinases (Sakurai et al., 1998). OxA binds to both Ox1 and Ox2 receptors with roughly equal affinity, but OxB primarily binds to the Ox2 receptor subtype with negligible effects at the Ox1 receptor (Scammell & Winrow, 2011). Both Ox1 and Ox2 receptors are found in similar quantities on neurons of the raphe nucleus, bed nucleus of the stria terminalis, thalamus, and hypothalamus (Cluderay et al., 2002; Trivedi et al., 1998). Ox1 receptors are preferentially expressed over Ox2 receptors in the LC, amygdala, HPC, basal ganglia, and ventromedial hypothalamic nucleus; meanwhile, Ox2 receptors are more highly expressed than Ox1 receptors in the pons, medulla, TMN, NAcc, BF, and subthalamic and paraventricular nuclei (Li & de Lecea, 2020; Marcus et al.,

2001). Within the cortex, Ox1 receptors are abundantly found in layers II through V, and Ox2 receptors are primarily localized in layer VI (Deutch & Bubser, 2007). Therefore, though both orexin receptors are co-localized in many areas, their overall expression patterns differ, resulting in a brain which is largely susceptible to orexin-mediated influence through either one or both receptor subtypes.

In 2006, Harris & Aston-Jones introduced the idea that orexin-generating cells of the LH/PFA have two primary functions: the instigation and maintenance of wakefulness and the motivated recruitment of survival- and reward-linked behaviors. Namely, it is believed that neurons of the PFA are predominantly responsible for modulating neurotransmitter systems implicated in consciousness and alertness via projections to and from brainstem nuclei, while other LH fibers travel to regions involved in the hedonic value of rewards as well as incentivized behaviors to attain those rewards (Harris et al., 2005; Willie et al., 2001). These functionally-distinct nuclei are often activated together, and this dichotomy in orexinergic function ultimately converges on psychological states and behaviors which are mutually beneficial in their outcomes, with adequate wakefulness and arousal enabling awareness of reinforcing stimuli as well as the perception of a rewarding stimulus or reward-associated cue boosting alertness and enhancing the motivation to attain the reward. Scammell & Winrow (2011) indicate that orexinergic activity in the cortex, BF, TMN, dorsal raphe, periaqueductal gray, and LC encourages wakefulness and boosts attention, and orexinergic neuromodulation of the NAcc, substantia nigra, and VTA promotes feeding, reward, motivation, and locomotion. Therefore, in the following sections, the role

of orexins in wakefulness and incentivized behaviors will be discussed as well as how, by boosting alertness and motivational activation, orexins offer significant support for normal attentional functioning especially in challenging circumstances.

The orexinergic system and wakefulness

Naturally, following the discovery of orexin-generating cells of the LH/PFA in the late 1990s, a significant volume of research emerged in the coming years in an attempt to elucidate the many roles of this widespread neuropeptide system. It was soon learned that these neurons are involved in arousal, with brain-wide administration of orexins dose-dependently inducing wakefulness and increasing arousal-linked behaviors such as locomotion, food-seeking, socialization, and grooming (Hagan et al., 1999). Orexin neuron firing rate naturally increases during periods of active wakefulness, lessens during periods of non-active wakefulness, silences during non-REM sleep, and rises near the end of each period of REM sleep before muting prior to the re-initiation of slow-wave NREM sleep (Estabrooke et al., 2001; Lee, 2005). The LH is an important node of the ARAS, receiving innervations from brainstem neuromodulatory systems implicated in arousal, including the norepinephrinergic LC, serotonergic raphe nucleus, and cholinergic neurons of the PPT/LDT (Horvath et al., 1999; Villano et al., 2017). The LH additionally communicates with histaminergic neurons of the TMN as well as cholinergic and non-cholinergic neurons of the BF and pyramidal neurons of the cortex (Eriksson et al., 2001; Fadel & Burk, 2010;

Yan et al., 2012), establishing itself as a critical link between brainstem arousal signaling and higher-order processing in the frontal lobe that relies on adequate wakefulness and alertness.

Perhaps the most compelling indicator of the critical role of orexins as sleep-modulating molecules is that the widespread loss of orexinergic function results in narcolepsy, a condition marked by profound fatigue, hypersomnia, and intermittent “sleep attacks” which typically range from 30 seconds to two minutes (Nishino et al., 2000; Roth, 1976; Siegel, 1999; Thannickal et al., 2000). A mutation in the Ox2 gene, HCRTR2, produces lapses in consciousness which are characteristic of narcolepsy, highlighting the necessity of Ox2-mediated inputs to neurons which promote and maintain wakefulness (Lin et al., 1999). A fundamental inability to sustain consciousness is at least partly addressed through the use of stimulant medications, with drugs such as methylphenidate, amphetamines, and modafinil increasing arousal in both humans and non-human studies (Challman & Lipsky, 2000; Salerno et al., 2019; Shindler et al., 1985; Wise et al., 2007). OxA, which is the most used orexin receptor-stimulating agent due to a relative paucity of orexin receptor agonists (Sakurai et al., 1998; Willie et al., 2001), is also able to significantly improve wakefulness and attentional performance in sleep-deprived animals and humans with narcolepsy (Deadwyler et al., 2007; Lim & Dinges, 2008; Weinhold et al., 2014). It is worth reiterating that OxB binds exclusively to Ox2 receptors and has virtually no effect at Ox1 receptors; therefore, while the influence of OxA is more widespread and robust through its actions at both orexin receptor subtypes, OxB plays a distinct role as

a wakefulness-enhancing neurochemical through its selective activation of Ox2 receptors. Much of this effect has been classically attributed to the predominantly Ox2 receptor-expressing histaminergic neurons of the TMN, the activity of which is highest during periods of alertness and high vigilance (Thakkar, 2011).

Conversely, orexin-inhibiting drugs are currently prescribed to treat insomnia, a condition which is characterized by difficulty falling and staying asleep. Like narcolepsy, insomnia involves aberrant orexin signaling, albeit at the opposite extreme, with Tang and colleagues (2017) reporting elevated plasma orexin levels - indicative of an overactive orexinergic system - in subjects with insomnia; however, it is not fully understood if the LH itself is the locus of insomnia-associated hyperarousal or if increased OxA in insomnia arises as a result of inputs from other overactive arousal circuits. Despite this, drugs which inhibit orexin receptor function have been shown to be as effective at reducing sleep onset time, reducing the number of wakes after sleep onset, and increasing sleep duration as GABA-mimetic sleep aids for those with insomnia as well as healthy controls (Neubauer, 2010; Patel et al., 2015; Sun et al., 2013). Dual orexin receptor antagonists (DORAs), which block the activity of both Ox1 and Ox2 receptors with varying receptor affinities, are currently prescribed to treat hyperarousal. Unlike other sleep aids which suppress consciousness through GABAergic mechanisms, the DORA suvorexant - which is sold under the brand name Belsomra - is described as instigating a natural transition into sleep from wakefulness through the direct suppression of the neuronal pathways directly responsible for producing arousal (Bennett et al., 2014). Thus, just as stimulating

orexin neurocircuitry promotes and maintains wakefulness in conditions like narcolepsy, the antagonism of these same neurons promotes and maintains sleep.

Interactions between the LH and BF form an important substratum linking wakefulness and vigilance and play a particularly important role in orexin-mediated frontocortical ACh release (Fadel & Burk, 2010). The LH sends a dense projection from orexinergic neurons to the BF, and cholinergic, GABAergic, and glutamatergic neurons in the BF express orexin receptors and are therefore sensitive to varying orexin levels (Arrigoni et al., 2010). The stimulation of orexin-producing neurons, such as with intrabasalis and intracerebroventricular (ICV) OxA administration, results in the release of cortical ACh from BF cholinergic terminals and augments cortical cholinergic efflux (Fadel et al., 2005; Calva et al., 2018). Orexins have also been shown to activate corticopetal wake-promoting parvalbuminergic GABA neurons (Anaclet et al., 2015; Arrigoni et al., 2010; Calva & Fadel, 2020). ACh-recipient glutamatergic and GABAergic neurons in the magnocellular preoptic nucleus and substantia innominata of the BF additionally send fibers back to LH orexin neurons and are believed to support arousal and wakefulness by quickly stimulating hypothalamic activity in a positive feedback loop between the two regions (Agostinelli et al., 2019; Henny & Jones, 2008; Yoshida et al., 2006). Ultimately, as two separate but inextricably interconnected nodes of the ARAS, the LH and BF communicate extensively to instigate and maintain arousal, with orexinergic outputs to BF

comprising a crucial pathway by which the cortex is stimulated during normal wakefulness.

Empirical evidence supports a more important influence of Ox2 receptors over Ox1 receptors in stimulating the BF as a whole. Eggermann et al. (2001) found that *in vitro* application of both OxA and OxB strongly excited BF cholinergic neurons; because OxB was found to be more effective than OxA in doing so, the authors suggested that orexins drive the release of ACh primarily through the agonism of Ox2 receptors expressed on cholinergic neurons of the BF. However, the Ox1 receptor does still contribute to BF-mediated cholinergic signaling, with some studies demonstrating more potent wakefulness-promoting and pro-cholinergic qualities of ICV and intrabasalis OxA (Dong et al., 2006; España et al., 2001). However, while Ox1 receptors localized to the BF likely play a role in this outcome, it has been suggested to largely result from the agonism of Ox1 receptors expressed on BF-synapsing glutamatergic projections from the PFC, IC, and other outlying regions (Fadel & Burk, 2010; Frederick-Duus et al., 2007). Orexinergic stimulation of corticopetal PV-expressing GABAergic neurons of the BF is also understood to be primarily driven by the Ox2 receptor subtype, with intranasal OxA administration putatively suppressing cortical inhibitory GABAergic interneuron activity through the stimulation of BF-PV cortical projections (Calva et al., 2018; Wu et al., 2002). Taken together, both orexinergic neuropeptides activate BF neurons, and cholinergic and PV+ GABAergic neurons are preferentially driven by orexinergic inputs at the Ox2 receptor subtype.

Because the timescale of cholinergic and parvalbuminergic signaling differs, it is likely that the effects of orexins at these distinct BF neuronal populations promote wakefulness and arousal in different ways. For example, following increased LH-orexin neuron activity, frontocortical cholinergic neurotransmission would result in prolonged bouts of wakefulness by contributing to a baseline state of cortical activation in which wakefulness can be maintained over an extended period of time. Meanwhile, BF-PV outputs to the cortex would produce near-immediate and transient excitation of pyramidal neurons, a mechanism which would be useful in situations that might require rapid alertness and quick responding. It is beneficial to have multiple arousal circuits subserving similar conscious states, particularly those which operate on dissociable timeframes, and by facilitating the depolarization of systems which work on the order of milliseconds (BF-PV) as well as on the order of seconds (BF cholinergic), orexins act as potent modulators of various conscious states which provide a foundation upon which more complex processing can occur.

The orexinergic system and motivation

In addition to homeostatic maintenance at the cellular level, lateral hypothalamic activity is instrumental for behaviors that promote energy homeostasis, such as food seeking and consumption. Though the role of the hypothalamus in appetitive- and reinforcement-linked behaviors was established in the mid-20th century, the specific cellular mechanisms mediating these behaviors remained elusive until the discovery of the orexinergic system in rat

brains in the late 1990s. In the 1950s, it was revealed that repeated electrical stimulation of the LH of cats significantly increased their food consumption, suggesting that natural activity of these neurons regulates energy homeostasis by facilitating food-seeking behaviors, and these behaviors can be experimentally evoked regardless of whether the animal is hungry (Delgado & Anand, 1952). The importance of orexinergic neuromodulation for the volitional engagement in reward-governed behavior has since grown to encompass not only behaviors relevant to homeostasis, but anything with hedonic value, such as non-homeostatic food consumption and the use of psychoactive drugs, solidifying that LH orexinergic activity encourages goal-directed behaviors related to the receipt of reward regardless of its necessity for physiological status.

Orexins are important for reward processing largely through their stimulatory actions at neurons of the VTA and adjacent midbrain nuclei. The LH sends one of its largest orexinergic projections to the midbrain - with these innervations being the only source of endogenous orexins to the VTA (Peyron et al., 1998) - and exerts its potent influence at both dopaminergic and non-dopaminergic ventral tegmental neurons (Korotkova et al., 2003). Orexinergic output to the VTA inspires the pursuit of reward largely by stimulating dopaminergic neurons which synapse with DA receptor-rich medial and lateral NAcc shell neurons in response to the perception of rewarding stimuli (Baimel et al., 2017). Intra-VTA administration of OxA directly increases DA efflux in the cortex and in the NAcc shell (Narita, 2006; Zahm, 1999) and promotes incentivized behavior, including conditioned place preference (CPP), an assay

which measures the amount of time an organism spends in a drug-paired chamber over a placebo-paired chamber (Shaw et al., 2017; Taslimi et al., 2012). There is also a direct VTA projection to the LH and PFA, but the constituent neurons of these nuclei very rarely express DA receptors, suggesting that any sort of VTA-to-LH/PFA influence is likely governed by non-dopaminergic co-transmitters (Bubser et al., 2005; Deutch & Bubser, 2006).

In addition to research showing that enhancing orexinergic functioning increases DA receptor expression in the NAcc and promotes DA efflux in the PFC (Morales-Mulia et al., 2020; Vittoz & Berridge, 2006), studies using orexin knock-out mice lacking the HCRT gene and the ability to produce orexin peptides reveal lower baseline dopaminergic activity as well as dampened dopaminergic tone in response to cues associated with acquisition of a drug (Chemelli et al., 1999); these deficits in DA efflux are associated with a reduction in CPP. A lack of CPP for a location repeatedly paired with administration of or access to a rewarding drug is interpreted in this context as a failure to form a hedonic association with the drug in the absence of orexinergic inputs to reward-active neurons. Drugs which antagonize both orexin receptor subtypes, such as suvorexant and almorexant, also abate sucrose- and drug-induced extracellular VTA DA efflux and self-administration, suggesting that the indiscriminate reduction of orexin activity reduces both the hedonic value of ordinarily-rewarding stimuli and the execution of the conditioned behaviors required to attain these rewards (Gentile et al., 2018; Shaw et al., 2017; Srinivasan et al., 2012). In this

regard, orexinergic inputs to midbrain reward circuits are not only important for normal reward processing, but are necessary for it (Harris et al., 2005).

Though both Ox1 and Ox2 receptor subtypes are highly expressed in the midbrain, reward-seeking behavior appears to be mostly mediated by the activity of Ox1 receptors. Selective orexin receptor antagonists (SORAs), which target either the Ox1 or Ox2 receptor with negligible effects at the other receptor subtype, are used to explore the unique contributions of each orexin receptor subtype to various neurobiological and behavioral processes. Ox1 receptor-specific SORAs like SB-334867 suffice to attenuate CPP for morphine-, cocaine-, and amphetamine-paired environments, but Ox2 receptor antagonists like TCS-OX2-29 do not have exert the same anti-reward effect (Steiner et al., 2013). It is important to note that suppressed orexinergic activity does not impair conditioned place avoidance - such as when an animal spends less time in a location where they have been exposed to a noxious stimulus (Narita et al., 2006). This suggests that orexinergic blockade does not impair memory formation, but rather, the integrity of the LH orexinergic system is more relevant to the acquisition of reward. The role of the Ox1 receptor subtype in reward-relevant responding is also reflected in findings that suggest orexinergic inputs via the Ox1 receptor may be most important when the requirements to attain reward are increased, such as in a progressive-ratio schedule of reinforcement during which the required number of responses required at an operand to gain access to a reinforcing stimulus gradually increases (España et al., 2010). Thus, here, it seems orexins are not only important for the subjective experience of a reward,

but also for the motivation to engage in effortful responding to attain the reward, and much of this is due to their effects at the Ox1 receptor subtype.

Orexinergic projections to BF ACh-producing neurons contribute to motivational processing and reward-seeking behavior by increasing cortical cholinergic signaling. The activation of BF cholinergic neurons in response to food-relevant cues in hungry animals was first recorded in the late 1970s, prior to the discovery of the orexin system (Rolls et al., 1977, 1979), with this research coinciding with experiments showing augmented cortical ACh efflux following the perception of food or food-paired stimuli (Fadel et al., 1996; Inglis et al., 1994). These findings were further validated upon the elucidation of an ascending lateral hypothalamic pathway projecting to the BF in 1991 (Cullinan & Záborszky, 1991; Záborszky & Cullinan, 1989) which was later confirmed to be largely orexinergic in nature. Additionally, cholinoceptive glutamatergic and GABAergic neurons in the magnocellular preoptic nucleus and substantia innominata of the BF synapse with LH orexin neurons to establish a positive feedback loop wherein increased ACh neurotransmission in these areas directly depolarizes orexin neurons and further increases brain-wide excitation (Agostinelli et al., 2019; Henny & Jones, 2006; Yoshida et al., 2006).

Mahler et al. (2014) suggests a hypothesis of motivational activation in the effects of orexinergic neurotransmission; namely, LH orexinergic neurons are preferentially recruited in situations of high motivational relevance, including hunger, thirst, fear, or opportunity to attain reward. In this sense, one could frame arousal, wakefulness, and motivated behaviors on a continuum, with orexins

instigating a state of heightened arousal which creates a foundation of cortical excitation upon which more complex psychological states and relevant behaviors, such as incentivized pursuit of reward, can be built. On one hand, orexin-facilitated wakefulness appears to be reliant on the integrity of Ox2 receptor functioning, while hedonic processing underlying motivated behaviors is more dependent on the Ox1 receptor subtype, highlighting overlapping yet dissociable roles in orexinergic network activity. In this regard, by enabling arousal and facilitating incentivized behavior, orexins contribute significantly to normal attentional functioning and performance.

The orexinergic system and attention

That the LH is a central hub for the integration of sensory signals into conscious awareness in order to inform behavior was established prior to the discovery of orexins. This notion has been expanded upon significantly since the initial characterizations of orexins. It acts as a conduit for physiological cues regarding internal states, such as hunger, thirst, pain, fatigue, and other information about an organism's internal state. Interoception, which is defined as the ability to identify, understand, and respond to physiological signals, sensations, and drives (Craig, 2002; Price & Hooven, 2018), is largely attributed to orexin-mediated stimulatory activity throughout the brain, with the LH imbuing the emotional salience of incoming sensory signals to be broadcast to brain areas associated with reward, fear, attention, memory, and decision-making. Internal drives and external stimuli are often tied to a rich variety of affective and

motivational states, and it is through the activity of these lateral hypothalamic orexinergic efferents - which synapse with and relay sensory information to neurons of a multitude of emotion-, cognition-, and motivation-relevant brain areas - that sensations can evoke and inspire relevant behavior sets in response to these internal or external cues (Li & de Lecea, 2020). The relay of physiological status to conscious awareness, which is largely attributed to reciprocal connections between LH orexin-producing neurons and the orexin receptor-expressing IC (Clascá et al., 1989; Peyron et al., 1998), biases exteroception - defined as the general awareness of external stimuli (Simmons et al., 2013) - by enhancing the salience of stimuli which are relevant to these bodily signals. Decisions based on these sensations are ultimately facilitated by the PFC, with LH orexin neurons enhancing PFC activity through direct projections to the PFC and innervations of other cortex-projecting regions of the brain (Jin et al., 2016).

In general, the exogenous activation of orexinergic neurotransmission has demonstrated attention-enhancing qualities, and many of these benefits stem from the aforementioned excitatory influence of orexins on corticopetal cholinergic signaling. The salience of an external stimulus enhances LH-facilitated activation of BF choline acetyltransferase-positive neurons, with interoceptive awareness of internal states biasing attentional resources towards internal state-relevant stimuli in the environment (Frederick-Duus et al., 2007; Fadel & Burk, 2010; Villano et al., 2017). This is particularly useful when attentional demands are increased, requiring further cortical ACh

neuromodulation to maintain adequate attentional performance. Zajo et al. (2016) found that intra-BF infusions of OxA sufficed to attenuate impairments in the SAT induced by a flashing house light for both intact rats and rats with 192 IgG-saporin-lesioned BF corticopetal cholinergic projections, and it was suggested that these improvements could be attributed to orexin receptor-mediated increases in cortical cholinergic efflux. Similarly, Lambe and colleagues (2006) discovered that orexins and nicotine act at overlapping thalamocortical synapses within the cortex - suggesting similar distribution of nACh and orexin receptors - and intra-PFC orexin (as well as nicotine) administration in rats improved attentional performance under high demand in a continuous performance task, offering further support that the recruitment of LH orexin inputs are paramount for ACh-dependent task performance.

These orexinergic-cholinergic interactions appear to be particularly crucial in distracting or otherwise challenging circumstances which necessitate a boost in cortical excitation to continue to pay attention. In experiments with rats, Zajo et al. (2016) revealed that neither intrabasalis nor ICV infusions of OxA improved well-trained performance in the SAT under normal testing conditions, but for rats whose ascending cholinergic projections were lesioned with 192 IgG-saporin, BF OxA administration sufficed to notably improve lesion-induced impairments in signal trial accuracy during a portion of testing where the house light was flashing. Similar outcomes were found in a continuous performance task, with improvements from OxA being specific to more demanding trials with shorter, but not longer, signal durations (Lambe et al., 2005). These findings further solidify

that the BF cholinergic system is a major mediator of the attention-enhancing outputs from orexin-producing nuclei, with elevated stimulation of Ox1 and Ox2 receptors in the BF potentially compensating for corticopetal cholinergic deafferentation. Furthermore, because OxA was specifically beneficial during a flashing visual distracter and not prior to its introduction or following its removal, the authors suggest that orexinergic inputs to the BF are most useful during periods of attentional strain, where increased output from cholinergic neurons is normally required to maintain satisfactory attentional performance.

The importance of this LH-BF connection in PFC-mediated cholinergic efflux has been documented using a variety of orexin receptor-inhibiting compounds. Yao et al. (2017) found that, in the absence of cognitive effort, inhibiting orexinergic inputs does not necessarily reduce cholinergic neuron activity. In particular, intracranial administration of DORA-22 reduces HA in the hypothalamus and cortex, but it does not have the same influence on hypothalamic or cortical cholinergic activity at these HA-reducing doses (Yao et al., 2017), suggesting that for normal and non-engaged baseline arousal, low to moderate cholinergic activity may not require inputs from orexin-producing nuclei to properly function. This idea is supported by findings that suggest that orexin neurons are most active in situations that necessitate increased awareness of and attention to the ongoings of the external world (Furlong et al., 2009). Lesion studies using the immunotoxin OxB-saporin - which eliminates most orexin neurons at the injection site - as well as antagonist studies with SB-334867 reveal that the normal cholinergic response to perception of a food cue is

significantly abated following loss of orexin functioning, suggesting that the BF requires orexinergic inputs to increase ACh efflux in the cortex following the perception of palatable or otherwise rewarding stimuli (Frederick-Duus et al., 2007).

An important quality of orexin receptor antagonists which dovetails with the above-mentioned hypothesis is that they do not appear to impair cognition at doses which have beneficial therapeutic qualities in the context of sleep. This is evidenced by experiments examining the efficacy of this class of drug in inducing sleep. At doses that are equally as effective as cognition-impairing GABA-A receptor-targeting sleep medications at inducing sleep, DORAs fail to worsen performance in tasks of cortex-mediated attention and HPC-relevant memory (Uslaner et al., 2013), highlighting a wider therapeutic margin between doses that suppress consciousness and doses that impair cognition. There is evidence that selective intrabasalis as well as systemic Ox1 receptor antagonism with SB-334867 can disrupt attentional performance in signal trials of the SAT (Boschen et al., 2009); however, because these impairments were particular to trials of the longest signal duration, reduced Ox1 receptor-mediated excitatory inputs to the BF could have interfered with the ability to reliably recall appropriate responses associated with signal-guided behavior (Sarter et al. 2005). These findings support the idea that, while orexinergic neurotransmission is especially valuable for cognitive performance, the reduction in orexin inputs does not necessarily worsen cognition at doses that have clinical value.

Taken together, the LH orexinergic system acts as an integrator of physiological sensations and information about an organism's environment and incorporates it into conscious awareness, particularly as it relates to enabling wakefulness as an intersection of the ARAS and processing stimuli and cues with homeostatic and hedonic value by way of the midbrain dopaminergic system. Though the role of orexins in cognition and attention are still being explored and elucidated, it appears that a particularly important function of LH orexinergic neurons is the processing and relaying of information about the demands of the immediate environment to multiple orexin-recipient brain systems, including to cortical areas involved in attention and decision-making, with increases in orexinergic signaling resulting in improved performance in distracting or otherwise challenging tasks. LH orexinergic innervations of cortically-projecting neurons of the BF form a key anatomical substrate of arousal and vigilance, with orexin-cholinergic and orexin-GABAergic interactions determining how limited attentional resources are spent and ultimately working together to produce an activated cortex that is prepared to respond to the happenings of the external world (*Figure 3*). The omnipresence of orexinergic projections and receptors, particularly in cognition-relevant forebrain and cortical regions, makes this system a viable target to treat a number of psychiatric disorders for which attention is deficient, including SZ.

The therapeutic potential of orexin receptor antagonists for the treatment of attentional impairments in SZ

Given its ubiquitous projections and broad influence over a variety of brain systems, psychological states, and behaviors, it can be expected that hypothalamic function would be affected in SZ, a condition which is also known for its widespread neuronal involvement. There is evidence of dysconnectivity of excitatory thalamocortical projections and abnormal volumetric increases in the hypothalami of SZ-affected individuals, including the paraventricular and mammillary body nuclei and associated regions like the pituitary gland, with the extent of these structural changes correlating with a severe psychopathology (Goldstein et al., 2007; Lambe et al., 2007). However, much of the evidence that orexin activity is altered in SZ is based on the known dysregulation of psychological and behavioral processes which rely on an intact orexinergic system. Such abnormalities, which are also detailed in the last chapter, include irregular circadian rhythms, impaired sleep quality, energy imbalance, motivational deactivation, and impaired cognition (Lu et al., 2021). The remainder of this chapter will discuss recent experimental discoveries at the intersection of orexinergic functioning and alternative antipsychotics for the treatment of SZ. Ultimately, the rest of this chapter as well as the remainder of the dissertation will explore the hypothesized therapeutic potential of orexin receptor-inhibiting compounds for the management of SZ symptoms, with emphasis on the historically treatment-resistant attentional deficits associated with SZ.

Very recent experiments using animal models of SZ and psychosis-like states have uncovered potentially antipsychotic qualities of orexin-inhibiting drugs, largely through their reduction of psychotogenic drug-induced hyperdopaminergia. In the methylazoxymethanol acetate (MAM) rodent model of SZ, MAM is administered to a pregnant rat or mouse at a specific time-point in the pregnancy during which key neuroblasts associated with brain regions associated with SZ - including the midbrain, HPC, and cortex - develop in utero; for rats, this critical period is gestational day 17 in rats and gestational day 16 in mice (Chalkiadaki et al., 2018; Lodge, 2013). In this model, it was found that intraperitoneal (ip) and intra-PVT infusions of the DORA TCS-1102 attenuated excessive DA neuron activity in the ventral tegmenta of rats who were exposed to MAM during development (Perez & Lodge, 2021); in parallel with additional findings that intra-PVT OxA and OxB administration significantly increases VTA DA dopaminergic output in MAM-naive rats suggest that orexinergic inputs to VTA-innervating and orexin receptor-rich PVT neurons may contribute to DA neuron hyperactivity observed in SZ. Similarly, in an inescapable footshock paradigm of post-traumatic stress disorder (PTSD)-associated psychosis, infusions of the DORA suvorexant, the Ox1 receptor-specific antagonist SB-334867, and the Ox2 receptor inhibitor EMPA suppressed excessive dopaminergic signaling and hypersensitivity to stimulant drugs stemming from a sensitized VTA, but only suvorexant and SB-334867 were able to provide relief for the behavioral indices of an overactive midbrain, including impaired sensorimotor gating (Elam et al., 2021). The latter discovery suggests that the

Ox1 receptor subtype plays a more important role in modulating brain-wide DA activity than the Ox2 receptor. This aligns with the notion that the function of orexin receptors, while largely overlapping, is more heavily involved in distinct processes, with Ox1 receptors mostly implicated in reward and Ox2 receptors more involved with wakefulness and arousal. Thus, these newly-published experiments suggest a putatively antipsychotic effect of compounds which suppress orexinergic inputs - with particular emphasis on Ox1 receptor-mediated neurotransmission - to SZ-involved dopaminergic neurons.

The notion that orexin receptor antagonists could be useful as antipsychotic agents has only been posited in the last few years (Han et al., 2020) and has thus far been solely based on findings from animal models of SZ; as such, there is an understandable paucity of human research to validate these findings. In 2017, Suzuki and colleagues reported that, alongside aripiprazole once-monthly treatment, suvorexant/Belsomra provided relief for one patient with SZ-linked insomnia and improved sleep quality for this individual, though it is not understood if these improvements in sleep sufficed to reduce the severity of primary SZ symptoms (Suzuki et al., 2017). Similarly, delirium, which is a temporary psychosis-like state of extreme confusion, disorganized thinking, and reduced situational and environmental awareness associated with elevated DA activity, is prevented with suvorexant administration when compared to placebo, and this DORA also performed as well as standard delirium treatment (Azuma et al., 2018; Hatta et al., 2017; Izuhara et al., 2021). Therefore, while it is still early in the exploration of the role of orexin receptor antagonists for the treatment of

SZ and other disorders for which psychosis is a symptom, emergent human evidence suggests that such drugs may offer relief for conditions which either exacerbate symptoms in SZ or produce psychosis-like states in otherwise SZ-free individuals.

Because both orexin receptor subtypes are amply expressed throughout the CNS - including in numerous arousal-active neurotransmitter systems which induce brain-wide excitation and produce enduring states of wakefulness and behavioral activation - their antagonism represents a potential antipsychotic pathway by which excessive stimulatory neurotransmitter release can be quelled. However, their ubiquity also makes it difficult to pinpoint an individual locus of its beneficial mechanisms of action, with a more likely scenario being that orexin receptor antagonists provide relief for symptoms of psychosis at multiple brain regions. One significant candidate for their neuroleptic potential is the lessening of heightened DA efflux in an active disease state. As has already been established, LH orexin neurons send a dense projection pathway to the orexin receptor-rich VTA, and recent evidence suggests DORAs and Ox1 receptor-specific SORAs can assuage higher-than-normal DA efflux in animal models of psychosis (Elam et al., 2021). A compound which lessens aberrant dopaminergic signaling without directly targeting DA receptors could be clinically effective in lessening psychosis symptom severity while bypassing the physiological side effects of extant antipsychotics which arise, to a large extent, due to their effects at D2 receptors.

Another antipsychotic mechanism of CNS-wide orexinergic antagonism that is particularly relevant for the attentional deficits in SZ involves their effects at orexin receptors expressed on ACh-generating neurons of the BF; namely, because orexinergic inputs to corticopetal cholinergic neurons directly stimulate the frontocortical release of ACh, and because these neurons are putatively overstimulated in SZ and produce a hypercholinergic state (Lustig & Sarter, 2015), it is possible that reducing orexinergic neurotransmission at these neurons would lessen the extent of cholinergic activity in the PFC and, as such, improve attentional functioning. Recall that the anticholinergic medication clozapine, which is the “gold standard” in antipsychotics for treatment-resistant SZ, is more effective in treating associated cognitive impairments, including attention and verbal fluency, than primarily D2-targeting drugs (Lee et al., 1994). Orexinergic suppression also demonstrates anticholinergic mechanisms of action (Frederick-Duus et al., 2007), introducing the possibility that, like clozapine, orexin receptor antagonists may improve symptoms of SZ which arise from hypercholinergia - including the attentional impairments - in a similar fashion. If the pro-cognitive effects of clozapine do indeed emerge from its anticholinergic traits, orexin receptor blockade may be able to produce similar beneficial psychological and cognitive outcomes as clozapine without the unpleasant and potentially dangerous side effects stemming from chronic M1-mACh receptor blockade (Young et al., 1998).

It is also important to consider the effects of orexin receptor inhibition on BF-PV neurons and the implication for cortical neurotransmission in SZ.

Depolarization of PV+ corticopetal GABAergic projections increases pyramidal neuron discharge within a matter of milliseconds, and low-wattage tonic stimulation of these neurons significantly increases the frequency of neuronal oscillations in the PFC in a manner which resembles what is observed in psychosis (McNally et al., 2021). If a substantial proportion of BF neurons are overactive as a downstream consequence of a hyperdopaminergic midbrain, it is possible that BF-PV neurons are overactive in the illness as well. Increased spontaneous gamma and decreased evoked gamma during trains of auditory stimuli in subjects with SZ offers support for BF-PV dysfunction in psychosis, as these neurons generate and ultimately control cortical gamma oscillations (Hirano et al., 2015; Kim et al., 2015). If this ascending arousal pathway is abnormally activated in the context of SZ, one could posit that limiting excitatory inputs to these neurons would lessen their output and, as a result, reduce BF-PV-mediated cortical activation. Whether orexin receptor blockade would reduce the activity of BF parvalbuminergic nuclei and improve attentional impairments associated with hyperfrontality and disrupted cortical E/I balance in SZ is unknown and is speculative at this time; however, it is an important potential mechanism when considering the therapeutic potential of orexin receptor antagonists for the treatment of SZ.

The cortex, too, is a pertinent target of orexin receptor-binding drugs. Ox1 and Ox2 receptors are found in each neocortical layer, and the presence of cortical orexins promotes cognitive arousal by directly stimulating pyramidal neurons (Yan et al., 2012). In theory, these same pyramidal neurons are

overactive in SZ due to hypofunctional GABAergic interneurons and widespread failure of cortical inhibitory circuitry. This simultaneous underactivation of cortical GABAergic nuclei and overactivation of glutamatergic pyramidal neurons results in aberrant signaling throughout the cortex and subcortex, disrupted cortical E/I balance, muddled signal-to-noise ratio, and worsened attentional performance. If unimpinged corticofugal glutamatergic signaling in SZ can be mitigated through the use of anti-orexinergic compounds, this could represent an important locus of beneficial action by which more complex processing dependent on balanced prefrontal cortical activity can be improved.

There are other neurotransmitter systems which are both affected in SZ and are heavily susceptible to orexinergic influence. For example, the norepinephrinergic system is primarily involved in stimulating arousal and alertness via projections from brainstem LC neurons to the frontal lobe and cortex (Aston-Jones & Bloom, 1981; Carter et al., 2010; Sara & Bouret, 2012). Activity of LC neurons is involved in the alerting aspect of attention, with NE mediating heightened responses to the happenings of the external world, especially in the context of stress (Beane & Marrocco, 2004). Cortical NE acts in a similar fashion as cortical ACh, with both contributing separately, not synergistically or competitively, to pyramidal neuron excitability in response to incoming sensory inputs and cortical signal-to-noise ratio in the cortex (Hasselmo et al., 1997). The LC shares synapses with LH orexin-producing neurons and also itself expresses orexin receptors, most notably the Ox1 receptor subtype (Hagan et al., 1999; Soya et al., 2013), with these appositional contacts between

orexin- and NE-releasing cells indirectly modulating cortical excitation in a separate ascending arousal pathway. LC norepinephrinergic neurons project to BF and cortical neurons as well, offering additional indirect avenues through which NE promotes arousal, wakefulness, and vigilance (Schwarz & Luo, 2015). In SZ, there are little to no reported anatomical changes or neuronal abnormalities in the LC (Craven et al., 2005), though there is evidence suggesting unusual norepinephrinergic neurotransmission occurs concomitantly with dopaminergic dysregulation in the disease; therefore, it is likely that anomalous NE neurotransmission, which has brain-wide consequences, is a result of abnormalities in afferent innervations from other systems.

Conclusion

The hypothalamus is a small but highly prolific structure with efferent projections spanning the entirety of the CNS. It exists at the junction of endocrine and nervous system functioning, acting as a critical link between hormones and neurotransmitters involved in arousal, wakefulness, motivation, and other survival-promoting psychological and behavioral processes. In enhancing these processes, orexins serve a significant role in supporting attention as well as the incentive to pay and maintain attention, both of which are invaluable for day-to-day life; this is especially true in situations where attentional demands are high, such as in distracting tasks or following exposure to performance-impairing drugs which necessitate increased effort to maintain attention. Important in this context is the expression of both orexin receptor subtypes on cholinergic and non-

cholinergic neurons of the BF, with increased activity of the orexinergic system evoking enduring cortical activation through its actions at BF ACh-producing neurons and inciting rapid excitation of cortical neurons by depolarizing BF-PV neurons. There is a new and growing case for the use of orexin-suppressing compounds to treat SZ symptom severity, and, in detailing the overlap of neurobiological aberrations, psychological processes, and associated behaviors which rely on orexinergic integrity and which are also abnormal in SZ, there is a strong case to continue the exploration of orexin receptors as novel antipsychotic targets to more effectively treat the notoriously treatment-resistant symptoms of SZ.

Experimental plan

Recent research has begun to elucidate a role of orexin receptor antagonists in improving neuronal and behavioral abnormalities in animal models of SZ (see Perez & Lodge, 2018; Perez & Lodge, 2021; Elam et al., 2021), suggesting that the inhibition of orexinergic activity has antipsychotic qualities. However, to date, there have been no published studies elucidating the effects of these compounds on attentional performance in SZ, nor has there been research examining DORAs specifically in the context of sustained attention. To address these gaps in the literature, each of the three experiments within this dissertation measured the effects of orexin receptor-blocking compounds on attention-relevant neurological processes and behaviors. In each experiment, orexin receptor antagonists were administered alongside the psychotomimetic NMDA

receptor antagonist MK-801 (dizocilpine). PV-positive interneurons are particularly sensitive to the effects of dizocilpine and other drugs of the same class (Bygrave et al., 2016; Xi et al., 2009), and similarly to sub-anesthetic doses of other NMDA receptor antagonists, dizocilpine increases monoaminergic and cholinergic efflux largely through the suppression of inhibitory systems when administered systemically and disrupts attentional performance in a number of paradigms, including tasks of sustained attention (Acquas et al., 1998; Howe & Burk, 2007; Jentsch, 1999; Paine & Carlezon, 2009). In each of the experiments, acute dizocilpine administration was anticipated to muddle the signal-to-noise ratio in regions associated with attentional processing, resulting in worsened performance for rats trained in a visual SAT (experiments one and two) and suppressed auditory steady-state response (ASSR) - an electrophysiological measure of neuronal synchronization to periodic trains of acoustic stimuli - in cortical and hippocampal tissues in mice (experiment three).

In the first and second experiments, orexin receptor antagonists were used to uncover the role of brain-wide orexin receptor inputs in attentional performance as well as their therapeutic potential in reducing the attentional detriments associated with dizocilpine-induced overstimulation of attentional circuitry. In experiment one, the effects of ICV infusions of the DORA MK-6096 (filorexant), which has roughly equal affinity for Ox1 and Ox2 receptors (Winrow et al., 2012), on performance in a signal detection task was determined with and without co-administration of dizocilpine. In doing so, the effects of dual orexin receptor antagonism on sustained attentional performance can be explored in

both dizocilpine-free and dizocilpine co-administered animals. In the second experiment, the importance of the Ox1-mediated neuronal inputs in attention was assessed in this same paradigm using the SORA SB-334867. Similarly to other non-site-specific routes of administration, ICV infusions demonstrate translational applicability by assessing the effects of DORAs in widespread brain regions because the drug disperses throughout the brain through the circulation of cerebrospinal fluid, enabling the opportunity to assess any unexpected deleterious effects from drug actions in brain regions outside of those that are the focus of this experiment (Turner et al., 2011). It was ultimately hypothesized that indiscriminate orexinergic suppression induced by intracranial filorexant as well as the targeted inhibition of Ox1 receptor-mediated activity through the use of SB-334867 would improve behavioral indicators of attentional impairment that are induced by stimulatory, psychosis-emulating drug, such as a failure to identify a visual signal and rates of in-task responding.

In the third and final experiment, mice were given various combinations of dizocilpine and filorexant and were repeatedly exposed to a 40 Hz auditory stimulus, with the dependent variables of this project measuring the effects of these compounds on phase separation and elicited GBOs stemming from a 40 Hz tone. Deficient ASSR is considered a translational biomarker for SZ (O'Donnell et al., 2012), and while it does not directly quantify attentional performance like the SAT, it measures the ability for the PFC and HPC to operate at frequencies which are known to be conducive for attention and cognition. Acute intracranial and intravenous dizocilpine in rodents has been

shown to weaken ASSR in a way that is reminiscent of impaired ASSR in human participants with SZ (Sivarao et al., 2013; Wang et al., 2020). Therefore, for the concluding study, it was hypothesized that, by quelling NMDA receptor antagonism-induced disruptions in cortical E/I balance, dual orexin receptor antagonism could improve indices of neuronal entrainment to a 40 Hz noise. However, He and colleagues (2015) noted that intra-mPFC infusions of SB-334867, but *not* TCS-OX2-29, sufficed to reduce cortical pyramidal neuron activity as well as power in the gamma band by the recording site. As such, it is possible that on its own, filorexant may lessen GBOs through its actions at the Ox1, but not the Ox2, receptor.

It is difficult to pinpoint a potential locus of beneficial action in these experiments at this time, as all drugs employed throughout the dissertation - dizocilpine, filorexant, and SB-334867 - are administered into the lateral ventricles in experiments one and two as well as intraperitoneally in experiment three as a way to emulate a clinical route of dispersal through target brain areas. Because of this, it is not possible to dissociate where, exactly, these compounds would exert their deleterious or beneficial effects. In theory, any brain region expressing NMDA and orexin receptors, which are both virtually ubiquitous in the CNS and have overlapping expression in many different brain areas, are potential loci of therapeutic benefit. Much of the discussions so far in this document have centered around the role of the BF cholinergic system in attention and how its dysfunction contributes to the negative and cognitive symptoms of SZ. Like other NMDA receptor antagonists, sub-sedative doses of

dizocilpine preferentially target PV-positive GABAergic neurons (Romón et al., 2011), suggesting that effects at BF-PV neurons may influence cortical excitability in these studies as well.

In conclusion, this dissertation attempts to address multiple unanswered questions relating orexinergic activity to attention-relevant neurotransmission, processing, and performance, both on its own and in congruence with an NMDA receptor antagonist used to model the neurobiology and attentional impairment in SZ. Namely, these works aim to 1. Replicate established findings that dizocilpine impairs attention-relevant neuronal activity and worsens performance in tasks measuring sustained attention, 2. Explore the unique effects of dual orexin receptor antagonism and Ox1 receptor antagonism on electrophysiological and behavioral indicators of vigilance, and 3. Measure the effects of dizocilpine and orexin receptor antagonist co-administration to determine if DORAs and Ox1 receptor-exclusive SORAs have pro-attentional qualities for rodents in a pharmacological model of SZ. In doing so, these experiments endeavor to build off of emergent research implicating orexin receptors in the possible treatment of SZ as well as further extend their pharmacotherapeutic value to the treatment of attentional impairments in SZ which remain largely untreated by extant antipsychotics.

CHAPTER 4. Experiment one: dual orexin receptor antagonism alleviates attentional deficits in an NMDA receptor hypofunction model of SZ

Introduction

The goal of the present experiment was to study the effects of orexin suppression on attentional performance for rats, both on its own and in the context of a commonly-used pharmacological model of psychosis. Each of the animals was trained in a previously-validated visual SAT (Bushnell & Strupp, 2009; McGaughy & Sarter, 1995). In general, this signal detection task measures the capacity for rats to correctly identify the presence of a brief, unpredictable visual stimulus during any given trial as indicated by a response at experimenter-determined operand, with the operand in this context being a retractable lever. It additionally measures their ability to correctly identify non-signal trials by responding at a second operand. It quantifies not only accuracy, but the time it takes to respond at either operand at the conclusion of any given trial. Ultimately, these measures of performance reveal how attentive rats are on a trial-by-trial basis as well as how effectively they can maintain focus over an extended period of time.

The NMDA receptor antagonist dizocilpine was the psychogenic agent employed in this experiment as well as throughout the remainder of this dissertation. The cognitively-impairing qualities of NMDA receptor-inhibiting compounds are robust, with administration of sub-anesthetic doses of dizocilpine and similar drugs resulting in deficient attentional performance in both humans

and non-human animals, although dizocilpine is poorly tolerated in humans and is almost exclusively used in animals (Smith et al., 2011). Like ketamine and PCP, dizocilpine binds non-competitively with NMDA receptors, but in contrast with ketamine and PCP – which have numerous off-site targets – its effects appear to be more exclusive to the NMDA receptor (Chen et al., 2009). Dizocilpine additionally has a delayed onset and longer half-life than ketamine, with the latter dissociating from the open NMDA receptor channel more quickly than the former (Johnson & Kotermanski, 2006; Zorumski et al., 2016). While ketamine reaches peak plasma concentration at around five minutes post-ip injection and has behavioral effects which can last upwards of 30 minutes following one-time administration in young adult rats (Mion & Villevieille, 2013), dizocilpine induces peak neurological and behavioral activation 30 minutes following exposure that lasts on the order of hours rather than minutes (Hargreaves, 1995). Therefore, the selection of dizocilpine as the psychosis-mimicking drug used in this experiment was strategic in order to reduce the likelihood of a loss of potency towards the end of a given 40-minute behavioral testing session.

The DORA filorexant, which was first explored for the treatment of insomnia, migraine, depression, and diabetes-linked neuropathy beginning in 2012, was chosen because it demonstrates equal affinity for both the Ox1 and Ox2 receptor subtypes (< 3 nM in binding) and has both a higher reported bioavailability and more rapid receptor binding than commonly-used predecessor DORAs, such as suvorexant and almorexant (Winrow et al., 2012). Using an

antagonist that inhibits the activity of both orexin receptors is prudent when attempting to parse the overall role of the orexin system in attention. Non-selective orexinergic blockade via a drug that binds with each receptor subtype equally allows for the behavioral findings to be attributed to the transient loss of general orexin function. The use SORAs is ideal for isolating the contributions of individual orexin receptor subtypes to attentional performance.

Both dizocilpine and filorexant were administered in a system-wide, rather than site-specific, fashion. Dizocilpine was injected into the peritoneal cavity while filorexant was infused directly into the cerebrospinal fluid-filled lateral ventricles of the brain. In doing so, changes in task performance in this experiment can be attributed to widespread, as opposed to localized, CNS activity. Though the use of ip and ICV administration of psychoactive compounds reduces the likelihood that the behavioral effects can be ascribed to particular regions of interest, such as the PFC or BF, these techniques have more clinical value, as hypoactive NMDA receptors in SZ are not exclusively localized to fast-spiking GABAergic interneurons in the PFC, and patients taking antipsychotics would experience diffuse neurobiological effects of these drugs throughout the brain. While the behavioral consequences of CNS-wide dizocilpine and filorexant administration were the primary interests in this experiment as well as the others in this dissertation, questions about how these drugs influence neuronal activity in distinct areas of the brain and how those translate to alterations of observable behaviors can be answered with direct regional administration.

Overall, it was hypothesized that acute NMDA receptor antagonism would worsen attentional performance in the SAT; specifically, injections of dizocilpine were expected to impair the capacity to identify the visual signal as evidenced by worsened correct responding in signal trials, increase the amount of time it took to press the correct lever following its extension into the testing chamber, and lessen the number of total completed trials in a given testing session. It was also anticipated to negatively impact task performance during and after the introduction of a distracting stimulus, a modification which will be explained in detail in the methods section. Although there is a paucity of literature on orexin receptor blockade and performance in attention tasks, it was postulated herein that ICV filorexant infusions would induce little to no SAT performance impairments at sub-sedative doses, and when co-administered alongside dizocilpine, they would improve upon dizocilpine-induced drops in accuracy, increases in reaction time, and elevations in trial omissions, potentially as a result of alleviated excitatory imbalances in regions important for attentional processing.

Material and methods

Subjects

A total of 14 adult male Fischer 344/Brown Norway F1 rats (Charles River Laboratories, Wilmington, MA), 12 weeks old upon arrival, were used in the present experiment. Subjects were housed in pairs with a 14-hour light/10 hour dark cycle (lights on 06:00-20:00) in a temperature- and humidity-controlled

vivarium, and all behavioral testing occurred 6-7 days per week between 09:00 and 16:00. The rats were allotted ad libitum access to rat chow, but water was restricted to 10 minutes a day during testing days and 20 minutes on non-testing days in order to establish water as a salient motivator throughout behavioral training and testing. The protocol for this research was approved by William & Mary's Institutional Animal Care and Use Committee.

Apparatus

Following the initiation of water restriction, subjects began behavioral testing in one of 14 chambers controlled by MED-PC-V data collection software (Med Associates, Inc., Georgia, VT). Each testing chamber was situated within a sound-attenuating cubicle and consisted of an intelligence panel with one retractable lever on either side of a water access port, a water dipper with a cup which could hold 0.01 ml of water, and a central panel light situated above the water port. A house light was located on the opposite panel of the chamber.

Presurgical behavioral training

Rats were trained in the previously-discussed visual SAT. The house light remained illuminated throughout the session prior to surgery. The task consisted of three training stages. During the first training stage, both levers were extended throughout testing, and subjects were shaped to press levers using a fixed ratio (FR)-1 reinforcement schedule. To prevent the development of a lever bias, if a rat pressed a particular lever five consecutive times, water access was withheld

until a press was made on the other lever. Rats were moved to the next training stage once 120 water rewards were obtained for three successive days. The second training phase consisted of 100 trials, during which rats were trained to discriminate between signal (1 second illumination of the central panel light) and non-signal (no central panel light illumination) trials. After illumination of central panel light (or no illumination), the levers were extended into the chamber. The dipper was raised following a response on one lever on signal trials and the other lever on non-signal trials. Half of the rats received reward access following a response on the left lever on signal trials and following a right lever press on non-signal trials. The correct levers for signal and non-signal trials were reversed for the other half of the animals. Pressing the rewarded lever during a signal trial was considered a hit, and pressing the rewarded lever during a non-signal trial was recorded as a correct rejection. Pressing the incorrect lever in signal trials was considered a miss, and pressing the incorrect lever during a non-signal trial was considered a false alarm. Failure to press either lever after their extension into the testing chamber for 3 seconds was recorded as an omission. Each trial was separated by an inter-trial interval (ITI) of 18 seconds. During this training stage, if the rat responded incorrectly or not at all, a correction trial occurred, which was identical to the previous trial. Pressing the incorrect lever for three consecutive correction trials resulted in a forced trial during which only the correct lever was extended into the chamber until a response was made or until 90 seconds elapsed. The central panel light was illuminated if the errors occurred on signal trials. Rats remained in this training stage until accuracy on signal and

non-signal trials was at least 70 percent on signal and non-signal trials for three consecutive sessions.

The final training stage consisted of 90 trials in each session. There were 45 total signal trials, with an equal number of trials with the 500, 100, and 25 ms signal durations, and 45 non-signal trials (*Figure 4a*). Each trial was separated by an ITI of 9 ± 3 seconds. The ITI was shortened and made variable in order to increase the attentional demands of the task. During any given trial, the signal light was either illuminated or not, after which both levers extended for three seconds. Lever pressing was rewarded in the same manner as during the previous training stage. Rats were considered eligible for surgery when they achieved the criteria of 70 percent or higher accuracy in successfully identifying 500 ms signals and at least 70 percent on non-signal trials for three consecutive days.

Surgical procedures

The night prior to surgery, rats were given free access to 2.7 mg/ml of acetaminophen (po). The following morning, they were anesthetized via an ip injection of 90 mg/kg of ketamine and 9 mg/kg of xylazine. Upon sedation, rats were shaved around the surgical site, placed in a stereotaxic apparatus (Kopf Instruments, Tujunga, CA), given an incision along the midline, and underwent unilateral ICV cannulation surgery wherein one 8 mm (22 gauge) guide cannula was implanted 1.0 mM above either the left or the right lateral ventricle (-0.8 mm anterior-posterior, ±1.6 mm medial-lateral from bregma; -2.5 mm dorsal-ventral

from dura; *Figure 4b*). The surgeries were conducted using aseptic conditions, and the cannulae were held in place with stainless steel screws and dental cement. After surgery, subjects were given a week-long period of ad libitum water access, with acetaminophen provided for the first three days, after which they resumed water restriction and were reintroduced to the SAT.

Postsurgical behavioral training

At least one week after baseline performance was re-established, rats were introduced to a modified version of the SAT wherein the house light flashed (0.5 Hz) during the middle set of trials. The 90-trial attention test session was divided into three blocks: the first 30 trials were identical to those of the standard where with the house light remained illuminated (pre-distracter block), the next 30 trials introduced the flashing house light distracter (distracter block), and the final 30 trials were a return to the standard task with the illuminated house light (recovery block). The rats were exposed to the modified task once before initial drug exposure and on drug administration days; on days when the rats did not receive drugs, they performed in the standard SAT with no distracter.

Drug preparation and administration procedures

Dizocilpine maleate (Tocris Bioscience) was dissolved in sterile saline to create a solution of 0.1 mg/ml that was stored at -40 °C and used within one week of preparation. Stock solutions of 0.1mM and 1.0 mM of filorexant (MedChemExpress) in dimethyl sulfoxide (DMSO) were stored at -40 °C and used within one month of preparation.

Rats received a randomized ip injection of either saline or 0.1 mg/kg dizocilpine (at a volume of 1.0 ml/kg) 30 minutes prior to placement in the chamber. This dose of dizocilpine was selected because it has been shown to induce cognitive impairments in rats while not completely precluding task performance, both in the literature (Hurtubise et al., 2017; Karasawa et al., 2008; Svoboda et al., 2015) and in pilot dosing studies from our lab. Fifteen minutes before testing, 2.5 µl of either 0 (DMSO vehicle), 0.1, or 1.0 mM of filorexant was infused at a rate of 1.0 µl per minute by way of an internal cannula (8 mm with 1.0 mM extension beyond the guide cannula; *Figure 4c*). There is no existing research that administered filorexant intracerebroventricularly, and the concentrations that were used in ip and sub-cutaneous injection studies were chosen because they were sedating; therefore, the doses for this experiment were selected based on preliminary findings testing a range of concentrations (up to 10 mM) showing that the lower doses used in this experiment did not induce motoric deficits or sleep in rats. The internal cannula was connected to a microsyringe on an infusion pump (Harvard Apparatus) via polyethylene tubing. Dizocilpine and filorexant dose combinations were randomized across rats, and a washout period of at least 48 hours separated drug administration sessions.

Histological procedures

Following the final drug administration session, each rat was anesthetized with a ketamine/xylazine cocktail of 100.0 mg/kg of ketamine and 10.0 mg/kg of xylazine and transcardially perfused at 300 mmHg with a 10 percent sucrose

solution followed by 4 percent paraformaldehyde. Brains were harvested, stored in the 4 percent paraformaldehyde solution, and rinsed with 0.1 M phosphate buffer solution on the day of sectioning. Each brain was sectioned using a vibratome (Thermo Scientific, Microm HM 650V) into 50 µm slices. Sections in the vicinity of the cannulation site were stained with cresyl violet acetate and guide cannula location was confirmed using an Olympus BX-51 light microscope.

Data analysis

Relative hits were calculated by dividing the number of correct signal trials by all presses on signal trials, and relative correct rejections were determined by dividing the number of correct rejections by the number of presses on non-signal trials. Relative hits, relative correct rejections, and trial omissions were further calculated for pre-distracter, distracter, and recovery blocks. Correct response latency measurements were calculated as the average time (out of 3000 ms) it took rats to press the correct lever following its extension into the testing chamber at the conclusion of a trial, and these were additionally split into blocks for block-specific analyses. Repeated-measures analyses of variance (ANOVAs) were used for each measure of accuracy and omissions, all of which were corrected using the Greenhouse-Geisser procedure when required. Interaction effects were further analyzed with one-way repeated-measures ANOVAs, and main effects revealed by these analyses were explored with multiple comparisons of paired-samples t-tests and corrected with the Bonferroni pairwise comparison procedure. All statistical analyses were conducted using SPSS

Statistics version 24.0. Statistical significance was determined using α = .05. Data are presented as the mean ± standard error.

Results

Effects of dizocilpine on SAT performance

Appropriate guide cannula placement was confirmed for all rats included in the behavioral analyses. A 2 (dizocilpine: 0 and 0.1 mg/kg) X 3 (block: pre-distracter, distracter, and recovery) X 3 (signal duration: 500, 100, and 25 ms) repeated-measures ANOVA was used to measure the influence of acute NMDA receptor antagonism on signal detection in the SAT. A main effect of dizocilpine ($F(1,13) = 9.14$, $p = .01$, $\eta^2p = .413$) revealed that dizocilpine decreased rats' accuracy in signal trials when compared to saline (Figure 3a). There was also a main effect of block ($F(2,26) = 6.06$, $p = .007$, $\eta^2p = .318$), with performance being better in the pre-distracter block than the distracter ($t(13) = 2.27$, p = .041. d = .608) and recovery blocks ($t(13) = 3.00$, $p = .011$, $d = .796$). No interactions between dizocilpine concentration and block suggest that the attentional detriments associated with NMDA receptor blockade are throughout the testing session rather than influenced by a particular period of testing. Furthermore, a main effect of signal duration ($F(2,26) = 25.87$, $p < .001$, $\eta^2p = .666$) revealed an aggregate signal duration-dependent decrease in hit accuracy as signal duration decreased (p < .002 between all signal lengths). The signal duration main effect was qualified by a dizocilpine X signal duration interaction ($F(2,26) = 27.98$, $p < .001$, $\eta^2p = .683$). Paired-samples t-tests at each of the three signal durations

showed that, compared to saline, dizocilpine decreased accuracy following the 500 ($t(13) = 4.26$, $p = .001$, $d = 1.137$) and 100 ms signals ($t(13) = 2.42$, $p = .031$, $d = .646$), but not the 25 ms signal (*Figure 4d*). A dizocilpine X block repeated-measures ANOVA for accuracy in non-signal trials failed to reveal a significant main effect or interaction including dizocilpine as a factor (*Figure 4e*).

A main effect of dizocilpine in a dizocilpine X block repeated-measures correct response latency ANOVA verified that dizocilpine notably increased response times when aggregating all trials during which rats responded correctly, $F(1,13) = 21.93$, $p < .001$, $\eta^2p = .628$ (*Figure 4f*). Response times also varied by block ($F(2,26) = 53.14$, $p < .001$, $\eta^2p = .803$); regardless of whether they were given saline or dizocilpine, rats were slowest to accurately respond in the recovery block when compared to the pre-distracter ($t(13) = 6.81$, $p < .001$, $d = 1.819$) and distracter blocks ($t(13) = 8.52$, $p < .001$, $d = 2.278$), and they were ultimately quickest to respond in the distracter block when juxtaposed with the pre-distracter block ($t(13) = 2.82$, $p = .014$, $d = .754$). This suggests that rats responded most assuredly during the distracter segment, but their performance slowed beyond that of pre-distracter speeds once the house light stopped flashing.

For trial omissions, a dizocilpine X block repeated-measures ANOVA revealed a main effect of dizocilpine ($F(1,13) = 46.72$, $p < .001$, $\eta^2p = .782$), with NMDA receptor antagonism significantly reducing lever-pressing behavior (*Figure 4g)*. The ANOVA also yielded a main effect of block ($F(2,26) = 20.59$, $p < .001$, $\eta^2p = .613$), with a block-dependent increase in omissions from pre-

distracter to distracter and from distracter to recovery (all $p < .01$). The dizocilpine X block interaction was not statistically significant, showing that the detrimental effect of dizocilpine on omissions was overall and not block-specific.

Effects of filorexant on SAT performance

To explore the unique effect of filorexant on attentional performance, a 3 (filorexant: 0, 0.1, and 1.0 mM) X 3 (block: pre-distracter, distracter, and recovery) X 3 (signal duration: 500, 100, and 25 ms) repeated-measures ANOVA was conducted for accuracy in signal trials for rats when they were given injections of saline and one of the three possible filorexant concentrations. In signal trials, there was neither a main effect of filorexant nor any interactions between filorexant and other variables of interest (*Figure 4h*). For non-signal trials and for trial omissions, there was additionally no main effect of filorexant or interactions with filorexant (*Figure 4i*). There were, however, main effects of block for correct rejections ($F(2,26) = 5.79$, $p = .008$, $\eta^2p = .308$) and for omission rates ($F(2,26) = 28.32$, $p < .001$, $\eta^2p = .685$). In non-signal trials, rats performed better in the pre-distracter block than the distracter block ($t(13) = 3.96$, $p = .002$, $d = 1.058$), and for omissions, rats omitted more in the recovery block than in the pre-distracter ($t(13) = 5.45$, $p < .001$, $d = 1.455$) and distracter blocks ($t(13) = 6.08$, $p < .001$, $d = 1.624$). Lastly, for response latencies in all correctly-responded trials, a filorexant X block repeated-measures ANOVA failed to detect the involvement of filorexant in reaction times (*Figure 4j*). Therefore, because the only notable effects to come from these analyses did not relate to filorexant, it can be surmised that dual orexin receptor antagonism at the present doses does

not necessarily disrupt performance in the SAT despite the involvement of both orexin receptors in cognition- and motivation-linked processes.

Effects of filorexant on dizocilpine-induced SAT impairments

A 2 (dizocilpine: 0 and 0.1 mg/kg) X 3 (filorexant: 0, 0.1, and 1.0 mM) X 3 (block: pre-distracter, distracter, and recovery) X 3 (signal duration: 500, 100, and 25 ms) repeated-measures ANOVA for signal trial accuracy revealed a main effect of filorexant, $F(2,26) = 4.42$, $p = .046$, $\eta^2p = .254$. When averaged across dizocilpine dose, signal duration, and testing block, no disparities in signal detection were found between the vehicle and the 1.0 mM filorexant dose, but the 0.1 mM filorexant dose improved performance compared with the former ($t(13) = 3.13$, $p = .008$, $d = .836$) and latter doses of filorexant ($t(13) = 3.54$, $p = .004$, $d = .946$), suggesting that the low concentration of filorexant predominantly drove the statistically significant improvement in vigilance (*Figure 4k*). As was similarly found with dizocilpine alone, filorexant alone did not affect non-signal trial accuracy.

For reaction times in all correct trials, a dizocilpine X filorexant X block repeated-measures ANOVA revealed a dizocilpine X filorexant interaction ($F(2,26) = 5.49$, $p = .021$, $\eta^2p = .297$) which was further qualified by a dizocilpine X filorexant X block three-way interaction ($F(4,52) = 5.22$, $p = .007$, $\eta^2p = .287$). When averaged across block, comparing saline and dizocilpine response speeds for each filorexant concentration showed a slowing of reaction times when rats were given dizocilpine paired with infusions of 0 mM ($t(13) = 4.68$, $p < .001$, $d = 1.251$) and 1.0 mM doses of filorexant ($t(13) = 2.44$, $p = .03$, $d = .652$); however,

no such difference was detected between saline- and dizocilpine-injected rats when they were infused with 0.1 mM of filorexant (*Figure 4I*). Dizocilpine X filorexant repeated-measures ANOVAs for each block revealed a main effect of dizocilpine in all three testing periods (all $p < .005$) where rats were slower to respond following NMDA receptor blockade regardless of the introduction of filorexant to the analyses. While no block had a main effect of filorexant, there were dizocilpine X filorexant interactions in the pre-distracter ($F(2,26) = 4.43$, $p = .039$, $\eta^2p = .254$) and recovery periods ($F(2,26) = 7.56$, $p = .002$, $\eta^2p = .654$). Dizocilpine concentration *t*-tests for each filorexant dose in these two blocks showed that, though rats were slower to press the correct lever when they were given dizocilpine than when they were given vehicle ($p < .003$ for both blocks), the 0.1 and 1.0 mM concentrations of filorexant normalized reaction times of dizocilpine-administered rats to that of baseline.

As revealed by a dizocilpine X filorexant X block repeated-measures omissions ANOVA, there was a main effect of filorexant on number of omitted trials ($F(2,26) = 5.17$, $p = .025$, $\eta^2p = .293$) and a filorexant X dizocilpine interaction ($F(2,26) = 12.14$, $p < .001$, $\eta^2p = .432$). Filorexant repeated-measures ANOVAs for each injection condition showed that there was no main effect of filorexant when paired with saline, denoting that orexin receptor antagonism did not suppress lever-pressing frequency by itself. Rather, when rats were given dizocilpine, performance did vary based on filorexant concentration ($F(2,26) = 8.68$, $p = .005$, $\eta^2p = .400$). When rats were injected with dizocilpine, trial omissions were statistically similar between 0 mM and 1.0 mM doses of

filorexant, but they were lower with infusions of the 0.1 mM concentration compared with vehicle ($t(13) = 3.55$, $p = .004$, $d = .950$) as well as with the 1.0 mM concentration ($t(13) = 4.46$, $p = .001$, $d = 1.193$; *Figure 4m*). Similarly, injection condition paired-samples t-tests for each of the three filorexant doses reveal that the low dose was sufficient to reduce trial omissions for rats given dizocilpine to a number comparable to when they were given saline, whereas dizocilpine-exposed rats omitted more when infused with vehicle ($t(13) = 6.84$, $p < .001$, $d = 1.827$) and the high filorexant dose ($t(13) = 3.36$, $p = .005$, $d = .898$, *Figure 4n*).

A dizocilpine X filorexant X block interaction ($F(4,52) = 3.90$, $p = .008$, $\eta^2p = .231$) suggests that the ability for filorexant to influence trial omissions for dizocilpine-exposed rats largely depends on testing period. Moreover, an interaction between filorexant and dizocilpine was observed prior to ($F(2,26) = 4.04$, $p = .03$, $\eta^2p = .237$) and during the distracter ($F(2,26) = 7.29$, $p = .003$, $\eta^2p = .359$). Dizocilpine x filorexant ANOVAs for the pre-distracter and distracter blocks revealed that omission rates relied on filorexant concentration only during the flashing distracter ($F(2,26) = 6.76$, $p = .004$, $\eta^2p = .359$). During the distracter, multiple comparisons *t*-tests revealed that, when rats were given dizocilpine, omissions were similar between 0 and 1.0 mM doses of filorexant, but the 0.1 mM dose reduced the number of omissions when juxtaposed with vehicle (*Figure 4o*; $t(13) = 3.34$, $p = .005$, $d = .893$). Taken together, these omission analyses highlight a robust ameliorative effect of the lower filorexant concentration.

Discussion

The findings from experiment one demonstrate that acute systemic administration of dizocilpine, a psychotomimetic often employed to emulate the NMDA receptor hypofunction observed in SZ, decreased accuracy in signal trials, increased response latency during correct trials, and increased trial omissions in the SAT. Because performance in non-signal trials remained intact, it suggests that rats were still able to respond based upon the task rules when dizocilpine was administered and that decreased signal detection accuracy is not due to a side or lever bias. Regardless of trial type, dizocilpine augmented response latency for trials during which rats responded at the correct lever, a well-established finding that has been replicated in other animal studies using single-dose administration of NMDA receptor antagonists in similar paradigms of signal detection, such as the 5-CSRTT (Amitai & Markou, 2010; Smith et al., 2011; Nikiforuk & Popik, 2014). Lastly, dizocilpine increased trial omissions in all task blocks compared to saline, suggesting that motivation to respond in the SAT may also be negatively impacted in this model of SZ. Motoric impairments cannot be fully discounted although no serious aberrations of movement were observed prior to and following removal from the task.

To date, this experiment is the first to explore the influence of dual orexin receptor antagonism on sustained attentional performance concurrently with a pharmacological model of SZ. It was speculated that filorexant would ameliorate decreases in accuracy as well as increases in correct response latency and omissions when co-administered with an NMDA receptor antagonist. As was

hypothesized, filorexant attenuated deficits in hit accuracy for rats administered dizocilpine, though the effects are modest here. Brain-wide blockade of orexin receptors - especially those located on cells which are known to proliferate frontocortical ACh efflux - may have slightly improved attention though reduction of dizocilpine-produced disturbances of E/I balance in sustained attention-relevant cortical areas. Additionally, increases in correct response latency induced by dizocilpine were abated following co-administration of the low dose, and occasionally the high dose, of filorexant in both signal and non-signal trials. This finding is clinically applicable, as some previous research using dizocilpine and other NMDA receptor antagonist models of SZ have shown that antipsychotic pretreatment either does not affect or can exacerbate increases in correct response and reward retrieval latencies (Amitai et al., 2007; Paine & Carlezon, 2009).

In addition to rescuing attentional accuracy, intracranial infusions of filorexant markedly reduced the number of omitted trials resulting from dizocilpine exposure. Based on our behavioral findings, it can be surmised that dual orexin receptor antagonism may have attenuated abnormally elevated prefrontal cortical stimulatory neurotransmission that precluded appropriate adjustment to increasing attentional load. In doing so, the incentive to maintain performance in this pharmacological model of SZ was partly restored. Interestingly, the 0.1 mM concentration of filorexant, but not the 1.0 mM concentration, was sufficient to restore in-task responding to levels observed with saline injections, with the high dose producing a similarly elevated number of omissions as dizocilpine alone.

The neurobiological mechanisms underlying the adverse outcomes regarding in-task responsiveness following the combination of dizocilpine and 1.0 mM of filorexant observed in this experiment remain unclear. However, the effects of orexin receptor blockade on the pursuit of reinforcement are heavily influenced by the effort-to-reward ratio (Shaw et al., 2019) - that is, high-effort, but not low-effort, response capacity is differentially impacted by orexinergic antagonists. Because dizocilpine made the performance in the SAT significantly more effortful, the exertion required to maintain performance across trials may have exceeded the drive to attain the water reward. While this motivational deactivation was reversed by a lower degree of orexin receptor antagonism, findings from the present experiment suggest that higher DORA concentrations may be insufficient in improving task engagement in this model of acute psychosis. It can therefore be surmised that lower concentrations of anti-orexinergic drugs do not necessarily impact incentivized performance or motoric functioning at a concentration that benefitted rats in the SAT in the context of NMDA receptor hypofunction.

In addition to putatively anticholinergic effects in the BF, dual orexin receptor antagonism may have indirectly addressed dizocilpine-induced dysfunctions of signal-driven input selection and cortical vigilance networks stemming via various non-cholinergic loci in the mesocorticolimbic system, including PV+ GABAergic neurons of the BF, which are depolarized by orexins and are themselves sufficient to stimulate cortical arousal when exposed to OxA in animals with lesions to corticopetal cholinergic projections (Arrigoni et al.,

2010; Blanco-Centurion et al., 2007). Thus, frontocortical activation may be suppressed when blocking orexin receptors expressed on these neurons as well as orexin receptors located on cortical glutamatergic outputs to the BF, which synapse exclusively with these PV+ GABAergic neurons (Záborszky et al., 1997; Sarter & Bruno, 2002).

Moreover, because muted GABAergic efferents from the NAcc to BF cholinergic neurons are hypothesized to contribute to the attentional deficits in SZ (Sarter et al., 1999), orexin receptor antagonism may mitigate the prevalence of SZ-linked behavioral correlates by modulating mesolimbic DA synthesis. This is supported by the Elam et al. (2021) findings that suvorexant, SB-334867, and EMPA reduced VTA DA neuron population activity in a rodent model of stress-induced psychosis, and the former two reversed dizocilpine-induced hyperlocomotion through presumed antidopaminergic mechanisms of action. Neurons in the cortex containing both Ox1 and Ox2 receptor mRNA also project to and synapse with A10 DA cells of the nucleus paranigralis subdivision of the VTA and the shell of the NAcc (Carr & Sesack, 2000; Murase et al., 1993; Sesack & Pickel, 1992; Thorpe & Kotz, 2005), so it is possible that DORAs may lessen BF hyper-reactivity through the inhibition of these orexin-sensitive corticofugal innervations.

It is also feasible that filorexant has attentionally-beneficial effects outside of the BF and dopaminergic midbrain, including through reciprocal connections between the LH and the PFC (Gabbott et al., 2005; Kita & Oomura, 1981), midline-intralaminar thalamic relay neurons (Lambe et al., 2007; Hay et al.,

2015), and norepinephrinergic neurons of the LC (Foote et al. 1991; Trivedi et al., 1998; Aston-Jones et al. 1999; Boschen et al., 2009; Mahler et al., 2014). Site-specific administration can provide better insight as to which vigilance-relevant brain circuits respond to and benefit the most from orexin receptor-targeting ligands.

In the absence of dizocilpine, neither dose of filorexant impacted accuracy or correct reaction times in the SAT, nor did they diminish lever-pressing behavior. This is a clinically- relevant finding, as ideal drug candidates to treat attentional impairment in SZ would not worsen cognition on their own. As has been discussed, functionality of Ox1 receptors is required for homeostasis-driven pursuit of food (Bingham et al., 2006; Choi et al., 2010; Sharf et al., 2010; Thorpe & Kotz, 2005), water (Hurley & Johnson, 2014; Kunii et al., 1999), and drug reinforcers (Ellis et al., 2005; Moorman et al., 2017), and Ox2 receptor activity plays a critical role in the instigation and maintenance of consciousness, behavioral arousal, and awareness in human and non-human animals (Mieda et al., 2013; Sasaki et al., 2011). The composite findings of this experiment suggest that in the absence of other psychoactive pharmacological compounds, widespread blockade of both orexin receptor subtypes neither interfered with fluid balance-related motivational activation in the SAT nor induced lethargy that precluded adequate responding. This is corroborated by research from Gentile and colleagues (2017) showing that orexin receptor antagonism is able to lessen cocaine-induced premature responses in the 5-CSRTT without de-incentivizing reward-contingent attentional performance. It also offers further support for the

aforementioned idea that orexin receptor blockade may primarily demotivate the pursuit of reinforcement during periods of augmented effort, such as when administered in tandem with other compounds known to disrupt focus-based performance (España et al., 2010; Brodnik et al., 2015; Shaw et al., 2019).

Though the presented findings highlight a putatively therapeutic benefit of DORAs for the treatment of attention-relevant deficits in the context of NMDA receptor hypofunction, the gap in the literature can be further addressed outside of the scope of the present experiment. For example, the inclusion of female rats is important to parse any sex-specific effects of the drugs used in the study; though less is known about sex differences in response to orexin receptor antagonists, it has been shown that female rats may be more sensitive to the influence of dizocilpine and other NMDA receptor-blocking compounds (Andiné et al., 1999; Hur et al., 1999). Site-specific, rather than ICV, administration of orexin receptor-targeting agents can offer insight regarding which particular brain regions and their associated behaviors are most responsive to anti-orexinergic compounds. The employment of SORAs can additionally elucidate the unique roles of the Ox1 and Ox2 receptor subtypes in influencing attentional outcomes in this model of acute psychosis. Histochemical techniques, such as c-Fos staining and immunofluorescence, can reveal neurobiological effects of DORA exposure that, together with behavioral interpretations, offer a more complete understanding of cellular and behavioral outcomes of orexinergic manipulations.

Conclusion

In an acute NMDA receptor antagonism model of SZ, dual orexin receptor blockade was able to alleviate dizocilpine-induced alterations of signal trial performance, reaction time, and trial omissions in a test of sustained attention. In particular, the 0.1 mM concentration of filorexant improved response accuracy, restored correct response latency, and lessened the number of omitted trials. Besides improving reaction times in the pre- and post-distracter periods, the 1.0 mM dose failed to demonstrate many of the same ameliorative qualities, suggesting that a higher degree of orexin receptor inhibition fails to improve upon or incentivize task performance for rats when they are co-administered dizocilpine. This experiment is the first to introduce orexin receptors as a potential novel pharmacotherapeutic target to treat the sustained attentional and perhaps motivational deficits associated with psychosis. The employment of SORAs to research the role of individual orexin receptor subtypes on brain physiology and behavior in this model is a logical next step towards a more complete picture of the therapeutic potential of orexin receptors for the treatment of attentional impairments in SZ.

CHAPTER 5. Experiment two: Ox1 receptor antagonism improves dizocilpine-induced attentional deficits

Introduction

The outcomes of experiment one uncovered a potentially ameliorative quality of indiscriminate orexin receptor blockade for attentional impairments in an NMDA receptor antagonist model of psychosis. Because the DORA filorexant binds with equal affinity to both the Ox1 and Ox2 receptors, it is not possible to ascribe receptor-specific responsibility for the benefits found in the previous study. A logical next step is to parse the unique contributions of the individual orexin receptor subtypes by using receptor-specific ligands. In the current study, the non-peptide SORA SB-334867 was selected to explore the contributions of the Ox1 receptor in the findings from the prior experiment. SB-334867 was the first Ox1 receptor-targeting ligand to be developed (Smart et al., 2001), and while it has demonstrated some affinity for targets outside of the Ox1 receptor, it has a 30- to 100-fold higher selectivity for the Ox1 over the Ox2 receptor subtype and is the most widely-used Ox1 receptor antagonist to date (Gotter et al., 2012; Haghparast et al., 2017; Porter et al., 2001; Socała et al., 2016). Despite this disparity, the methodological techniques as well as the research hypotheses of this experiment mirrored what was done for the experiment prior in most ways; rats were given ip injections of either 1.0 ml/kg of saline or 0.1 mg/kg of dizocilpine, followed shortly thereafter by ICV infusions of vehicle or the orexin receptor antagonist, and then underwent attentional testing in the modified

distracter version of the SAT. Based on experiment one, it was believed that dizocilpine would worsen measures of performance in the attention task, and SB-334867 would both fail to notably impair them on its own and alleviate attentional deficits induced by dizocilpine.

Another key difference separating this study from the one in the last chapter is the use of Sprague Dawley rats. The FBNF1 hybrid rats which were included in the last experiment were outbred and outsourced all-male cohorts, thus precluding the exploration of sex-specific behavioral effects of concurrent NMDA and orexin receptor suppression. The switch from an outbred strain to rats which were bred in-house enabled the use of both male and female rats and, as such, allowed for the exploration of performance outcomes which depended on the sex of the subject. Additionally, anecdotal evidence suggests that FBNF1 hybrid rats are less motivated for the water reward and complete significantly less trials, on average, than Sprague Dawley rats, therefore necessitating a version of the task with less trials. Upon the inclusion of Sprague Dawley rats, the total number of trials in the SAT was increased from 90 to 126, with Sprague Dawley rats omitting less often than FBNF1 hybrid rats despite the augmented number of trials. A second slight adjustment of the SAT from experiment one to the current experiment is an increase in the frequency of the flashing distracter – from 0.5 Hz to 1 Hz – for the purpose of augmenting the attentional demands of the task.

Lastly, rats were sacrificed two hours after the final drug administration procedure because the expression of c-Fos - the *fos* oncogene which is

considered a genetic marker of cellular activation (Herrera & Robertson, 1996) - peaks two hours following drug exposure (Kaczmarek, 1992). By euthanizing the subjects within this critical window, task performance can be considered in parallel with immunohistochemical analyses to parse disparities in neuronal activity induced by various combinations of the compounds of interest in attention-associated regions of the brain, including the PFC and the BF. For example, as will be detailed in the discussion section, it might be expected that, due largely to glutamatergic disinhibition, systemic administration of sub-sedative doses of dizocilpine would increase the activity of wake-active neurons, including ascending cholinergic, glutamatergic, and PV+ GABAergic neurons; conversely, intracranial SB-334867 infusions could be hypothesized to attenuate the number of c-Fos-positive cells in cortical and subcortical attention-promoting neurons, as has been found in the hypothalamic nuclei, prelimbic cortices, BFs, and other CNS areas of rats (García-Brito et al., 2018; Vanderhaven et al., 2015; Zhang et al., 2012). If acute NMDA receptor antagonism increases genetic markers of neuronal activation, and Ox1 receptor antagonism has the opposite effect, it could be postulated that SB-334867 may be able to reduce dizocilpine-induced elevations in c-Fos expression in the PFC and BF in such a way that results in rescued attentional performance.

Material and methods

Subjects

17 adult Sprague Dawley rats (9 male, 8 female) were bred in house and housed in a vivarium on a 14-hour light/10 hour dark cycle (lights on 6:00 - 20:00). They were kept in groups prior to surgery and single housed following surgery. Behavioral testing was conducted between 09:00 and 16:00 for six to seven days per week. Throughout the duration of the experiment, rats were allowed *ad libitum* access to rat chow but were on a water restriction schedule where they were given free access to water for 10 minutes on testing days and 20 minutes on non-testing days. This research was approved by William & Mary's Institutional Animal Care and Use Committee.

Apparatus

The rats in this experiment were trained in the same behavioral testing chambers and with the same data collection software as experiment one (Med-PC V Software Suite; Med Associates, Inc., Georgia, VT). Within each operant box were two retractable levers, one on either side of a water access port, a 0.01 ml water cup attached to a water dipper, a signal light located above the water port, and a house light on the other side of the testing chamber.

Presurgical behavioral training

Like the previous experiment, rats were trained in the signal detection SAT, with a number of small adjustments to increase the attentional demands.

This version of the SAT, similarly as the one used in experiment one, consisted of three stages of training. The first stage introduced the levers and established pressing the lever (on an FR-1 schedule of reinforcement) as a means to attain the water reward, with progression to the next stage of training requiring 120 rewards for three days in a row. In the second stage of training, which consists of 100 trials separated by an ITI of 18 seconds, rats were trained to press one lever following a 1 second signal light illumination (hit) and the other lever if the signal did not appear (correct rejection) at the conclusion of any given trial. Responses at the appropriate lever were rewarded while trials that were answered incorrectly - such as pressing the non-signal lever in a signal trial (miss), pressing the signal lever at the conclusion of a non-signal trial (false alarm), or failing to press either lever during their three-second extension into the testing chamber (omission) - were repeated for correction. To progress to the last stage of training, rats must be at least 70 percent accurate in signal trials and non-signal trials for three consecutive sessions.

In the current experiment, the number of trials in the final version of the task was increased from 90 to 126, with 63 non-signal trials and 63 signal trials which were equally divided into 500, 100, and 25 ms signal trials. Trials were separated by variable ITIs between six and 12 seconds. Rats were considered eligible for surgery when they achieved the criteria of 70 percent or higher accuracy in successfully identifying 500 ms signals and at least 70 percent on non-signal trials for three consecutive days.

Surgical procedures

All surgical procedures in this experiment match what was done for the prior experiment (*Figure 4b*). Rats were sedated with a ketamine/xylazine cocktail (90 mg/kg ketamine and 9 mg/kg xylazine, ip) after which their heads were shaved and they were placed in the stereotaxic apparatus (Kopf Instruments, Tujunga, CA), given an incision along the midline, and implanted with a cannula (8 mm, 22 gauge) which terminated 1.0 mM above either the left or right lateral ventricle (-0.8 mm anterior-posterior, ±1.6 mm medial-lateral from bregma; -2.5 mm dorsal-ventral from dura). After one week of recovery, rats recommenced behavioral testing, and baseline performance was monitored for at least two weeks before experimentation began.

Postsurgical behavioral training

In advance of the first drug administration session, rats were exposed to the modified distracter version of the SAT with the flashing house light for a portion of testing. In this version, the 126 trials were divided into pre-distracter, distracter, and recovery blocks composed of 42 trials each, which increased from 30 trials per block in experiment one. Additionally, in this version of the task, the frequency of house light flashing was doubled from 0.5 Hz in experiment one to 1 Hz in the present experiment to slightly increase the saliency of the distracter. After the initial exposure, rats only experienced the distracter on drug administration days; all other testing sessions were conducted with the normal SAT.

Drug preparation and administration procedures

Dizocilpine maleate (Tocris Bioscience) was dissolved in saline to create a 0.1 mg/ml solution that was stored at -40 °C and used within one week. SB-334867 (Tocris Bioscience) was suspended in vehicle comprised of saline (1 ml), Hydroxy-beta-cyclodextran (200 mg), and DMSO (125 µl) to produce 3 µg and 6 µg concentrations which were kept at -40 °C and used within a month of preparation.

On drug administration days, rats were given an ip injection of either 1.0 ml/kg of saline or 0.1 mg/kg of dizocilpine 30 minutes before behavioral testing began. Fifteen minutes before placement in the task, rats received 2.5 µl ICV infusions of either 0 µg (vehicle), 3 µg, or 6 µg of SB-334867 at a rate of 1.0 µl per minute via an internal cannula (8 mm with 1.0 mM extension beyond the guide cannula) attached to a microsyringe on an infusion pump (*Figure 5a*; doses adjusted for ICV administration from Boschen et al., 2009). All combinations of dizocilpine and SB-334867 were randomized across rats, and a minimum of 48 hours separated drug administration sessions.

Histological procedures

On the last day of drug exposure, rats were given their final treatment and underwent behavioral testing in the modified distracter version of the SAT. Two hours after drug administration, they were sedated with ketamine and xylazine (100 mg/kg and 10 mg/kg, respectively), transcardially perfused, and debrained using the same procedures as experiment one. Both cresyl violet acetate and c-

Fos staining on these brains is forthcoming. Quantification of c-Fos in brain areas of interest will allow for a better understanding of cellular activity at the time that these drugs were active in the CNS, including when they were performing the SAT.

Data analysis

The data collected in this experiment were analyzed in the same manner as experiment one. Of interest were relative hits, which are calculated by dividing number of hits by the sum of hits and misses, and relative correct rejections, which divides the number of correct rejections by a summation of correct rejections and false alarms. Also of interest was the amount of time it took rats to depress the correct lever in signal and non-signal trials following its extension into the testing chamber (out of 3000 ms) as well as the number of omitted trials during a session. Repeated-measures ANOVAs and follow-up t-tests were used to analyze relative hits, relative correct rejections, reaction times, and trial omissions were done for overall performance as well as for pre-distracter, distracter, and recovery blocks. Statistical analyses were conducted with SPSS Statistics version 24.0, and statistical significance was determined using $\alpha = .05$. Data are presented as the mean ± standard error.

Results

Effects of dizocilpine on SAT performance

A 2 (sex: female and male) X 2 (dizocilpine: 0 and 0.1 mg/kg) X 3 (block: pre-distracter, distracter, and recovery) X 3 (signal duration: 500, 100, and 25 ms) repeated-measures ANOVA was used to parse the effects of dizocilpine on signal trial accuracy in the SAT. There was a main effect of dizocilpine ($F(1,15) = 8.45$, $p = .011$, $\eta^2p = .360$) where rats that were given the NMDA receptor antagonist prior to placement in the task performed less accurately than when they were given saline. A lack of a sex effect suggests that this deficit was present regardless of the sex of the animal. A main effect of testing block ($F(2,30) = 18.90$, $p < .001$, $\eta^2p = .557$) was further explored with paired-samples *t*-tests comparing the three blocks, revealing that signal trial performance was higher in the pre-distracter block than the distracter ($t(16) = 3.92$, $p < .001$, $d = .951$) and recovery blocks ($t(16) = 5.99$, $p < .001$, $d = 1.452$). No interaction between dizocilpine and block indicates that attentional impairments stemming from NMDA receptor blockade occur equally throughout the task and are not specific to a particular testing block. A main effect of signal duration was also found ($F(2,30) = 47.69$, $p < .001$, $\eta^2p = .761$); follow-up *t*-tests revealed, a signal length-dependent decrease in hit accuracy ($p < .001$ between 500, 100, and 25 ms signal durations). A dizocilpine X signal duration interaction ($F(2,30) = 8.28$, $p = .001$, $\eta^2p = .356$) showed that, as revealed by injection condition *t*-tests per signal duration, dizocilpine made rats' performance worse at the 500 ($t(16) = 2.85$, $p = .011$, $d = .692$) and 100 ms signals ($t(16) = 3.77$, $p = .002$, $d = .915$), but

performance did not differ at the 25 ms signal between saline- and dizocilpine-administered rats (*Figure 5b*). For non-signal trials, there was neither a main effect of dizocilpine nor an interaction between dizocilpine and any other variables (*Figure 5c*), though there was a main effect of block ($F(2,30) = 6.86$, $p = .004$, $\eta^2p = .314$) for which *t*-tests comparing the three blocks revealed a decrease in performance from the pre-distracter to the distracter block to the distracter block ($t(16) = 3.43$, $p = .003$, $d = .831$) but an overall resurgence in performance in the recovery period.

A sex X dizocilpine X block X signal duration repeated-measures ANOVA for signal trial correct response latencies in the SAT found a main effect of sex ($F(1,15) = 4.93$, $p = .042$, $\eta^2p = .248$) where, when averaged across dizocilpine dose, testing block, and signal duration, females took longer to press the signal lever following its extension into the testing chamber than males (*Figure 5d*). There was additionally a main effect of dizocilpine ($F(1,15) = 20.69$, $p < .001$, $\eta^2p = .580$) that showed a slowing of response times following NMDA receptor antagonism (*Figure 5e*). Though there was a main effect of block ($F(2,30) = 12.69$, $p < .001$, $\eta^2p = .458$), there were no significant follow-up pairwise comparisons. Interestingly, when divided into signal duration *t*-tests, a main effect of signal duration ($F(2,30) = 23.20$, $p < .001$, $\eta^2p = .607$) revealed that rats were faster to correctly respond following the presentation of the 100 ms signal than both 500 ($t(16) = 3.10$, $p = .007$, $d = .752$) and 25 ms signals ($t(16) = 4.61$, $p < .001$, $d = 1.119$).

Though accuracy in non-signal trials was not impaired when rats were given dizocilpine, there was a main effect of dizocilpine for non-signal trial correct response latency (*Figure 5e*; $F(1,15) = 24.66$, $p < .001$, $\eta^2p = .622$) where rats were slower to respond when given dizocilpine. No other main effects or interactions were uncovered in these analyses. Thus, while dizocilpine only worsened accuracy outcomes for signal trials and not non-signal trials, it did increase correct response latencies regardless of trial type.

For trial omissions, a sex X injection condition X block repeated-measures ANOVA yielded a main effect of injection condition ($F(1,15) = 16.70$, $p < .001$, $\eta^2p = .527$), showing that rats omitted more when they were given dizocilpine than when they were given saline, and this was true regardless of sex (*Figure 5f*). An interaction between dizocilpine and block ($F(2,30) = 3.92$, $p = .031$, $\eta^2p = .207$) was broken down into injection condition ANOVAs comparing each of the three testing blocks, revealing that while saline-administered rats omitted similarly across blocks, there was a main effect of block for dizocilpine-administered rats ($F(2,30) = 3.92$, $p = .031$, $\eta^2p = .207$); the only difference was an increase in omissions from the pre-distracter to the recovery block ($t(16) = 2.81$, $p = .013$, $d = .681$). Injection condition paired-samples *t*-tests for each block showed that rats omitted more when given dizocilpine in pre-distracter ($t(16) = 3.42$, $p = .003$, $d = .830$), distracter ($t(16) = 4.23$, $p < .001$, $d = 1.026$), and recovery testing periods ($t(16) = 4.23$, $p < .001$, $d = 1.025$).

Effects of SB-334867 on SAT performance

A 2 (sex: female and male) X 3 (SB-334867: 0, 3, and 6 µg) X 3 (block: pre-distracter, distracter, and recovery) X 3 (signal duration: 500, 100, and 25 ms) repeated-measures ANOVA was used to examine the effects of Ox1 receptor antagonism alone on signal trial accuracy in the SAT. There was no overall main effect of SB-334867, meaning that this drug did not influence the rats' ability to correctly identify the signal (*Figure 5g*). However, as suggested by a SB-334867 X block X signal duration interaction ($F(8,120) = 2.05$, $p = .046$, $\eta^2p = .120$), the relationship between block and signal duration in signal trials depended partly on SB-334867 dose. This interaction was further elucidated with SB-334867 X block ANOVAs for each signal duration, and it was found that SB-334867 only had an influence for the 25 ms signal as evidenced by a SB-334867 X block interaction, $F(4,64) = 2.62$, $p = .043$, $\eta^2p = .141$. SB-334867 concentration ANOVAs per block at the 25 ms signal were not significant for any of the three testing blocks, though it was trending towards significance in the recovery block, $F(2,32) = 2.96$, $p = .066$, $\eta^2p = .156$. This trend was further investigated with follow-up *t*-tests between the three SB-334867 doses, but all comparisons were non-significant. Additionally, as determined by a SB-334867 X block repeated-measures ANOVA, Ox1 receptor antagonism did not influence accuracy in non-signal trials, as a main effect of SB-334867 was not present, nor were there any interactions between SB-334867 or any other variables of interest (*Figure 5g*).

A sex X SB-334867 X block X signal duration repeated-measures ANOVA was used to explore the unique effects of SB-334867 on correct response latencies in signal trials, and while there was neither a main effect of sex nor a main effect of SB-334867 (*Figure 5h*), there was an interaction between SB-334867 and sex ($F(2,30) = 3.96$, $p = .03$, $\eta^2p = .143$). Sex *t*-tests for each SB-334867 concentration revealed that males were faster to respond than females only when they were given infusions of vehicle ($t(15) = 2.39$, $p = .031$, $d = 1.161$); reaction times were not different between the sexes when they were either dose of SB-334867 (*Figure 5i*). Taken together, in the absence of dizocilpine, males are faster than females at pressing the signal lever following its extension into the testing chamber when they are given infusions of 0 µg of SB-334867, though these sex differences did not persist following either SB-334867 dose. Similarly for correct response latencies in non-signal trials, a sex X SB-334867 X block repeated-measures ANOVA uncovered a sex X SB-334867 interaction ($F(2,30) = 3.07$, $p = .023$, $\eta^2p = .170$) but no effect of SB-334867 or sex by themselves. However, independent samples *t*-tests comparing the sexes at each of the three SB-334867 doses found no differences in non-signal trial response times between males and females, highlighting only a marginal difference between the sexes.

For omission rates, a sex X SB-334867 X block repeated-measures ANOVA failed to find a main effect of SB-334867 on the number of omitted trials (*Figure 5j*). There was a main effect of block ($F(2,30) = 3.39$, $p = .047$, $\eta^2p = .184$) as well as an SB-334867 X block interaction ($F(4,60) = 2.74$, $p = .037$, η^2p

= .155). When averaged across SB-334867 dose, pairwise comparisons between the three blocks did not uncover any significant differences. Therefore, Ox1 receptor antagonism does not necessarily lessen the incentive to continue performing for the water reward in the SAT.

Effects of SB-334867 on dizocilpine-induced SAT impairments

A 2 (sex: female and male) X 2 (dizocilpine: 0 and 0.1 mg/kg) X 3 (SB-334867: 0, 3, and 6 µg) X 3 (block: pre-distracter, distracter, and recovery) X 3 (signal duration: 500, 100, and 25 ms) repeated-measures ANOVA aimed to explore the relationship between dizocilpine and SB-334867 on accuracy in signal trials. The main effect of dizocilpine that was present in the absence of SB-334867 disappeared when SB-334867 was included in the analyses ($F(1,15) = 2.72$, $p = .120$, $\eta^2p = .154$). Therefore, when averaged across all other variables, animals performed similarly when they were given dizocilpine as they did when they were given saline, suggesting that Ox1 receptor antagonism protected against attentional impairments associated with NMDA receptor blockade. A main effect of SB-334867 ($F(2,30) = 5.10$, $p = .012$, $\eta^2p = .254$) was further qualified by a dizocilpine X SB-334867 interaction ($F(2,30) = 6.60$, $p = .004$, $\eta^2p = .305$). To follow up on the significant interaction, one-way ANOVAs with SB-334867 as a factor were conducted for each dizocilpine dose, revealing a main effect of SB-334867 for rats given dizocilpine and not vehicle ($F(2,32) = 7.62$, $p = .002$, $\eta^2p = .323$). Follow-up *t*-tests showed that the hit accuracy of dizocilpine-administered rats was comparably high following infusions of both 3 and 6 µg of SB-334867, but only infusions of 3 µg were able to significantly improve signal

trial performance from that of dizocilpine alone ($t(16) = 3.30$, $p = .005$, $d = .800$). To break down the interaction differently, dizocilpine *t*-tests for each SB-334867 dose showed that, despite a significant drop in performance for dizocilpine-administered rats in the absence of SB-334867 ($t(16) = 2.88$, $p = .011$, $d = .699$), no differences in performance were found between when rats were given dizocilpine and when they were given saline when they were also co-administered either SB-334867 concentration (*Figure 5k*). This suggests that, while the low SB-334867 concentration may have been more effective, both doses had beneficial effects on attention in this model of acute psychosis.

For reaction times in correct signal trials, a main effect of dizocilpine ($F(1,15) = 18.29$, $p = .001$, $\eta^2p = .549$) shows that despite the addition of SB-334867 to the analyses, rats were still slower to respond, on average, when they were given dizocilpine than when they were given saline. An interaction between dizocilpine and sex ($F(1,15) = 16.14$, $p = .001$, $\eta^2p = .518$) and an interaction between dizocilpine, SB-334867, and sex ($F(2,30) = 3.39$, $p = .047$, $\eta^2p = .184$) were also observed. When averaged across sex and divided into paired-samples *t*-tests for each of the three SB-334867 doses, both 3 and 6 µg of SB-334867 sufficing to equalize signal trial correct response latencies, with the only difference in response speeds being between saline- and dizocilpine-administered rats co-administered the ICV vehicle, $t(16) = 4.58$, $p < .001$, $d = 1.110$ (*Figure 5l*). SB-334867 X sex ANOVAs found no effects for rats given saline, but when they were given dizocilpine, there was main effect of SB-334867 on reaction times for only male rats ($F(2,16) = 7.70$, $p = .005$, $\eta^2p = .491$). Follow-

up pairwise comparisons revealed that the only significant difference was a decrease in response times from male rats injected with dizocilpine and infused with 0 µg of SB-334867 to when they were co-administered dizocilpine and the 6 µg dose of SB-334867, $t(8) = 3.73$, $p = .006$, $d = 1.243$. This same interaction was also analyzed with dizocilpine dose *t*-tests within each of the three SB-334867 concentrations for male and female rats, showing that female rats took longer to press the signal lever during signal trials regardless of SB-334867 dose ($p < .015$ for all three possible SB-334867 concentrations; *Figure 5m*); however, while male rats were slower when co-administered dizocilpine and SB-334867 vehicle ($t(8) = 3.11$, $p = .015$, $d = 1.036$), there were no differences in reaction times between saline and dizocilpine when they were also given 3 and 6 µg of SB-334867 (*Figure 5n*). Thus, SB-334867 was beneficial for normalizing response times only for males, as the degree of Ox1 receptor antagonism in this experiment was not ameliorative for females.

For correct rejections, a dizocilpine X SB-334867 X block repeated-measures ANOVA revealed main effects of both dizocilpine ($F(1,15) = 7.71$, $p = .014$, $\eta^2p = .340$) and sex ($F(1,15) = 9.57$, $p = .007$, $\eta^2p = .390$), neither of which was present prior to the inclusion of SB-334867 in the analyses; these main effects revealed that rats performed worse in non-signal trials when they were injected with dizocilpine than when they were injected with saline, and female rats tended to perform worse than males (*Figure 5o*). Correct response latencies in non-signal trials, as determined by a sex X dizocilpine X SB-334867 X block repeated-measures ANOVA, found a main effects of sex ($F(1,15) = 6.93$, $p =$

.019, η^2p = .316) and dizocilpine ($F(1,15) = 37.75$, $p < .001$, η^2p = .716) as well as a sex X dizocilpine interaction ($F(1,15) = 12.96$, $p = .003$, η^2p = .463). Independent samples *t*-tests comparing male and female rats at each dizocilpine dose showed that, while males and females did not differ regarding their response times in non-signal trials when they were administered saline, females took significantly more time to respond than males when they were given dizocilpine ($t(15) = 3.70$, $p = .002$, $d = 1.796$; *Figure 5p*). The effects of dizocilpine on non-signal trial correct response latencies also depended on SB-334867 concentration as determined by a dizocilpine X SB-334867 interaction, $F(2,30) = 3.74$, $p = .036$, η^2p = .199. When averaging across sex, injection condition *t*-tests for each of the three SB-334867 doses revealed that, when rats were given infusions of vehicle, they tended to take longer to press the correct signal when they were administered dizocilpine than when they were administered saline ($t(16) = 4.92$, $p < .001$, $d = 1.194$), but when given infusions of 3 and 6 µg of SB-334867, there were no differences in reaction times between saline- and dizocilpine-injected animals *(Figure 5q*).

A 2 (sex: female and male) X 2 (dizocilpine: 0 and 0.1 mg/kg) X 3 (SB-334867: 0, 3, and 6 µg) X 3 (block: pre-distracter, distracter, and recovery) repeated-measures ANOVA for trial omissions uncovered a main effect of dizocilpine ($F(1,15) = 27.46$, $p < .001$, η^2p = .647); even with SB-334867 in the analyses, rats still omitted more trials when they were given dizocilpine than when they were given saline. There was no main effect of SB-334867, nor was there an interaction between SB-334867 and dizocilpine, indicative of a failure of

Ox1 receptor antagonism to attenuate dizocilpine-induced errors of omission (*Figure 5r*). There was additionally a main effect of sex ($F(1,15) = 8.31$, $p = .011$, $\eta^2p = .357$) and an interaction between dizocilpine and sex ($F(1,15) = 8.92$, $p = .009$, $\eta^2p = .389$). On average, females omitted more than males, and when further divided into sex *t*-tests for saline- and dizocilpine-injected animals, it was revealed that this sex-dependent difference was specific to when rats were given dizocilpine (*Figure 5s*; $t(15) = 3.05$, $p = .008$, $d = 1.483$). Similarly, when juxtaposing omissions between saline- and dizocilpine-administered male and female rats, omissions increased for both males ($t(8) = 2.47$, $p = .038$, $d = .825$) and females ($t(7) = 4.42$, $p = .003$, $d = 1.561$) from when they were given injections of saline to when they were given injections of dizocilpine; however, this effect was much more pronounced for females. This suggests that Ox1 receptor blockade was overall unhelpful in improving on-task behavior regardless of sex, but especially for female rats.

Discussion

The results in experiment two verify many of the findings in the first experiment. For example, as was observed in experiment one, 0.1 mg/kg of dizocilpine was sufficient to impair performance in signal, but not non-signal, trials, indicative of an input selection-specific deficit without affecting the remembrance of the rules of the task. This decline of signal trial performance when rats were administered dizocilpine was specific to trials with longer signal durations; while accuracy at the 500 and 100 ms signals was worsened following

ip dizocilpine, detection of the 25 ms signal remained stable. This is likely because there was not much room for detriment at the 25 ms signal, which was already being correctly identified around 25 percent of the time in the absence of dizocilpine. It can therefore be surmised that dizocilpine impairs the identification of longer signals which are typically easy to detect. It was also detrimental regardless of testing block in both experiments, with widespread impairments observed in both the presence and absence of the flashing distracter, highlighting the capacity for NMDA receptor antagonism to worsen attentional performance regardless of environmental distraction.

Also akin to experiment one, experiment two established dizocilpine as a compound that slows reaction times in trials that were answered correctly. Namely, in both signal and non-signal trials, 0.1 mg/kg of dizocilpine notably increased the amount of time it took the rats to press the lever upon its extension into the testing chamber, with rats taking nearly twice as long to accurately respond in non-signal trials. In a similar vein, dizocilpine had a profound effect on number of omitted trials, resulting in an increase from an average of less than five omissions in the absence of NMDA receptor blockade to rats failing to respond in over one-thirds of the 126 trials when they were injected with dizocilpine. These response speed and omission results go hand-in-hand, as they are relevant to not only attention, but motivation and locomotion as well. Nothing definitive can be said about the effects of dizocilpine on movement or coordination during the SAT, as locomotion was not quantified throughout the testing sessions, but 0.1 mg/kg of dizocilpine does not reliably induce substantial

motoric aberrations in rodents like higher concentrations do (Hönack & Löscher, 1993), making the changes in reaction time and omission rates in this study less likely to stem from movement abnormalities. It may instead relate to motivational processing and incentivized responding, which are highly reliant on the integrity of cortical neurotransmission and a balanced E/I ratio. If sub-anesthetic amounts of dizocilpine disrupts normal cortical activity through its stimulant properties, it may have increased the effort required to maintain adequate performance in the task, resulting in animals that are responding less quickly and less often than when they were instead given saline.

Neither dose of SB-334867 influenced overall accuracy or correct response latencies for any signal duration, or for any testing block, in the SAT. These findings parallel those of experiment one in that neither dual orexin receptor antagonism nor selective blockade of the Ox1 receptor subtype worsened sustained attentional performance - but oppose findings from Boschen et al. (2009) which revealed Ox1 receptor antagonism-linked attentional impairments following ip and intrabaslis infusions of SB-334867 at doses which are known to attenuate cortical cholinergic neurotransmission in rats (Frederick-Duus et al., 2007) as well as impaired performance in an attentional set-shifting task in female mice (Durairaja et al., 2022). In a similar vein, SB-334867 did not increase the number of omitted trials, a result that conflicts with outside evidence suggesting that the Ox1 receptor subtype is critical for motivation and reward-seeking behavior. Of particular relevance are findings from Wiskerke et al. (2020) demonstrating that ip SB-334867 had no effect on response inhibition or

attentional functioning in a rat stop-signal reaction time task but reduced the number of trials completed to attain the sucrose reward; therefore, it would not have been surprising if rats given ICV infusions of SB-334867 continued to respond correctly but omitted more trials in the present experiment, signifying unaffected attentional capacity but reduced motivation to perform for the water reward. The fact that ICV SB-334867 did not deter rats from responding in the majority of trials is not to suggest that the Ox1 receptor is not required for attentional performance and motivation-contingent responding, but rather, it is possible that the doses used in the present experiment were low enough to avoid negatively impacting attentional and incentivized responding in dizocilpine-free and well-trained animals.

The deficits in attention induced by acute ip dizocilpine were largely counteracted with the co-administration of ICV SB-334867 to a greater extent than filorexant in experiment one. For rats given dizocilpine, 3 and 6 µg of SB-334867 similarly improved signal trial performance and quickened overall correct response latencies in the SAT. However, treatment with SB-334867 did not ameliorate dizocilpine-induced increases in trial omissions. As was similarly found with dual orexin receptor antagonism, Ox1 receptor blockade in the absence of dizocilpine did not affect omissions at the chosen doses. This may be because increased orexinergic activity is crucial during times of distraction and attentional duress, which may include when attentional effort increases following dizocilpine exposure. It is also possible that the combination of dizocilpine and a higher dose of SB-334867 might produce unforeseen physiological or

psychological side effects that would result in reduced task engagement. Overall, SB-334867 was restorative in the context of attentional performance and reaction times in an NMDA receptor hypofunction model of psychosis, and while it could not improve increased omissions stemming from NMDA receptor antagonism, rats were still more accurate and quicker when they did respond.

Unlike experiment one, which was comprised of only male rats, there were a number of sex-specific outcomes in the current study. For example, in the total absence of SB-334867 and when averaged across dizocilpine concentration, female rats were slower than males to press the signal lever at the conclusion of signal trials. This disparity in correct response latencies was not accompanied by worsened accuracy in the task, suggesting that, while males were quicker than females to press the lever, both sexes performed equally well in these trials. Bayless et al. (2012) found that in the 5-CSRTT, male rats were more likely to "jump the gun" and respond prematurely, and, in contrast, female rats missed the signal more frequently, highlighting a propensity for males and females to demonstrate reduced inhibitory control and lapses in vigilance, respectively. Though this was not the case in this experiment, it suggests an overall trend in response speeds which is influenced by the sex of the subject. Namely, despite male rats being quicker to respond within the three-second window of lever availability than female rats, it had no bearing on the overall capacity to respond correctly in the SAT.

How dizocilpine influenced the frequency of lever-pressing behavior in the SAT also depended on sex. When given ip saline, omissions between males and

females were virtually identical, and when given ip dizocilpine, omissions increased for both sexes; however, this change was much more profound for females than males, with dizocilpine-exposed female rats omitting over one-third of all trials on average. There is evidence to suggest that female rodents are more sensitive to the neurological and behavioral alterations associated with dizocilpine (Andiné et al., 1999; Hur et al., 1999), with Hönack and Löscher (1993) reporting that, while ip administration of 0.1 mg/kg of dizocilpine failed to evoke locomotor abnormalities for male rats, it produced enduring motoric effects - such as hyperlocomotion, ataxia, and head weaving - for female rats. Thus, though distance traveled was not directly measured in the present experiment, it is possible that 0.1 mg/kg of dizocilpine disproportionately affected locomotor control in females, resulting in more omitted trials when compared to male rats exposed to acute dizocilpine.

Interestingly, in the absence of dizocilpine, there were multiple interactions between sex and SB-334867 concentration. Specifically, though there was not a main effect of dizocilpine on correct rejections, there was an effect when SB-334867 was included in the analyses, with males doing better than females in correctly rejecting the signal. Also, while male rats were faster to respond than females in the all-vehicle condition, this sex-dependent disparity disappeared when they were given the 3 and 6 µg doses of SB-334867. This produced a slight slowing of reaction times for males that, while not sufficient for a main effect of sex or SB-334867 alone, was enough to induce a subtle interaction effect between the two variables. For dizocilpine-administered animals, it

appears that, while both doses of SB-334867 normalized correct response latencies for males, it failed to have the same beneficial effect for females. It is unlikely here that Ox1 receptor antagonism was detrimental for females, as no increase in reaction time was found between when they were given ICV infusions of vehicle and when they were given either dose of SB-334867 in the absence of dizocilpine. Instead, it can be interpreted that the restorative qualities of Ox1 receptor antagonism for correct response latencies for dizocilpine-injected animals may be particular to male, but not female, rats.

Because all analyzed variables in this study were measures of behavior, the neurobiological correlates of the impairments and improvements in attentional performance induced by dizocilpine and SB-334867 can only be hypothesized at this time. In the context of c-Fos staining - which is a future direction of this experiment - there is evidence that systemic dizocilpine and sub-anesthetic doses of other NMDA receptor antagonists increase c-Fos expression in numerous brain areas relevant to SZ and psychosis, including but not limited to entorhinal, motor, and prefrontal cortices as well as midline thalamic nuclei, HPC, and VTA (De Leonibus et al., 2002; Dragunow & Faull, 1990; Panegyres & Hughes, 1997; Väisänen et al., 2004; Zhang et al., 2019), though the dizocilpine doses included in these studies were higher than the one used in the present experiment. On the other hand, despite limited research concerning the effects of Ox1 receptor antagonism on c-Fos expression throughout the brain, it has been shown that SB-334867 dampens stressor- and drug-linked increases in c-Fos expression in hypothalamic and ventral tegmental neurons as well as disrupts

morphine-induced c-Fos in the HPC (Merlo Pich & Melotto, 2014; Riahi et al., 2013; Sharf et al., 2008; Vanderhaven et al., 2015). The DORA suvorexant lessens Fos-like immunoreactivity in the LC, which exclusively expresses the Ox1 receptor, as well as in the TMN, for which the Ox2 receptor is the dominant orexin receptor subtype (Etori et al., 2014), underscoring a putatively anti-norepinephrinergic effect that may underlie some of the Ox1 receptor antagonism-mediated behavioral outcomes of this experiment. Ultimately, empirical evidence supports the notion that systemic administration of sub-sedative concentrations of dizocilpine yields neuronal activation in numerous areas throughout the brain and Ox1 receptor blockade through the use of SB-334867 and DORAs exerts the opposite effect.

Based on the behavioral findings of this experiment as well as evidence from outside studies quantifying changes in c-Fos expression using NMDA receptor antagonists or orexin receptor antagonists, one could speculate about the hypothetical changes in neuronal activation associated with the two drugs used throughout the study. Immunohistochemical stains for genetic markers of cellular activity will focus on neurons of the PFC and neurons of the BF, two attention- and SZ-involved systems with demonstrated sensitivity to both dizocilpine and SB-334867. Because ip dizocilpine is known to promote widespread cortical and subcortical neuronal depolarization that results in c-Fos induction just prior to debraining (Dragunow & Faull, 1990), and because there were clear behavioral and attentional changes induced by dizocilpine, it can be hypothesized that it would increase the number of c-Fos-containing cells in

sections of the PFC and BF in the present study. However, it is also possible that the dose used in this experiment did not suffice to significantly increase the number of c-Fos-expressing cells compared to saline-injected animals, as the lowest reported ip dose to result in a notable increase in Fos-immunoreactive cortical and forebrain neurons is 0.5 mg/kg (Dragunow & Faull, 1990). The SAT is a somewhat complex task for rodents and is sensitive to subtle aberrations in cortical network activity, suggesting that the low dose of 0.1 mg/kg of dizocilpine may have been sufficient to worsen attentional outcomes without inducing significant increases in c-Fos expression. Additionally, female rats have demonstrated dizocilpine concentrations in the CNS and plasma that are up to 25 times more than what are observed in males (Andiné et al., 1999), and locomotor abnormalities induced by 0.1 mg/kg are specific to females (Hönack & Löscher, 1993), suggesting that they may be more neurobiologically sensitive to the effects of NMDA receptor antagonists and could thus have a greater quantity of c-Fos-expressing neurons than males. Forthcoming c-Fos staining efforts will determine if the dose of dizocilpine used throughout this experiment was sufficient to influence this particular indicator of neuronal activation.

Conversely, because SB-334867 did not have much of an effect on any of the measures of attention and motivation in the SAT on its own, one might expect that it might also have negligible effects on genetic markers of cellular activity in excitatory neurons of the PFC and BF. As was discussed in the previous experiment, burgeoning research supports the idea that orexinergic inputs are not required for normal, non-effortful attention, as would be the case for well-

trained and high-performing rats in the SAT; rather, orexins and their constituent receptors serve to support attention in distracting or otherwise demanding scenarios, largely by promoting cholinergic efflux in vigilance-reliant cortical areas. Thus, it does not appear likely that SB-334867 would have a marked influence on normal cortical neurotransmission on its own. Based on the capacity for orexin receptor blockade to quell drug-induced activation of excitatory neurotransmitter systems throughout the brain, it might be postulated that, if 0.1 mg/kg of dizocilpine increases Fos-immunoreactivity in the PFC and BF, co-administration of dizocilpine and SB-334867 might result in reduced cortical and forebrain c-Fos induction when compared to dizocilpine by itself. As was mentioned previously, cholinergic and parvalbuminergic neurons may be more potently influenced by Ox2 receptor-mediated inputs (Eggermann et al., 2001); if this is the case, Ox1 receptor antagonism with SB-334867 may have less of a putative c-Fos-dampening effect than if an Ox2 receptor-specific antagonist, such as TCS-OX2-29, were used in its place.

Conclusion

Taken together, in the second experiment, the NMDA receptor antagonist dizocilpine worsened accuracy in signal trials, but not non-signal trials, for rats engaged in the SAT, and these deficits were present in both the presence and absence of a flashing distracter. It also slowed response times and increased omission rates, highlighting a potentially demotivating component of dizocilpine. On its own, the Ox1 receptor antagonist SB-334867 did not affect overall

performance in the task; accuracy in signal and non-signal trials remained intact, and despite the Ox1 receptor being involved in incentive-linked behaviors, it did not increase omissions at the doses used in this experiment. SB-334867 was also sufficient to improve changes in signal trial performance and reaction times induced by dizocilpine, perhaps by reducing excessive cortical stimulation. Ox1 receptor antagonism did not reduce the number of omitted trials, revealing a key difference in the capacity of filorexant and SB-334867 to restore on-task behavior which is disrupted by NMDA receptor inhibition. Additionally, males given dizocilpine, but *not* females given dizocilpine, exhibited improved signal trial performance, suggesting that the beneficial effects of SB-334867 for rats administered dizocilpine depended on sex.

CHAPTER 6. Experiment three: Dual orexin receptor antagonism does not improve dizocilpine-induced deficits in cortical and hippocampal gamma synchronization

Introduction

Thus far, both dual orexin receptor and Ox1 receptor-specific blockade have demonstrated pro-attentional and potentially pro-motivational qualities for rats given sub-anesthetic doses of a psychotomimetic NMDA receptor antagonist. Each of the dependent variables in these experiments indicated behavioral differences produced by various combinations of the drugs of interest; however, there were no measures of neurological activity during the period that these compounds were psychoactive. As such, the discussions about the brain circuits that are potentially involved in these behavioral outcomes have been based on existing literature detailing how these drugs influence attention-relevant regions of the CNS. To address this limitation, the goal of the present and final experiment in this dissertation was to use electrophysiological techniques to determine the capacity for neurons to fire at frequencies which are known to coincide with focused attention. In particular, because neuronal oscillatory activity in the gamma frequency is closely associated with attentional effort, this experiment aimed to determine how various combinations of dizocilpine and filorexant influence neuronal entrainment in the gamma band.

Prior research has revealed abnormal gamma oscillatory activity for individuals with SZ. As was previously discussed, higher baseline gamma power

has been observed in the cortices of SZ patients when compared to compared to healthy controls (Spencer, 2012; White & Siegel, 2016). Normal attention depends on flexible levels of cortical neuronal activation, with sub-40 Hz oscillations being common during sleep and relaxed wakefulness and the generation of 40 Hz GBOs frequently coinciding with alertness, vigilance, and cognitive effort (Jing et al., 2016; Li et al., 2017; Mably & Colgin, 2018); thus, elevations in baseline gamma activity that are not task-dependent underscore E/I imbalances that contribute to perceptual disturbances and dysfunctional information processing in psychosis (McNally & McCarley, 2016). In support of this, increases in resting state cortical gamma activity coincide with decreases in evoked GBOs in both humans with SZ and animal models of psychosis, with ASSR being a commonly-used indicator of gamma entrainment in this context (Brenner et al., 2009; McNally et al., 2021). The ASSR is an electrophysiological measure of the evoked potential of neurons to generate narrow-band oscillations – which occur independently of broadband oscillatory activity – in relative synchrony with a periodically-repeating auditory stimulus, peaking at approximately 40 Hz in humans (Picton et al., 2003; Thuné et al., 2016). Deficient neuronal entrainment to a 40 Hz auditory stimulus has been noted in SZ patients as well as following NMDA receptor antagonism (O'Donnell et al., 2013; Thuné et al., 2016; Tsuchimoto et al., 2011; Wang et al., 2020), establishing reduced ASSR as a translational biomarker for cortical circuit dysfunction in SZ (Sivarao et al., 2016). Therefore, the ASSR in the context of

NMDA receptor antagonism and orexin receptor antagonism, both separately and concurrently, was of interest in the present experiment.

The local field potential (LFP) in the PFC and HPC was recorded in this pilot study to determine the ASSR during auditory steady-state stimulation. LFP is the measure of the electrical output of neurons as determined by the temporal overlap in multiple local electrical signals in the extracellular space (Kajikawa & Schroeder, 2011). Unlike EEG, which is popular in human electrophysiology research because it is recorded via a non-invasive macroelectrode placed on the scalp, LFP microelectrodes are intracerebrally implanted and terminate within the brain tissue of interest, rendering them less susceptible to interference from brain areas closer to the surface. LFP signals can be analyzed and interpreted in various ways – including phase-locking factor (PLF), which compares phase coupling between two LFP signals over time, and power in the gamma band, which measures the degree of synchronized firing of local cell assemblies – to determine the efficacy of 40 Hz neuronal entrainment. Both evoked PLF and gamma power are common measures of gamma synchrony and are found to be deficient in subjects with SZ (Spencer, 2012; Roach & Mathalon, 2008; Rutter et al., 2009; Winterer et al., 2004), and, as such, were the dependent variables of interest in the current study.

An additional difference between this study and the two previous studies detailed in this dissertation is the use of mice rather than rats. Rats are a popular study species for cognitively-demanding behavioral experiments and were initially used to validate the rodent version of the SAT (McGaughy & Sarter,

1995). Mice, which are the most commonly-studied species in biomedical research (Keifer & Summers, 2016), have a well-established history of use in both basic and applied neuroscience research. Transgenic mice in particular account for over two-thirds of all mice used in neuroscience research and are especially advantageous for more precise and targeted neuromodulatory techniques, including optogenetics and chemogenetics. While time constraints precluded the use of optogenetics, the PV-positive GABAergic neurons of the transgenic mice included in this experiment expressed the tyrosine recombinase enzyme, cre recombinase, and were administered intrabasalis infusions of adeno-associated viral vectors containing the light-sensitive protein channelrhodopsin-2 (ChR2) at the time of surgery. Upon exposure to ChR2, which results in the expression of light-sensitive ion channels on host neurons, transduced PV cells can then be rapidly depolarized following exposure to 473 nm blue light. In the future, optogenetic stimulation of corticopetal BF-PV neurons can be explored as a novel psychotomimetic manipulation (see McNally et al., 2021).

Ultimately, while this experiment did not directly quantify attentional performance like experiments one and two, determining the capability of neurons in the PFC and HPC to synchronize to frequencies in the gamma range is relevant to the underlying neurological mechanisms which support and promote attentional effort. Unimpaired entrainment to a 40 Hz tone, such as during auditory steady-state stimulation, demonstrates that those neurons are available and able to respond to incoming information pertinent to important stimuli in the

immediate environment. In cases where inhibitory networks are deficient and the cortical E/I ratio is imbalanced, such as with psychosis and psychotomimesis, it would be expected that overstimulated neurons would be rendered less capable of reliably synchronizing with the tone, indicating suboptimal flow of information-bearing signals in cognition-associated areas. Dual orexin receptor and Ox1 receptor antagonism were both shown to improve attentional impairments stemming from acute NMDA receptor antagonism, but it is still not understood through what mechanisms orexin receptor inhibition exerted its pro-cognitive qualities. By measuring neuronal entrainment to a 40 Hz tone, it could be determined if orexinergic suppression improved dizocilpine-linked attentional deficits by restoring the capacity for prefrontal cortical and hippocampal neurons to fire at frequencies which coincide with vigilance and attentional effort.

Material and methods

Subjects

5 adult (3 male, 2 female) 5XFAD/PV-Cre (B6.129P2-*Pvalb*$^{tm1(cre)Arbr}$/J) mice were originally acquired from Jackson Laboratory (Bar Harbor, Maine) and were bred in house. They were housed with a 12-hour light/dark cycle (lights on 7:00 - 19:00) and were allowed *ad libitum* access to mouse chow and water throughout the duration of the experiment. Mice were group housed until they underwent surgery, after which they were single housed. All procedures were performed in accordance with the National Institutes of Health guidelines and in

compliance with the animal protocol approved by the VA Boston Healthcare System Institutional Animal Care and Use Committee.

Stereotaxic surgery

Mice were anesthetized with 5 percent isoflurane, placed in a stereotaxic frame (Kopf Instruments), and maintained with 1 to 2 percent isoflurane throughout the duration of the surgery. Though optogenetic techniques were ultimately not used in the present experiment, the BF (AP + 0.4 mm, ML ± 1.6 mm, DV - 5.4 mm) was infused with a total of 1 µl (500 nl per hemisphere at a rate of 50 nl per minute) of double-floxed adeno-associated viral vectors (AAV, serotype 5) containing a fusion protein of ChR2 and enhanced yellow fluorescent protein (EYFP; AAV5-DIO-CHR2-EYFP, University of North Carolina Vector Core, Chapel Hill, NC). Intrabasalis injections of the AAV were administered via a Hamilton syringe connected to an injector pump (model 250; KD Scientific). The transduction of BF-PV neurons with AAV ChR2 requires them to express cre-recombinase (Sohal et al., 2009), making this technique very highly selective for these neurons and, therefore, an attractive approach that allows for the targeted stimulation of PV+ GABAergic neurons at the exclusion of neighboring BF nuclei or other PV-expressing neurons in the brain.

Once the virus was administered in both hemispheres, 200 µm fiber optic cannulae (Doric Lenses; Quebec City, Quebec, CA) were bilaterally implanted 0.2 mm above the viral injection site (AP + 0.4 mm, ML ± 1.6 mm, DV - 5.2 mm),

stainless steel LFP electrodes were unilaterally implanted in the right mPFC (AP + 1.8 mm, ML ± 0.45 mm, DV - 2.0 mm) and right dorsal HPC (dHPC; AP - 2.0 mm, ML ± 1.8 mm, DV - 1.2 mm; *Figure 6*a). The mPFC and dHPC were chosen as electrophysiological recording sites because they are both relevant to attention, with prefrontal cortical neurons being primarily responsible for information processing and hippocampal neurons contributing to memory-guided attention (Goldfarb et al., 2016; Hutchinson & Turk-Browne, 2012). EEG/EMG head mounts (Pinnacle Technology Inc., part # 8402-SS, Kansas, USA) were then affixed to the skull, with EMG leads terminating in the nuchal muscle, and all equipment was secured to the skull with dental cement. Mice were allowed at least one week of recovery before drug administration and electrophysiological recording sessions began.

Drug preparation and administration

Dizocilpine maleate (Tocris Bioscience) was dissolved in sterile saline to create concentrations of 0.3, 0.5, and 1.0 mg/ml. Quantities of 1, 3, and 6 mg/ml of filorexant (MedChemExpress) were suspended in 1 ml saline, 125 µl DMSO, and 200 mg sulfobutyl ether-beta-cyclodextrin. All prepared drugs were stored at -20 °C and used within one week. On data acquisition days, mice were intraperitoneally injected with a randomized order of 0, 10, 30, or 60 mg/kg of filorexant 30 minutes before testing, and they were then injected with either 0, 0.3, 0.5, and 1.0 mg/kg of dizocilpine 20 minutes prior to testing (*Figure 6a*). The route of administration for filorexant administration was changed from ICV

infusions to ip injections because of prior issues with cerebrospinal fluid leakage from the lateral ventricles following ventricular cannulation surgery in mice. Like experiments one and two, this experiment employed a within-groups design wherein each animal received each possible combination of dizocilpine and filorexant.

Acoustic stimulation and in vivo electrophysiology

Twenty minutes after the second injection, the head stages of the mice were connected via a flexible tether to the EEG recording equipment. Mice remained in their home cages, which were placed in a sound attenuating chamber which contained a speaker, for the duration of the session. To measure ASSR, LFP signals were amplified with a 3 Channel-EEG System (#8200-K1-SL, Pinnacle Technologies) and recorded at a 2000 Hz sampling rate with a secondary digitizer (Digidata 1440, Molecular Devices) using WinWCP electrophysiology software. WinWCP was also used to generate the time-to-live signals that controlled the auditory stimuli, consisting of 10 ms trains of 90 dB white noise clicks. Each recording session was composed of six second trials which were repeated 100 times for a total recording time of 10 minutes. In each of these trials, a two-second period of auditory stimulation was preceded by two seconds of silence - which served as the baseline condition with which auditory stimulation was juxtaposed - and followed by a two-second silent post-stimulation recovery period.

Histological procedures

Upon completion of the experiment, mice were anesthetized with 50 mg/ml of sodium pentobarbital and underwent a transcardial perfusion with a 10 percent formalin solution. The brains were stored in this 10 percent formalin overnight, after which they were transferred to a 30 percent sucrose solution for at least 24 hours and sectioned into 40 µm-thick coronal slices. LFP electrode and fiber optic cannula placement were verified.

Data analysis

Analyses of prefrontal cortical and hippocampal LFP data were conducted offline using custom scripts for MATLAB R2021b (Mathworks, Natick, MA). PLF was quantified as the absolute value of the mean phase difference between the 40 Hz tone and evoked neuronal oscillations (see Aydore et al., 2013, for a review on PLF). Complex Morlet wavelet analyses were used to derive phase values for each individual trial, and circular variance was then computed across trials to generate PLF between 35 and 45 Hz during thepresentation of the auditory stimulus. This calculation results in a value between 0 and 1, with 0 suggesting no phase synchrony and 1 implying identical phase synchrony with the 40 Hz signal. Elicited gamma was calculated by computing average power in the gamma band between 35 and 45 Hz during the two-second period of steady-state stimulation and dividing it by gamma band power during the two-second pre-stimulation period. This yields a number that represents the proportion above

baseline power that occurred during the window of 40 Hz stimulation, with values close to 0 signifying little to no change in GBOs from baseline to stimulation, and values close to 1 indicating a near-doubling of gamma power from baseline to stimulation.

Repeated-measures one-way ANOVAs were used to compare PLF and evoked gamma values produced by dizocilpine and filorexant both separately and together, and pairwise comparison procedures were conducted using the Because the sample size used in this pilot study was small, Dunnett's test was selected over the more conservative Bonferroni pairwise comparison procedure – which was used in the first two experiments – for the purpose of contrasting each possible combination of these two compounds with the vehicle control rather than with each other. Data were analyzed using SPSS version 24.0 and GraphPad Prism version 9.3.1 and are graphically displayed as the mean ± standard error. Statistical significance was determined using $\alpha = .05$.

Results

Effects of dizocilpine on PLF and elicited gamma oscillations

Dizocilpine dose (0, 0.3, 0.5, and 1.0 mg/kg) repeated-measures one-way ANOVAs for both PLF and elicited gamma in each brain region were used to examine the impact of NMDA receptor antagonism on measures of neuronal synchronization during the auditory steady-state stimulation. For PLF, there were

significant effects of dizocilpine on neuronal phase coherence in both the mPFC ($F(3,12) = 10.39$, $p = .001$, $\eta^2p = .722$) and dHPC ($F(3,12) = 14.21$, $p < .001$, $\eta^2p = .780$). In the PFC, the only dose which differed from vehicle injections in its effects on PLF was the 0.5 mg/kg dose, $t(4) = 5.54$, $p = 0.012$, $d = 2.477$. In the HPC, however, all three doses of dizocilpine worsened PLF (all $p < .05$ compared to vehicle), demonstrating a more profound effect of dizocilpine on the activity of hippocampal neurons than those of the cortex at the doses included in the experiment.

Regarding elicited gamma, there was a significant effect in the mPFC ($F(3,12) = 13.32$, $p < .001$, $\eta^2p = .769$), with follow-up *t*-tests showing differences between vehicle and the 0.3 mg/kg dose ($t(4) = 4.31$, $p = .028$, $d = 1.926$) as well as between vehicle and the 0.5 mg/kg dose ($t(4) = 3.78$, $p = .043$, $d = 1.692$), but the same result was not found for the 1.0 mg/kg concentration, though it was very close to achieving statistical significance ($t(4) = 3.61$, $p = .05$, $d = 1.615$). Dizocilpine also had a similar effect on gamma power in the dHPC ($F(3,12) = 25.47$, $p = .003$, $\eta^2p = .680$), with follow-up *t*-tests uncovering suppressed gamma at all three concentrations of dizocilpine (all $p < .03$ compared to vehicle) when juxtaposed with saline injections. These findings suggest that hippocampal neuron discharge was disproportionately affected by NMDA receptor blockade when compared to what occurred in the PFC following exposure to the same dizocilpine doses (*Figure 6b*).

Effects of filorexant on PLF and elicited gamma oscillations

Filorexant dose (0, 10, 30, or 60 mg/kg) repeated-measures one-way ANOVAs exploring effects on PLF and elicited GBOs for the mPFC and the dHPC revealed that none of the concentrations of filorexant had any effect on PLF or elicited GBOs in the mPFC during auditory steady-state stimulation. For the dHPC, while there was no effect of filorexant on PLF, there was a significant effect of filorexant dose for hippocampal elicited gamma in the ASSR, $F(3,12) = 6.83$, $p = .006$, $\eta^2p = .631$. These differences were between vehicle and 10 mg/kg ($t(4) = 4.99$, $p = .017$, $d = 2.230$) as well as vehicle and 30 mg/kg ($t(4) = 4.97$, $p = .017$, $d = 2.221$), but *not* between saline and 60 mg/kg, highlighting a HPC-specific effect of indiscriminate orexin receptor antagonism (*Figure 6c*).

Effects of filorexant on dizocilpine-induced deficits of PLF and elicited gamma oscillations

Thus far, it has been determined that dizocilpine impairs measures of neuronal entrainment to the steady-state stimulation, with the 0.5 mg/kg concentration being the only concentration to worsen both PLF and elicited GBOs in the mPFC and dHPC. As such, this impairing dose was paired with the various quantities of filorexant for the purpose of examining the capacity for dual orexinergic suppression to reverse dizocilpine-induced abnormalities in gamma synchrony. Repeated-measures one-way ANOVAs comparing four key combinations of the drugs of interest (0 mg/kg dizocilpine + 0 mg/kg filorexant,

0.5 mg/kg dizocilpine + 10 mg/kg filorexant, 0.5 mg/kg dizocilpine + 30 mg/kg filorexant, and 0.5 mg/kg dizocilpine + 60 mg/kg filorexant) to see if orexin receptor antagonism can equalize phase locking for dizocilpine co-administered animals when compared to the all-vehicle condition. These analyses uncovered a main effect in the prefrontal cortical region ($F(3,12) = 18.38$, $p < .001$, $\eta^2p = .821$), and when comparing each of the levels to the all-vehicle condition, every possible combination was significant (all $p < .02$ compared to vehicle), indicating that none of the filorexant doses sufficed to normalize PLF for prefrontal cortical neurons in response to the 40 Hz tone. To see if perhaps filorexant had an ameliorative effect when compared to the 0.5 mg/kg of dizocilpine by itself rather than the all-vehicle condition, a repeated-measures one-way ANOVA comparing 0.5 mg/kg of dizocilpine alone with this same concentration combined with 0, 10, 30, and 60 mg/kg of filorexant did not uncover an interaction, suggesting that filorexant was largely unable to improve neuronal phase locking in dizocilpine-administered animals when compared to vehicle or when compared to dizocilpine alone.

In a similar vein, repeated-measures one-way ANOVAs for PLF in the dHPC examining the all-vehicle condition juxtaposed with the 0.5 mg/kg dizocilpine concentration paired with 10, 30, and 60 mg/kg of filorexant uncovered a significant effect between them ($F(3,12) = 13.06$, $p < .001$, $\eta^2p = .766$), once again revealing that phase locking for every dizocilpine-filorexant combination included in this analysis was markedly reduced when compared to that of the all-vehicle condition (all $p < .05$ compared to vehicle). Also similarly to

mPFC PLF, when comparing dizocilpine alone with dizocilpine paired with a variety of filorexant concentrations, there was no difference to be found, indicating that filorexant was incapable of improving NMDA receptor antagonism-induced deficits in GBO activity.

Many of these findings were recapitulated in analyses examining evoked power in the gamma band in the PFC and HPC. For prefrontal cortical elicited gamma, a repeated-measures one-way ANOVA (all-vehicle, 0.5 mg/kg dizocilpine + 10 mg/kg filorexant, 0.5 mg/kg dizocilpine + 30 mg/kg filorexant, and 0.5 mg/kg dizocilpine + 60 mg/kg filorexant) revealed a main effect ($F(3,12) = 8.52$, $p = .003$, $\eta^2p = .680$) which, when analyzed with paired-samples *t*-tests corrected with Dunnett's comparison procedure, revealed that each condition was significant when compared with the control condition (all $p < .05$ compared to vehicle), highlighting a failure of dual orexin receptor antagonism in adequately treating dizocilpine-induced suppression of evoked gamma power in the cortex. Again, when replacing the vehicle condition with the 0.5 mg/kg dose of dizocilpine alone, the significant effect disappeared, meaning that filorexant did not elevate elicited gamma compared with dizocilpine alone. Lastly, in the dHPC, all of the aforementioned results were paralleled; a significant outcome of a repeated-measures one-way ANOVA which compared the vehicle condition with 0.5 mg/kg of dizocilpine paired with 10, 30, and 60 mg/kg of filorexant ($F(3,12) = 13.06$, $p < .001$, $\eta^2p = .777$), which, when further analyzed with *t*-tests, showed significant differences between all possible combinations when juxtaposed with vehicle (all $p < .05$ compared to vehicle). Finally, when comparing the 0.5 mg/kg

concentration of dizocilpine to each of the dizocilpine and filorexant combinations with a repeated-measures one-way ANOVA, there was no effect found, solidifying the lack of benefit of orexin receptor antagonism for the treatment of ASSR-relevant deficits in this animal model of SZ (*Figure 6d*).

Discussion

In the present and final experiment of the dissertation, NMDA receptor blockade once again demonstrated detrimental effects on neurobiological mechanisms pertinent to attentional processing. In particular, 0.5 mg/kg of dizocilpine was the singular dose that was able to impair both measures of gamma synchrony in the brain areas of interest. This dose has been shown to have the same effect in hippocampal neurons and is accompanied by various behavioral parallels to SZ in humans, including deficient PPI and hyperlocomotion (Ma & Leong, 2007); however, while 0.5 mg/kg also sufficed to weaken ASSR in this study, the literature on the influence of this specific dose on gamma activity in the PFC is inconsistent (McNally et al., 2013; Shokry et al., 2019). It is generally understood that systemic administration of sub-anesthetic quantities of NMDA receptor antagonists induces a generalized disinhibition of Glu-producing neurons, resulting in a state of brain-wide excitation; however, because ascending BF PV+ neurons are key regulators of frontocortical high-frequency oscillatory activity in the gamma band (Kim et al., 2015; Hwang et al., 2019; McNally et al., 2020), it is hypothesized that these neurons played a role in

the presented findings. Otherwise, the antagonism of NMDA receptors expressed on cortical GABAergic interneurons as well as those expressed in the HPC have also been shown to disrupt normal oscillatory activity in the cortex (Hunt & Kasicki, 2013; Roopun et al., 2008), with a likely explanation being that dizocilpine had significant effects in numerous locations throughout the brain that culminated in ASSR impairments.

One possible reason for the suppression of narrowband gamma signaling in the ASSR following exposure to dizocilpine is that acute administration of non-sedative doses of NMDA receptor antagonists increases broadband gamma activity during auditory stimulation. As has been previously discussed, widespread abnormalities of stimulatory neurotransmission in the CNS produce E/I imbalances that muddle the signal-to-noise ratio in the frontal cortex and a resultant impairment of attention-pertinent processing (Kehrer, 2008) For individuals with and without SZ as well as for animals given psychomimetic compounds, increased prefrontal cortical noise negatively correlates with cognitive performance, underscoring an inadequacy of information processing-relevant pyramidal neurons to synchronize during cognitive effort (Winterer et al., 2004). Pertinent to the findings of the current study, both humans with SZ and NMDA receptor antagonist-administered animals demonstrate heightened resting-state GBOs in tandem with dampened ASSR, highlighting a putatively causal relationship between elevated high-frequency, non-stimulus-evoked oscillations at baseline and stimulus-evoked oscillations (Hirano et al., 2015). Thus, by increasing prefrontal and hippocampal noise, dizocilpine exposure

yields a consequential increase in broadband gamma activity that would be expected to interfere with frontal lobe-reliant cognitive functioning.

Unlike the PFC, for which only 0.5 mg/kg of dizocilpine was effective in impairing phase locking to the auditory stimulus and only the 0.3 and 0.5 mg/kg doses able to suppress power in the gamma band, all three quantities of dizocilpine significantly reduced both PLF and elicited gamma in the HPC. Like the cortex and BF, the HPC contains fast-spiking PV+ GABAergic interneurons which are acutely sensitive to low doses of NMDA receptor antagonists, and suppressing their inhibition of glutamatergic activity through NMDA receptor blockade results in increased activity of local and projecting glutamatergic neurons both *in vivo* and *ex vivo* (Lemercier et al., 2017). In support of this, ketamine and dizocilpine both increase power in the gamma band while simultaneously reducing sleep- and relaxation-associated theta oscillations in CA1 and dentate gyrus (Kittelberger et al., 2012). The relationship between cortical attention and hippocampal memory systems is most commonly framed as attention dictating what is learned and remembered; however, perhaps equally as important is memory-guided attention, with learned experiences dictating what is given our attention. Therefore, attention-adjacent cognitive processes which highly depend on balanced hippocampal neurotransmission - such as reinforcement learning and context memory (Goldfarb et al., 2016) - might be more susceptible to deterioration following NMDA receptor antagonism than those which are predominantly reliant on prefrontal cortical integrity.

On its own, filorexant had no effect on electrophysiological indicators of prefrontal cortical gamma entrainment. This outcome is in agreement with the previous two experiments in that orexin receptor antagonism does not necessarily impede upon normal prefrontal cortical functioning despite drugs of this class being prescribed to suppress wakefulness for individuals with insomnia. While filorexant at these doses did not affect elicited gamma in the HPC, it suppressed evoked gamma power, suggesting that although dual orexin receptor antagonism dampened overall gamma activity in this region, the phase coherence of neurons that were responsive to the 40 Hz stimulus remained unimpinged. LH orexinergic projections abundantly synapse with neurons of the HPC, particularly those of CA1-3 regions as well as entorhinal and subicular areas, and both orexin receptors are interspersed throughout hippocampal tissue, with the Ox1 receptor subtype being most prolific in the CA1 region and the Ox2 receptor more common in the CA3 area (Salmani et al., 2022; Nambu et al., 1999). It is therefore not surprising that the HPC would be sensitive to the blockade of orexin receptors and that deficits in gamma synchronization would occur as a result, with these findings having potential clinical implications for the use of DORAs in memory and cognition.

Unlike experiments one and two, which established orexin receptor antagonism as a putative pharmacotherapeutic avenue to treat the attentional deficits induced by hypofunctional NMDA receptors, this experiment failed to uncover a similar benefit when contextualizing deficient gamma activity as an impairment of attention-critical neural synchronization. It was originally

hypothesized that the indiscriminate inhibition of orexinergic neurotransmission through the blockade of both Ox1 and Ox2 receptor subtypes would be similarly advantageous for dizocilpine-induced impairments in ASSR. Additionally, because optogenetic inhibition of BF-PV neurons party attenuates ketamine-induced increases in cortical broadband power (McNally et al., 2020), it was speculated that, perhaps primarily by way of Ox2 receptor blockade, filorexant would have a similar suppressant effect on corticopetal BF-PV activity by assuaging elevated resting-state high-frequency oscillatory activity and enhancing the neuronal capacity to synchronize to gamma-inducing stimuli. However, this was not the case, as none of the three selected dosages of filorexant improved either measure of ASSR in the mPFC nor in the dHPC.

Though the underlying reasons for this inability of filorexant to reverse or even partially address dizocilpine-linked ASSR deficits is currently unknown, it may be because the 0.5 mg/kg concentration of dizocilpine induces profound E/I imbalances throughout the entire brain that could not be sufficiently addressed through orexin receptor antagonism. Despite being the smallest amount of dizocilpine that was effectively detrimental across all pertinent measures of the 40 Hz ASSR in the PFC and HPC, this concentration is five times higher than what was used in experiments one and two; in fact, 0.5 mg/kg of dizocilpine would actively prevent performance for rats in the SAT. As such, the non-success of filorexant to adequately ameliorate aberrant gamma synchrony stemming from systemic NMDA receptor inhibition could be a result of a significant increase in dizocilpine dose without a similarly proportional increase in

filorexant. Assuming 0.5 mg/kg of dizocilpine exists at the lower end of concentrations that disrupt ASSR despite its highly intoxicating effects, it may be worthwhile to increase the range of tested filorexant doses to include quantities that would otherwise be highly sedating for stimulant-free animals, with research on similar DORAs such as almorexant reporting sleep-promoting effects at upwards of 300 mg/kg (Black et al., 2013). Put another way, doses of filorexant or similar orexin antagonists which would ordinarily facilitate sleep in intact animals may be protective when co-administered with doses of dizocilpine which impair the capacity for neurons to fire at frequencies conducive for information processing and vigilant attention.

Due to time constraints, the presented data are from a small number of mice as part of a pilot study, with intentions to use these findings to guide future research directions. In addition to measuring spontaneous gamma activity and using higher doses of filorexant, increasing the sample size is an obvious next step that will allow for more precise estimates of treatment effects and, as such, more confident generalizations about the capacity - or lack thereof - of orexinergic suppression to reverse dizocilpine-induced deficits of PLF and elicited gamma power. Ensuing research would also benefit from investigating sex-specific effects of these drugs on cortical and hippocampal GBO generation. Sensitivity to NMDA receptor antagonists appears to vary depending on estradiol fluctuations in female rodents; in particular, while ketamine-induced cortical GBOs were similar between the sexes when females were in the luteal phase, Picard et al. (2019) found that this result did not replicate for female animals

during the follicular phase. This estrous cycle-dependent disparity in cortical gamma activity was accompanied by a notable loss of grin2A mRNA on PV+ neurons, suggestive of a temporary reduction of NMDA receptors on these neurons that precludes the typical cortical response to drugs of this class. When considered alongside the sex-dependent attentional benefits of SB-334867 following dizocilpine exposure in experiment two, it can be surmised that the efficacy of orexin receptor antagonism for the treatment of attention-relevant neurotransmission aberrations in this particular model of SZ relies, in part, on the sex of the subject.

Conclusion

Well-timed gamma oscillations in the brain are critical for the fast and efficient transfer of feature-specific information to areas responsible for a variety of conscious states, with cortical activity in the gamma band coinciding with enhanced wakefulness, alertness, and attentiveness to the happenings of the external world. The 40 Hz ASSR, which is a bioelectric response to rapid auditory stimulus that reveals the capacity of target neurons to fire at high frequencies which coincide with attentional and informational processing, is robustly impaired in patients with SZ. In the present study, the dissociable and combined effects of dizocilpine and filorexant on the entrainment of medial prefrontal and dorsal hippocampal neurons to 40 Hz rhythmic auditory inputs were explored. It was found that dizocilpine-mediated NMDA receptor blockade was detrimental for both phase locking and GBOs evoked by the tone, and dual orexin receptor

antagonism through the administration of filorexant was not able to improve these indicators of disrupted E/I balance in brain regions relevant to attentional processing. It was also found that, on its own, filorexant suppressed power in the gamma band only in the dHPC, unveiling the possibility that hippocampal synchrony may be more strongly impacted by orexin receptor antagonism than in the cortex.

Overall, these data revealing no influence of filorexant on the deleterious effects of dizocilpine in this paradigm are disparate from what was found in the two previous experiments - especially experiment one - and some potential explanations have been posited. Namely, the lowest dose of dizocilpine that was able to have any effect on the measures of interest may have been too high for orexin receptor antagonism to adequately address; or, conversely, the doses of filorexant included in this study could have been too low to sufficiently abate dizocilpine-induced ASSR impairments. If these findings are reflective of how orexin receptor antagonism would interact with NMDA receptor hypofunction-induced deterioration of ASSR in the human disorder, it can be suggested that, while the inhibition of orexinergic inputs throughout the brain could perhaps be beneficial to treat inattention for those with SZ through indirect mechanisms, it is unable to remediate aberrant excitatory activity of brain circuits directly involved in attentional processing. Multiple future directions, such as exploring higher doses of filorexant and considering the implications of biological sex in the effects of these drugs, can improve upon this pilot experiment in order to make more

accurate generalizations about the potential for orexinergic inhibition to normalize oscillatory abnormalities stemming from NMDA receptor hypoactivity in SZ.

CHAPTER SEVEN. Overarching discussion and future directions

Emergent research has begun to elucidate various neurochemical and behavioral properties of orexin receptor antagonists that are recognized as antipsychotic in nature. Because the notion of orexinergic suppression as an alternate therapeutic route to treat aberrant excitatory neurotransmission in SZ is a novel but steadily-growing idea, there is an understandable lack of research regarding the use of such compounds to address the attentional impairment in SZ. Disrupted attention is a pervasive cognitive symptom of SZ which remains relatively resistant to commonly-prescribed medications, underscoring a clinical impetus to investigate alternative chemicals with neurobiological mechanisms of action that differ from standard pharmacological treatments. The experiments detailed herein explored the potential of orexin receptor blockade to improve attentional impairments relevant to SZ in both a behavioral paradigm of sustained attention and an electrophysiological test of evoked gamma synchronization in areas associated with attention. Overall, ICV administration of the DORA filorexant and the Ox1 receptor-binding antagonist SB-334867 were both able to attenuate deterioration of accuracy, correct response latencies, and in-task responding associated with a commonly-employed rodent model of psychosis in a visual SAT. However, indiscriminate reduction in orexinergic activity through the use of filorexant did *not* normalize deficient evoked GBOs caused by the same psychogenic compound, suggesting a capacity for these compounds to reverse the anomalous behavioral, but not necessarily electrophysiological,

measures of attentional processing. In the remainder of this document, the reconciliation of these opposing findings as well as ongoing efforts to continue the exploration of orexin receptor antagonists as potential pharmacotherapeutics for the treatment of attentional dysfunction in SZ will be discussed.

Dichotomous effects of orexinergic blockade in an NMDA receptor hypofunction model of SZ

When considered together, these findings can be interpreted in a number of ways. Perhaps the most parsimonious evaluation is that, during active attentional processing, suppressing orexinergic inputs to overstimulated cortical neurons improves E/I imbalances and enhances attentional processes reliant on balanced excitatory neurotransmission. Antagonism of orexin receptors has been shown to exert a “calming” effect on both the brain and behavior. As an example, for psychiatric conditions such as anxiety disorders or insomnia, which cause or are caused by excessive arousal, orexin receptor antagonism has been shown to be particularly effective in subduing output from arousal and fear centers of the brain (Merlo Pich & Melotto, 2014; Sears et al., 2013; Winsky-Sommerer et al., 2005). In this context, the antagonism of the Ox1 receptor subtype is believed to play a more important role in treating anxiety-like behaviors, and Ox2 receptor blockade helps to lessen the activity of wake-active arousal systems and promote sleep. As both psychosis and sub-anesthetic concentrations of dizocilpine induce states of hyperarousal, and established and emergent research directly implicates orexin receptor antagonism in the reduction of

hyperdopaminergia in the VTA, it makes sense that widespread reduction in orexinergic neuromodulation would at least partly mitigate the psychological disturbances of SZ arising from imbalances in excitatory neurotransmission and, relevant to these experiments, negate some of the behavioral abnormalities caused by dizocilpine. Immunohistochemical staining of sections containing the PFC and BF of the brains of rats in experiment two can shed light onto this speculation, as we might expect that, if Ox1 receptor antagonism suppresses excessive excitatory neurotransmission, this would be evidenced by a reduction in cholinergic, parvalbuminergic, and pyramidal neurons that express c-Fos in these key regions. Otherwise, more research needs to be done to elucidate the relationship between neurobiological changes associated with orexinergic suppression and attentional outcomes in this model of SZ.

The disparity in the beneficial effects of orexin receptor antagonists in the behavioral and electrophysiological studies may be a product of the different dizocilpine doses used. The 0.1 mg/kg concentration administered prior to placement in the SAT is located at the low end of the psychotomimetic range and, as such, was more easily reversed with drugs that have diametrically opposing actions on excitatory neurons. While dizocilpine was able to disturb sustained attentional performance in experiments one and two, it was likely too low of a dose to notably impair PLF or elicited gamma in the ASSR paradigm of experiment three, as the differences between saline and 0.3 mg/kg of dizocilpine - which was the lowest concentration administered in the final study - failed to achieve statistical significance for both measures of gamma synchronization in

the mPFC. Because a reduced concentration of dizocilpine was used in the behavioral experiments, lower doses of filorexant and SB-334867 provided relief for the dizocilpine-induced attentional abnormalities. On the other hand, dizocilpine concentrations higher than 0.1 mg/kg have been shown to be detrimental to SAT accuracy for rats and produce profound locomotor abnormalities, leading to the omission of a majority of trials in a given testing session. On the other hand, only the 0.5 mg/kg dose of dizocilpine, which would be an impairing dose for more complex cognitive tasks, suppressed evoked GBOs stemming from trains of a 40 Hz auditory stimulus. This elevation in dizocilpine concentration necessitated a similar increase in the quantity of filorexant used, including a 60 mg/kg dose, which is around the sedative threshold for better-studied DORAs such as almorexant and suvorexant/Belsomra (Gelegen et al., 2018; Parish & Lee-Iannotti, 2016). In this regard, the included doses of filorexant may be incapable of restoring prefrontal and cortical GBOs that are impaired from such a high dose of dizocilpine, with one possible future direction being to include higher doses of filorexant or other similar sedative-hypnotics of this class. In this regard, the seemingly contrary outcomes of these experiments and the usefulness of orexin receptor antagonism can be partly contextualized by the various dizocilpine doses which differ in their neurobiological and behavioral profiles.

The fact that dizocilpine doses lower than 0.3 mg/kg fail to consistently impair gamma synchronization in the brain but still manage to worsen attentional performance in the SAT is an important disparity to reconcile in the present

research. Unimpeded synchronization of neuronal firing in the gamma range would suggest that attentional apparati remain relatively intact at this dose; thus, worsened attentional performance may be indicative of motivational, rather than attentional, deficits. If dizocilpine exposure augmented the effort required to pay attention beyond the desire to attain reinforcement by even mildly disrupting communication between attention-pertinent regions and neurons, an expected result which was demonstrated in both behavioral experiments would be increased trial omissions, as there would be a reduced incentive to make a response for the water reward. Another likelihood is that, if the rats were not sufficiently motivated to remain focused, they may take longer to press the lever when they do decide to respond, and they may also be more liable to miss the signal and err towards the non-signal lever at the conclusion of the trial. Hence, while 0.1 mg/kg of dizocilpine may not have been intoxicating enough to notably disrupt primary attentional circuitry, it was enough to affect performance in the SAT, meaning it may have, to some extent, precluded the motivated recruitment of attentional resources in a way that at least superficially resembles what is observed in humans with SZ.

It is also important to consider that experiments one and two were conducted with rats while experiment three used mice. The ways in which rats and mice differ have implications for the generalizability of behavioral and pharmacological outcomes between the two species, including capacity to perform certain cognitive tasks and how quickly exogenously introduced compounds are processed in the brain and periphery. In general, smaller animals

like mice have faster metabolisms and elimination rates when compared to larger animals like rats, primates, and humans, leading to significantly shorter half-lives of CNS-active compounds; therefore, they oftentimes require higher doses of the same drug to get comparable behavioral and neurological outcomes (Demetrius, 2005; Radermacher & Haouzi, 2013; Zhao et al., 2016). In this case, though a five-fold increase in the dizocilpine dose used from rats to mice appears substantial at a surface level, the difference may not be as extreme in terms of induced brain-wide excitatory dysfunction and behavioral outcomes. Endeavors to establish effective doses across species can benefit future animal research into the therapeutic potential of orexin receptor-binding drugs.

The cognitive and perhaps motivational benefits revealed herein could also be most relevant to simple, well-trained attention tasks. In experiments one and two, rats began drug administration sessions only once they demonstrated consistent proficiency in the SAT. NMDA receptor antagonism is robustly disruptive to not only tasks that measure attention, but learning and memory as well, and, in general, the more complicated or difficult the task, the more susceptible it is to NMDA receptor antagonist-induced impairments (Lee et al., 2020). In this sense, though the SAT is a non-spatial attention task which makes it more challenging, it is a simple signal detection task with few rules and a high degree of predictability, suggesting that impairments may be more easily reversed than if animals were engaged in more complicated and challenging cognitive tasks. In this sense, it is important to consider that attentional integrity is a prerequisite for learning new information and is therefore pivotal for memory

formation. What is given our attention determines what is ultimately encoded, and if attention is fragmented for any reason, more complex cognitive processes which rely upon adequate attention are compromised. Thus, if it is the case that quelling CNS-wide orexinergic inputs is only ameliorative in simpler tasks, this still has implications for cognition as a whole. An interesting direction would be to employ these drugs during the training stages of the SAT, such as when the rats are learning the difference between the signal and non-signal levers.

Due to the nature of drug administration throughout each of the studies detailed in this dissertation, it is likely that their attentional performance-enhancing qualities in an animal model of psychosis stem from numerous orexin-recipient nuclei, which are ubiquitous throughout the CNS. The ascending BF cholinergic and PV+ GABAergic systems are obvious candidates for key loci of these benefits, as the two systems are critical for a variety of attentional and motivational processes, amply express orexin receptors, and are involved in the psychopathology of SZ. As has been discussed in great detail throughout this document, balanced and flexible cortical ACh increases the signal-to-noise ratio by amplifying the response of pyramidal neurons to salient stimuli, including the cue light in the SAT. The heightened cholinergic neurotransmission which is known to emerge as a result of systemic NMDA receptor antagonism would presumably dampen the signal-to-noise ratio by also invoking the activity of non-task-related neurons, leading to impaired signal detection and, as a result, worsened performance in signal trials. Similarly, when transiently stimulated, fast-acting corticopetal BF-PV neurons produce rapid excitatory effects that

optimize information processing speeds by synchronizing the firing of pyramidal neurons, but prolonged stimulation - such as what might occur as a result of NMDA receptor hypofunction in SZ and dizocilpine-induced hyperglutamatergia in animal models - could exacerbate the E/I ratio to an extent that would extinguish the signal-to-noise ratio in the cortex and impair information processing capabilities. If filorexant and SB-334867 were able to preclude enough of this speculated BF-exacerbated frontocortical overstimulation, then they could theoretically attenuate psychological and behavioral outcomes of hypercholinergia and overactive BF-PV outputs to some extent. Site-specific administration can better parse the influence of orexin inhibition in various SZ-affiliated regions, including distinct populations of BF neurons.

The included research explicitly measured the effects of filorexant and SB-334867 for the attentional and putatively motivational deficits in a rodent model of SZ. Filorexant antagonizes both orexin receptors with relatively equal affinity, and SB-334867 is Ox1 receptor-specific with negligible affinity for the Ox2 receptor; because both drugs have demonstrated beneficial effects in the context of NMDA receptor antagonist-induced attentional impairments, it is possible that the therapeutic effects are primarily due to Ox1 receptor suppression, as it is the shared mechanism of action of these two drugs. As such, the role of the Ox2 receptor subtype in these circumstances remains unknown. While not in the context of attention, Elam et al. (2021) very recently revealed that the selective suppression of Ox1 and Ox2 receptors with SB-334867 and EMPA, respectively, both result in a reduction of aberrant mesolimbic dopaminergic system activity in

an inescapable footshock model of psychosis; however, of these compounds, only SB-334867 was able to reverse the behavioral abnormalities in this paradigm. Though it may have less of an obvious effect as the Ox1 receptor subtype in addressing the primary symptoms which stem from imbalances in cortical excitation, Ox2 receptor blockade is still worthy of exploration as a potential therapeutic avenue to treat symptoms associated with psychosis. It is co-expressed with Ox1 receptors in numerous shared regions, including the attention- and SZ-pertinent VTA, NAcc, BF, HPC, and PFC (Marcus et al., 2001) and is directly involved in promoting the activity of brainstem, midbrain, forebrain, and cortical networks associated with alertness and vigilance. Their antagonism in these same areas could, in theory, dampen overexcitability of these neurons in an active disease state and provide some relief for hyperarousal-induced symptoms.

Indeed, perhaps the strongest case for the therapeutic potential of the Ox2 receptor in this context is its role in the sleep-wake cycle. It was briefly mentioned in the introduction that SZ is strongly correlated with markedly dysfunctional sleep which interferes with day-to-day functioning, including by impairing attention, learning, memory, and emotional processes reliant on adequate arousal (Cohrs, 2008; McCoy & Strecker, 2011). A characteristic feature of SZ is sleep-onset and maintenance insomnia (Monti & Monti, 2005), and one could posit that arousal system overactivity would produce a state of excessive wakefulness that makes falling and staying asleep difficult for someone with the disorder. Additionally, regardless of whether it originates from SZ, prolonged and

excessive wakefulness can lead to the induction or worsening of a psychotic state (Waters et al., 2018), suggesting that, by disturbing activity in consciousness-relevant brain areas, sleep dysfunction contributes to both primary and secondary symptom phenomena. Therefore, if excessive wakefulness in SZ worsens sleep quality and aggravates the severity of the illness, directly targeting arousal-relevant neurons may improve sleep quality, treat sleep deprivation-relevant symptoms, and perhaps yield clinically significant improvements in attention and cognitive processing.

In further support of this idea, recall that there is evidence that the BF may be more potently influenced by the activity - and lack thereof - of Ox2 receptors (Eggermann et al., 2001). As a terminating branch of the ARAS, the BF contains multiple populations of excitatory, cortex-innervating neurons which receive and integrate inputs from other brainstem arousal networks, acting to enhance wakefulness and promote awareness of and attention to the external world. Assuming it is the case that the activation of BF cholinergic and non-cholinergic nuclei is driven by orexins primarily through the Ox2 receptor subtype, the blockade of these receptors would produce sedative effects by preventing or stunting Ox2 receptor-mediated promotion of wakefulness and alertness. Then, by quelling outputs from arousal systems which are abnormally active and promoting sleep in vulnerable individuals with SZ, antagonism of the Ox2 receptor can indirectly improve cognitive and motivational processing. Preclinical experiments which administer Ox2-specific SORAs - particularly those which

employ site-specific infusions of these drugs, including in the BF - can better elucidate the hypothesized benefit described here.

When taken together, the findings of this dissertation illustrate that the ameliorative quality of orexin receptor-suppressing compounds in an NMDA receptor model of psychosis depends on the degree of NMDA and orexin receptor antagonism. A comparatively low dose of dizocilpine, which was able to incite deficits in attentional performance in a task of sustained visual attention, likely could not impair the synchronization of prefrontal cortical and hippocampal neurons in the gamma frequency, indicating that these neurons are still capable of firing at frequencies which coincide with attentional integrity. In fact, five times the amount of dizocilpine was ultimately required to reduce power and phase locking in the gamma band evoked by a 40 Hz tone, and the selected doses of filorexant were unable to restore cortical and hippocampal GBOs. In this regard, orexin receptor antagonism aided attention following doses of dizocilpine which were too low to significantly alter cortical neuron firing rates, perhaps indicating that the worsened attentional performance being normalized may be an outcome of NMDA receptor blockade-induced motivational deactivation. Quantities of dizocilpine that *do* incite significant aberrations in cortical activity are not negated by elevated filorexant in the same manner as the low dizocilpine concentration was addressed by the low filorexant and SB-334867 doses. These findings, when considered together, introduce a complicated, dose-dependent relationship between these compounds which are worthy of further exploration.

Current and future directions

There is an ongoing experiment which aims to expand upon the findings of this dissertation; in particular, it aspires to measure the behavioral and electrophysiological effects of psychomimetic manipulations and orexin receptor antagonism, allowing for a more holistic understanding about how these drugs impact both neurobiology and attention-dependent task performance. Presently, a cohort of mice is being trained in a lever-press version of the rPVT, which, as discussed previously, is a signal detection task that quantifies sustained attentional capacity by the amount of time it takes for mice to release the lever following the presentation of a visual cue which signifies reward availability. Each operant box in which the rPVT takes place consists of a panel with two retractable levers on either side of a liquid reward access port, lights situated above each lever and the reward port, and a house light on the opposite side of the chamber. Following an initial habituation session, mice are shaped to press the left lever to receive access to a super-saccharin solution (1.5 percent glucose and 0.04 percent saccharin in distilled water) on an FR-1 schedule of reinforcement. The light above the left lever, which is the active lever, remains illuminated until the lever is depressed, at which point it deactivates and the light above the reward port becomes illuminated. This indicates to the mouse that reinforcement is ready to be retrieved, and breaking the infrared (IR) beam in front of the water spout results in the recording of a correct response and switches the activated light from above the reward port to above the lever for the

next trial to commence. This repeats until 75 rewards are retrieved or until 40 minutes pass.

After subjects consistently retrieve over 75 rewards over a period of three consecutive testing sessions, cue training will begin, during which mice must hold the lever until the cue light above the left lever activates, alerting mice that they have five seconds to break the IR beam and retrieve the super-saccharin reward. A failure to do so in a timely manner results in an omission. The minimum time that they must depress the lever gradually increases until they can reliably hold it for a minimum of 700 ms for at least 75 percent of total lever presses in a given testing session. If the mouse releases the lever before the cue light appears, the levers retract for five seconds, and it is recorded as a premature response. After demonstrating proficiency here, randomized delays will be introduced to the minimum hold times; in each trial, mice must press and hold the lever for at least 700 ms with a random delay between 0 and 5300 ms - with the maximum possible hold time being six seconds - until the cue light above the lever activates and the reward becomes available.

Once mice are well-trained and performing reliably in the rPVT, they will undergo surgery using the same methods as experiment three: upon sedation with isoflurane, ChR2 will be bilaterally infused into the BF, optic fibers will be implanted above the virus injection site, LFP electrodes will be placed in the mPFC and dHPC, and EEG/EMG head mounts will be affixed to the skull. They will be allowed at least one week of surgical recovery before being reintroduced to the rPVT. Once stable baseline performance is achieved, drug administration

sessions will commence. Here, dizocilpine can once again be used as a psychotomimetic agent, and the antipsychotic qualities of both DORAs and SORAs can be explored.

In terms of behavioral findings, it is speculated that the effects of dizocilpine and orexin receptor antagonists would mirror what was found in the SAT. Namely, dizocilpine is expected to reduce the number of answered trials and increase response latencies in the trials that are completed. Orexin receptor antagonists - with particular emphasis on those which target the Ox1 receptor subtype - are expected to at least partly address these NMDA receptor antagonist-induced impairments of vigilant attention. The quantity of dizocilpine may need to be adjusted from the 0.1 mg/kg dose used in the SAT to the rPVT; unlike the SAT, which cycles through trials at a predetermined rate regardless of whether or not responses are actively being made, the rPVT employs self-initiated trials, meaning subjects engage in the task and pay attention when they are motivated to do so. This may potentially require a higher dizocilpine dose to exert a comparable performance detriment which might, as a result, necessitate a proportional increase in the degree of orexin receptor antagonism to exert similar pro-attention benefits that were demonstrated in the SAT.

This experiment will also incorporate optogenetic stimulation of corticopetal BF-PV neurons as a second psychotomimetic manipulation. Recent findings from McNally et al. (2020) demonstrate that 5 mW tonic optogenetic stimulation of BF corticopetal PV-positive GABAergic neurons for 60 seconds, repeated every five minutes, significantly enhanced cortical GBO and weakened

auditory steady-state stimulation-linked evoked gamma oscillations, both of which also occur following administration of ketamine. In this sense, as opposed to brief optogenetic activation of BF PV neurons, which improves vigilant attention (Schiffino et al., 2021), prolonged stimulation of these neurons represents a psychotogenic technique that has similar outcomes on cortical GBOs as a commonly-employed pharmacological model of psychosis. It was also found that 20 mW tonic inhibition of this same neuronal population for five minutes using archaerhodopsin was sufficient to lessen reductions in broadband gamma induced by ketamine, highlighting a potential antipsychotic quality of BF-PV suppression and, as a result, offering further support for the antipsychotic qualities of blockade of ascending arousal pathways of the BF. Hence, in the current rPVT experiment, it is possible to investigate the effects of low-wattage, longer-duration BF-PV stimulation, which mimics one aspect of the putative hyperactivity of the BF in SZ, on performance of the rPVT. Using similar procedures as McNally et al. (2020), it is hypothesized that prolonged parvalbuminergic stimulation will impact task-relevant gamma oscillations and worsen performance in the task in a comparable manner as dizocilpine, determined by increased reaction times and reduced number of completed trials.

Similarly as experiment three, the placement of the LFP electrodes in the mPFC and dHPC will allow for electrophysiological recordings of GBOs in brain regions relevant to attentional processing during task performance as well as relevant to the psychopathology of SZ. Research has shown that the synchronization of cortical pyramidal neuronal firing in the gamma range

increases during periods of focused and selective attention (Benchenane et al., 2011; Fell et al., 2003); as such, we might expect that in drug- and optogenetic stimulation-free performance in the rPVT, resting-state gamma power would be lower than when the mice were actively engaged in the task, such as when they perceive and respond to the cue light. Furthermore, cortical gamma generation just prior to the occurrence of the visual cue is hypothesized to coincide with faster behavioral acknowledgement of the signal. The latter speculation is supported by findings from Schiffino et al. (2021) who found that stimulating cortical gamma shortly before cue presentation resulted in speedier responding in the rPVT. Based on both the behavioral and electrophysiological outcomes from all three of the experiments of this dissertation, acute dizocilpine on its own would be expected to disturb synchronous firing in the gamma frequency in the mPFC and dHPC and result in worsened sustained attentional performance. Though there is a paucity of research on the effects of orexin receptor blockade on GBO generation during attentional engagement, it might be expected that, because orexin receptor antagonism alone neither worsened task accuracy in the SAT nor suppressed gamma power around implanted LFP electrodes, drugs of this class are therefore not expected to have notable effects on power in the gamma range during task performance. Compounds which bind primarily with Ox2 receptors, such as TCS-OX2-29, may have more of an effect on cortical GBOs because of their ample expression on BF-PV neurons, though this has yet to be determined.

The inclusion of extant antipsychotics, such as haloperidol and clozapine, alongside various orexin-targeting ligands can further strengthen the argument that orexin receptor antagonists are antipsychotic in their mechanisms of action. For example, while both typical and atypical antipsychotic medications reverse deficient evoked gamma stemming from NMDA receptor antagonism in rodents, clozapine was unique in that it was the only one shown to also ameliorate behavioral correlates of psychotomimesis, such as deficient PPI (Hudson et al., 2016). If it is true that antipsychotics which are more heavily anticholinergic in nature can stabilize anomalous neurotransmission which impedes upon attention-relevant gamma synchronization, orexin receptor-blocking medications may have a similar outcome, and this possibility can be explored in future experiments.

Electrophysiological measures outside of task-associated gamma oscillations in the rPVT can also be used to further delineate the potential of orexin receptor antagonism to treat neurological and behavioral aberrations caused by these psychotogenic manipulations. Spontaneous GBOs, which interfere with evoked gamma synchronization during auditory steady-state stimulation, are elevated in patients with SZ and in animals in an NMDA receptor antagonist model of psychosis (Hirano et al., 2015; Hiyoshi et al., 2014). In order to test for this in the present study, drugs would be administered 30 minutes prior to recording to ensure that they have achieved peak activity at the start of recording, and GBOs in the PFC and HPC not linked to a rhythmic stimulus can be computed over an extended period of time. Thanks to the EMG element of the

head mount, it is also possible to measure locomotion - which is known to be increased in SZ - in an open field arena. By measuring distance traveled during a given recording session, EMG data can be used to make generalizations about how varying doses of dizocilpine might affect movement and the ability for mice to coordinate and perform in the rPVT. Pairing either dizocilpine or tonic BF-PV stimulation with different orexin suppressing agents during these recording sessions can help determine if orexin receptor blockade has the ability to quell hyperlocomotion and potentially the task impairments associated with movement abnormalities in these models of SZ.

Conclusion

Attention is the lens with which living organisms perceive, interpret, and respond to the happenings of the external environment. It is the psychological mechanism that filters and processes numerous streams of sensory information every waking moment, allowing us to focus on important stimuli at the exclusion of irrelevant noise in order to make sense of a complex, dynamic, and unpredictable world. The BF corticopetal cholinergic system plays an inextricable role in attentional processing by facilitating prolonged changes to pyramidal neuron sensitivity to incoming sensory information, and PV+ GABAergic neurons of the BF have recently been discovered to serve a similar pro-vigilance role through a more rapid and transient mechanism. SZ is a chronic and at times debilitating disorder which is characterized by, among many other symptoms, deficient attentional processing that is believed to be exacerbated by aberrant

excitatory outputs from the BF to the cortex. Current medications are efficacious in treating the hallucinations, delusions, and other positive symptoms in SZ, but they do not provide this same relief for the negative and cognitive symptoms - including those relevant to attention and motivation - and are also associated with a litany of unpleasant side effects which make them difficult to take on a regular basis. Because of the omnipresence of orexin receptors - particularly in regions that are known to be overactive in SZ - the idea that compounds which suppress orexin inputs throughout the CNS have antipsychotic qualities has begun to gain experimental traction in the last few years. Their expression on neurons in areas involved in attentional processing is of particular clinical interest when considering that attentional dysfunction in SZ arises as a consequence of an abnormally stimulated brain with deficient inhibitory circuitry.

The experiments conducted in this dissertation endeavored to address this gap in the literature and explore the potential for indiscriminate and targeted orexin receptor antagonism through the use of the DORA filorexant and the Ox1 receptor-exclusive SORA SB-334867, respectively, for the purpose of counteracting the neurological and behavioral outcomes of excessive brain-wide stimulation in a pharmacological model of SZ which reproduces the observed NMDA receptor hypofunction. In a nutshell, the results of these experiments suggest that the route of administration of both drugs, which suppress orexinergic inputs throughout the brain, can reverse deficient accuracy, reaction times, and in-task responding in the SAT induced by acute administration of a low doses of dizocilpine; however, these benefits were not recapitulated for the

electrophysiological anomalies produced by a higher dose of dizocilpine. These disparate findings can be resolved by exploring a range of concentrations of dizocilpine, filorexant, SB-334867, and other anti-orexin compounds, because how effective lessening orexinergic activity is in this context may depend on where a given quantity of dizocilpine lies on the psychotomimetic spectrum. Because the Ox1 receptor subtype is the common mechanism of action between these two drugs, the beneficial effects described herein are posited to arise from Ox1 receptor inhibition, and, as such, more research needs to be conducted regarding the extent that the Ox2 receptor subtype can help in this paradigm. Therefore, while only the beginning, the sum of this work will hopefully contribute to the growing literature in support of orexin receptor blockade as a potential pharmacological intervention for SZ, and ongoing research efforts aim to further explore the possibility of orexinergic suppression to provide better relief for the treatment-resistant negative and cognitive symptoms of this disorder.

APPENDIX

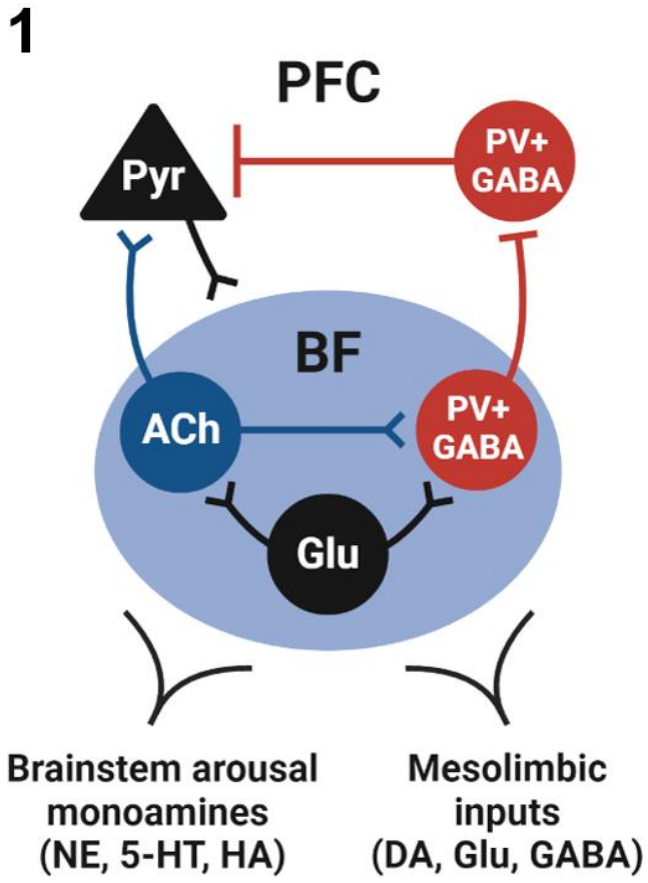


Figure 1. Circuit diagram of the different populations of neurons in the BF and how they promote attention in the PFC. There are three known types of neurons contained within the BF - cholinergic, GABAergic, and glutamatergic - which are sensitive to inputs from numerous regions throughout the brain. For example, the BF is a terminating branch of the ARAS, and, as such, receives signals from wake-active neurons that produce NE, 5-HT, HA, and other arousal-promoting chemicals. Additionally, the mesolimbic system, which sends dopaminergic, glutamatergic, and GABAergic projections to the BF, is involved with the motivated recruitment of attentional systems and the incentive to remain vigilant. Corticopetal cholinergic neurons stimulate the cortex by amplifying the response of pyramidal neurons to inputs regarding a salient stimulus. BF-PV+ neurons predominantly synapse with cortical GABA interneurons and indirectly promote cortical activity by inhibiting these GABAergic neurons and, as a result, disinhibiting pyramidal neurons. Lastly, in this context, glutamatergic neurons primarily subserve attentional processes by stimulating cholinergic and parvalbuminergic neurons.

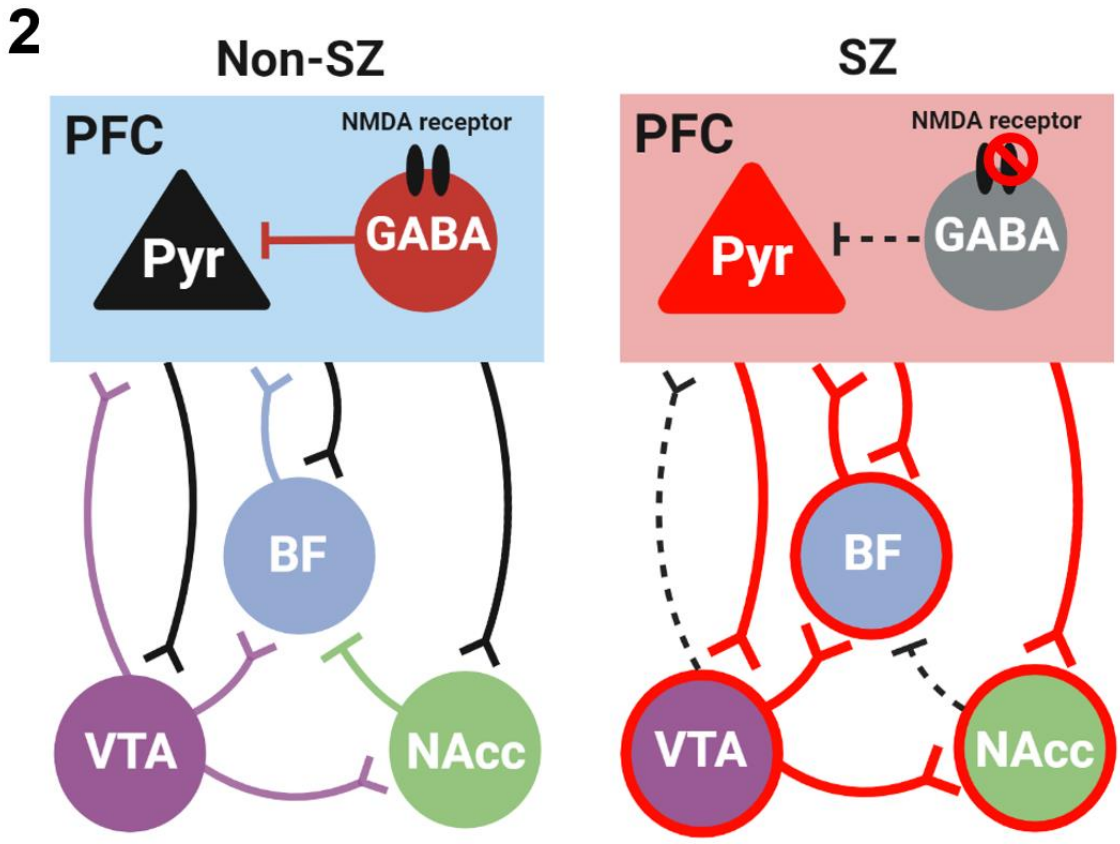


Figure 2. Circuit diagram of the hypothesized relationships between midbrain, forebrain, and cortical circuits in the normal brain and the brain of someone with SZ. In the typical brain, outputs from pyramidal neurons to various subcortical brain areas are mitigated by GABAergic interneurons, the inhibitory influence of which requires adequate glutamatergic inputs from their NMDA receptors. In SZ, NMDA receptors expressed on these cortical GABAergic interneurons are hypofunctional, leading to disinhibited corticofugal projections that produce a mesocorticolimbic circuit that is overstimulated and overactive at baseline. These disturbances together result in the positive, negative, and cognitive syndromes of SZ. Regarding the putative role of the BF in SZ, it is believed that hyperdopaminergia-induced suppression of GABAergic outputs from the NAcc to corticopetal cholinergic projections, rendering them abnormally active during non-attentive states and unable to accommodate changing attentional demands. This dysfunctional NAcc-BF/ACh relationship is posited to be the primary mediator of the attentional impairments in SZ, with other network aberrations - such as overactive inputs from the cortex and VTA - likely worsening these outcomes.

3

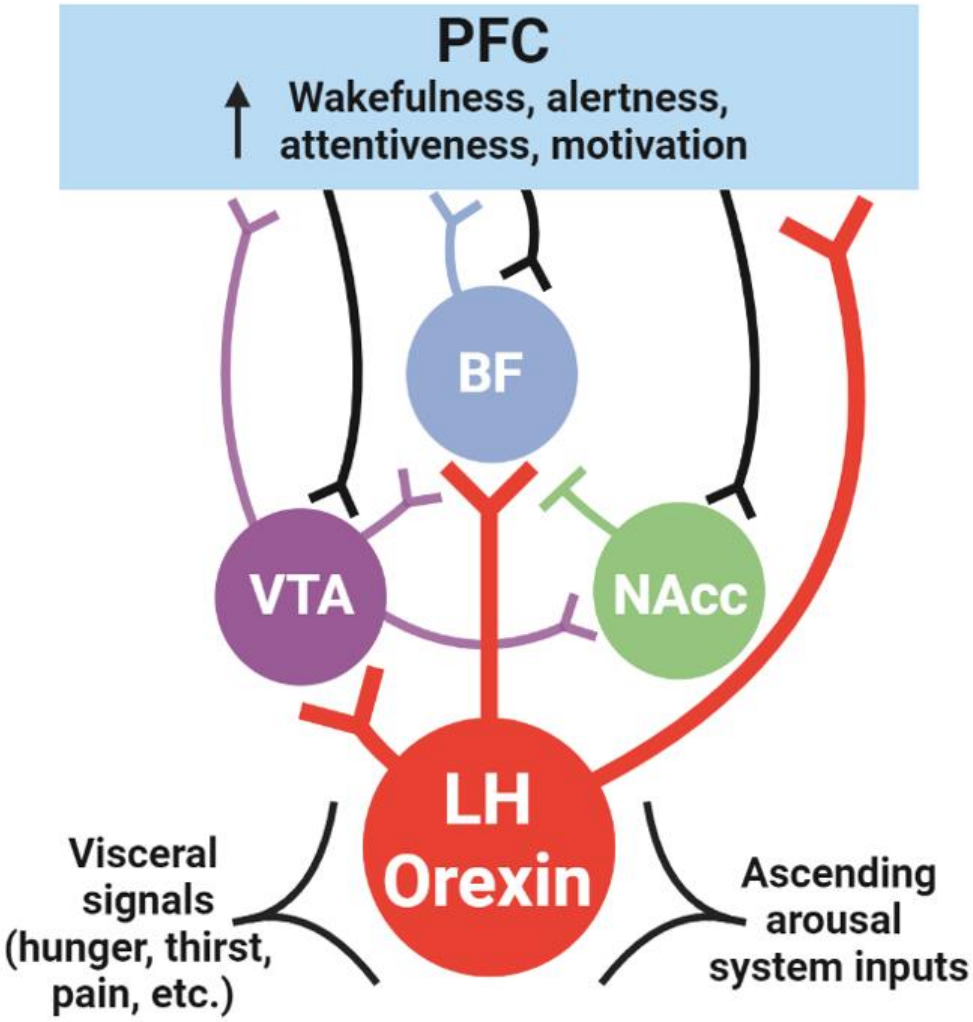


Figure 3. Circuit diagram of lateral hypothalamic orexinergic innervations of attention- and SZ-relevant regions of the midbrain, forebrain, and cortex. The LH sends projections of orexin peptide-producing neurons throughout the entire brain, including to the VTA, BF, and PFC. Orexinergic efferents are activated in response to physiological signals such as hunger, thirst, and pain, thereby informing behavior based on the saliency of these internal cues. They are also recipient to fibers from brainstem arousal nuclei, suggesting that they play an important role in instigating wakefulness and motivated behaviors through pro-dopaminergic, pro-cholinergic, and other pro-stimulatory mechanisms of action. Conversely, the blockade of orexin receptors has been shown to suppress the release of DA from the VTA and ACh from the BF, findings that are relevant to the antipsychotic potential of orexin receptor antagonists.

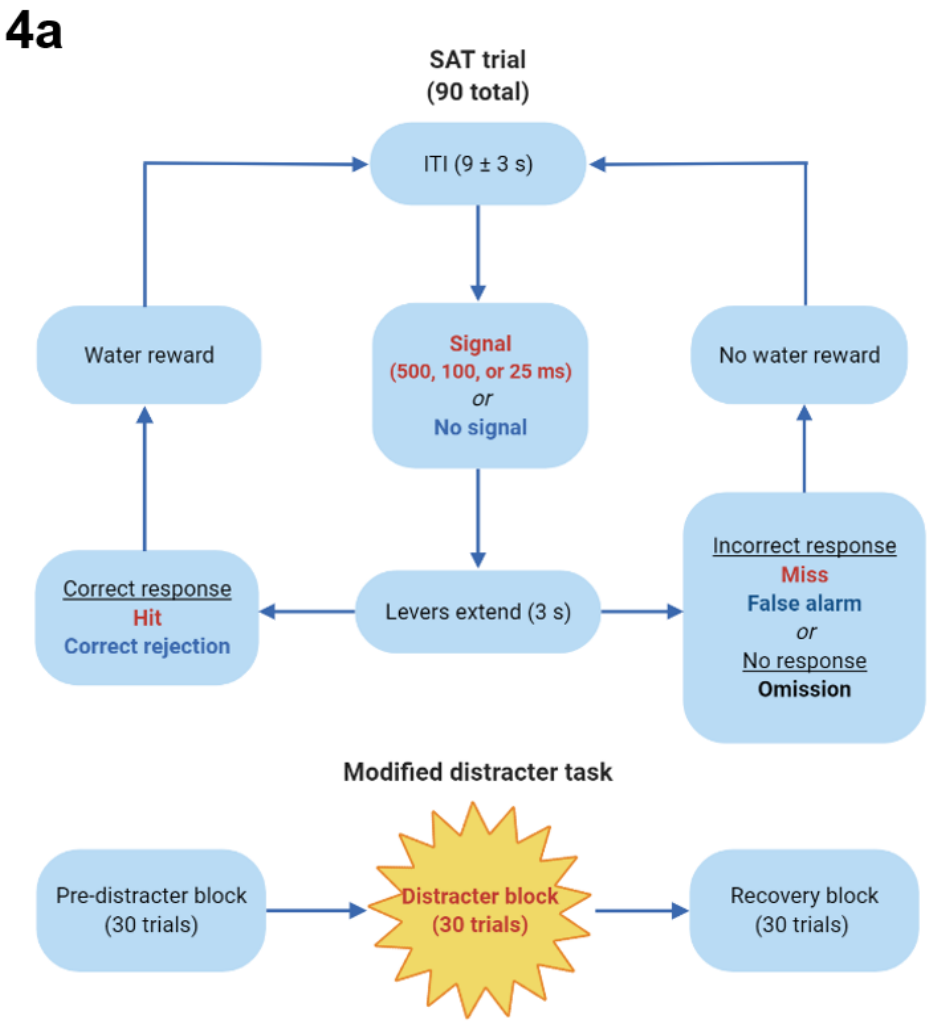
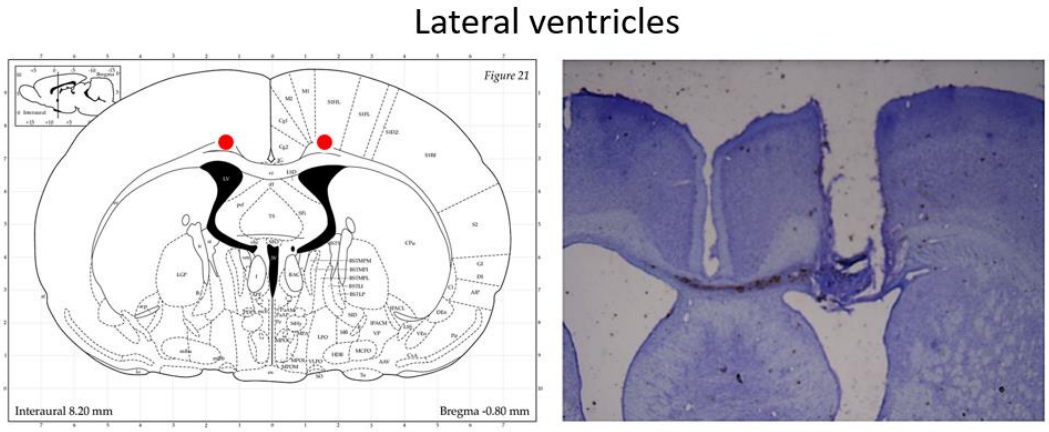


Figure 4a. Schematic representation of the sustained attention task (SAT) which is comprised of 90 total trials. During a given trial, a signal either flashes (500, 100, or 25 ms) or does not, after which both levers extend into the testing chambers for 3 seconds. The water reward is contingent upon correct responding. If rats press the signal lever at the conclusion of a signal trial, it is recorded as a hit, and they are given the water reward. Similarly, if the non-signal lever is pressed at the conclusion of a non-signal trial, it is considered a correct rejection, and they are rewarded. However, if they press the non-signal lever following the appearance of the signal, it is recorded as a miss, and if the signal lever was pressed at the end of a non-signal trial, it is considered a false alarm. If they press neither lever, it is marked as a trial omission. On drug administration days, the 90 trials are divided into three distinct testing blocks: the pre-distracter block, during which the house light remains illuminated; the distracter block, wherein the house light continuously flashes (0.5 seconds on, 0.5 seconds off); and the recovery block, during which the house light returns to its typical illuminated state. Image created with BioRender.

4b



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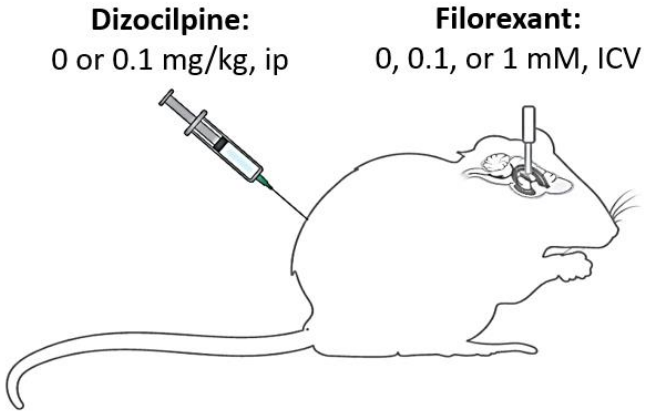
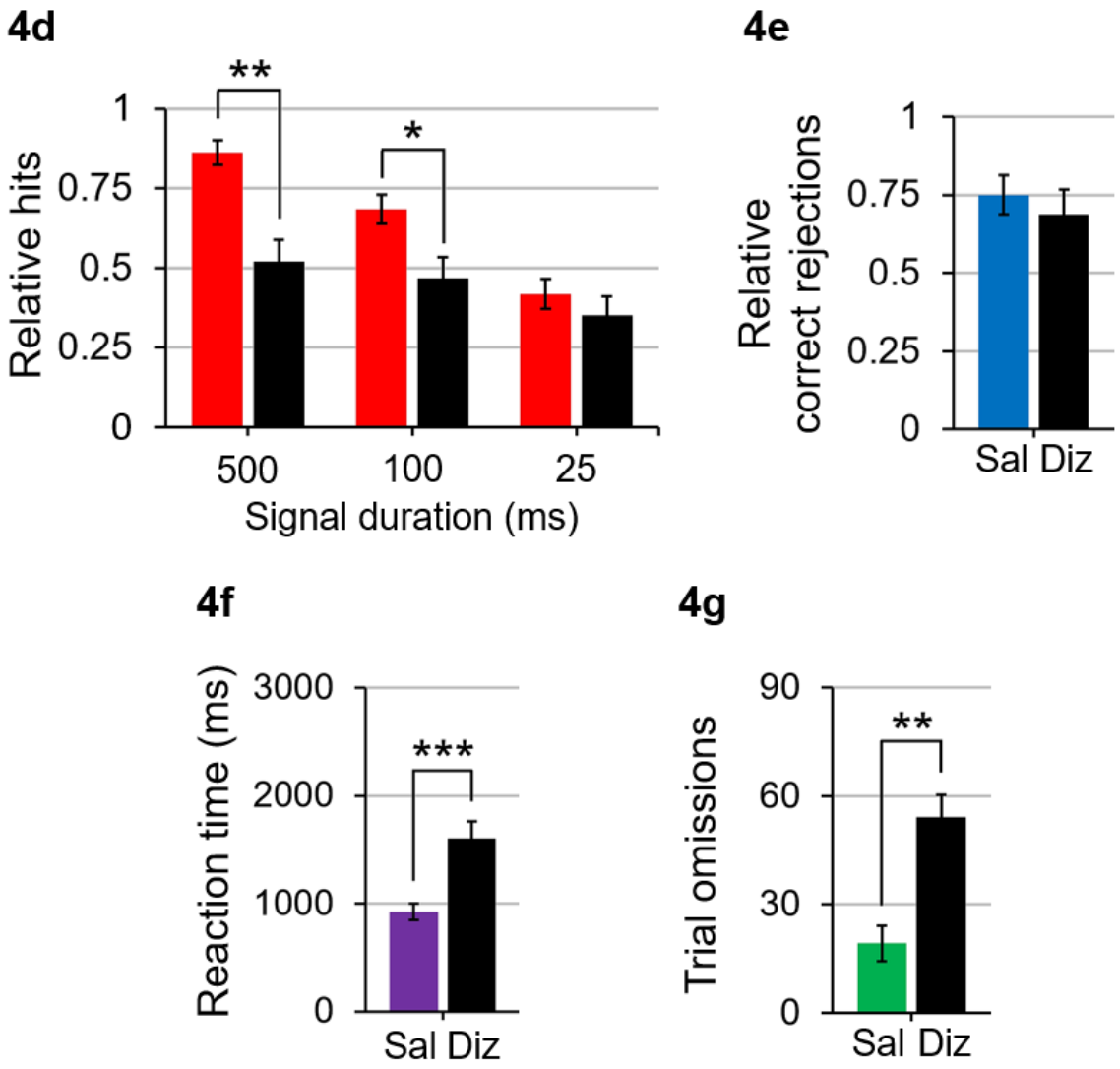
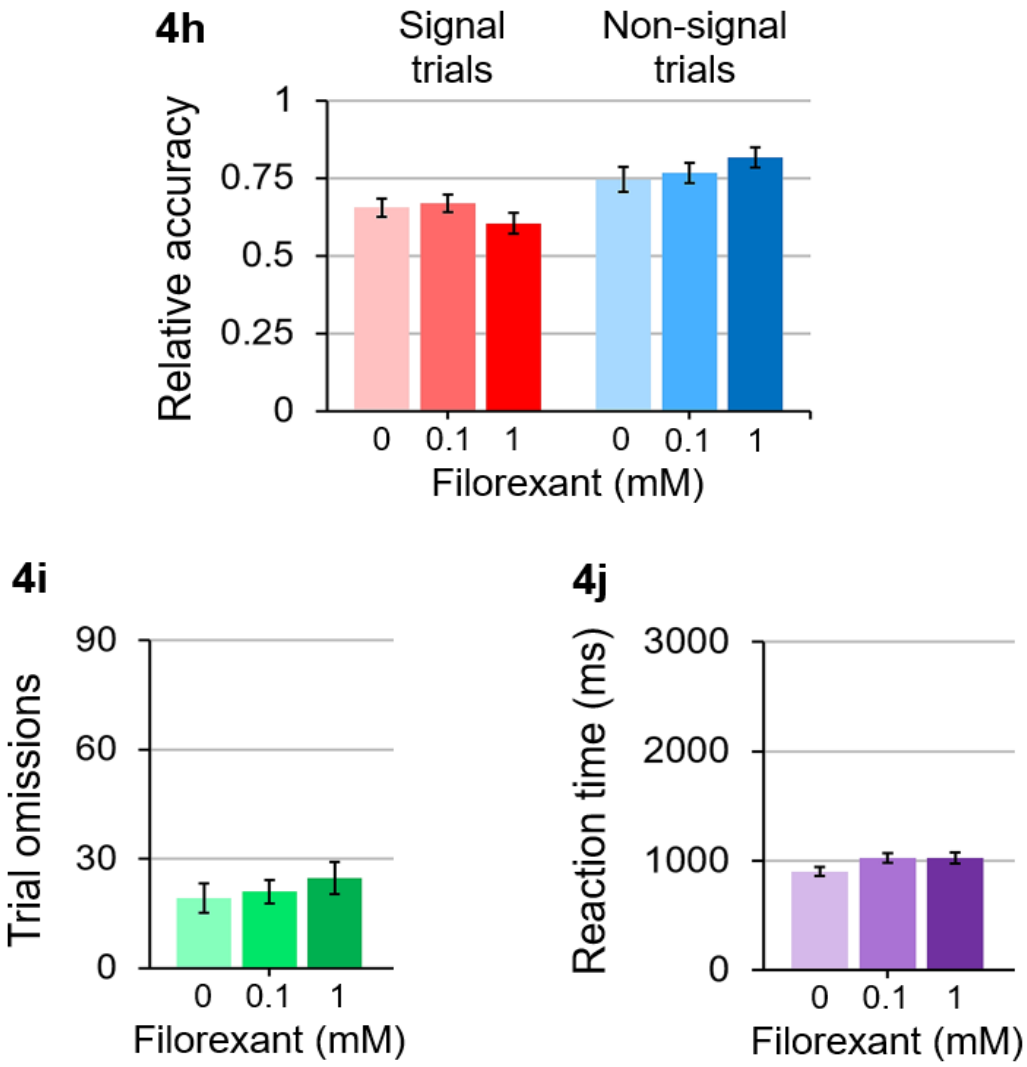


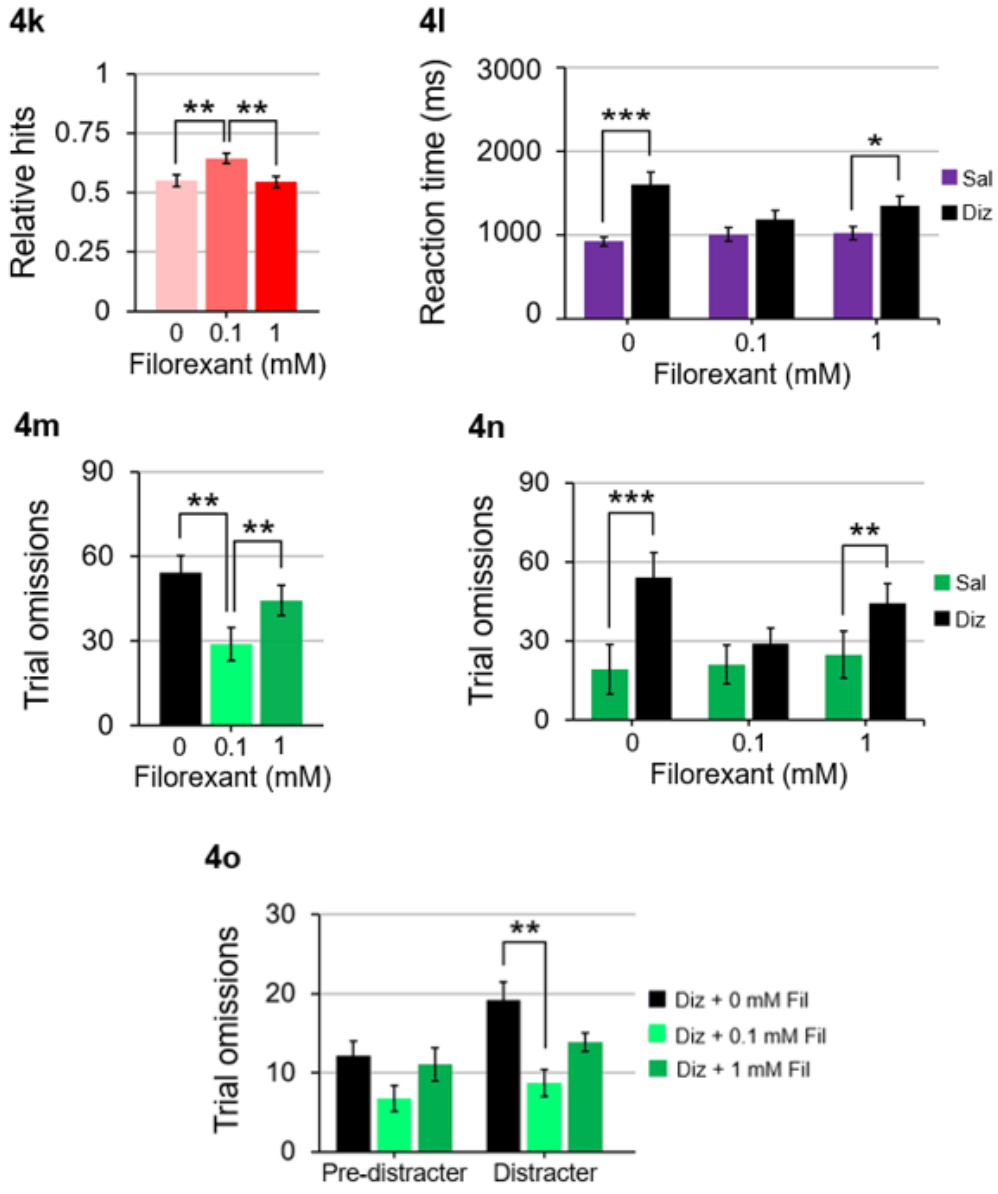
Figures 4b and 4c. Stereotaxic surgery and drug administration procedures. **4b.** Stereotaxic atlas for ICV cannulation and cresyl violet acetate-stained 50 µm section of the lateral ventricles showing cannula tract. Rats underwent unilateral cannulation surgery during which a guide cannula (8 mm, 22 gauge) was placed 1.0 mM above either the right or left lateral ventricle; internal cannulae extended 1.0 mM beyond guide cannula into the ventricle. Adjusted from Paxinos & Watson's *The Rat Brain in Stereotaxic Coordinates*. **4c.** Following surgery, on drug administration days, rats were given ip injections of either 0 or 0.1 mg/kg of the NMDA receptor antagonist dizocilpine as well as ICV infusions of either 0, 0.1, or 1.0 mM of the DORA filorexant prior to placement in the SAT.



Figures 4d - 4g. The effects of dizocilpine on signal trials, non-signal trials, reaction times, and omissions in the SAT. **4d.** Compared to when they were given saline, rats given dizocilpine demonstrated a worsened ability to correctly identify the 500 and 100 ms signals, but performance was undisturbed at the 25 ms signal. **4e**. Dizocilpine did not impair performance in non-signal trials. **4f.** Dizocilpine slowed the speed with which rats pressed the correct lever following its extension into the testing chamber at the conclusion of any given trial. **4g.** Dizocilpine significantly increased the number of omitted trials when compared to saline. For all graphs, colored bars indicate 1 ml/kg of saline, and black bars indicate 0.1 mg/kg of dizocilpine. Error bars are displayed as mean ± SEM. *p < .05, **p < .01, ***p < .001



Figures 4h – 4j. The effects of filorexant on signal trials, non-signal trials, omissions, and reaction times in the SAT. **4h.** Filorexant did not influence accuracy in signal or non-signal trials when rats co-administered saline in lieu of dizocilpine. **4f.** Filorexant did not increase the number of omitted trials across doses on its own. **4g.** Filorexant did not slow correct response latencies. For all graphs, the leftmost lighter colors indicate DMSO infusions, the rightmost darker colors indicate 1.0 mM infusions of filorexant, and the middle intermediate colors indicate 0.1 mM infusions of filorexant. Error bars are displayed as mean ± SEM. **p* < .05, ***p* < .01, ****p* < .001



Figures 4k – 4o. The effects of filorexant and dizocilpine co-administration on signal trial accuracy, reaction times, and omissions in the SAT. **4k.** When averaged across dizocilpine dose, signal trial performance was higher when rats were given 0.1 mM of filorexant than when they were given 0 and 1.0 mM. The leftmost light red bar indicates vehicle infusion, the rightmost darker red bar indicates 1.0 mM infusion of filorexant, and the middle intermediate red bar indicates 0.1 mM infusion of filorexant. **4l.** 0.1 mM of filorexant, but not 1.0 mM, is able to quick correct response latencies for dizocilpine-administered animals compared to dizocilpine alone. Purple bars indicate 1 ml/kg of saline, and black bars indicate 0.1 mg/kg of dizocilpine. **4m.** When rats were given dizocilpine, they omitted less often when they were also given 0.1 mM of filorexant, but not when they were co-administered the 1.0 mM concentration. The leftmost black bar indicates dizocilpine in the absence of filorexant, and the lighter and darker

green bars represent dizocilpine + 0.1 and 1.0 mM of filorexant, respectively. **4n.** When comparing saline- and dizocilpine-injected rats, only the 0.1 mM concentration of filorexant was able to normalize omissions between the two injection conditions. Colored lines indicate 1.0 ml/kg of saline, and black lines indicate 0.1 mg/kg of dizocilpine. Green bars indicate 1 ml/kg of saline, and black bars indicate 0.1 mg/kg of dizocilpine. **4o.** When analyses were separated by pre-distracter and distracter blocks, the 0.1 mM dose of filorexant, but not the 1.0 mM dose, sufficed to significantly improve dizocilpine-induced omissions during the distracter block. For each testing block, the leftmost black bar indicates dizocilpine in the absence of filorexant, and the lighter and darker green bars represent dizocilpine + 0.1 and 1.0 mM of filorexant, respectively. Error bars are displayed as mean ± SEM. *$p < .05$, **$p < .01$, ***$p < .001$

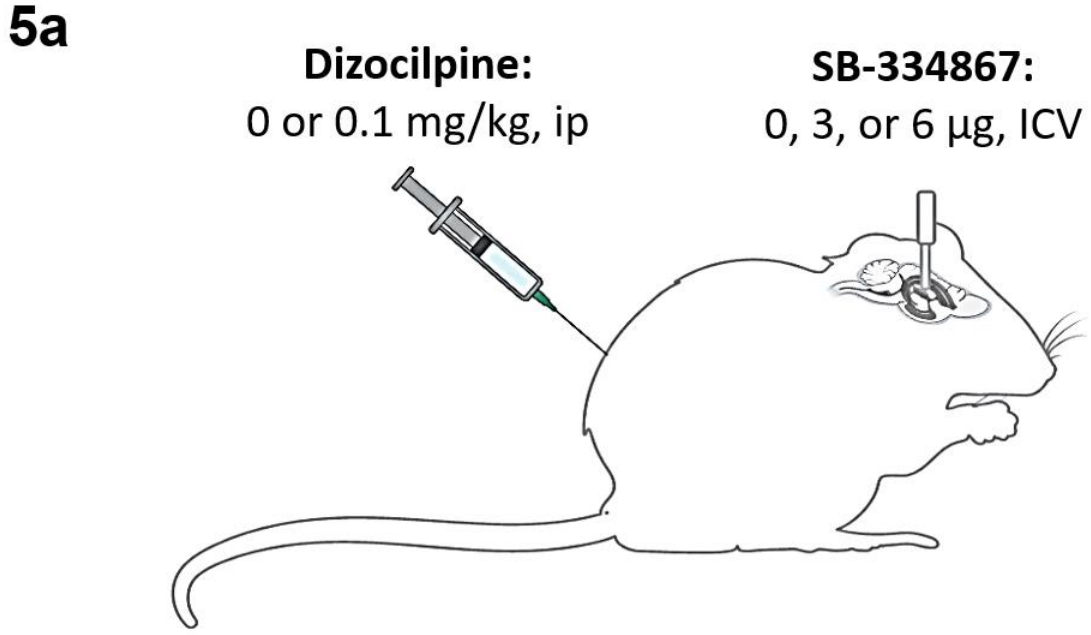
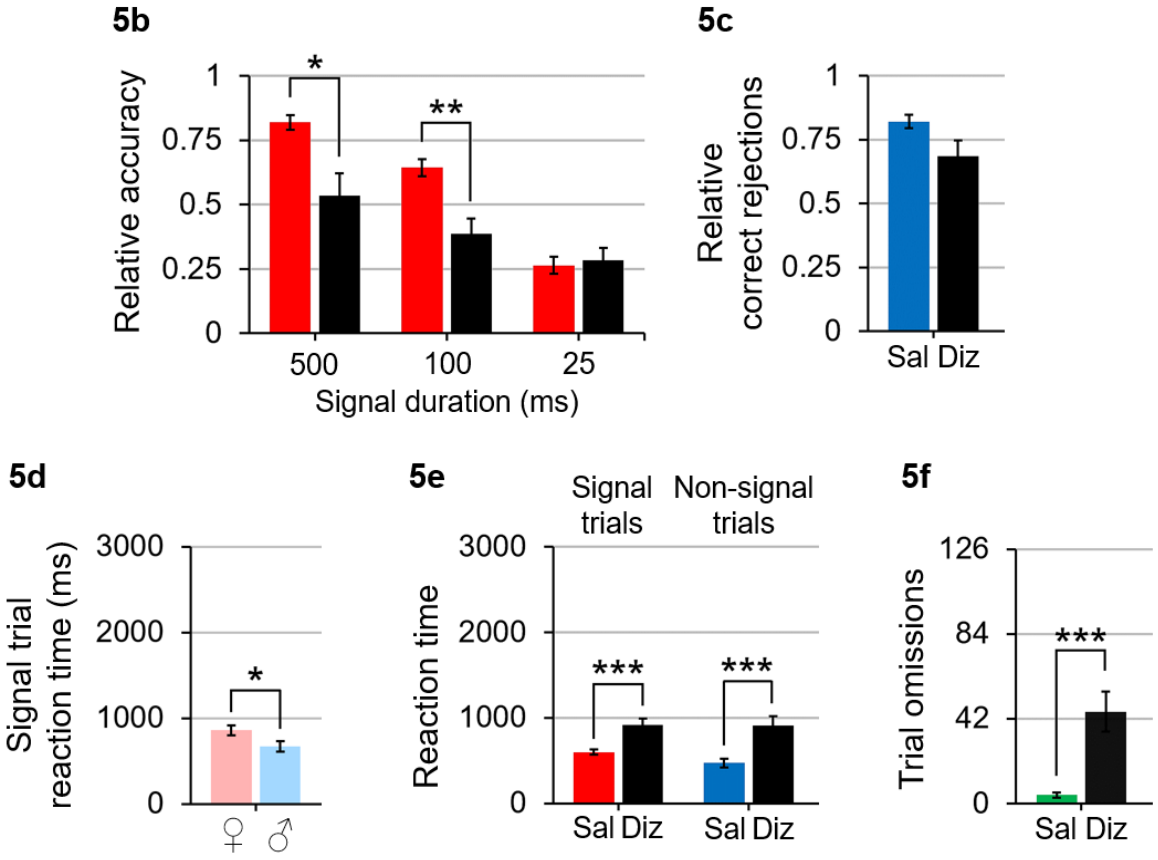
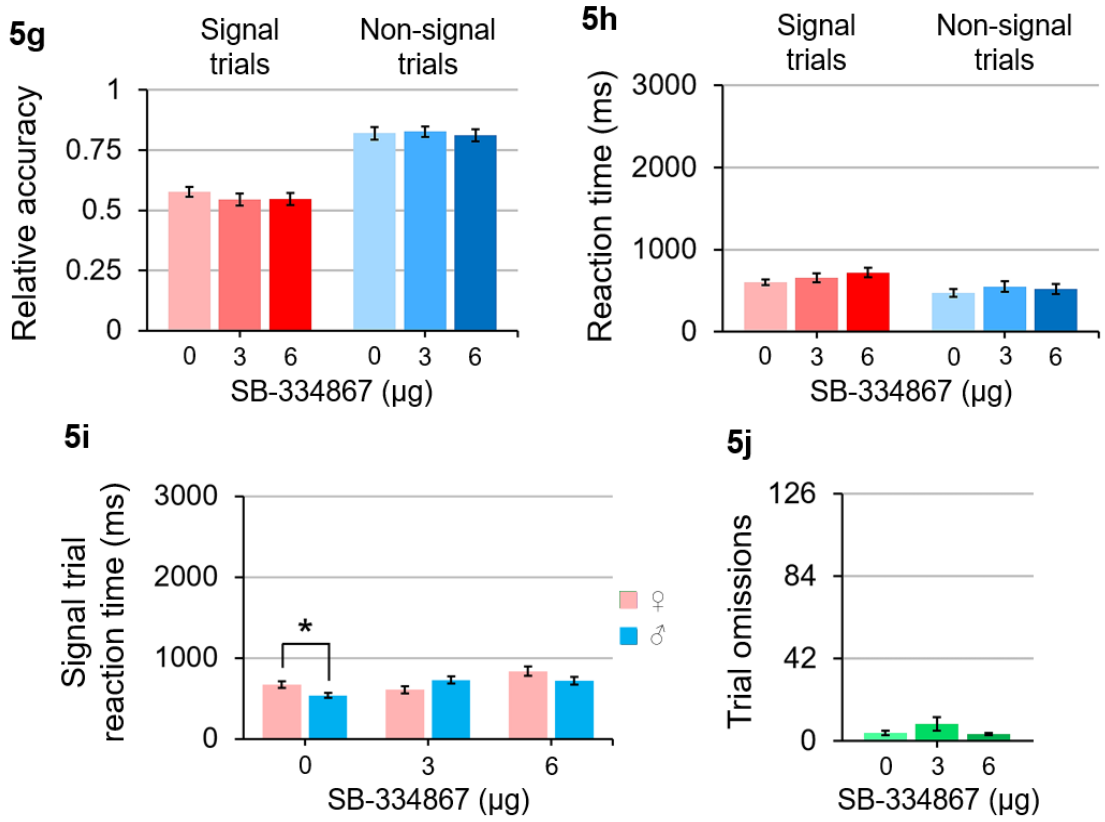


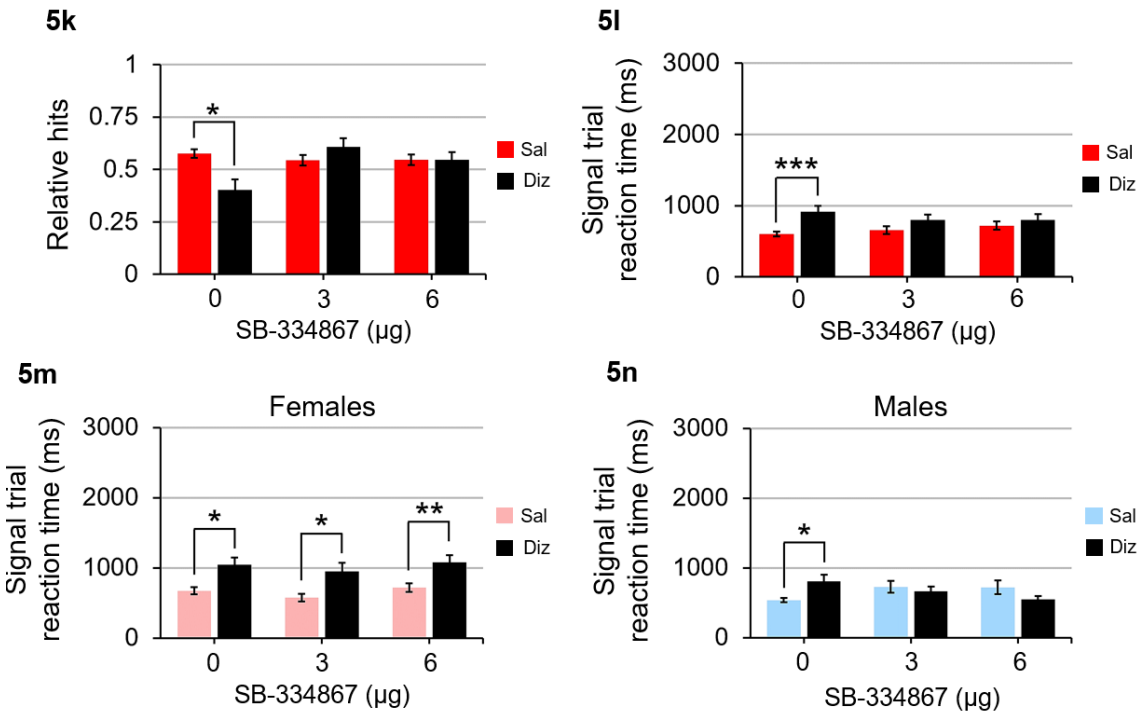
Figure 5a. Dizocilpine and SB-334867 administration procedures. Following recovery from the same stereotaxic surgical procedures in experiment one, rats were given ip injections of either 0 or 0.1 mg/kg of the NMDA receptor antagonist dizocilpine and ICV infusions of either 0, 3, or 6 µg of the Ox1 receptor-specific SORA SB-334867 prior to placement in the SAT with the modified distracter.



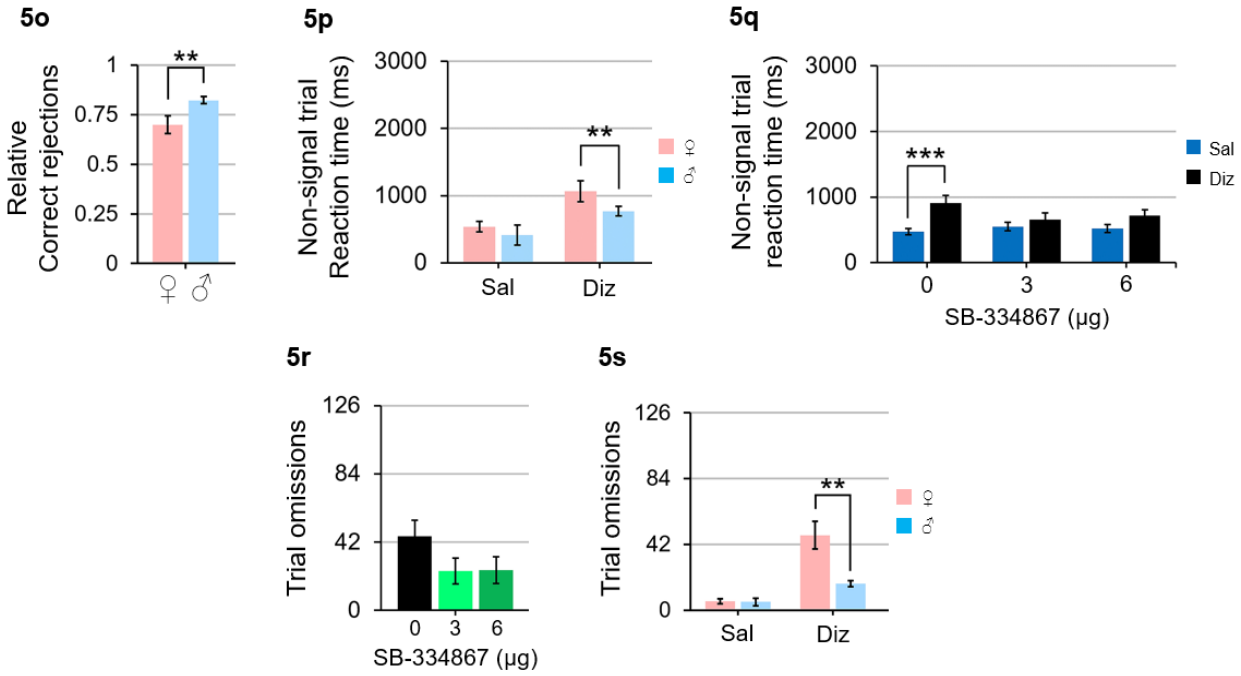
Figures 5b – 5f. The effects of dizocilpine on task accuracy, reaction times, and omissions in the SAT. **5b.** Dizocilpine worsens performance in signal trials with 500 and 100 ms signals, but performance at the 25 ms signal was unaffected. Red bars indicate 1 ml/kg of saline, and black bars indicate 0.1 mg/kg of dizocilpine. **5c.** NMDA receptor antagonism had no effect on accuracy in non-signal trials. The blue bar indicates 1 ml/kg of saline, and the black bar indicates 0.1 mg/kg of dizocilpine. **5d.** When averaging across dizocilpine dose, females took longer than males to press the correct lever following its extension into the testing chamber at the conclusion of a trial. The pink bar indicates female rats, and the blue bar indicates male rats. **5e.** Rats took longer to respond at the correct lever in both signal and non-signal trials when they were administered dizocilpine than when they were administered saline. Colored bars indicate 1 ml/kg of saline, and black bars indicate 0.1 mg/kg of dizocilpine. **5f.** Dizocilpine-administered rats omitted significantly more trials than when they were given saline. The green bar indicates 1 ml/kg of saline, and the black bar indicates 0.1 mg/kg of dizocilpine. Error bars are displayed as mean ± SEM. *$p < .05$, **$p < .01$, ***$p < .001$



Figures 5g – 5j. The effects of SB-334867 on task accuracy, reaction times, and omissions in the SAT. **5g.** Ox1 receptor antagonism failed to impair accuracy in signal or non-signal trials on its own. The leftmost light bars indicate vehicle infusion, and the medium- and dark-colored bars indicate infusions of 3 and 6 µg infusion of SB-334867, respectively. **5h.** SB-334867 did not have an effect on correct response latencies in either trial type. The leftmost light bars indicate vehicle infusion, and the medium- and dark-colored bars indicate infusions of 3 and 6 µg infusion of SB-334867, respectively. **5i.** While females tended to be slower than males, on average, in correctly-answered trials in the all-vehicle condition, this disparity disappeared when they were given both doses of SB-334867. The pink bars indicate female rats, and the blue bars indicate male rats. **5j.** SB-334867 did not significantly alter omission rates. The leftmost light green bar indicates vehicle infusions, the rightmost dark green bar indicates 6 µg infusions of SB-334867, and the middle intermediate green bar indicates 3 µg infusions of SB-334867. Error bars are displayed as mean ± SEM. *$p < .05$, **$p < .01$, ***$p < .001$



Figures 5k – 5n. The effects of SB-334867 on dizocilpine-induced impairments of task accuracy, reaction times, and omissions in the SAT. **5k.** When rats were given dizocilpine, both 3 and 6 µg of SB-334867 improved accuracy in signal trials when compared to dizocilpine and infusions of vehicle. **5l.** Both concentrations of SB-334867 improve reaction times for dizocilpine-administered animals. **5m and 5n.** When divided by sex, SB-334867 was not able to quick response times for females, but it did so for males. For all graphs, colored bars indicate 1 ml/kg of saline, and black bars indicate 0.1 mg/kg of dizocilpine. Error bars are displayed as mean ± SEM. **p* < .05, ***p* < .01, ****p* < .001



Figures 5o – 5s. The effects of SB-334867 on dizocilpine-induced impairments of task accuracy, reaction times, and omissions in the SAT, cont. **5o.** When averaging across dizocilpine and SB-334867 concentrations, females performed worse in non-signal trials than males. The pink bar indicates female rats, and the blue bar indicates male rats. **5p.** In non-signal trials, males and females performed similarly when they were given saline, but when they were given dizocilpine, females were slower than males to correctly respond at the conclusion of a trial when averaged across SB-334867 dose. The pink bars indicate female rats, and the blue bars indicate male rats. **5q.** Regardless of sex, dizocilpine-administered rats took longer to respond than saline-administered rats in non-signal trials, but this was mitigated by both 3 and 6 µg of SB-334867. Blue bars indicate 1 ml/kg of saline, and black bars indicate 0.1 mg/kg of dizocilpine. **5r.** Ox1 receptor blockade was not able to improve omission rates for dizocilpine co-exposed animals. The leftmost black bar indicates dizocilpine in the absence of SB-334867, and the lighter and darker green bars represent dizocilpine + 3 and 6 µg of SB-334867, respectively. **5s.** Females omitted more than males when they were injected with dizocilpine than when they were injected with saline. The pink bars indicate female rats, and the blue bars indicate male rats. Error bars are displayed as mean ± SEM. *$p < .05$, **$p < .01$, ***$p < .001$

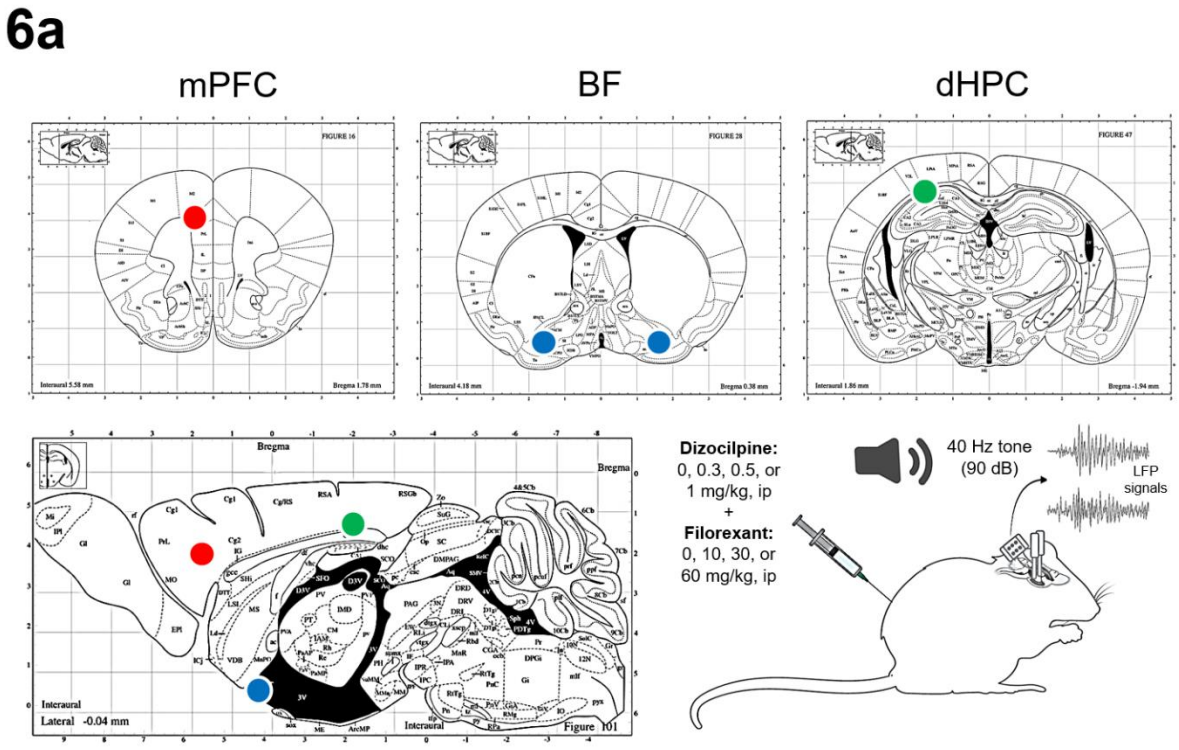


Figure 6a. Stereotaxic atlas of targeted brain areas and experimental procedures. AAV-ChR2 was bilaterally injected into the BF, and optogenetic fibers were implanted slightly above the site of viral transduction. LFP electrodes were placed in the right mPFC and the right dHPC to record the activity of prefrontal cortical and hippocampal neurons during testing. On drug administration days, mice were given a combination of one of four possible doses of filorexant (0, 10, 30, or 60 mg/kg, ip) 30 minutes prior to auditory steady-state stimulation, and 20 minutes beforehand, they were administered dizocilpine (0, 0.3, 0.5, or 1 mg/kg, ip). Testing sessions were divided into 100 repeating intervals of six seconds which are comprised of a two-second pre-stimulation period, a two-second stimulation period during which a 40 Hz tone plays, and a two-second post-stimulation recovery period. Adjusted from Paxinos & Watson's *The Rat Brain in Stereotaxic Coordinates*.

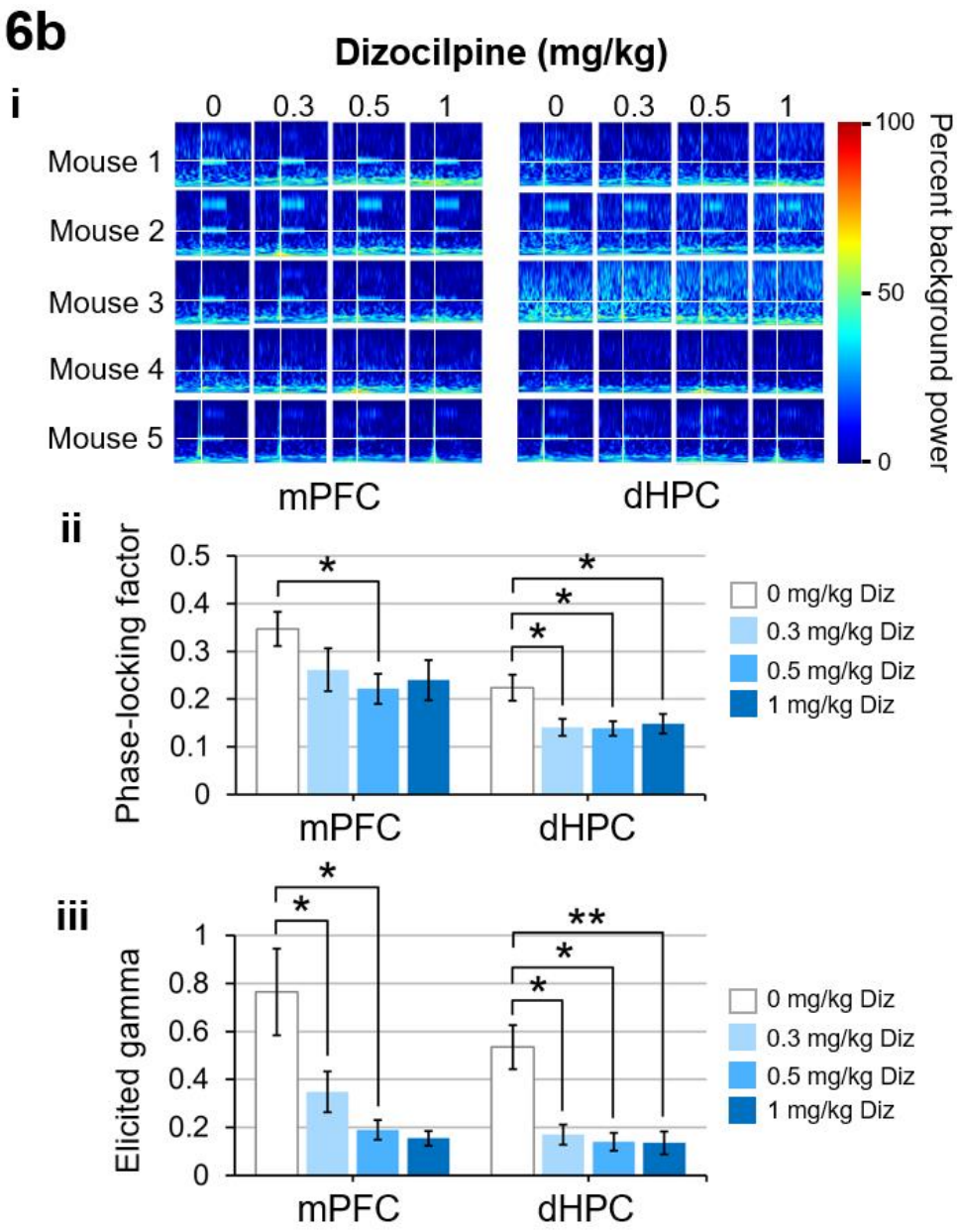


Figure 6b. The effects of dizocilpine alone on PLF and elicited gamma in the ASSR. **i.** Average time-frequency spectrograms of the LFP response to the 40 Hz tone in the mPFC and dHPC of each mouse, separated by dizocilpine dose. The vertical line represents the start of auditory steady-state stimulation (2 seconds), and the horizontal line represents the 40 Hz frequency (scale from 0 to 100 Hz). **ii.** In the PFC, only the 0.5 mg/kg dose of dizocilpine suppressed PLF, whereas in the HPC, all three doses were effective in doing so. **iii**. Both 0.3 and 0.5 mg/kg, but not 1 mg/kg, of dizocilpine reduced power in the gamma band in the PFC, and all three doses did so in the HPC. For all graphs, white bars indicate vehicle injection, and light, medium, and dark blue bars indicate injections of 0.3, 0.5, and 1.0 mg/kg of dizocilpine, respectively. Error bars are displayed as mean ± SEM. *$p < .05$, **$p < .01$, ***$p < .001$

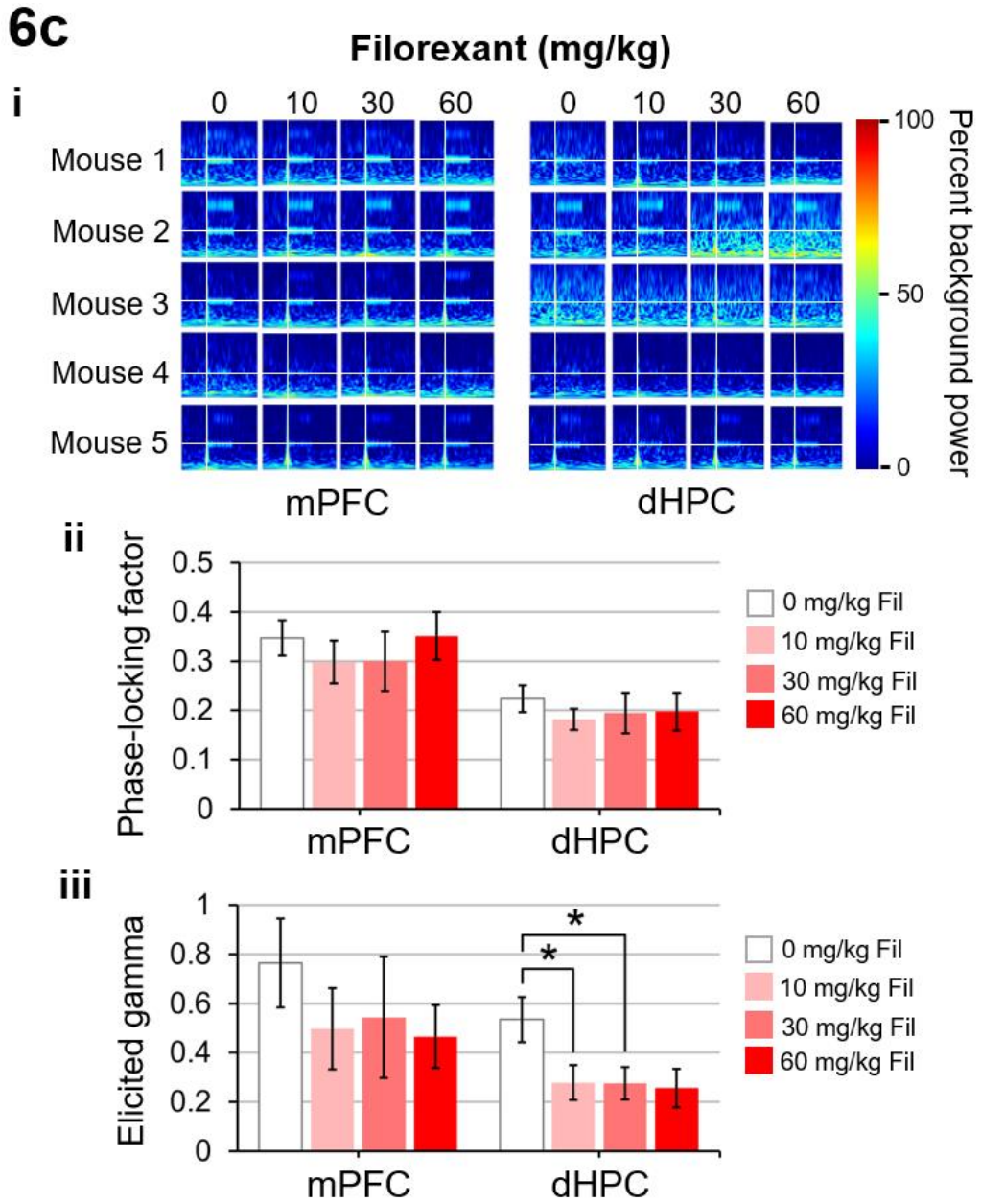


Figure 6c. The effects of filorexant alone on PLF and elicited gamma in the ASSR. **i.** Average time-frequency spectrograms of the LFP response to the 40 Hz tone in the mPFC and dHPC of each mouse, separated by filorexant dose. The vertical line represents the start of auditory steady-state stimulation (2 seconds), and the horizontal line represents the 40 Hz frequency (scale from 0 to 100 Hz). **ii.** None of the filorexant concentrations impacted PLF in the PFC or the HPC. **iii**. Filorexant did not influence evoked gamma power in the PFC, but 10 and 30 mg/kg of filorexant weakened hippocampal generation of GBOs. For all graphs, white bars indicate vehicle injection, and light, medium, and dark red bars indicate injections of 10, 30, and 60 mg/kg of filorexant, respectively. Error bars are displayed as mean ± SEM. **p* < .05, ***p* < .01, ****p* < .001

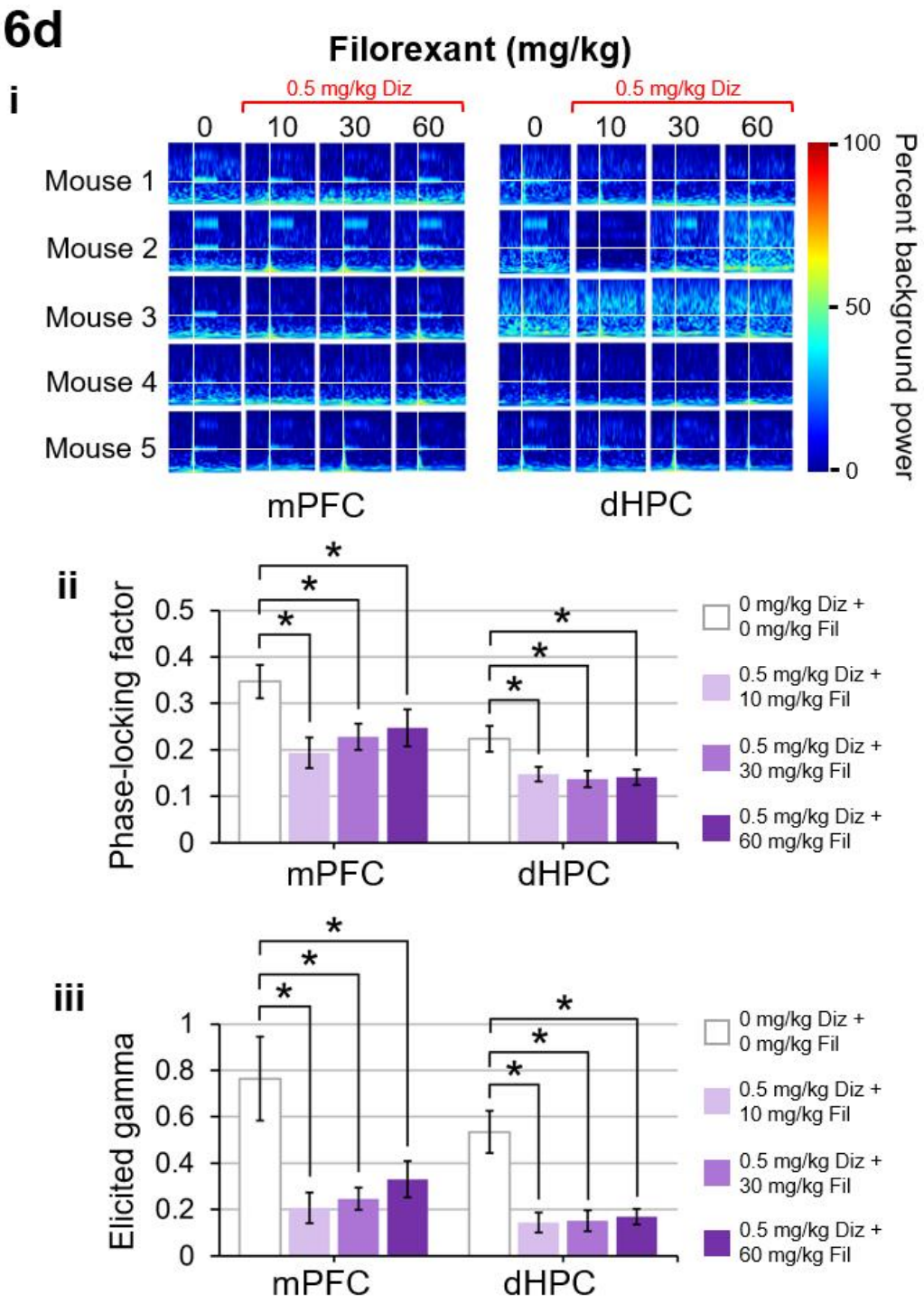


Figure 6d. The effects of dizocilpine and filorexant on PLF and elicited gamma in the ASSR. **i.** Average time-frequency spectrograms of the LFP response to the 40 Hz tone in the mPFC and dHPC of each mouse, separated by the four dizocilpine-filorexant dose combinations of interest. The vertical line represents the start of auditory steady-state stimulation (2 seconds), and the horizontal line represents the 40 Hz frequency (scale from 0 to 100 Hz). **ii.** In neither the PFC

nor the HPC were any of the doses of filorexant able to improve phase locking for dizocilpine co-administered mice. **iii**. Similarly, no concentration of filorexant ameliorated dizocilpine-induced suppression of phase locking and elicited GBOs. For all graphs, white bars indicate vehicle injection, and light, medium, and dark purple bars indicate injections of 0.5 mg/kg of dizocilpine alongside 10, 30, and 60 mg/kg of filorexant, respectively. Error bars are displayed as mean ± SEM. *p < .05, **p < .01, ***p < .001

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EDUCATION

2022	**Doctor of Philosophy in Neuroscience**, William and Mary Dissertation: Orexin receptor antagonism and schizophrenia: addressing attentional impairments in an NMDA receptor hypofunction model of psychosis
2017	**Master of Arts in Experimental Psychology**, William and Mary Thesis: The effects of intranasal orexin-A on sustained attention in an NMDA receptor hypofunction model of schizophrenia
2015	**Bachelor of Arts in Psychology** *(Cum Laude)*, James Madison University Concentration: Behavior Analysis Minor: Biological Anthropology

HONORS AND AWARDS

2020	**Excellence in Scholarship in the Natural and Computational Sciences** Office of Graduate Studies and Research, William and Mary
2017	**Excellence in Scholarship in the Sciences** Office of Graduate Studies and Research, William and Mary
	S. Laurie Sanderson Award for Excellence in Undergraduate Mentoring Office of Graduate Studies and Research, William and Mary
2015	**President's List** James Madison University

	Psi Chi International Honor Society in Psychology James Madison University
2011 to 2015	**Dean's List** James Madison University

GRANTS AND FELLOWSHIPS

2020	**Student Research Grant** Roy R. Charles Center, William and Mary
2017 to 2019	**Recruitment Fellowship** Department of Applied Science, William and Mary

GRANTS AND FELLOWSHIPS (cont.)

2017 to 2019	**Office of Graduate Studies and Research Semesterly Grant** Office of Graduate Studies and Research, William and Mary

RESEARCH EXPERIENCE

Psychiatry Research Fellow, Harvard Medical School, 2021 to present
Principal Investigator: Dr. Robert Strecker, Ph.D.
Species: Mouse (C57BL/6)

Design and conduct experiments using techniques such as stereotaxic optogenetic and local field potential surgery, drug administration, electrophysiology, behavioral training and testing, tissue sectioning and histochemistry, and statistical analyses. Mentor and train students through the Stonehill Undergraduate Research Experience (SURE) program at Stonehill College. Collaborate with other principal investigators at Harvard Medical School/VA Boston Healthcare System.

Graduate Research Assistant, William and Mary, 2015 to 2021
Principal Investigator: Dr. Joshua Burk, Ph.D.
Species: Rat (Sprague Dawley, Fischer 344-Brown Norway F1 hybrid)

Designed and conducted experiments using techniques such as stereotaxic cannulation surgery, drug administration, behavioral training and testing, tissue sectioning and histochemistry, and statistical analyses. Presented at local, regional, and national conferences. Mentored and trained students as well as oversaw honors thesis experiments. Managed students' lab schedules and oversaw behavioral testing shifts. Planned and led weekly lab meetings to discuss ongoing projects and articles related to our research.

Undergraduate Research Assistant, James Madison University, 2013 to 2015

Behavioral Neuroscience Lab, 2014 to 2015
Principal Investigator: Dr. Jeffrey Dyche, Ph.D.
Species: Rat (Sprague Dawley, Spontaneously Hypertensive, Wistar Kyoto)
Shift leader: created lab schedules and coordinated students' lab shifts. Participated in animal training and testing for multiple experiments as well as presented at local, regional, and national conferences.

Experimental Analysis of Behavior Lab, 2013 to 2015
Principal Investigator: Dr. Daniel Holt, Ph.D.
Species: Pigeon (White Carneau)
Participated in animal training and testing for projects related to delay discounting and magnitude effects as well as presented at local, regional, and national conferences.

RESEARCH AND TEACHING EXPERIENCE (cont.)

Cognition and Critical Thinking Lab, 2013 to 2014
Principal Investigator: Dr. Richard West, Ph.D.
Instructed and supervised participants during a computerized test of critical thinking. Assigned Participant Pool credits.

TEACHING EXPERIENCE

Graduate Teaching Assistant, William and Mary, 2015 to 2017

2017	Normal and Pathological Aging (Spring); Cognition and Language (Spring)
2016	Research in Physiological Psychology (Fall); Interplay of Nature and Nurture (Spring); Introduction to Psychology as a Social Science (Spring)
2015	Psychological Statistics (Fall)

Undergraduate Teaching Assistant, James Madison University, 2014 to 2015

2014 to 2015	Psychology of Learning and Behavior (Fall and Spring)

PUBLICATIONS

- **Maness, E.B.**, Burk, J.A., Schiffino, F.L., McKenna, J.T., Strecker, R.E., and McCoy, J.G. (2022). Role of the locus coeruleus and basal forebrain in arousal and attention. *Brain Research Bulletin, 188,* 47-58.

- Schiffino, F.L., McNally, J.M., **Maness, E.B.**, Brown, R.E., and Strecker, R.E. (2022). Basal forebrain parvalbumin neurons modulate vigilant attention and rescue deficits produced by sleep deprivation. *Under review*.
- Burk, J.A., **Maness, E.B.**, Blumenthal, S.A., and Fadel, J.R. (2019). Orexins in cognition: Neuroanatomical and neurochemical substrates. In J.A. Burk and J.R. Fadel (Eds.), *The Orexin/Hypocretin System: Functional roles and therapeutic potential* (pp. 139-153). Academic Press.
- Burk, J.A., Blumenthal, S.A., and **Maness, E.B.** (2018). Neuropharmacology of attention. *European Journal of Pharmacology, 835*(15), pp. 162-168.

TALKS AND PRESENTATIONS

Maness, E.B., Little, P.C., and Burk, J.A. (2021). Orexin-1 receptor antagonism alleviates dizocilpine-induced attentional impairments in an NMDA receptor antagonist model of schizophrenia. Poster presented at the virtual Society for Neuroscience conference.
Maness, E.B. (2021). In search of better treatment of schizophrenia. Talk given for William and Mary's Emergent Scholar Series, Williamsburg, VA.
Maness, E.B. and Burk, J.A. (2021). SB-334867, a selective orexin-1 receptor antagonist, alleviates dizocilpine-induced attentional impairments in an NMDA receptor hypofunctional model of schizophrenia. Poster presented at the Society for Neuroscience Virtual Connectome.

TALKS AND PRESENTATIONS (cont.)

Maness, E.B., Blumenthal, S.A., and Burk, J.A. (2019 and 2020). Dual orexin receptor antagonism attenuates dizocilpine-induced attentional impairments in a rat model of acute psychosis. Poster presented at the Society for Neuroscience, Chicago, IL. Virtual talk given at William and Mary's Graduate Research Symposium.
Blumenthal, S.A., **Maness, E.B.**, Fadel, J.R., and Burk, J.A. (2019). Effects of an orexin-2 receptor agonist on attention following loss of cortical cholinergic inputs. Poster presented at the Society for Neuroscience, Chicago, IL.
Burk, J.A., Patel, R., **Maness, E.B.**, Blumenthal, S.A., and Fadel, J.R. (2019). Effects of medial prefrontal cortical administration of the orexin-1 receptor antagonist, SB-334867, on attentional performance in rats. Poster presented at the Society for Neuroscience, Chicago, IL.
Maness, E.B., Blumenthal, S.A., Fadel, J.R., and Burk, J.A. (2018 to 2019). The effects of manipulating orexinergic neurotransmission on attentional performance in an NMDA receptor hypofunction model of schizophrenia. Poster presented at the Society for Neuroscience (San Diego, CA) and the Central Virginia Chapter of the Society for Neuroscience (Charlottesville, VA).
Blumenthal, S.A., Tapp, A., **Maness, E.B.**, and Burk, J.A. (2018). Effects of medial prefrontal cortical orexin-2 receptor blockade on attention. Poster presented at the Society for Neuroscience, San Diego, CA.

Burk, J.A., Feldmann, J., **Maness, E.B.**, and Blumenthal, S.A. (2018). Effects of intranasal orexin-A on attentional performance. Poster presented at the Society for Neuroscience, San Diego, CA.

Blumenthal, S.A. and **Maness, E.B.** (2018). Effects of infusions to the medial prefrontal cortex of an orexin-2 receptor antagonist on attention. Poster presented at the International Behavioral Neuroscience Society, Boca Raton, FL.

Maness, E.B., Fadel, J.R., and Burk, J.A. (2017 to 2018). Effects of intranasal orexin-A on MK-801-induced attentional deficits. Poster presented at the Society for Neuroscience (Washington, D.C.) and the International Behavioral Neuroscience Society (Boca Raton, FL). Talk given at William and Mary's Graduate Research Symposium, Williamsburg, VA.

Vij, P., **Maness, E.B.**, and Burk, J.A. (2017). The role of orexin-2 receptors in the basal forebrain, characterized by attentional performance in adult rats. Poster presented at the Society for Neuroscience, Washington, D.C.

Tapp, A., **Maness, E.B.**, Vij, P., and Burk, J.A. (2017). Effects of medial prefrontal cortical administration of the orexin-2 receptor antagonist, TCS-OX2-29, on attentional performance in rats. Poster presented at the Society for Neuroscience, Washington, D.C

Maness, E.B., Leong, C.S., and Burk, J.A. (2016 to 2017). Effects of *N*-Desmethylclozapine on attentional performance following loss of basal forebrain corticopetal cholinergic inputs. Poster presented at the Society for Neuroscience (San Diego, CA) and the Central Virginia Chapter of the Society for Neuroscience (Roanoke, VA). Talk given at William and Mary's Graduate Research Symposium, Williamsburg, VA.

Leong, C.S., **Maness, E.B.**, Baraki, D.I., and Burk, J.A. (2016). Effects of protein kinase C activation on attention deficits following loss of corticopetal cholinergic neurons. Poster presented at the Society for Neuroscience, San Diego, CA.

Maness, E.B. and Burk, J.A. (2016). Effects of muscarinic-1 receptor stimulation on attentional deficits induced by loss of cortical cholinergic projections. Poster presented at the Central Virginia Chapter of the Society for Neuroscience (Charlottesville, VA) and William and Mary's Graduate Research Symposium (Williamsburg, VA).

TALKS AND PRESENTATIONS (cont.)

Ponder, K., Sequira, S., Cowan, C. Contreras, M., Gangsaas, A., Krause, B., Mack, N., Pointon, G., Bates, E.B., **Maness, E.B.**, Shoup-Knox, M., and Dyche, J. (2015). Sleep deprivation and voluntary alcohol consumption: The neuroplasticity of chronic behaviors. Poster presented at the Society for Neuroscience, Chicago, IL.

Bates, E., Bivens, D., Carnes, A., Cowan, C., Howard, K., Keith, R., Mack, N., **Maness, E.B.**, Mangalmurti, N., Meccariello, M., Pointon, G., Rutter, D., Stewart, M., Ponder, K., Sequeira, S., Dyche, J. (2015). Sleep Deprivation and Voluntary Alcohol Consumption in Adolescent Rats. Poster presented at the L. Starling Reid Undergraduate Psychology Conference at the University of Virginia (Charlottesville, VA) and James Madison University's Psychology Student Symposium (Harrisonburg, VA).

Bates, E., Brown, J.M., Cousins, V., Foote, E., Herr, S.P., Livesay, T.W., **Maness, E.B.**, Phelan, M.J., Ricotta, J., Rutter, D., Wigley, B.M., Williams, D., Wolf, M.R., Worrell, R.D.,

and Holt, D.D. (2015). Delay Discounting in Pigeons. Presented at James Madison University's Psychology Student Symposium, Harrisonburg, VA.
O'Malley, J.J., Ponder, K., Sequiera, S., Shemery, A., Bates, E., Cowan, C., Mack, N., **Maness, E.B**, Meccariello, M., Vassallo, M., Holt, D., and Dyche, J. (2014) Auditory Masking in Spontaneously Hypertensive Rats: An Examination of the Continuum of Impulsivity. Poster presented at the Society for Neuroscience, Washington, D.C.

SERVICE AND OUTREACH

- **Graduate Advisor**, First Generation Low Income (FGLI) Student Organization, William and Mary
- **Applied Science Representative**, Graduate Student Association, William and Mary
- **"Scientist"**, Skype-A-Scientist
- **Member and Speaker**, Emergent Scholar Series, William and Mary
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