mPFC and Its Communication with NAc Support Inhibitory Control of Approach Action

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THESIS

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For my dad

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LIST OF ABBREVIATIONS

Ach	Acetylcholine
ADHD	Attention deficit hyeractivity disdorder
BIS	Barrat impulsivity scale
BA	Broadmann's Area
DA	Dopamine
dlPFC	Dorsal lateral prefrontal cortex
fMRI	Functional magnetic resonance imaging
mPFC	medial prefrontal cortex
MGLu2/3	Metabotropic glutamate 2/3 receptor
NE	Norepinephrine
NAc	Nucleus accumbens
OFC	Orbital frontal cortex
preSMA	Presupplimentary motor cortex
5HT2A	Serotonin 2A receptor
SDT	Signal detection theory
SSRT	Stop signal reaction time
SST	Stop signal task
vlPFC	Ventral laterl prefrontal cortex

SUMMARY

Environmental cues associated with rewards, such as food or substances of abuse, often prompt approach and consummatory actions that are difficult to override, even when restraint would be beneficial in the short- or long-term. As such, much research has focused on the neural underpinnings of behavior driven by cues, directed at obtaining reward. However, the neural systems that underlie restraint of behavior in response to reward related cues are not well understood, but play a critical role in maladaptive, impulsive actions. I hypothesized that medial prefrontal cortex (mPFC) and its communication with nucleus accumbens (NAc) play vital roles in such behavioral restraint. I implanted multiwire electrode arrays in the mPFC and recorded the activity of single neurons and characterized firing rate responses to task cues. Neurons in mPFC showed populations of neurons either increased or decreased firing rates transiently in responses to the onset of cues when the animal preformed correctly on both Go and NoGo trials; a small population of neurons showed transient increases that were higher for NoGo compared to Go cues. I then pharmacologically inactivated mPFC and showed that accuracy on NoGo trials was largely reduced. I then used chemogenetics to facilitate firing of mPFC neurons and show increased accuracy on NoGo trials. Together these finding suggest that mPFC is both necessary and sufficient to support inhibitory control on NoGo trials.

mPFc sends strong excitatory, glutamatergic connections to NAc. Previous work from our lab showed restraint of approach behavior on NoGo trials was substantially reduced when glutamatergic AMPA/kainite receptors were blocked in NAc, suggesting that excitatory inputs inform NAc to inhibit approach behavior. I hypothesized that

mPFC is one origin of the excitatory signal. To investigate this hypothesis, I pharmacologically disconnected the functional communication between mPFC and NAc and found that bilateral and ipsilateral disconnection of mPFC communication with NAc caused an increase in NoGo errors. These results suggest that mPFC signals the appropriate action needed for optimal performance and that NAc integrates this signal to render appropriate approach/withhold behavior.

1. Introduction

Appetitive stimuli in our environment often elicit approach and consummatory responses that can be hard to effectively direct or override. For example, one may go for one too many cookies from the holiday spread or purchase that sale item even though they are low on funds. This difficulty is the phenotypic expression of one's impulsiveness, and conversely, the ability to optimally perform in the face of these appetitive stimuli is one's phenotypic impulse control; together these two aspects make up the personality trait of one's impulsivity. Proper balance in impulsivity, between impulsiveness and impulse control, can be beneficial to an organism's survival. Unbalanced impulsivity, however, can be detrimental to individuals and lead to injury or death. The behavioral nature of impulsivity has been studied at length. However, we still do not have a complete picture of the neural circuitry that supports impulsivity and we are therefore at loss to combat the detrimental contributions of impulsiveness. In this dissertation, I seek to elucidate multiple, but distinct, avenues in which this impulsivity is expressed in human and animal models. I will then focus on the neurobiological underpinnings that influence impulsivity. Finally, I will propose a series of experiments to illuminate a role of for medial prefrontal cortex (mPFC) of the rat, and its communication with the subcortical nucleus accumbens (NAc), in a specific type of impulsivity: behavioral restraint.

Much of our lives are guided by impulses that direct behavior toward or away from stimuli in the environment. Indeed this impulsivity pervades even the smallest of life's scenarios: we see something that we'd like to eat, hear someone in the hall that we'd like to talk to, or click on an interesting website, for example. Because of the ubiquity of impulsivity's influence over behavior, it has become easy to refer to it in the

vernacular as a homogenized construct; a unitary underlying personality trait that influences how (well) one interacts with their environment. Furthermore, references to impulsivity have become connoted with maladaptive or destructive behaviors. As such, it is easy to forget that impulsivity can be beneficial to an organism individually and to the evolution of a species as a whole. Dickman (1990) points to two different types of impulsivity: Dysfunctional impulsivity in which individuals execute action without proper forethought in scenarios that lead to detriment. He distinguishes that phenomenon from Functional impulsivity in which individuals similarly execute action without forethought but in scenarios that lead to optimal outcomes, such as those scenarios in which one must act immediately lest they miss a good, but fleeting opportunity. Cale & Lilienfeld (2006) further this notion of a dichotomy in impulsivity by explaining that functional impulsivity can be evolutionarily beneficial by promoting organisms to reasonably test risks in the environment that could lead to better than usual outcomes. Functional impulsivity also fosters exploration in the environment that could result in unexpected opportunities, as well as promotes extroversion and sociability. Interestingly, these two impulsivity personality traits, functional and dysfunctional, appear to be unrelated as persons that exhibit higher occurrences of one type do not necessarily exhibit more occurrences of the other.

Even though sometimes beneficial, the negative connotation of impulsivity has persisted in subsequent studies and this persistence becomes apparent when one examines existing functional definitions used by researchers in their attempts to capture the breadth of impulsivity's impact on behavior and cognition. In a classic definition, Durana, Barnes, Johnson, & Shure (1993) describe impulsivity as "actions which are

poorly conceived, prematurely expressed, unduly risky or inappropriate to the situation and that often result in undesirable consequences". Other researchers, though, opt for more vague language, presumably to not exclude behaviors and decisions that do not fall nicely under the more detailed definitions. For example, Winstanley (2011) describes impulsivity broadly as "acting, or making decisions, without appropriate forethought, there enhancing the potential for negative consequences". These negative implications of impulsivity have likely been perpetuated, at least in part, by the deleterious manner in which impulsiveness contributes to both maladaptive behavior and psychiatric disorders. For example, substance abuse and impulsivity are intimately intertwined, with each component influencing the other to create a vicious cycle that perpetuates addiction. In order for substance users to modify or terminate substance consumption, they must engage effortful voluntary inhibition of impulsive approach toward substances and substance-related cues. Moreover, impulsiveness must be tempered throughout all stages of the addiction life-cycle as it increases the likelihood that one will start using drugs, maintains the addiction by the facilitating increases in drug consumption and hindering the ability to reduce consumption, and finally precipitates relapse (for review see Jentsch et al. 2014). In addition, impulsivity is a hallmark, transdiagnostic criterion for many psychiatric disorders including obesity, impulsive shopping, problem gambling, attention deficit/hyperactivity disorder (ADHD), kleptomania, borderline personality disorder, bipolar disorder, impulse control disorders, among others (American Psychiatric Association, 2013). Therefore, its fundamental properties have been extensively studied, both behaviorally and neurobiologically, with hope to derive effective therapies to combat damaging impulsiveness.

With the ubiquity of impulsivity has come the elucidation of nuances in the behavioral phenomena associated with the construct. Early on, Buss & Plomin (1975) postulated that impulsivity is a multidimensional construct for which behavioral control is the fundamental root. As well, Dickman (1993) proposed three dimensions of impulsivity: attentional, reflection-impulsivity, and disinhibition. Indeed for sometime, researchers have turned their attention to capturing distinctions in impulsive behaviors through questionnaires in humans and behavioral tests in both humans and animal models. For example, the Barrat Impulsivity Scale (BIS) was an early questionnaire that set out to describe the complexities of impulsivity as it existed in a “normal” person. The questionnaire sought to understand impulsivity’s role in psychopathology and relate the construct to other personality traits (Barratt, Monahan, and Steadman 1994). Since its inception, the scale has gone through a number of iterations to evolve with our understanding of the multidimensionality of impulsivity and produce fruitful results. For example, analysis of a later form of the BIS lead Patton (1995) to dissociable second order factors of impulsivity: attentional stimulation, motor impulsivity, and non-planning (for a review of early work, see Evenden, 1999). Over time and much study, the larger, more nebulous constructs promoted by Patton et al. have been further broken down into more definite categories. For example in a recent review, Fineberg et al. (2014) depict impulsivity as comprised of concepts relating to response, choice, reflection, and decision-making. The fact that impulsivity is a conglomerate construct that encompasses numerous sub-constructs should not be surprising, nor should it detract from the validity of impulsivity as a whole. After all, many psychological constructs amalgamate multiple sub-constructs, with memory being the most notable (Kesner and

Rogers 2004). Such distinctions have paved the way for contemporary works that investigate both impulsive behavior and the neurobiology that supports it, or the neural underpinnings that have gone awry to detriment it (see (Winstanley, 2011 and Dalley, Everitt, & Robbins, 2011 for reviews). Indeed, these neurobiological studies have helped to establish the modern divisions of impulsivity into those behaviors that fall under the umbrellas of impulsive choice and those behaviors that fall under impulsive action (Figure 1.1). These two phenomena can then be parsed apart even further to their sub-constructs and experimental paradigms designed to investigate them both behaviorally and neurobiologically. Although the sub-constructs sometimes share similar properties, the neural underpinnings of each can differ, giving credence to the ontology of their existence as dissociable constructs. Moreover, these constructs can also predict, and contribute, differentially to the maladaptive behavior and psychiatric disorders mentioned earlier. Therefore it is important to discern the behaviors associated with the term impulsivity (impulse control) as well as their neural underpinning before laying out the behavioral paradigm used to model impulse control in the later series of proposed studies in this document.

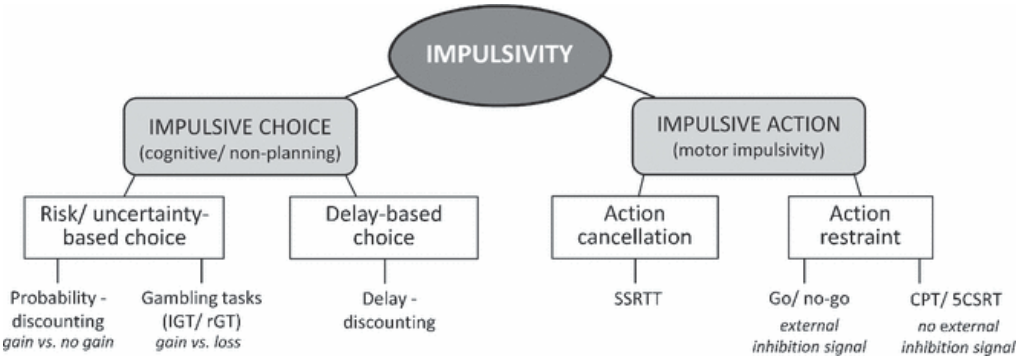

Figure 1.1 Diagrammatic subdivisions of impulsivity (Winstanley 2011).

1.1 Choice Impulsivity

Impulsivity can be split into impulsive action and impulsive choice (Figure 1). One type of impulsive choice (or Choice Impulsivity) typically refers to decisions made between options that deliver payouts at different time points: a sooner, but smaller payout versus a larger payout that delivered a longer time interval (Bickel and Marsch 2001). Choice impulsivity encompasses aspects of impulsivity's definition that pertain to lack of planning and neglect of future consequences. This type of decision has been referred to as intertemporal choice, delay-based choice, delay discounting, temporal discounting. Here, I will refer to it as temporal discounting. The category of impulsive choice in Figure 1 also encompasses risk/uncertainty-based decision-making. These are choices made between options from which at least one outcome is uncertain and delivered probabilistically: choices between an option that delivers a small, certain outcome versus an option that delivers a larger reward at varying levels of probability, for example. In recent literature, however, it has been suggested that although risk/uncertainty-based decisions share some qualities with temporal discounting, this uncertainty-based decision-making should be separated into its own category of impulsivity (see Fineberg et al., 2014; Hamilton et al., 2015). This "decision-making impulsivity", like other forms of impulsivity (e.g. attentional or reflection impulsivity) lies outside the scope of this dissertation.

1.1.1 Temporal Discounting. In temporal discounting paradigms, subjects are given the choice between two options: one that gives a smaller outcome sooner (smaller-sooner) and one that produces a larger outcome later (larger-later). For

example, would one prefer five dollars now or ten dollars in a week, or five dollars now or 100 dollars in a year? The amount of payout and time to delivery can then be manipulated. A rational decision maker would always choose the larger-later reward as time has no tangible effect on the objective value of the payout (for review of rational choice theory, see Rawling & Mele, 2004). However, both humans and animals tend to make decisions under the influence of internal biases, such as impulsivity. These biases can be illuminated in temporal discounting paradigms by manipulating the payout amount and length of time it takes to receive it. Experimenters present numerous repetitions of these decisions with multiple payouts and delivery times to quantify the extent to which time discounts the larger payout to the point that the subjects switch their preference from larger-later payouts to the smaller-sooner ones. This temporal discounting can be measured in several ways. By providing multiple payouts and delays, experimenters determine the indifference point between two the options; the point at which the subjects switch their preference that can then be used to establish discounting curves (Mazur 1988; Mendez et al. 2010; Richards et al. 1997). These curves represent the rate at which the value of the payout is reduced as a function of the time it takes to receive it. Steeper discounting curves mean that only a short amount of time is needed to reduce the value of the larger-later outcome to the point that subjects switch their preference to the smaller-sooner option and this steepness represents the subjects' level of choice impulsivity (for review see Hamilton et al., 2015). Alternatively to mathematical functions, experimenters also use more straightforward calculations such as the percent of choices subjects make for one option over the other.

In addition to human paradigms, temporal discounting tasks have been adapted for investigations using animal models. These animal models are especially important when investigating the neural substrates/processes associated with choice impulsivity as they allow for more invasive approaches. Although some paradigms have been designed for use in non-human primates (see Woolverton, Myerson, & Green, 2007), a majority of animal models are tailored to rodents and thus will be the focus here. Paradigms for rodent impulsive choice are modeled closely to those paradigms designed for humans. In rodent models, the animal is often placed in an operant chamber and given the choice between an option (e.g. a lever to press or port to nose-poke in) that delivers a small reward (or more precisely, a reinforcer) quickly or an option that provides a larger reward that the animal must wait for. As is typical with rodent paradigms, the reward is often food or water, but has also been carried out with intracranial self-stimulation (Rokosik and Napier 2011). Like human-based paradigms, rodent choice impulsivity is indexed based on the delay of reward delivery that precipitates the animal to switch from the larger-later to the smaller-sooner option. Also similar to human-based paradigms, the timing/reward size can be presented within session or across sessions. In within session designs, animals are often presented with blocks of trials with several trials of same reward/time pairing per block. The blocks then switch to a new reward/time paring. For example, the blocks may start out with the larger reward associated with no delay, then a increase the delay to 3 seconds, 5 seconds, 10 seconds, and so on (see Evenden, 1999; Hamilton et al., 2015; Mitchell & Wilson, 2012; Winstanley, Dalley, Theobald, & Robbins, 2003 for review). Before choice blocks, animals are typically given a series of forced choice blocks to ensure they learn

the behavior-payout contingencies of both options. They are then presented with a series of free choice trials in which the animals chooses between the two options. Alternatively, the delay/reward contingencies can be altered between sessions. Both within and between designs construct a discounting curve to represent the animals' level of choice impulsivity (for an argument against the validity of discounting paradigms in animals, see Hayden, 2015).

Together, human and animal investigations have made it possible to investigate how impulsive choice is associated with psychiatric and behavioral disorders, as well as their neural underpinnings (which will be addressed below). Discounting tasks have proven beneficial in understanding an array of problems, some being psychiatric (e.g Cáceda, Nemeroff, & Harvey, 2014; Rogers, Moeller, Swann, & Clark, 2010) and others being maladaptive behaviors that lead to detriment of individuals or those people around them. Indeed, discounting tasks show impulsivity that is both predictive of some behaviors and/or is a result of other maladaptive behaviors. For example increased discounting is associated with problem gambling (for review see Leeman & Potenza, 2012). As well, choice impulsivity may have deleterious effects an individual's ability to manage their finances through several domains. Particularly, individuals with high discounting tendencies may abuse credit cards as goods can be acquired immediately, rather than at a later time when the individual has the cash in hand (Hamilton and Potenza 2012). Temporal discounting proclivities also correlate with behavioral health choices. For example, Johnson & Bruner (2012) adapted a temporal discounting paradigm using hypothetical sexual encounters and found that those participants that engaged in riskier sex practices discounted delayed sexual gratifications more than

those participants that did not engage in risky sex. Choice impulsivity is also complexly intertwined with ingestive behaviors: Increased discounting of delayed rewards is associated with binge eating disorder, for example (Davis et al. 2010). Additionally in a network analysis, Barlow, Reeves, McKee, Galea, & Stuckler (2016) found higher discounting rates for individuals that consumed an unhealthy diet and for people who were overweight or obese. They also found that increased discounting was associated with higher energy intake and negatively associated with weight loss. Interestingly, discounting was reduced when individuals practiced mindful eating. Discounting is also complexly associated with substance abuse and addiction, as was mentioned above. In a meta-analysis, Amlung, Vedelago, Acker, Balodis, & Mackillop (2016) found that steeper discounting curves were associated with addictive behaviors with alcohol, tobacco, cannabis, and stimulants. Moreover, increased discounting was correlated with severity and frequency of use. Substance abuse poses a particularly complex interaction with choice impulsivity as discounting is not only associated with substance abuse, but can also be a result of substance abuse that then feeds forward to maintain addictive behaviors (Petry 2001; Sweitzer et al. 2008).

Because of the detrimental influence of choice impulsivity, it has become pertinent to understand the neurobiological underpinnings of discounting behavior. The structure of temporal discounting paradigms makes them ideal for human neuroimaging studies: distinct trials are presented to participants that can then be analyzed using event-related neuroimaging analysis to identify cortical and subcortical activity correlates associated with each choice. In seminal work, McClure, Laibson, Loewenstein, & Cohen (2004) used functional magnetic resonance imaging (fMRI) while

participants made a series of binary choices in a temporal discounting experiment. They found greater activation in limbic structures and paralimbic cortices associated with choices for more immediate rewards: ventral striatum, medial orbital frontal cortex (OFC), mPFC, posterior cingulate cortex, and left posterior hippocampus. From this activation, the authors concluded that these structures make up a dissociable system responsible for eliciting choices toward the smaller-sooner choice. However, participants likely do not execute choices toward one option over another based solely on the delay during a given trial. Instead, they likely (automatically) construct a more abstract subjective value of each option that underlies their choice. Experimenters can then correlate that subjective value with measures of neural activity derived from functional imaging. With that in mind, Kable & Glimcher, (2007) refuted the findings that there are separate systems for immediate versus delayed rewards. They found that those areas previously thought to be associated with immediate rewards, in fact, tracked the subjective value of the delayed option; the activity in these areas increased as the objective amount of the reward changed as a function of the associated delay. However, how the brain influences impulsive choice may not be so easily reduced to the activity of just this handful of brain regions. Hamilton et al. (2015) describe the process as an imbalance of activity between structures that are closely associated with reward, like some of those described by Kable and Glimcher (ventral striatum and mPFC), and structures that are often associated with control like in McClure et al.'s findings (dorsal lateral prefrontal cortex [dlPFC] and ventral lateral prefrontal cortex [vlPFC]). Evidence for the role of the latter has been shown using transcranial magnetic stimulation (TMS) in human subjects. Sheffer et al. (2013) used TMS to increase activity in lateral

prefrontal cortex and found decreased impulsive choice while Figner et al. (2010) used the same technique to reduce activity in dorsal prefrontal cortex and found an increase in impulsive choice. Communication between the above the structures is also important as is suggested by findings that show that lower white matter tract integrity between the mPFC and ventral striatum is associated with increased impulsive choice.

Human imaging and TMS studies provide evidence for structural correlates of discounting behavior. However the activity within and between these structures is likely rendered through modulation through complex interstructural communication and neurotransmitter release. For example, van Gaalen, van Koten, Schoffelmeer, & Vanderschuren (2006) showed that blocking dopamine D1 receptors and alpha-2 adrenergic receptors systemically increases choice impulsivity in rats. Findings from Winstanley, Eagle, & Robbins (2006) further the notion of transmitter involvement with results showing real time increases in serotonin release in mPFC and a dopamine metabolite (3, 4-di-hydroxy-phenylocetic acid) in OFC. This indicated not only the involvement of these transmitters, but also indicated a double dissociation for the involvement of dopamine and serotonin in these brain areas. Also in OFC, Wischhof et al. (2011) showed that a serotonin 2A (5-HT2A) agonist increased impulsive choice but this increase prevented when the drug was coadministered with also a metabotropic glutamate 2/3 (mGlu2/3) receptor agonist, suggesting that metabotropic glutamate receptors may regulate the effect of serotonin on impulsive choice. Floresco, St Onge, Ghods-Sharifi, & Winstanley (2008) also implicated glutamate's involvement in discounting through systemic injection of the noncompetitive NMDA receptor antagonist ketamine. These results were furthered by Cottone et al. (2013) who showed that

administration of ketamine, a non-competitive glutamate antagonist, increased discounting in low discounting rats, but had no effect on high discounting animals. Together, these results suggest a complex relationship between structural localizations in the brain and that honed through specific neurotransmitter interactions.

1.2 Impulsive Action/Inhibitory Control

The other side of the impulsivity coin is Impulsive action, which is also called rapid response impulsivity (Figure 1). These behaviors generally involve motoric actions, usually approach actions, that are poorly thought out or executed automatically in a manner out of context with the situation that lead to suboptimal or detrimental outcomes. Impulsive action has also been characterized as an inability to inhibit prepotent responses (Moeller et al. 2001). Prepotent responses are strong, automatically activated behavioral biases that have exceptional power over action such that the biased behavioral tendency takes precedence over other behavioral possibilities that could be performed in a given scenario. Bari & Robbins (2013) specify that voluntary inhibition is subcomponent of cognitive control (executive control), a construct that organizes and regulates lower order cognitive functions: updating working memory, shifting between sets, changing behavior based on task contingencies, and inhibition. Still, there is contention as to whether inhibition is, in fact, its own subconstruct of executive control or whether it is a fundamental and unifying component of all executive control constructs (Barkley 1997; Dempster and Corkill 1999; Zacks and Hasher 1994), while others believe inhibition is only made possible by through the aforementioned faculties of executive control (Alderson et al. 2010; Friedman and

Miyake 2004): a “chicken or the egg” problem. Such circularity may be indicative of a more complex relationship, or balance, between inhibition and the other executive control components, like cognitive flexibility and attention. To borrow words from Bari & Robbins (2013), in order to restrain behavior within context “we need to pay attention to cues that signal a sudden change in the environment in order to inhibit the current flow of thoughts and actions when they are no more appropriate, and then select and shift to a new cognitive/behavior set”. As is indicated by Bari and Robbins, inhibition is not the sole contributor to impulsive action. However, inhibition of action is easily measured in behavioral paradigms and stands a good proxy of impulsive actions. Therefore, paradigms that measure behavioral inhibition will be the focus of this literature summary (although there will be some mention of the other influential cognitive constructs in the later explication of the neural underpinnings of inhibitory control).

In broad strokes, inhibition can be thought of as restraint of behavior: the voluntary prevention of a behavior from being carried out or halted once initiated. Generally, it is approach behavior toward an environmental object that is put in check and has been referred to as behavioral restraint, inhibitory control, or “stopping”. Such restraint can allow a subject to avoid negative consequences or restraint can be engaged in order to receive an outcome that is more beneficial than the outcome of immediate approach. It could be argued that inhibitory control is a balance between motivation and control (Jentsch & Pennington, 2014) and we seek to understand inhibition in order stop ourselves from engaging in practices that are immediately gratifying but that ultimately net in the negative. For example, one may want to restrain oneself from taking one more cookie because they looking to shed a few pounds, to

stop themselves from having that cigarette because they have lung problems, or refrain from purchasing that sale item because they can't afford it. Indeed failure to restrain is seen as a problem because it often leads to detriment. Because of this, inhibitory control paradigms have been a favorite of substance abuse, behavioral addiction, and obesity researchers with the goal to understand inhibitory control in each domain; to identify the underlying cause of failed inhibitory control that leads to each of these diseases, and then find therapeutics to reinstate control and eradicate the pathology (See Jentsch et al., 2014; Winstanley et al., 2010)

As indicated in Figure 1, impulsive action can be bifurcated into two behavioral subcategories: action cancellation and action restraint (Schachar et al. 2007). Poor planning and motor control influence both of these constructs, but the paradigms differ on the point at which they elicit action inhibition. In action cancellation, subjects inhibit an action response after they have initiated it, whereas in action restraint the subject inhibits the action from the outset, preventing themselves from initiating the action. As well, action cancellation and action restraint may be further delineated by their separable neural underpinnings, which will be discussed in further detail below. These two behavioral constructs can be reflected in a number of different experimental paradigms that have been fruitful in distinguishing both overlapping and distinct neural substrates between the two. As well, impulsive action paradigms are highly translatable between species and have been developed for both humans and rodents (see Eagle, Bari, & Robbins, 2008 for review). A few of these constructs will be discussed in further detail below.

Experimental paradigms that model impulsive action at times share behavioral

components that are similar to those behaviors seen in impulsive choice paradigms. Such similarities may confuse the distinction between the two constructs and therefore I will clarify their distinction further before explicating impulsive action models. A number of the following paradigms that measure inhibition incorporate a delay on “inhibit trials” that the subject must endure while also inhibiting action in order to be rewarded, avoid punishment, or move on to the next trial. These trials, however, are distinct from trials in impulsive choice tasks (which are derived from delay-based behavior) even though they both draw on the similar attributes of the impulsivity definition, such as poor planning. And although these trials in the inhibition paradigms may seem like a choice between sooner and later, the sooner options (i.e. acting without waiting) does not result in a smaller reward; it results in nothing or punishment. Additionally, the behavioral outcome on impulsive choice task trials more directly indicates the subject’s preference for one outcome over the other: smaller-sooner or larger-later outcomes. However in inhibitory control paradigms, animals are often provided with distinct trial types that are delineated by the behavioral contingencies that lead subjects to acquire rewards or avoid punishment. Furthermore, the subject is cued as to which trial type they are currently participating in with either, otherwise arbitrary, cues (such as lights and sounds) or behaviorally relevant cues (such as distinct levers or nose-poke ports) that lead to outcomes when an operant behavior is performed on them (e.g. reward vs. punishment). This setup in action restraint paradigms establishes a set of rules by which the subject must follow in order to perform optimally on the task. Such rule-based behavior is not pertinent to performing optimally on impulsive choice paradigms, as the most optimal strategy relies on the preference of the subject.

Empirically, impulsive action and choice impulsivity are very weakly correlated, if at all. Lane, Cherek, Rhoades, Pietras, & Tcheremissine (2003) investigated relationships between psychometric, questionnaire measurements of impulsivity traits and experimental procedures meant characterize an individual's impulsivity traits: both choice impulsivity tasks and response inhibition tasks (action restraint). As well, they investigated relationships between the experimental measures of impulsive choice and impulsive action. They found significant correlation among the psychometric measures of impulsivity, but no correlation with experimental procedures (save for one). Additionally, they found that although measures of impulsive choice were positively correlated with response inhibition measures, none of these correlations were significant. Reynolds, Ortengren, Richards, & de Wit (2006) bolstered the previous finding by also showing that most of the questionnaire measure were correlated, but again found no correlation between impulsive choice with either action cancellation or action restraint. Moreover, Reynolds et al. conducted principal component analysis that revealed that the variance across impulsivity measures loaded differentially between impulsive action and impulsive choice, giving further credence that these two constructs capture dissociable impulsivity traits.

1.2.1 Stop Signal Task (SST). SST is a paradigm designed to model action cancellation, the ability to inhibit an action after it has been initiated. Typically, the subject is cued to initiate a response and then periodically is presented with a second cue that instructs them to inhibit the initiated response. These "Stop" cues are presented at variable delays after action initiations. In their seminal work, Logan & Cowan (1984) established a paradigm using human participants and developed a

working model and theory to help better characterize the nature in which action cancellation was carried out. In the primary “Go” task, subjects were presented with a series of four letters displayed on a cathode ray tube and then asked to respond as fast as possible on one of two telegraph keys that they pressed with either their index or middle fingers. In the task, the subjects categorized the presented letter by using their index finger to respond to two of the four letters and their middle finger to respond the other remaining two. Because the subjects respond as quickly as possible, their responses become strongly biased toward the Go, approach response . On 25% of the trials, after the letter was displayed, subjects were presented with a tone that indicated that they were to inhibit their press response on either key. That is, they were given a Stop signal. This Stop signal was presented at variable delays across the session. The main dependent variable was the probability of responding on the primary task when a stop signal was presented. The variable delays allowed the experimenters to measure the probability of responding as a function of the delay to determine the effect of timing on the ability to cancel actions. They also measured the Stop Signal Reaction Time (SSRT) it took for the subject to inhibit pressing relative to the reaction time on Go trials. The authors showed that the farther in time the Stop signal was presented after the Go, the greater the probability that the subject would press the key; that is, not be able to inhibit the action. The authors theorized that this effect was due to two independent, but competing cognitive faculties: one that drives the completion of the Go action and one that drives the Stop action. They argued that whichever of these faculties won the race to completion was the one most able to influence the motor outcome. Therefore the SSRT can be thought of as the relative time it takes to complete the Stop process

relative to the Go process. Additionally, they theorized that longer reactions were indicative of more difficulty in inhibiting responding and thus were a measure of inhibitory control. This “race horse” theory spawned an increase in SST studies that used SSRT to measure underlying inhibitory control tendencies that were previously unobservable. Later studies evolved the original paradigm beyond finger tapping responses to a raft of behavioral response methods, for example moving the arms (Henry and Harrison 1961) squeezing (De Jong et al. 1990), typing (Logan, 1983; Rabbitt, 1978), speaking (Ladefoged P, Silverstein R 1973; Levelt 1983). As well, these studied employed alternative response stimuli (both Go cues and Stop signals), such as shapes and auditory stimuli.

Using human subjects, the SST has been fruitful in revealing correlative and predictive associations with both maladaptive behavior, such as maladaptive food consumption and substance abuse, and psychiatric disorders. Oosterlaan, Logan, & Sergeant (1998) indicated that ADHD patient showed longer SSRTs (they took longer to stop) compared to non-ADHD controls. Alderson, Rapport, Sarver, & Kofler (2008) conducted a meta-analysis that bolstered those previous findings, but went on to show that ADHD patients showed slower and more variable reaction times to both the stop signal and the Go signals which may be due to deficits in lower level cognitive processes and motor execution that are necessary to adequately perform the SST. In addition to ADHD, other psychiatric patients show deficits on the SST. Patients with OCD exhibit longer SSRT along with patients that suffer from compulsive disorders such as trichotillomania (compulsive hair pulling) and Tourette’s syndrome. Unlike ADHD, though, these latter patients show longer reaction times that are isolated to the

stop signal, perhaps indicative of the hallmark poor behavioral control associated with the each disorder (Chamberlain et al. 2006; Goudriaan et al. 2006; Verbruggen and Logan 2008). In addition to psychiatric disorders, a number behavioral disorders are marked by their inability stop approach actions and SST (and SSRT) has been beneficial in revealing underlying inhibitory deficits that may contribute to these problems. For example, SST has been studied at length in addiction (both substance abuse and behavioral addictions). In the case of addiction, however, inhibitory control results varied or were contradictory across studies and thus muddied the waters, so to speak, as to the contribution action cancellation played as a correlate of addiction. The reason for these variations may have been due to low samples sizes with low statistical power or to the restriction to a single type of substance abuse that may have over confined interpretations (Smith et al. 2014). To address these concerns, Smith et al. conducted a meta-analysis of 97 published papers to illuminate the association of inhibitory control deficits with addiction across both substance abuse and behavioral addictions (such as problem gambling and Internet addictions). This meta-analysis allowed for meaningful inclusion of studies that used small sample sizes. Their analysis suggests SSRT cannot be taken as uniform correlate of addiction behavior irrespective of the abused substance or behavior. In substance abusing populations, they found medium-large deficits associated use of the stimulant methamphetamine, but only small-medium deficits with use of the stimulant cocaine. Additionally, they only found small-medium deficits in alcohol abusers, and nodeficits in either nicotine dependent subjects or cannabis users. They also found medium-large deficits in problem gamblers.

In addition to work with human subjects, SSRT has also been adapted for use in non-human animals. For this review, I will focus on the work in rodents. Rodent models of SST were developed with the primary intention to study the underlying neural circuitry that supports action cancellation as these paradigms allow for more invasive methods that are not possible in studies with human subjects (Eagle & Robbins, 2003). Eagle and Robbins designed a task in which rats are placed in an operant chamber and trained to sequentially press two levers to obtain food rewards. In the task, rats nose-poke in a center port to start a trial. After the nose-poke, a lever on the left side of the chamber is presented and the rat must press the lever. When the lever is pressed, a second lever on the right side of the chamber is presented for a brief time that the rat must rapidly press in order to receive a food reward (Go trials). The right lever is only extended for a short time to promote the rat to respond as quickly as possible and establish the strong bias toward the Go, approach response. On 20% of trials, stop trials, a tone is sounded after the right lever is extended to instruct the animal that they are not to press the right lever. The tone is sounded at variable delays to prevent the animals from anticipating the tone. If the animal successfully cancels/inhibits the approach behavior, they are rewarded. The authors measured the mean reaction time to both Go and Stop trials. They found that rats perform the task in a manner comparable to humans such that when the Stop signal was presented later, closer to the time the rat completed pressing on the right lever, it was more difficult to inhibit the approach. As well, the mean reaction time on either Go or Stop trials did not vary as a function of the delay. This work established the rat version of the SSRT as a valid

homologous model of action cancellation to be used to uncover the complex neural underpinnings of this type of inhibitory control (to be discussed later).

1.2.2 Go/NoGo task. In seminal work, Iversen & Mishkin, (1970) developed the Go/NoGo task to characterize neural substrates necessary for a primate to be able to discriminate approach responses from withholding responses. They trained monkeys to associate one tone with lifting a door to receive a food reward (Go trial) and a second, distinct tone with no reward (NoGo trial). They then tested the animals on how well they were able to withhold approach responding when the NoGo trials were interleaved among Go trials. Since its inception, this Go/NoGo paradigm has been modified and used at length to study action restraint behavior across numerous domains in both normal and psychiatric patients (see Wright, Lipszyc, Dupuis, Thayapararajah, & Schachar, 2014). In studies with humans, participants are trained to respond as rapidly as possible (using a variety of response methods: key pressing, touch screens, speaking, etc) to an array of Go cues. Such repetition is thought to establish a strongly biased approach response action. Periodically, the participant is presented with a distinct cue (NoGo trials) to which they are to withhold, or inhibit, responding. For example, the subject might be required to respond to letters or shapes that are presented in blue, but are to withhold pressing when the letter or shape is presented in red. The level of inhibitory control is then measured through the number of commission errors made; that is, the number of times they inappropriately provided a response on NoGo trials. Those participants with more commission errors are ostensibly more impulsive. In additions, the number of omission errors (inappropriately withholding on Go trials) is sometimes calculated and is often indicative of lack of attention in the task

or misunderstanding of the behavioral contingencies of the task. Mean reaction time can also be calculated for correct approach responses on Go trials and commission errors on NoGo trials, but it is less clear how this measure captures processing in the task.

Like the SST, Go/NoGo has been used to examine psychiatric and behavioral disorders, especially those disorders that are characterized by lack of restraint. In a meta-analysis, Wright et al. examined deficits in Go/NoGo performance across psychiatric illnesses. Like SST, however, Wright et al. found that Go/NoGo cannot be taken as a unitary contributor, or indicator, across illnesses, as there are varied effect sizes for Go/NoGo deficits across disorders. Wright et al. examined 318 studies by calculating mean effect size in ADHD, anxiety, autism, bipolar disorder, depression, OCD, personality disorder, reading disorder, schizophrenia, and Tourette's syndrome. These authors found no large effects in commission errors across disorders and only found medium effect sizes for commission errors in bipolar disorder (which is marked by highly impulsive manic periods) and reading disorder. They also found significant, but small, effect sizes in ADHD, anxiety, autism, bipolar, depression, and OCD, but importantly, these were marred by significant heterogeneity across study findings rendering Go/NoGo an insufficient diagnostic tool to discern psychiatric patients from healthy individuals.

In addition to psychiatric disorders, the Go/NoGo paradigm has been used extensively to characterize deficit in inhibitory control across substance abusing populations. In a meta-analysis, Smith et al. (2014) examined deficits in commission errors across studies of substance-abusing participants. These authors synthesized

results from two versions of the Go/NoGo paradigm: one with equal numbers of Go and NoGo trial presentations, and one in which Go trials frequent and NoGo trials were rare. They also examined results across a number of different substances of abuse. Similar to findings in SST, Smith et al. found that deficits in inhibitory control were not unitary across substances. In the Frequent Go/Rare NoGo paradigms, the authors found significantly increased commission errors in cocaine users, MDMA users, and tobacco smokers. Moreover, these participants did not show increased omission errors on Go trials, suggesting an inhibitory control deficit (for recent conflicting results with smokers, see Zhao, Liu, Zan, Jin, & Maes, 2016). In addition, alcohol dependent participants showed highly significant increases in commission errors on NoGo trials with nonsignificant levels of omission errors. However, nondependent heavy drinkers did not show these effects. Interestingly, the effects seen in Frequent Go/Rare NoGo paradigms were not present in paradigms that presented Go and NoGo trials equally. What is unclear however is whether these deficits are indicative of underlying traits that predispose some people to use these substances or whether the deficits are a product of the substance abuse, although certain inhibitory control deficits have been shown to index susceptibility to addictions (for review see Jentch & Pennington, 2014). It could also be that the small effects sizes seen in Smith et al.'s analysis are indicative stimuli involved in the task. For example, in a Go/NoGo task subjects that are obese, Price, Lee, & Higgs (2015) found that participants showed significantly more frequent commissions compared to healthy controls, but only when the Go/NoGo stimuli were food related and not when the cues were neutral.

The Go/NoGo paradigm has also has been modified for use in rodent models. Typically in the task, animals are placed in a chamber and operantly trained to respond to a stimulus in the environment to receive a reward (Go trials): a lever, nose poke port, etc. Often the operanda are presented briefly to encourage the animal to respond as fast as possible which in turn is intended promote the animals to develop a strongly biased, approach response. If the animal does not respond on Go trials they are punished by one of several means, such time-outs or electric shocks to the feet. The animal is also trained to withhold responding to a second operanda, a different lever for example. If they successfully withhold responding, they are moved on to the next trial. If they do not withhold, they are also punished (for review see Bari & Robbins, 2013). Like studies in humans, inhibitory control is indexed through number of commission errors on NoGo trials. Omission errors can also be quantified to inform whether commission errors on NoGo trials are specific to inhibitory control; increases in both omission and commission error would suggest a more general deficit in understanding or attending to the task contingencies.

Rodent studies using the Go/NoGo task are often conducted with little variation from human subject paradigms and have been used to understand the implications of inhibitory control performance in experiments that are impossible to conduct with humans, such as controlled investigations into the influence by substances of abuse on the behavior, novel pharmaceutical development to restore healthy inhibitory control, and invasive approaches to uncover the neural underpinnings of the behavior. However, even though the paradigm can be translated with little variation, rodent work using the Go/NoGo task has produced seemingly contradicting results that lead one to

question the extent to which the traditional version task is useful. For example, Paine, Dringenberg, & Olmstead (2003) trained rats on a variant of the Go/NoGo paradigm in which both Go and NoGo trials were administered in interleaved blocks (or intervals) of ten trials each. Rats were trained to lever press and upon reaching criterion were tested on a session in which they received 0-20 mg/kg of cocaine immediately prior to the start of the session. The authors found that at 15 mg/kg, animals showed a significant increase in lever pressing on NoGo trials and suggested this cocaine dose reduced inhibitory control in these animals. This finding, however, is likely due to immediate effects of cocaine on the animals behavior as Paine et al. found no significant increase in commission errors in rat chronically exposed to cocaine, but tested without cocaine on board. Additionally, Blackburn & Hevenor (1996) found that when they administered the stimulant amphetamine, rats produced more commission errors. These results are counterintuitive as amphetamine is used to treatment ADHD, a disorder marked by poor inhibitory control. The influence of these drugs of abuse and drugs used as therapeutics rely on the underlying interactions with neural structures and neurotransmitters, however the neural underpinnings that support action restraint are still unclear. Such a lack of clarity may help explain why, at times, we see counterintuitive effects of therapeutic drugs on action restraint, like amphetamine, that bely the drugs' effects on impulsivity as a whole construct. Another explanation could be that traditional Go/NoGo tasks render it hard to know precisely when the subject inhibits the biased approach actions. In the traditionally Go/NoGo paradigms subjects provide a Go response in one operant context, for example to a lever on the right of the operant chamber, and NoGo withholding of response in a different context, to a lever on the

opposite side of the chamber. In addition, the animal is always rewarded in the Go and never rewarded in the NoGo contexts. Therefore, it is possible that the animal never developed the biased response in the NoGo context that needed to be inhibited in the first place. Or, it could be that any tendency to respond on the NoGo was extinguished early on such that inhibitory control is no longer needed to prevent responding because the animal is no longer motivated to press. In order to hone in on when the inhibition takes place, the Go/NoGo paradigm will need to be modified to establish a biased approach response tendency that will need to be inhibited on NoGo trials.

1.3 Neural underpinnings of inhibitory control of action

PFC subserves many higher order cognitive functions that likely play influential roles to support action cancellation and action restraint in the changing world. PFC can be broadly defined at the anterior pole of cortex that is directly innervated by the medial dorsal nucleus of the hypothalamus (for extensive review PFC anatomy, see Fuster, 2009). In humans, the prefrontal cortex extends back to the third frontal convolution and can be subdivided into the following areas: mid dorsal (Broadmann's Areas [BA], 9), dorsal lateral (BA 46), ventro lateral (BA 12, 45) and orbital frontal/medial (BA 10,11, 13, 14, (Earl K Miller and Cohen 2001). The rat, however, possesses a less convoluted PFC, due to less extensive temporalization, and can be subdivided by its cytoarchitechtonics (similarly to BA) in anterior cingulate cortex, prelimbic cortex, infralimbic cortex, and orbital frontal cortex. Whether or not the structures of the PFC are homologous between humans and rats, though, is still a matter of debate; although, some work has been done to suggest functional

homologues, rather than anatomical, between the two (Seamans, Lapish, and Durstewitz 2008).

PFC has been shown to support foundational cognitive constructs that likely play a role in both action cancelation and action restraint. For example, PFC has been shown to be important for executive control, decision-making, reinforcement learning, instrumental learning, and goal directed behavior (Corbit and Balleine 2003; Rita Z Goldstein and Volkow 2002; J D Jentsch and Taylor 1999; Ostlund and Balleine 2005). PFC also receives dense dopaminergic projections from the ventral tegmental area that is necessary for reward processing (Ishikawa et al. 2008). Moreover, PFC supports an organism's ability to shift behavioral strategies/behavioral sets in order to optimally navigate within a dynamic environment and inhibit action on the fly when behaviors are no longer appropriate to the given context (as is experienced in the aforementioned experimental paradigms). In particular, the dorsal lateral cortex (dlPFC) of humans and mPFC (prelimbic and infralimbic cortices) in rat play a key role in set shifting (see (Bissonette, Powell, & Roesch, 2013 for review), giving further credence to functional homologues between the two species.

Importantly, PFC has long been proposed to play an important, regulatory role in inhibitory control (Brutrowski and Mempel 1961; Drewe 1975a, 1975b; Mishkin 1964; Stanley and Jaynes 1949). In early observations, Mishken et al. (1962) theorized lesions in the PFC to lead to a lack of suppression of behaviors that fit the description of prepotent responses, based findings in studies of reaching behavior in monkeys. How the PFC is exerting that influence over inhibitory control is a topic of much investigation, as the basic functions of cortex rely on complex circuitry both within cortex and with

subcortical structures. In human, PFC's role is made even more complex due to the highly convoluted nature of the cortex in general and thus its extensive interconnectivity. Extensive studies in human, though, have pointed to areas of cortex that are seemingly associated with inhibitory control, although more extensive work has pointed to these areas actually supporting basic cognitive functions necessary for inhibitory control (like working memory). For example, dlPFC has long been suggested as a key player in inhibitory control (Fassbender et al. 2004; Garavan et al. 2006; Hester et al. 2004; Menon et al. 2001). However, as mentioned above, dlPFC seems to play a critical role in cognitive functions that foundational to inhibitory control, like set shifting and working memory (Mostofsky et al. 2003; Simmonds, Pekar, and Mostofsky 2008), that are necessary in order for the participant to remember task rules and recognize that they need to inhibit an action as the task changes.

Numerous studies have implicated the inferior frontal cortex (IFC), an area of the ventral lateral cortex, as important for inhibitory control. Indeed, imaging studies have shown this area to be strongly associated with action restraint in Go/NoGo paradigms and in SST (Aron, Robbins, and Poldrack 2004; Konishi et al. 1998; Rubia et al. 2003). It thought that IFG exerts this control over inhibition through communication with areas more directly tied to motor output, such as pre supplementary motor area of the cortex (preSMA); an area that generally understood to be involved in complex motor movement and planning. For example, Duann, Ide, Luo, & Li (2009)used Granger analysis to establish functional connectivity of neural regions visualized in an fMRI experiment while subjects performed an SST. They found that right IFC is functionally connected to preSMA that then communicates with subcortical structures to promote

stopping behavior. However, as with dlPFC, there is still debate as to whether IFC is in fact responsible inhibitory control or whether it too is supports basic cognitive functions that are necessary for inhibitory control to be executed (see Aron et al., 2004; Bari & Robbins, 2013 for review).

Even though the PFC has been subdivided, it may be folly to think of any one structure as the locus of the inhibitory control faculty. Instead, PFC areas may be better thought of as nodes within necessary circuits, both cortico-cortical and cortico-subcortical, whose streams of activity support inhibitory control. This type of circuit influence, however, is difficult to study in humans due ethical restraints on methodology. To that end, neural investigations with rodent models have been fruitful in providing valuable information on how PFC, its circuitry, and neuropharmacology contribute to inhibitory control behavior. Much of this research has investigated the role of the mPFC, prelimbic and infralimbic cortex, of the rat, an area that has been suggested to be a functional homologue of the lateral areas of human PFC (Seamans, Lapish, and Durstewitz 2008). Indeed, Ragozzino, Detrick, & Kesner (2002) found that prelimbic cortex, and to a lesser degree infralimbic cortex, is supports shifting behavioral strategies and inhibition prepotent responses, faculties that are supported by the dlPFC in humans.

Chemical neurotransmitters play a critical role in brain function and neuronal communication through modulation of neuronal activity in both localized microcircuits within the prefrontal cortex and long-range neural circuits between cortex and subcortical structures. Cortical pyramidal cells release the excitatory neurotransmitter glutamate and are the primary source of excitatory communication within cortex and out

to subcortical structures. Additionally, pyramidal cells form microcircuits within cortex through connections with interneurons that release the inhibitory neurotransmitter GABA onto pyramidal cells to gate the excitatory signal. The emergent signal that is then produced by these circuits is further modulated by other neurotransmitters released from local axon terminals originating from cells whose bodies are distant from cortex (See Tremblay, Lee, & Rudy, 2016 for review). For example, norepinephrine (NE) and dopamine (DA) are heavily released in PFC but the cells that release them originate in the locus coeruleus and ventral tegmental area, respectively. Because these long-range transmitters shape connectivity and signaling within circuits, they may be better referred to as neuromodulators. NE and DA appear to play critical roles in inhibitory control, albeit within different regions of the brain (Andrea Bari et al. 2009).

The catecholamine NE appears to play an important role in inhibitory control, particularly in PFC. It is thought that NE produces its effect on inhibitory control by modulating the gain of the neuronal signals. For example, Eagle et al. (2008) found that administration of NE reuptake inhibitor atomoxetine improves inhibitory control. As a reuptake inhibitor, atomoxetine blocks the cell's reuptake NE to leave higher concentrations of NE in the synaptic cleft where it has more time to affect the postsynaptic cell. In addition, methylphenidate has been shown to increase inhibitory control (Tannock, Schachar, Carr, Chajczyk, & Logan, 1989; Tannock, Schachar, & Logan, 1995). Methylphenidate produces increases in extracellular DA and histamine, but induces preferential release of NE when administered in low therapeutic doses, with marked increases in PFC (Koob and Bloom 1988; Segal and Kuczenski 1997). Importantly, when DA1 and DA2 receptors are blocked, methylphenidate's effect of

increasing inhibitory control is not attenuated, which suggests theses increases inhibitory control are driven by NE or histamine. The role of NE is further bolstered by studies with the awake-inducing drug monafinil, which also increases inhibitory control. Although the exact mechanisms of action for monafinil are still not clear, it is thought that at least one of these mechanisms is that monafinil increases firing of NE neurons in the locus coeruleus, the only origin of forebrain NE (Minzenberg and Carter 2008). Additionally, both methylphenidate and atomoxetine also increase firing rates of neurons in the locus coeruleus (A Bari and Aston-Jones 2013; Devilbiss and Berridge 2006).

DA appears to play a complex role in inhibitory control by way of the structures in the dorsal and ventral striatum, but not in the PFC. For example, blocking DA2 receptors in dorsal striatum negatively affected SST performance but this effect was not seen when DA2 receptors were blocked in PFC (Bari et al., 2011). Additionally, Eagle et al 2011 explored the role of DA in both the dorsal and ventral striatum using a SST. They found that antagonizing DA1 and DA2 receptors in this area had contrasting effects: Blockade of DA1 receptors reduced SSRT, allowing the animal to stop more efficiently, whereas blockade of DA2 receptor increased SSRT. These authors claimed their findings are evidence that the role of DA1 receptors is to prevent inhibition and that DA2 receptors facilitate it. Interestingly, these findings with DA2 receptors were not seen the NAc of the ventral striatum. Findings using human neuroimaging also support these results (Ghahremani et al. 2012). DA seems to play a complex role as it pertains to action cancellation in the Go/NoGo task. Syed et al. (2015) used a novel discrimination task that incorporated a NoGo option to measure DA responses in NAc

associated with behavior in the task. After the animals learned the behavioral contingencies of the cues that instructed whether a trial was a Go right, Go left, or NoGo trial, this group found transient release of DA to the cue is shaped by correct motor initiation. That is, transient increases in DA appear to be associated with actions that lead to reward.

Serotonin may also play some role in inhibitory control, but its contribution is not well worked out; although, this neurotransmitter may help differentiate action cancellation and action restraint. Serotonin appears to have little effect on action cancellation as measured by SST in PFC. However, blockade of serotonin signaling in NAc decreases stopping in SST (Korte et al. 2017). As well, serotonin does appear to play in an important role in action restraint as measured by tasks that require an animal to withhold operant responding until cued to perform the response; a task that is slightly different than the Go/NoGo paradigm (for review see Bari and Robbins, 2013).

Although mPFC activity and neurotransmission has been implicated in inhibitory control, it is still unclear whether this structure is both necessary and sufficient to support inhibition of strongly biased approach action tendencies. In addition, it is unclear which subcortical connections are playing a critical role in inhibiting strongly biased approach action tendencies.. mPFC is strongly connected to the NAc through dense glutamatergic projections which may facilitate action restraint in operant tasks like Go/NoGo. NAc supports reward-directed behavior NAc has also been suggested to gate approach behavior by integrating excitatory inputs to facilitate action selection leading to the favorable outcome: either approach or restraint behaviors (Cardinal et al. 2009; Christakou, Robbins, and Everitt 2001; Hikosaka, Nakamura, and Nakahara

2006; Saleem M. Nicola 2007; Pennartz, Groenewegen, and Lopes da Silva 1994; Redgrave, Prescott, and Gurney 1999). Moreover, the mPFC projection to NAc is important for context specific actions and action-related cost-benefit evaluations that are necessary to correct performance on inhibitory control tasks. Whether or not the mPFC connection with NAc is critical for restraining strongly biased approach, though, is not known (Hauber and Sommer 2009).

1.4 Experimental Justification

For an individual to optimally survive, it is sometimes important to forgo immediate action in favor of restraint that will be more beneficial in the long run. This restraint can be difficult, though, because reward-related cues in the environment often elicit a strongly biased approach and consummatory actions that are hard to override. For example, humans may find it challenging to withhold consuming high calorie foods, alcohol, or drugs when they encounter cues that indicate these items are available, like a baker's showcase or flashing beer sign. Frequent lapses in this inhibitory control can ultimately lead to detrimental states such as obesity, addiction, or disease and it is therefore important to understand the behavioral and neurological mechanisms that support inhibitory control in the face of cues. Neuroscience studies have illuminated the neurological substrates responsible for the drive to engage in such rewarding, consummatory behaviors (Regina M. Carelli 2004; Goto and Grace 2008; Schultz 2007). But, it is far less clear how these neurological substrates are involved in inhibition of action, especially when inhibition is more beneficial than immediate approach. Indeed, programs that reward restraint have shown promise is treating certain disorders marked by poor inhibitory control. For example, Contingency Management programs

frequently test patients for drug use and each time the patients' test are negative, the program rewards them in gift cards and goods. These programs make inhibiting the biased approach response toward the drugs immediately beneficial and have shown that rewarding inhibition of that impulsive drug seeking is an effective method of maintaining abstinence in substance abusing populations (García-Fernández et al. 2013). Currently, there are few experimental paradigms that model this type of beneficial inhibition and therefore we are at a loss in understanding how the brain supports such beneficial inhibition.

Multiple behavioral paradigms have been derived as models through which to examine the neural substrates associated inhibitory control, but these paradigms fall short when modeling beneficial inhibition of approach responses. Indeed, inhibitory control of behavior has been studied at length and shown to have a complex relationship with disorders like obesity and addiction. Such complexities have given rise to contradictions in findings due to the multifaceted nature of inhibitory control behaviors; stopping behavior is not behaviorally uniform from one scenario to the next. Because of this lack of uniformity, researchers have developed individual paradigms to capture the nuances of inhibitory control and have identified two major categories: action cancelation and action restraint (See Winstanley et al., 2010). The current, well-established paradigms that make these behavioral characterizations have provided much insight into the nature of inhibitory control behaviors and the differential neural underpinnings that support each type. However, these existing experimental approaches fail to accurately model inhibitory control over biased approach responses that is ultimately beneficial, as many of these models only support inhibitory control in

the paradigm through negative reinforcement or by punishing lapses in inhibitory control. Additionally, the current paradigms pose problems that make it difficult to interpret neural signals: they often provide asymmetrical reward structures between trial types that create differences in reward prediction errors that confound interpretation of signals associated with prediction errors versus signals associated with inhibitory control.

The SST is the most common paradigm used to study action cancelation. In SST models, inhibition of the approach response comes after the initiation of action and therefore is a measure of how well one can cancel action, rather than restraining the action from the outset (for review Winstanley et al 2010). The SST cues subjects to make an approach response, but periodically presents an additional stop cue to instruct them to cancel that response. This stop signal is presented at variable delay intervals from which a SSRT can be calculated to indicate difficulty in inhibitory control. Slower SSRT are indicative of more difficulty in inhibiting action and have been shown to correlate with other maladaptive behaviors.

The Go/NoGo paradigm has become the prototypical paradigm to model action restraint. Typically in this task, subjects are given Go trials in which they are cued to approach and perform an operant behavior to receive a reward (for example, press a button or lever). On NoGo trials they are presented with a different set of stimuli from which they are to withhold their approach behavior. If they do not withhold, they are punished. If they withhold correctly, however, they are not rewarded but are simply moved on to the next trial. Traditional Go/NoGo paradigms, though, fall short of modeling inhibitory control of biased approach responses, as approach (Go) and

inhibition (NoGo) are associated with different operant contexts (two distinct levers on opposite side of chamber, for example). More specifically, subjects apply inhibition in one context over the other, not at the moment they encounter the operandus and have to act upon it or not, which is arguably the time point one must inhibit the biased response. Therefore, the subject can simply learn which option is the "good" one to approach and which option is the "bad" one to avoid. For example in human foraging, one may learn that it is appropriate to acquire food from the aisles in a grocery store, but that it is inappropriate to acquire food from the dumpster behind the grocery store. Such structures make it hard to know exactly when the inhibition has taken place and therefore make it difficult to hone in on the neural signals associated with that inhibition. In addition to these confounds in timing, traditional Go/NoGo paradigms also typically consist of asymmetric reward structures between trial types: correct Go is always rewarded and correct stop/NoGo is never rewarded. This structure produces differences in reward prediction errors between trial types and makes it impossible to delineate neural signals associated with the prediction errors versus signals associated with inhibition of action.

To address these pitfalls, our lab developed a Symmetric Go/NoGo task that rewards both correct Go and NoGo behavior (Roitman & Loriaux, 2014; for an alternative symmetric Go/NoGo tasks, see Harrison et al., 1999; Syed et al. 2016). In the task, rats are trained to press a lever immediately upon its presentation to receive a reward (Go trials). This trial type makes up the vast majority of trials presented to the animal (75% of trials) and the many repetitions develop this Go behavior into a biased approach response. On the remaining trials, the same lever is accompanied by a

distinct NoGo cue that indicates to the rat it should inhibit withhold pressing on these trials. Rats receive a reward when they successfully inhibit the approach response and restrain pressing the lever. These cues that instruct Go or NoGo are presented simultaneously with the lever presentation, and in the case of NoGo it instructs the rat to inhibit the initiation of the biased Go response. Like Go cues, the NoGo cue in this paradigm predicts reward, but requires behavioral inhibition to receive it. Thus, it establishes a symmetric reward delivery structure that circumvents differences in reward prediction errors between trial types that is problematic in traditional Go/NoGo tasks, allowing for isolation of neural activity associated with inhibition.

The structure of the Symmetric Go/NoGo task consists of matched reward expectations between Go and NoGo cues and requires rats to inhibit a biased approach response on NoGo trials in order to receive the reward. With this structure, we are able to isolate and examine the neural underpinnings that are associated with, and support, inhibition on NoGo trials. As mentioned in the previous sections, inhibitory control appears to be largely an mPFC dependent behavior and the symmetric Go/NoGo provides an ideal setup to examine mPFC's role in beneficial inhibitory control. PFC has long been implicated as critical for executive control over behavior and to play a role in the control of reward/value-based choices. As well, dysfunctions in PFC activity results in impulsive behavior, with the medial portion of prefrontal cortex (mPFC) implicated as closely associated with inhibitory control (Ghahremani et al. 2012; E K Miller 2000; Passetti, Chudasama, and Robbins 2002). mPFC makes broad connections with subcortical structures to communicate information that supports reinforcement/instrumental learning and executive control of goal-directed behavior

(Corbit and Balleine 2003; R Z Goldstein and Volkow 2012; Rita Z Goldstein and Volkow 2002; J D Jentsch and Taylor 1999; Ostlund and Balleine 2005). Importantly for inhibitory control, mPFC sends glutamatergic projections to subcortical areas like the nucleus accumbens (NAc), which then projects to other basal ganglia structures well situated to integrate information about environmental cues and rewards to influence (approach) motor behaviors (Costa et al., 2006; Floresco, Blaha, Yang, & Phillips, 2001; Grace et al., 2007). It is still unclear, though, how mPFC neurons respond to cues in the Symmetric Go/NoGo task and whether those responses influence inhibitory control and how this area is integrated into a larger inhibitory control circuit.

We hypothesize that mPFC is necessary for rewarded inhibitory control and that it is communicating with subcortical structures to provide the restraint signal. NAc stands a good candidate as one recipient of the signal produced from mPFC. In recent work, Roitman and Loriaux (2014) used extracellular electrophysiological recordings in NAc to investigate how MSNs in NAc respond to cues that instruct Go and NoGo behavior in the Symmetric Go/NoGo task. NAc integrates excitatory afferents from cortical and subcortical structures to render information about context, memory, associative and instrumental learning of reward predictive cues, reward delivery, as well as to gate behaviors that lead to reward through communication with downstream basal ganglia structure via MSN projections (Carelli & Deadwyler, 1994; Carelli, 2002; Chang, Paris, Sawyer, Kirillov, & Woodward, 1996; Costa et al., 2006; Floresco, Blaha, Yang, & Phillips, 2001a; Grace, Floresco, Goto, & Lodge, 2007; S M Nicola, Yun, Wakabayashi, & Fields, 2004; Syed et al., 2016). Roitman and Loriaux found that NAc neurons exhibited transient increases in average firing rate to both Go and NoGo cues and that

these increases were greater when animals correctly inhibited responding on NoGo trials compared to approach behavior on Go trials. These authors suggested the augmented neuronal activity on NoGo trials acts as an inhibition signal that is transmitted to downstream basal ganglia structures to gate the animals' biased motor response. It is unclear, though, how this increase in NAc reaches this augmented excitation. The cytoarchitecture of NAc does not allow this structure to increase firing rates of neurons within itself, as these neurons predominately release the inhibitory neurotransmitter GABA; unlike cortical neurons that release the excitatory transmitter glutamate and form intracortical connections to promote increased firing and synchronicity. Thus, NAc requires excitatory afferents to increase the firing rates of its neurons (see Floresco, 2015 for review). Indeed, work from our lab has shown that rats' ability to inhibit their approach behavior on NoGo trials was significantly reduced when excitatory glutamate AMPA/kainate receptors were blocked in NAc (Ebner, dissertation). It is still unclear, though, which brain structures are providing the excitatory signals to NAc that are necessary for inhibitory. As mentioned above, mPFC sends dense glutamatergic projections to NAc that could incite the increased excitation seen in NAc and thus we hypothesize the mPFC is one origin of this necessary excitatory signal.

The studies proposed here are designed to illuminate the contribution of excitatory neurons within mPFC as they pertain to inhibitory control using a rat model, specifically when that control results in a beneficial outcome. These studies will utilize the Symmetric Go/NoGo task and will employ *in vivo* extracellular electrophysiology to record and compare neuronal firing in these awake-behaving animals as they respond to both Go and NoGo cues. I will then employ pharmacological inactivation of mPFC

neurons and excitatory chemogenetics (designer receptors exclusively activated by designer drugs, DREADDs) to establish that mPFC signal is both necessary and sufficient to support inhibitory control. Finally, I will use pharmacological manipulations to disconnect the functional communication between mPFC and NAc to uncover the role of this communication in inhibitory control.

2. General Materials and Method

2.1. Subjects

All aims of this dissertation utilized Long-Evans rats (Charles River Laboratories, Chicago, IL) housed individually in plexiglass tubs (56 x 34 x 22cm), provided with chow to maintain them at no less than 90% of ad libitum body weight, and kept on a 12:12 hour light/dark cycle (lights on at 7:00 am). Experiments were conducted during the light phase between 8:00 am and 6:00 pm. All surgical procedures were performed under ketamine hydrochloride (100 mg/kg, i.p.) and xylazine hydrochloride (10 mg/kg i.p.) anesthesia. Animals were handled in accordance with guidelines set by the National Institutes of Health and under the supervision of the University of Illinois at Chicago's Animal Care Committee.

2.2 Apparatus

Animals were tested in operant chambers enclosed in sound attenuated cubicles. Each operant chamber was equipped with a house light, sound generator for white-noise and tones, pellet dispenser, food receptacle well, two retractable levers (one on either side of the food well), and two cue lights (one above each of the levers; Med Associates, St Albans, VT) and controlled by PC to monitor task events.

2.3 Behavioral training

All animals were trained in several stages to perform the Symmetric Go/NoGo as previously described in detail by Roitman and Loriaux (2014). In this task, a lever was presented on each trial simultaneously with a Go or NoGo cue, which instructs the rat to

either press the lever (Go), or withhold pressing (NoGo). All correct responses were rewarded and all errors were followed by a time-out. Initially, animals underwent magazine training and operant conditioning to lever press on an FR1 schedule for one 45mg sugar pellet (Bio-Serv, Beltsville MD). Next, animals were trained to produce two behaviors – pressing and withholding – on a *Go+/NoGo- Two Lever task.* On each trial (150 per session), one of two levers was presented, with one side assigned as Go+ and the other as NoGo-. The assignment of one side as "Go" was randomized for each animal and maintained throughout all training/testing. A lever press on a Go+ trial (75% of trials) yielded a reward of one sucrose pellet and a lever press on a NoGo- trial (25% of trials) yielded no programmed outcome. Incorrect behavior on either trial type (i.e. withholding pressing on Go+ trials or pressing on NoGo- trials) resulted in a 40 s timeout. Once animals reached a criterion of 50% correct NoGo- trials, they were moved to the next phase of training, the *Go+/NoGo+ Two Lever* task. In this phase, withholding pressing on NoGo+ trials led to a reward. Sessions were similar to the *Go+/NoGo-* task, but a cue light and brief white noise (0.5s) were presented simultaneously with the NoGo+ lever and withholding pressing for 4.5s resulted in a tone paired with a sucrose pellet. The NoGo+ cue was introduced to form an association between it and subsequent reward delivery, and to distinguish NoGo from Go trials. Contingencies for Go+ trials remained the same as the *Go+/NoGo-* task. After rats reach behavioral criterion of 50% correct NoGo+ trials for three consecutive days, they began performing the Symmetric Go/NoGo Task.

2.4 Symmetric Go/NoGo task.

The goal of the Symmetric Go/NoGo task was to examine the neural substrates of inhibitory control over biased approach behavior. “Go” behavior was encouraged by rewarding presses of the Go lever during training, and by presenting it more frequently. In this way, animals become strongly biased to approach and press the lever and this approach must be inhibited when the NoGo cue was presented. Each session of the Symmetric Go/NoGo task consisted of 150 trials. All trials began with the extension of the same, single lever – that which had previously been extended for Go+ trials, so that rats were required to use the cues lights and white noise to instruct appropriate behavior on each trial type (Fig. 2.1). On 75% of the trials, the cue light above the lever was illuminated at the time of lever presentation to indicate a “Go” trial in which the animal should press. When pressed (Go correct), the lever retracted, cue light extinguished, and a tone was paired with a 45 mg sugar pellet delivery. If the animal did not press the lever within 4 s (Go error), the lever retracted, cue light extinguished, and the animal received a 40 s timeout. On the remaining 25% of trials, the same lever extended but the cue light on the opposite side of the food well was illuminated and white noise associated with the previous NoGo+ lever were presented to indicate a “NoGo” trial in which the animals should withhold pressing. The lever was extended for 4.5 seconds or until the animal pressed it. If the animal successfully withheld pressing for the 4.5 seconds, a tone paired with a sucrose pellet was immediately delivered. If the animal pressed the lever, the lever was retracted and a 40 s time out followed. For sessions in which electrophysiological activity of mPFC neurons were recorded, lever presses on Go trials were followed by a four second delay to establish congruent timing

of reward delivery between Go and NoGo trials. All trials were followed by a 5-13s intertrial interval.

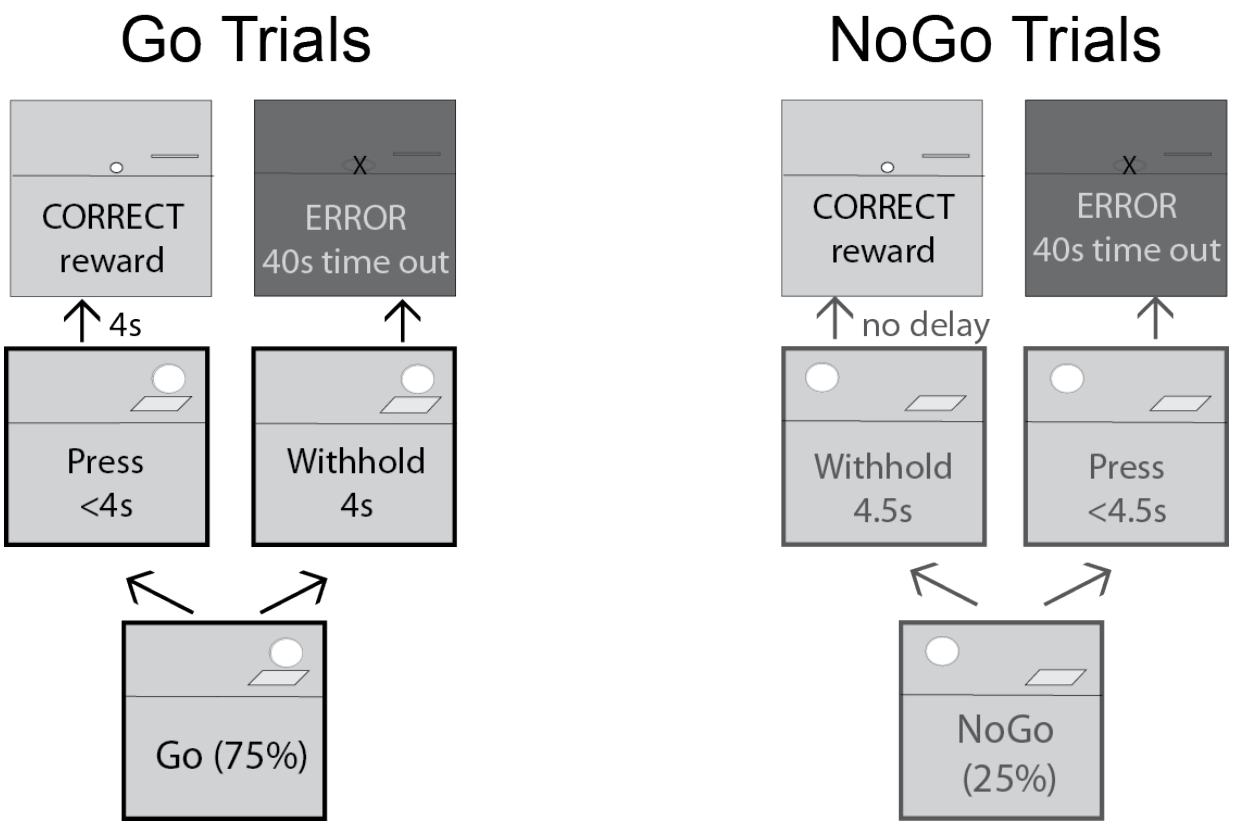

Figure 2.1 Symmetric Go/NoGo task design

3. mPFC shows transient changes in neuronal firing in response to task related cues in the Symmetric Go/NoGo task

3.1 Rationale

PFC, broadly, has long been implicated as critical for executive control over behavior and to support foundational cognitive faculties that are necessary for effective inhibitory control in a dynamic environment; for example, reward/value-based decision-making. The germane role of PFC in impulse control is supported through evidence that disrupted PFC function results in higher rates of impulsive behavior, and specifically, damage to the medial portion of prefrontal cortex reduces inhibitory control (Ghahremani et al. 2012; E K Miller 2000; Passetti, Chudasama, and Robbins 2002). Given these associations of mPFC with inhibitory control, it stands to reason that the neural activity in this area should show changes in activity that correspond to cues that indicate the relevant behavioral contingencies on Go and NoGo trials in the Symmetric Go/NoGo task. It is still unclear, though, what patterns of neuronal activity in mPFC are associated with the behaviorally relevant cues.

3.2 Specific Aim 1: Establish a neural correlate of inhibitory control in mPFC

To measure how mPFC encodes different aspects of the Symmetric Go/NoGo task, we performed extracellular recordings from individual neurons in the prelimbic subdivision of the rat mPFC while rats performed the Go/NoGo task and correlated their patterns of firing rate with behaviorally-relevant events. This method allowed me to isolate single units (neurons) within the mPFC and calculate changes in patterns of neuronal firing. Using this method, I was also able to align these changes in firing rates

to task-related events during task performance (for example, cue presentation and lever press).

3.3 Hypothesis and predictions

I hypothesized that excitatory signaling within prelimbic cortex of rat mPFC is associated with inhibitory control of behavior. If prelimbic cortex is important for inhibitory control, neurons in this area should show phasic responses at the time of NoGo cue onset, as this cue instructs the animal that inhibition is the appropriate response to obtain a reward. Additionally, I hypothesized that prelimbic cortex is one origin of the excitatory signal propagated subcortically to augment neuron firing in NAc. Roitman and Loriaux (2014) showed that NAc MSNs showed large transient increases in neuronal firing rate in response to both Go and NoGo cues, but this response was higher to NoGo cue when animals successfully inhibit approach behavior. If neuronal firing rates in prelimbic cortex produce a signal that discriminates Go and NoGo cues that could then be propagated to NAc, I would expect to see larger transient increases in neuronal firing rates in response to the NoGo cue versus the Go cue.

3.4 Method

3.4.1 Surgery. Rats were first trained to perform the Symmetric Go/NoGo task. In the task, they encountered 75% Go trials in which they were presented with a lever along with an environmental cue instructing them to approach and press the lever in order to receive a sucrose reward. Twenty-five percent of the time, though, they were presented with NoGo trials during which they were given the same lever along with a

distinct cue indicating they were to withhold pressing to receive the sucrose reward. After reaching the behavioral criterion of 50% correct NoGo trials, Rats were implanted with custom-designed stainless steel, Teflon insulated, electrode arrays (MicroProbes, Gaithersburg, MD). Arrays were organized into two columns of four microwires (50μm diameter; tip separation 0.25mm), and stereotaxically guided bilaterally into the prelimbic subdivision of mPFC (+3.2 AP, ±1.2 ML relative to bregma, and −3.5 DV relative to brain surface at 10° lateral angle). Ground wires for each array were inserted into the ipsilateral hemisphere, at a location several millimeters caudal to the electrodes. Connectors were anchored to the skull via stainless steel screws and dental acrylic. Animals were given at least one week to recover before testing.

3.4.2 Electrophysiological recording. Each animal was connected to a flexible recording cable attached to a motorized commutator (Plexon, Dallas, TX), to allow for relatively free movement. Electrical signals in the vicinity of the electrode tips were amplified and transduced via the OmniPlex system (Plexon, Dallas, TX). In addition, the time of trial events, such as cue and lever presentation, lever press, and sucrose pellet delivery, were time-stamped onto the neural spike data. During recording, individual waveform statistics, including principal components and inter-spike intervals, were used to identify waveforms belonging to individual neurons (PlexControl), which were then subsequently refined offline (Offline Sorter). The data were then exported to Matlab (Mathworks) for further analysis.

3.4.3 Analysis of neuronal data. For each neuron, I aligned the timing of action potentials relative to cue onset of each trial and calculated the firing rate of the neuron in 0.2s bins on each trial from -4s to +4s. The four seconds preceding cue onset were

used to calculate baselinefiring rate on each trial. I then used a two-tailed, paired t-test to screen for neurons whose firing rates changed significantly from baseline during the one second following cue onset (cue period) for correct Go trials, correct NoGo, or all correct trials. This analysis identified neurons that increased or decreased activity in response to Go, NoGo, or both cues. I then tested whether increasing and decreasing neurons responded differentially to Go and NoGo cues. For neurons in each group (increasing to Go, NoGo, or both and decreasing to Go, NoGo, or both) we calculated the time-course of the average firing rate from -4s to 4s relative to cue onset. For neurons with phasic responses to both cues, we used 2 X 2 ANOVA to determine if responses during the first second after cue onset depended on cue type (Go/NoGo) or outcome (correct/error) for increasing and decreasing neurons separately.

3.4.4 Histology. When animals completed the test sessions, they were injected with a sublethal dose of sodium pentobarbital (100mg/kg). Electric current was passed (100μA) through each electrode for 4 s with a lesion-making device (Ugo Basile, Comerio, Varese, Italy) to mark placement. Rats were then transcardially perfused with phosphorous-buffered saline followed by formalin. Brains were extracted and stored in formalin with 10% potassium ferrocyanide for 24 h, then changed to a 30% sucrose solution for at least another 24 h. Potassium ferrocyanide reacts with iron deposited after lesions and causes a Prussian blue reaction product, which was used to help visualize electrode placements. Brains were then sectioned at 50μm in a cryostat (-20°C). Tissue was mounted on slides and viewed under a light microscope to verify electrode placement based on visual landmarks (Figure 3.8, Paxinos & Watson, 1997)

3.5 Results

3.5.1 Medial prefrontal cortex neurons show selective transient responses to Go and NoGo cues. I implanted 6 rats bilaterally with microwire electrode arrays into mPFC to measure changes in neuronal firing that corresponded to the Go and NoGo cues. Rats showed higher accuracy on Go trials (90.0 ± 1.4%) compared with NoGo (Figure 3.1, 76.5 ± 6.4%, p=0.0014). The average response time (RT) to press the lever on correct Go trials (707 ± 127ms) and NoGo error trials (770 ± 183ms, *n.s.*) was comparable (Figure 3.2). The high level of accuracy combined with short latencies on Go trials indicates that pressing the lever upon its presentation was a biased response. However, when instructed to withhold pressing in response to the NoGo cue, the biased approach response was successfully overridden on the majority of NoGo trials.

I recorded from 91 neurons in the prelimbic region of mPFC while rats performed the Symmetric Go/NoGo task to examine their responses to the cues that instructed behavior. I identified neurons that responded to cue onset with a phasic change in firing rate by comparing the firing rate in the 1-s epoch aligned to cue onset with the baseline firing rate in the 4-s preceding cue onset. I found 32 neurons that showed phasic increases in activity to the cue and 29 neurons that showed phasic decreases. The baseline firing rate in the 4s prior to cue onset did not differ between these groups of neurons (Figure 3.3, increasing: 3.99±0.05 sp/s vs. decreasing: 4.02±0.05 sp/s, p=0.70).

For neurons with phasic increases, I compared responses to Go and NoGo cues to determine if they responded preferentially to one cue. Figure 3.4 shows the average change in response from baseline of each increasing neuron to the NoGo cue as a

function of the change in response to the Go cue. The line of unity depicts equal changes in firing to both Go and NoGo cues. A subset of 7 neurons (red) had significant increases in firing rate for NoGo cues only, and another subset of 13 neurons responded to the Go cue only (green). The remaining 12 neurons showed increased responding to both cues (black). Figure 3.5A-3.5C show the time-course of activity for these subpopulations of increasing neurons (time of cue onset = 0s), with the average activity on correct Go and NoGo trials plotted separately. The 'Go' and 'NoGo' panels (figure 3.5A & 3.5C) show the transient response at the time of lever presentation/cue onset for neurons that only increased activity for one trial type. Neurons that responded on both trial types (figure 3.5B) showed a greater increase at the onset of NoGo trials compared to Go ($p<0.05$), a pattern that is similar the pattern of activity described by Roitman and Loriaux (2014). Although the majority of neurons recorded were identified as being located in the prelimbic region of mPFC, 4 of the 32 increasing neurons were recorded from the infralimbic cortex. Of these 4, 2 increased only to the Go cue, and 2 only to the NoGo cue.

A separate group of neurons showed reductions in neural activity at the time of cue onset. Figure 3.6 shows the average change in firing rate from the baseline period to cue onset for each of the decreasing neurons, with a subset of 6 that decreased only to the NoGo cue (red), 10 that decreased only to the Go cue (green), and 13 that significantly decreased for both cues (black). The time course of responses for each of these subgroups of decreasing neurons is shown in Figure 3.7A-3.7C. In contrast to the increasing neurons, decreasing neurons that responded to both cues did not differentiate them (figure 3.7B; Go vs. Nogo: *n.s.*). Of the 29 decreasing neurons

recorded, 2 of those that decreased to both Go and NoGo cues were located in the infralimbic cortex, as were 1 with Go only and 1 with NoGo only responses.

3.6 Discussion

Using extra-cellular electrophysiological recording, I found that neurons in mPFC of the rat show transient changes in firing rate that correlate with the behaviorally relevant cues (lights) in the Symmetric Go/NoGo task. More specifically, these findings provide evidence that subsets of mPFC neurons selectively encode Go cues and NoGo cues by either transiently increasing their firing rate, while additional subpopulations transiently decrease their firing rate relative to cue onset. Two additional subsets of mPFC neurons transiently respond to both Go and NoGo cues with one population increasing their firing and the other decreasing. Importantly, the increasing subpopulation appeared to differentiate the between Go and NoGo cues such that higher increases in firing rate preceded correct inhibition on these trial. The decreasing neurons, however, did not show the same pattern of differentiations. We show transient changes in mPFC activity are associated with Go and NoGo cues, but a subpopulation appears to differentiate Go and NoGo. It is still unclear, though, if these signals are strictly correlational or if they play a necessary supporting role in inhibitory control.

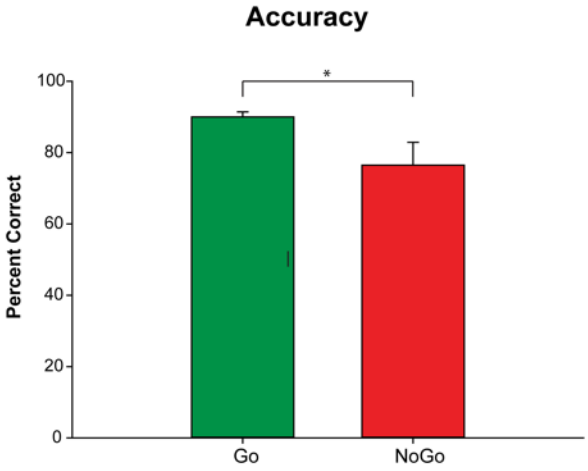

Figure 3.1. Average percent correct for Go and NoGo. Rats showed higher accuracy on Go trials.

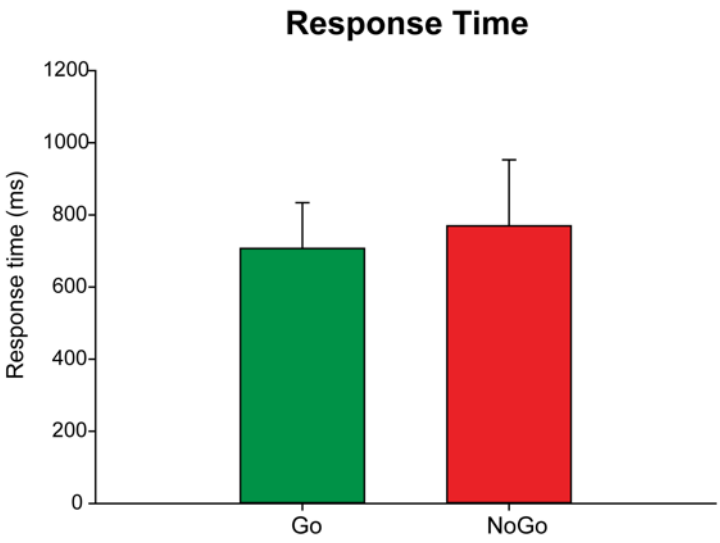

Figure 3.2. Average time to respond on correct Go trials and incorrect no go trials.

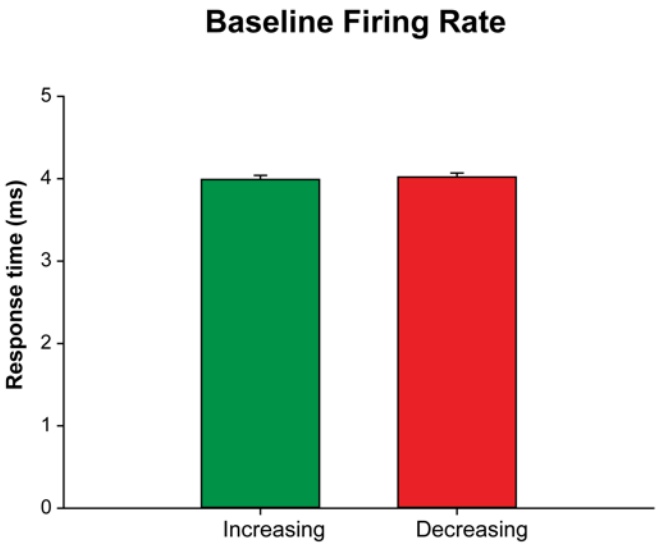

Figure 3.3. Shows the average baseline firing rate between neurons that exhibited increases and decreases in firing rate at he time of cue onset. Baseline firing rate was calculated from the firing rate, partitioned into 0.2 second bins, of the four seconds preceding cue onset.

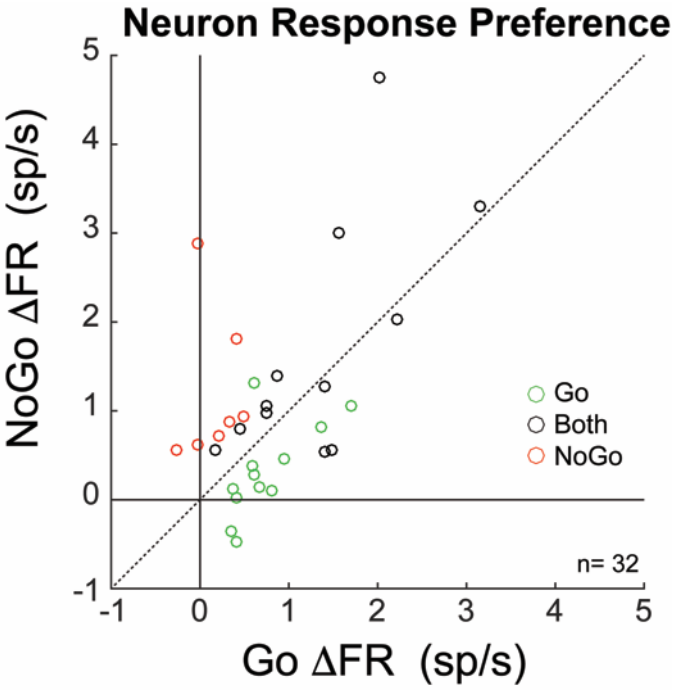

Figure 3.4. One population of mPFC neurons (n=32) show transient increases in firing to Go, NoGo, or both cues. The change in neural activity was measured in the 1s epoch aligned to cue onset for Go and NoGo trials separately for each neuron. For each neuron, the average NoGo response is plotted as a function of its average Go response. The central unity line marks equal responding to both cues. The color of each point indicates whether the neuron responded significantly to only Go cues (green), only NoGo (red) or both (black).

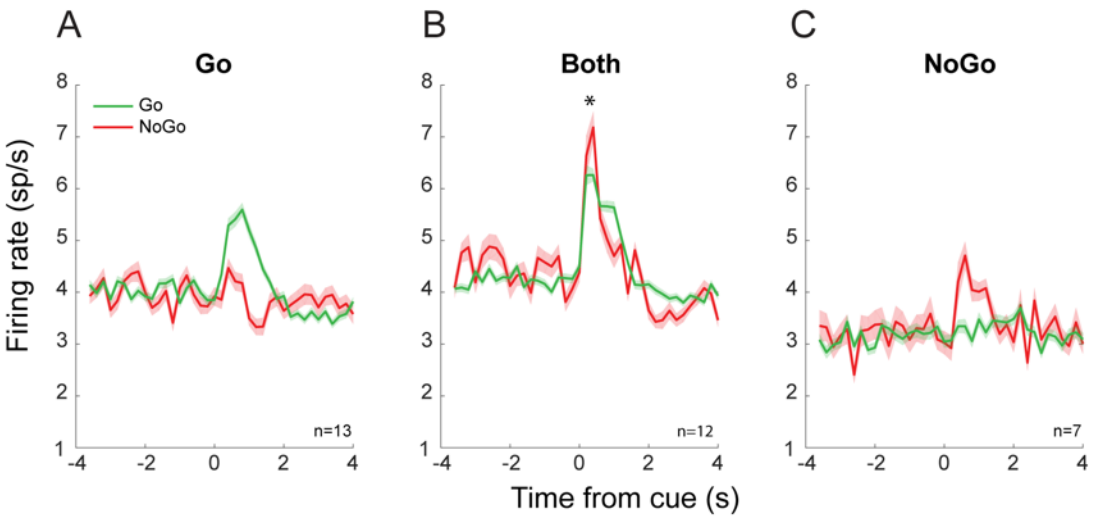

Figure 3.5. (A) Time-course of activity of neurons that responded with a transient increase only to Go cues, the average firing rate across trial calculated in 0.2-s bins for Go (green) and NoGo (red) trials separately. Shading indicates ± 1 s.e. of mean firing rate. (B) Time-course of activity for neurons showing a transient increase to both Go and NoGo cues. Same conventions as A. In this subpopulation, the average response to NoGo cues was higher than that to Go cues. (C) Time-course of average firing rate for neurons that show a transient increase only to NoGo cues.

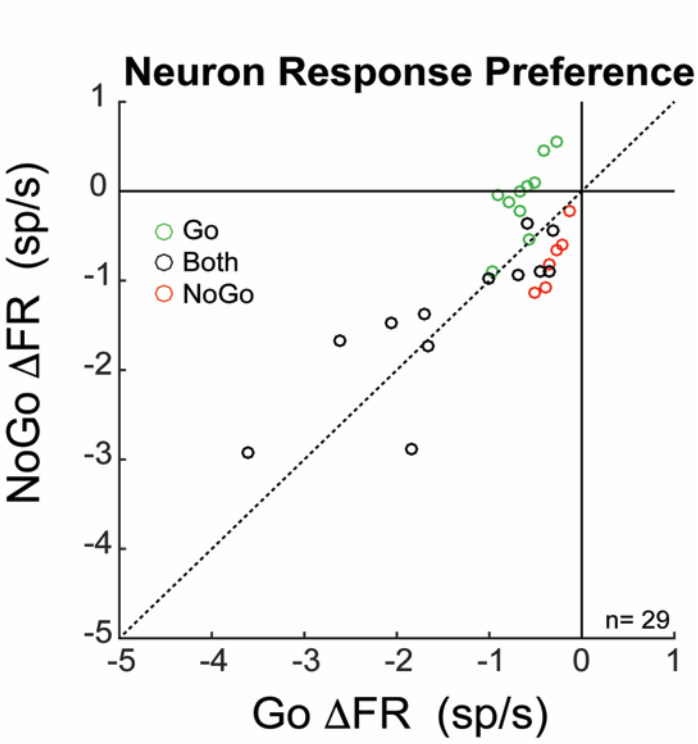

Figure. 3.6. A second population of mPFC neurons (n=29) show transient reductions in firing to Go, NoGo, or both cues. Same conventions as Figure 3.4.

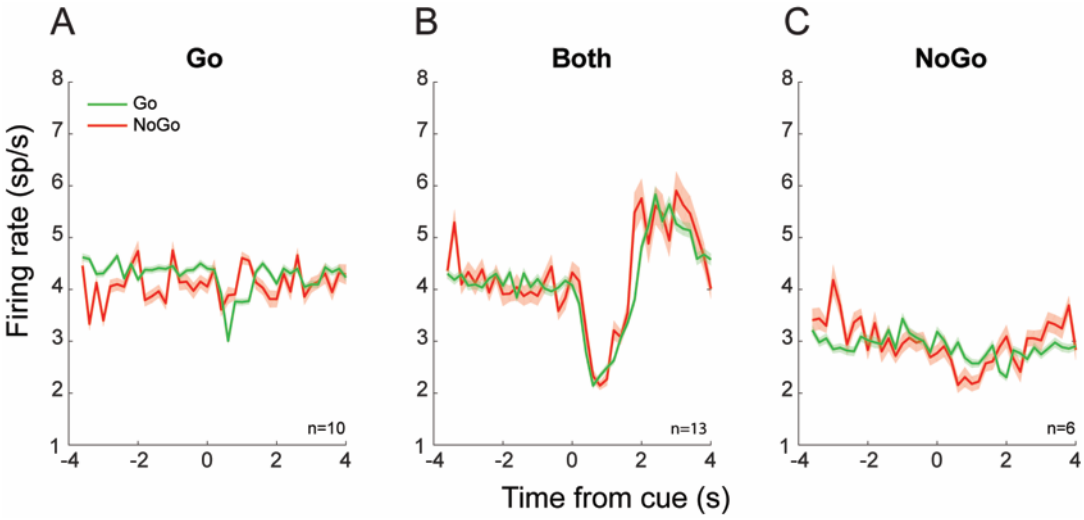

Figure 3.7. A) Time-course of activity of neurons that responded with a transient decrease only to Go cues, the average firing rate across trial calculated in 0.2-s bins for Go (green) and NoGo (red) trials separately. Shading indicates ± 1 s.e. of mean firing rate. (B) Time-course of activity for neurons showing a transient decreases to both Go and NoGo cues. (C) Time-course of average firing rate for neurons that show a transient deccrease only to NoGo cues.

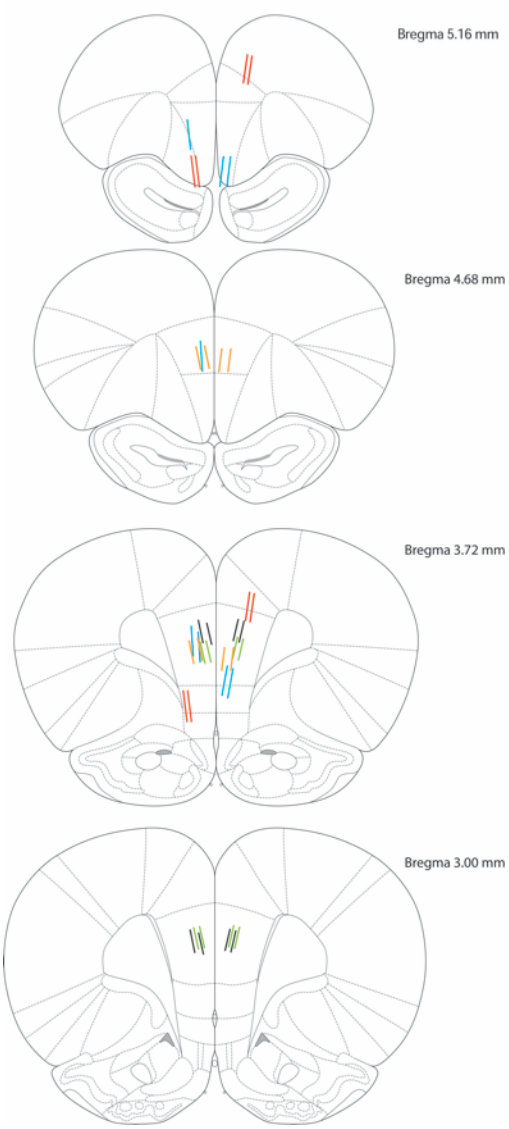

Figure 3.8. Histological verification of the electrode placement in mPFC.

4. mPFC is both necessary and sufficient to support inhibitory control on the Symmetric Go/NoGo task

4.1 Rationale

In the previous chapter I found that mPFC neurons showed transient changes in activity that correlated with the onset of task relevant cues that instructed the animal as to which behavior, approach or inhibition, would lead to reward on the each trial. It is still unclear, though, whether these signals play a causal role in influencing behavior on Go and NoGo trials.

4.2 Specific Aim 2a: Show that mPFC is necessary to support inhibitory control

To establish that mPFC is necessary to support inhibitory control, we temporarily inactivated the prelimbic cortex of the rat while the animal performed the Symmetric Go/NoGo task. Rats were trained on the task until they reach asymptotic levels of accuracy. Prelimbic cortex was then infused with a baclofen/muscimol that held excitatory cells in a hyperpolarized state reducing the likelihood of firing; in essence, inactivating them. I then quantified behavior on both Go and NoGo trials to compare accuracy between a drug treatment session and the following no treatment, washout session.

4.2.1 Hypothesis and predictions. PFC has long been implicated as critical for executive control. Dysfunctions in PFC activity are associated with impulsive behavior, with the mPFC implicated as necessary for inhibitory control. If mPFC is necessary for inhibitory control in the Symmetric Go/NoGo task, then inactivating it should result in a reduction of animals' ability to inhibit pressing on NoGo trials. However, inactivation of

prelimbic cortex should not affect accuracy on Go trials, as once this behavior becomes strongly biased, the burden of maintaining the behavior is shifted to other subcortical regions, such as the dorsal striatum (for review see Balleine & O'Doherty, 2010).

4.4 Method

4.4.1 Surgery. Rats performed the Symmetric Go/NoGo task as described above. After reaching the behavioral criterion of 50% correct NoGo trials, rats were each implanted with bilateral guide cannulae for delivery of pharmacological agents into mPFC. Bilateral cannulae were stereotaxically guided into the prelimbic region of mPFC at +3.3 AP, ±1.2 ML relative to bregma and -3.0 DV relative to brain surface at a 10° lateral angle. Cannulae were anchored to the skull via stainless steel screws and dental acrylic. Animals were given at least one week to recover before testing.

4.4.2 Pharmacology and testing. Animals were treated with a mixture of the $GABA_A$ agonist Muscimol and the $GABA_B$ agonist Baclofen. The drug cocktail of 250 ng/µl Muscimol and 250 ng/µl Baclofen was administered in a volume of 0.5µl a rate of 0.25µl/m in physiological saline such that 125ng of each drug was delivered per site. Data were omitted from analysis if the animal did not complete at least half of the trials (75) of the session under drug administration. After drug infusion, the animals were immediately tested on the Symmetric Go/No Task. Test sessions with drug treatment were followed a day without drug treatment to ensure recovery of behavior. If drug effects were still present, the animals were tested an additional day without drug treatment.

4.4.3 Analysis of behavioral data. For each treatment condition, performance on Go trials and NoGo trials was analyzed separately, comparing accuracy on the drug treatment session to that on the recovery, no-treatment sessions using a paired samples t-test.

4.4.4 Histology. When animals completed the test sessions, they were injected with a sublethal dose of sodium pentobarbital (100mg/kg). Electric current was passed (100μA) through each cannula injector for 4 s with a lesion-making device (Ugo Basile, Comerio, Varese, Italy) to mark placement. Rats were then transcardially perfused with phosphorous-buffered saline followed by formalin. Brains were extracted and stored in formalin for 24 h then changed to a 30% sucrose solution for at least another 24h. Brains were then sectioned at 50μm in a cryostat (-20°C). Tissue was mounted on slides and viewed under a light microscope to verify cannula placement based on visual landmarks (Figure 4.4, Paxinos and Watson, 2007).

4.5 Results

4.5.1 Bilateral mPFC inactivation impairs NoGo accuracy. To investigate mPFC's role in performance of the Go/NoGo task, rats were implanted with bilateral cannula in mPFC and infused bilaterally with a mixture of the $GABA_A$/$GABA_B$ agonists muscimol/baclofen to temporarily inactivate this area. Accuracy for Go and NoGo trials was calculated separately. Performance on each inactivation session was compared with its no drug treatment session on the following day. A paired samples t-test showed a small, but statistically significant reduction in Go accuracy following administration of drug (Figure 4.1, inactivation mean = 92.15 ± 1.62%, vehicle mean = 96.91 ± 1.07%,

t(18) = -3.09, p < 0.01). The animals' ability to withhold pressing on NoGo trials, however, was strongly reduced (Figure 4.1: inactivation mean accuracy= 32.49 ± 6.26%, no treatment mean accuracy= 74.83 ± 4.32%, t(18) = -6.97, p < 0.001). Following bilateral mPFC inactivation, RT was 752 ± 16ms for Go presses and 967 ± 40ms for NoGo errors. In the No Treatment session, RT was 552 ± 12ms for Go correct presses and 661 ±516ms for NoGo errors. Thus, across treatment conditions, RT on NoGo errors was significantly slower than correct Go lever presses (F(1,5037)=27.71, p<0.0001). Under bilateral inactivation of mPFC, overall RT was slower compared with the following no treatment day (Figure 4.2, F(1,5037)=67.64, p<0.0001). There was no significant interaction between trial type (Go/NoGo) and drug treatment (F(1,5037)=3.02, *n.s.*) on RT. These results implicate activity in mPFC as necessary for supporting inhibitory control on NoGo trials.

4.6 Specific Aim 2b: Show that mPFC is sufficient to support inhibitory control

To establish that mPFC is sufficient to support inhibitory control, I transfected neurons in prelimbic cortex of the rat with an excitatory (Gq)DREADD that selectively transfected excitatory, projection neurons (pyramidal cells) in cortex. DREADD technology utilizes human muscarinic receptors to that have been genetically modified to no longer bind Acetylcholine (Ach) and instead bind to clozapine-n-oxide (CNO). Without one another, both CNO and the DREADD receptor are inert and do not affect neurophysiology. In the case of excitatory (Gq) DREADD, when CNO binds to the DREADD receptor it triggers a G-protein signaling cascade that ultimately increases cyclic adenosine monophosphate and increases the excitability of the neuron, making it

more likely to fire. Rats received a peripheral injection of CNO. I then tested the animals before they reached their behavioral asymptote in order to observe changes in performance accuracy. Behavior on both Go and NoGo trials was quantified and compared between a pretreatment day, a CNO treatment day, and the following no treatment, washout day.

4.6.1 Hypothesis and predictions. If the excitatory signal in mPFC plays a causal role in supporting inhibitory control, then facilitating the firing of excitatory neurons should increase inhibitory control on NoGo trials. I also hypothesized that facilitating neurons within prelimbic cortex would not affect accuracy on Go trials, as once this behavior becomes strongly biased, the burden of maintaining the behavior is shift to other subcortical regions, such as the dorsal striatum (for review see Balleine & O'Doherty, 2010)

4.7 Method

4.7.1 Surgery. Rats received injections of the excitatory DREADD AAV8-CaMKII-hM3D(Gq)-mCherry (UNC Vector Core) into the prelimbic subdivision of mPFC. We used a 10µl Hamilton microinjection syringe attached to a stereotaxic pump. I infused using a 28-gauge injector (Plastics One) at +3.2 AP, ±0.8 ML relative to bregma and -3.6 DV relative to skull surface. Virus was injected at 1 µl per side at a rate of 0.1 µl per minute for 10 minutes. The promoter gene for Ca2+/calmodulin-dependent protein kinase II (CaMKII) allowed for selective transfection and receptor expression in glutamatergic, pyramidal projection neurons. The gene sequence also contains a gene for the flourophore mCherry that tagged receptors for later histological visualization.

The injector was left in place for ten minutes after infusion before being removed. Surgical wounds were sutured closed and animals were given one week to recover prior beginning training for the Symmetric Go/NoGo task.

4.7.1 Pharmacology and testing. Rats were initially trained to perform the Symmetric Go/NoGo task after recovering from surgery. Similar to the pharmacological manipulations described above, rats were administered the drug clozapine-N-oxide (CNO, 2mg/kg dissolved in 0.9% saline, i.p.) in a within subject design, tested on a treatment session, and then a follow-up no-drug session. It usually takes several weeks for the animals to reach their maximum level of NoGo accuracy over the course of training. Administration of CNO was conducted while performance on NoGo trials was not yet asymptotic, which allowed me to observe both improvements and impairments in performance on Go and NoGo trials.

4.7.2 Analysis of behavioral data. Accuracy was analyzed separately for Go and NoGo trials using a repeated-measures ANOVA and Holm-Sidak post-hoc test for pairwise comparisons (nonparametric tests were substituted for data that did not hold up to the normality assumption).

4.7.3 Histology. When animals completed the test sessions, they were injected with a sublethal dose of sodium pentobarbital (100mg/kg). Brains were extracted and stored in formalin for 24 h then changed to a 30% sucrose solution for at least another 24h. Brains were then be sectioned at 50μm in a cryostat (-20°C). Tissue was mounted on slides and cover slipped using Cryoseal 60 (Richard-Allen Scientific) and viewed under a light microscope connected to a X-Cite xLED laser (Lumen Dynamic) to verify

transfection placement based on visual landmarks (Figure 4.5, Paxinos and Watson, 2007).

4.8 Results

4.8.1 Facilitating excitability of mPFC projection neurons increases inhibitory control. Eight Long-Evans rats received injections of the excitatory DREADD AAV8-CaMKII-hM3D(Gq)-mCherry into mPFC to test whether enhancing excitability in mPFC improved performance on NoGo trials. The promoter gene for Ca2+/calmodulin-dependent protein kinase II (CaMKII) allowed for selective transfection and receptor expression in glutamatergic, pyramidal projection neurons. Seven of the 8 rats showed transfection in prelimbic cortex and were used for analysis. Unlike the previous pharmacological manipulations, I administered peripheral CNO to rats while they were still learning to inhibit pressing on NoGo trials in the Go/NoGo task. CNO was administered when rats had shown stable performance on NoGo trials for three consecutive days, but typically below criterion of 50% correct NoGo performance. As such, the CNO was administered on sessions 46-49 of the Go/NoGo tasks (the range of days is due to differences between rats advancing between stages of training based on criteria). A repeated-measures ANOVA on ranks showed no difference in performance on NoGo trials between pretreatment sessions (χ^2 (2) = 0.33, p = 0.96) indicating stable performance. CNO was then administered in a within subjects design. I compared performance on Go and NoGo trials separately for one session pretreatment, the CNO session, and the post-CNO treatment session. There was no difference in Go performance across the three sessions (Figure 4.3, repeated-measures ANOVA on

ranks: χ^2 (2) = 3.08, p = 0.24). However, there was a significant difference in the animals' ability to withhold pressing on NoGo trials (Figure 4.3, repeated-measures ANOVA: *F* (2,6) = 8.29, p < 0.01). NoGo accuracy significantly improved under CNO treatment compared to pretreatment session (Figure 4.3, post-hoc pair-wise Holm-Sidak test: t(6) = 4.03, p < 0.01) and trended toward a significant decrease in performance between CNO treatment and post treatment (Figure 4.3, t(6) = 2.50, p = 0.055). There was no difference in accuracy on NoGo trials between pre and post treatment days (Figure 4.3: t(6) = 1.53, p = 0.15). Together, these data show that inhibitory control was enhanced when projection neuron excitability was facilitated with treatment of CNO, implicating excitatory signaling in mPFC as sufficient for supporting inhibitory control.

4.9 Discussion

In this chapter I tested whether activity in mPFC was causally related to behavior on Go and NoGo trials. To test this, I temporarily inactivated mPFC to establish the necessity of the activity toward behavior. I found that temporarily inactivating mPFC resulted in a modest reduction in correct approach behavior on Go trials, but the high level of accuracy maintained on these trials indicated that activity in mPFC was less involved in maintaining the biased approach behavior. Inactivating this area, however, did dramatically reduce accuracy on NoGo trials implicating the activity in this area as crucial for sustaining inhibitory control. Furthermore, I tested the causal role of mPFC in inhibitory control by facilitating firing of pyramidal cells and found that increased excitatory signaling in mPFC strengthened inhibitory control accuracy on NoGo trials; bolstering the implication that this area plays a causal role influencing inhibitory control.

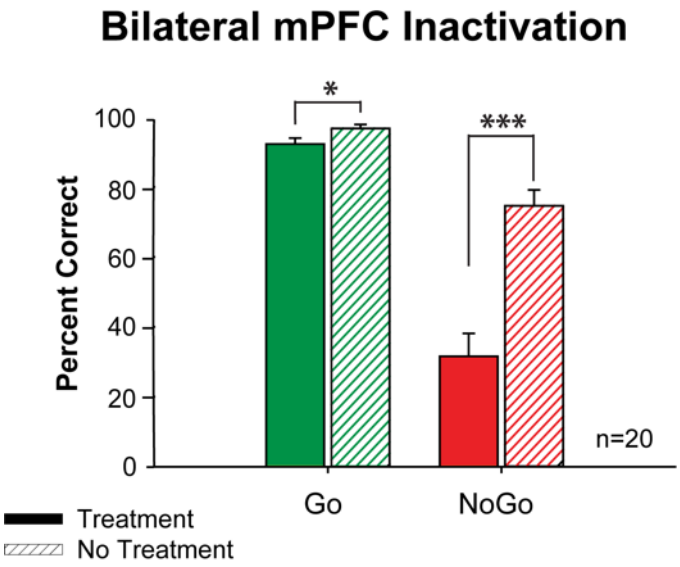

Figure 4.1. Bilateral inactivation of mPFC with muscimol/baclofen (hashed bars) results in a small reduction in accuracy on Go trials and large decrease in accuracy on NoGo trials compared with the 'No Treatment' condition on the following day. mPFC appears to play a necessary role for the animal to inhibit biased approach behavior.

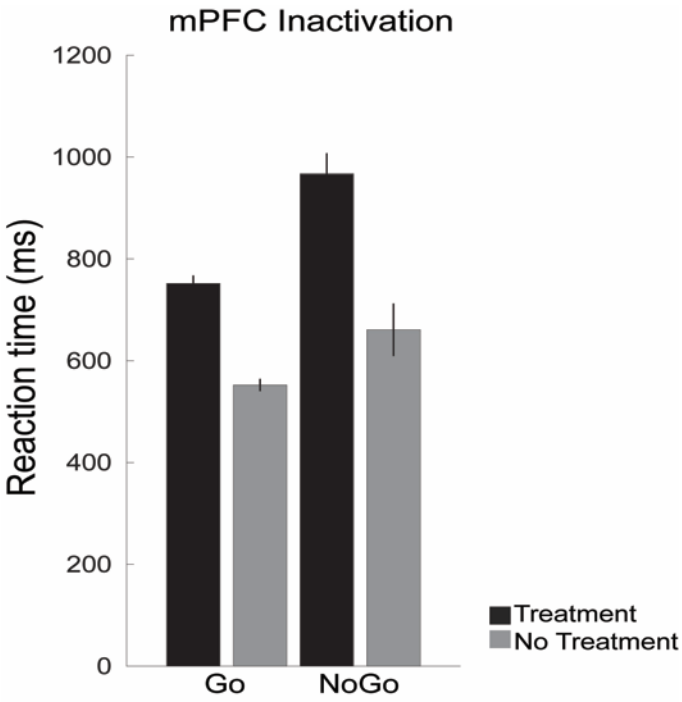

Figure 4.2. RT depended on trial type (Go/NoGo) and/or condition (Treatment/NoTreatment). Bar shading indicates Treatment (black) or NoTreatment (gray), with average Go and NoGo RT shown separately (error bar = ± 1 s.e). NoGo RT was significantly slower than Go RT in the mPFC inactivation. RT was slower than the NoTreatment session in the mPFC inactivation.

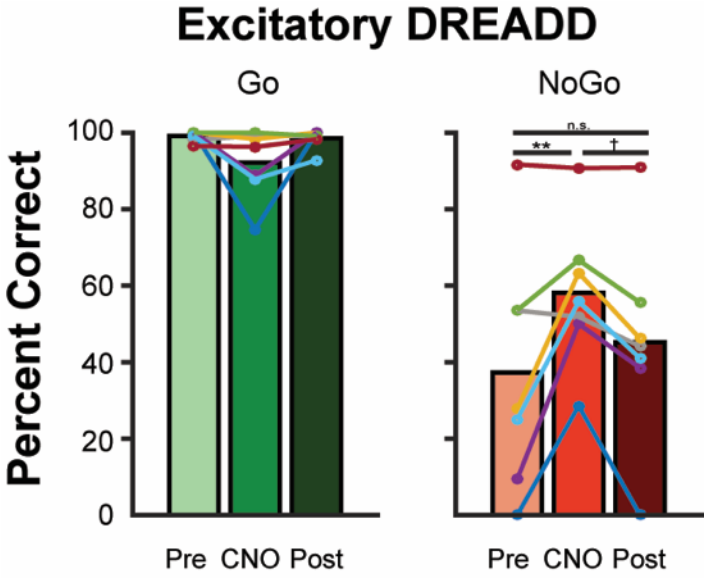

Figure 4.3. Facilitating excitatory output from mPFC during training, before rats are proficient at inhibiting NoGo responses, increases accuracy on NoGo trials. Rats were transfected in prelimbic cortex of mPFC with an excitatory DREADD AAV8-CaMKII-hM3D(Gq)-mCherry. Rats were administered CNO while still learning to inhibit approach behavior in response to NoGo trials. During the CNO treatment session (red bars, center) rats showed a significant increase in accuracy on NoGo trials compared to the pretreatment session ('Pre', $p<0.01$) and a trending decrease on post treatment ('Post', $p = 0.055$) compared to treatment day. There were no significant changes in Go performance (green bars).

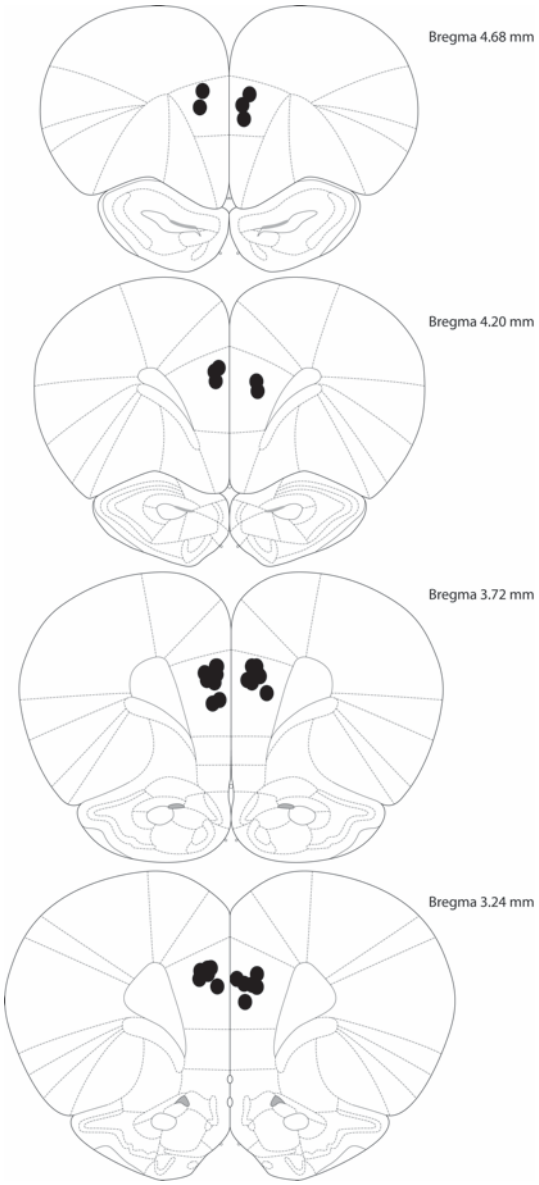

Figure 4.4. Histological verification of the cannula placement for mPFC inactivation.

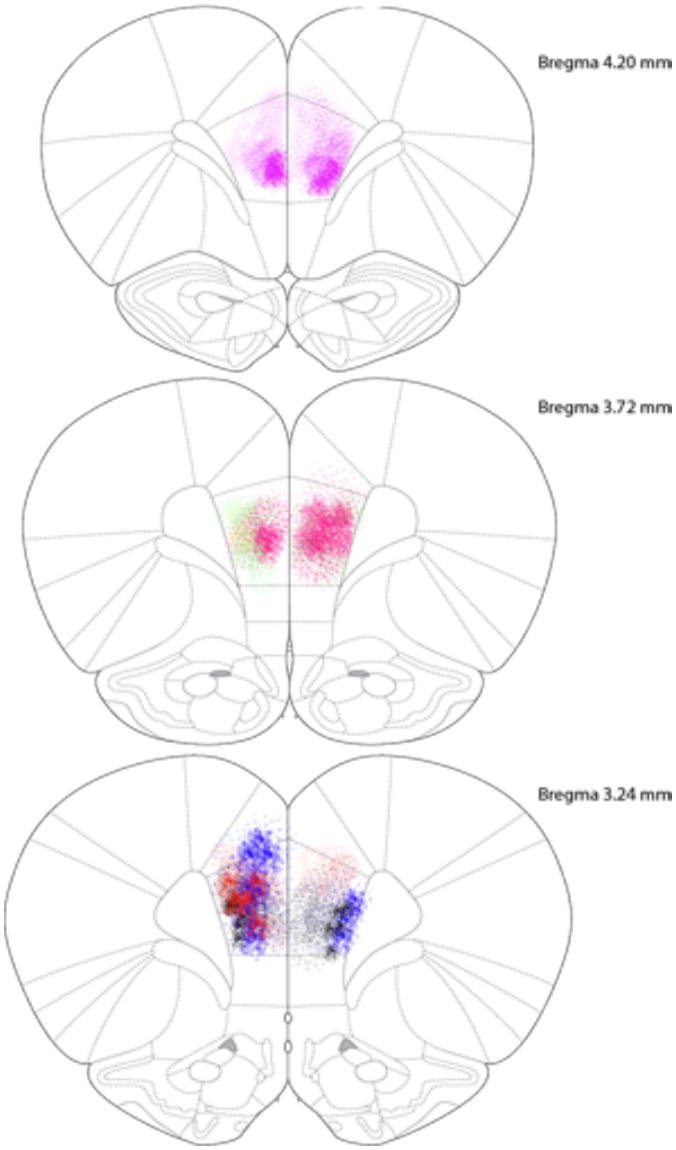

Figure 4.5. Histological verification of the DREADD transfection. Clouds represent density of transfection in area. Dots do not represent individual cells.

5. Functional communication between mPFC and NAc supports inhibition of approach behavior in a Symmetric Go/NoGo task

5.1 Rationale

In the previous chapters I showed that mPFC signaling is correlated with inhibitory control expressed on NoGo trials and that activity in mPFC is both necessary and sufficient to maintain inhibitory control. How mPFC activity, though, sits within a larger circuit to influences inhibitory control is still unclear. One target of mPFC signaling that stands as a good candidate for inhibitory control is the NAc. mPFC sends glutamatergic projections to the NAc. NAc integrates information about environmental cues and rewards and then projects to other basal ganglia structures to influence (approach) motor behaviors (Costa et al., 2006; Floresco, Blaha, Yang, & Phillips, 2001; Grace et al., 2007). Additionally, previous work from our lab has shown that NAc shows augmented neuronal firing on NoGo trials and that blocking excitatory signaling through AMPA receptors resulted in animals' reduced ability to inhibit approach on NoGo trials (Roitman and Loriaux, 2014; Ebner, dissertation). Whether mPFC is an origin of this excitatory signal, though, is still unclear.

5.2 Specific Aim 3: Determine whether mPFC communication with NAc supports inhibitory control.

I tested whether the functional connectivity from mPFC to NAc is necessary for successful inhibitory control while rats performed the Symmetric Go/NoGo task. Rats were trained on the task until they reached an asymptotic level of accuracy. Brain structures were centrally infused with baclofen/muscimol that held excitatory cells in a

hyperpolarized state, reducing the likelihood that they would fire. Drug was infused to a unilateral mPFC and to the contralateral NAc creating a bilateral disconnection of communication between the two structure; that is, it disrupted the functional communication between mPFC and NAc on both sides of the brain, but left one of each structure intact that could presumably support behavior. In addition to dense ipsilateral projections to NAc, mPFC also sends less dense contralateral projections to NAc. To test whether these full circuits are necessary for inhibitory control, I also conducted an ipsilateral disconnection by inactivating one mPFC and the ipsilateral NAc. I then quantified behavior on both Go and NoGo trials to compare accuracy between each drug treatment session and its following no treatment, washout session.

5.3.1 Hypothesis and predictions. If the functional communication between mPFC and NAc is necessary for behavioral restraint, then rats should show reduced accuracy on NoGo trials, indicating an impairment of inhibitory control.

5.4 Methods

5.4.1 Surgery. After reaching the behavioral criterion of 50% correct NoGo trials on the Symmetric Go/NoGo task, rats were each implanted with two pairs of bilateral guide cannulae for delivery of pharmacological agents into mPFC and NAc. Bilateral cannulae were stereotaxically guided into the prelimbic region of mPFC at +3.3 AP, ±1.2 ML relative to bregma and -3.0 DV relative to brain surface at a 10° lateral angle. One cannula was stereotaxically guided into the left NAc at -2.45 AP, -1.1 ML relative to bregma and -7.1 DV relative to brain surface at a 25° posterior angle. One cannula was stereotaxically guided into the right NAc at +0.4 AP, +1.2 ML relative to bregma and -

6.4 DV relative to brain surface at a 10° posterior angle. Cannulae were anchored to the skull via stainless steel screws and dental acrylic. Animals were given at least one week to recover before testing.

5.4.2 Pharmacology and testing. Animals were treated with a mixture of the $GABA_A$ agonist Muscimol and the $GABA_B$ agonist Baclofen in a counter balanced design that included four test conditions: contralateral infusions in which one mPFC was inactivated along with the contralateral NAc (bilateral disconnection), ipsilateral infusions in which one mPFC was inactivated along with the ipsilateral NAc (ispsilateral disconnection), a unilateral mPFC inactivation, and a unilateral NAc inactivation. Note that each animal can be tested twice in the disconnection conditions by alternating the sides of the infusions. The drug cocktail of 250 ng/µl Muscimol and 250 ng/µl Baclofen was administered in a volume of 0.5µl a rate of 0.25µl/m in physiological saline such that 125ng of each drug was delivered per site. If motor effects following infusions into the NAc are witnessed, the dosage into NAc was reduced at increments of 25% of the original dosage until no motor deficits were observed. If motor effects were still observed at 50% the original dose, data from these conditions were omitted from analysis. Additionally, data were omitted from analysis if the animal did not complete at least half of the trials (75) in each session. After drug infusion, the animals were immediately tested on the Symmetric Go/No Task. Test sessions with drug treatment were followed by a session without drug treatment to ensure recovery of behavior. If drug effects were still present, the animals were tested an additional day without drug treatment.

5.4.3 Analysis of behavioral data. For each treatment condition, performance on Go trials and NoGo trials was analyzed separately, comparing accuracy on the drug treatment session to that on the recovery, no-treatment sessions using a paired samples t-test.

5.4.4 Histology. When animals completed the test sessions, they were injected with a sublethal dose of sodium pentobarbital (100mg/kg). Electric current was passed (100μA) through each cannula injector for 4 s with a lesion-making device (Ugo Basile, Comerio, Varese, Italy) to mark placement. Rats were then transcardially perfused with phosphorous-buffered saline followed by formalin. Brains were extracted and stored in formalin for 24 h then changed to a 30% sucrose solution for at least another 24h. Brains were then sectioned at 50μm in a cryostat (-20°C). Tissue was mounted on slides and viewed under a light microscope to verify cannula placement based on visual landmarks (Figures 5.6 & 5.7, Paxinos and Watson, 1997).

5.5 Results

5.5.1 Communication from mPFC to NAc supports behavioral restraint on NoGo trials. I tested whether the functional communication between mPFC and NAc is necessary to support inhibitory control on NoGo trials. To do this I implanted infusion guide cannulae in mPFC and NAc and infused a mixture of muscimol/baclofen in multiple configurations to disrupt communication between the two regions both bilaterally and ipsilaterally. Twelve bilateral disconnections were analyzed to establish the role of the mPFC's communication with NAc. Performance on the Symmetric Go/NoGo task was calculated as percent correct on both Go and NoGo trial types.

Animals were tested with drug treatment and then again the following day with no drug treatment for comparison and to examine whether there were lasting effects of the central infusions. As in the bilateral inactivation of mPFC, there was a small, but statistically significant reduction in Go accuracy following bilateral disconnection (Figure 5.1, disconnection mean = 87.36 ± 2.93%, no treatment mean = 95.15 ± 1.67%, t = -2.55, $p < 0.05$). The animals' ability to withhold pressing on NoGo trials, however, was strongly reduced (Figure 5.1, disconnection mean = 38.05 ± 8.36%, no treatment mean = 77.76 ± 5.65%, t = -5.58, $p < 0.001$). Following bilateral disconnection of mPFC from NAc, RT was 729 ± 26ms for correct Go presses and 762 ± 51ms for NoGo errors. On the No Treatment session, RT was 540 ± 17ms for correct Go presses and 652 ± 79ms for NoGo errors. Across treatment conditions, there were no reliable differences in RT between correct Go lever presses and NoGo (Figure 5.2, $F(1,2770)=2.51$, *n.s.*). Overall RT, was slower during the disconnection compared with the following no treatment day ($F(1,2770)=10.77$, $p<0.01$). There was no significant interaction between trial type and drug treatment ($F(1,2770)=0.74$, *n.s.*).

With ipsilateral disconnection of mPFC-NAc, there was no change in Go accuracy (Figure 5.3, disconnection mean = 91.05 ± 3.28%, no treatment mean = 94.38 ± 2.43%, t = -0.77, $p =0.46$). However, animals showed a significant decrease in accuracy on NoGo trials following ipsilateral disconnection (Figure 5.3: disconnection mean = 31.22 ± 9.79%, no treatment mean = 74.64 ± 5.83%, t = -5.71, $p <0.001$). Following ipsilateral disconnection of mPFC from NAc, RT was 474 ± 18ms for correct Go presses and 651 ± 49ms for NoGo errors. On the No Treatment session, RT was 516 ± 18ms for correct Go presses and 901 ± 104ms for NoGo errors. Overall, RT was

slower for error NoGo presses than correct Go (Figure 5.4, $F(1,2336)=52.84$, $p<0.0001$). RT across trial types was faster during the disconnection compared with the following no treatment day (Figure 5.4, $F(1,2336)=14.25$, $p<0.01$). In addition, there was a significant interaction between trial type (Go/NoGo) and drug treatment ($F(1,2336)=7.21$, $p<0.01$).

Single, unilateral inactivations of mPFC (N = 7) or NAc (N = 5) both failed to alter Go accuracy (Figure 5.5A & 5.5B, single mPFC: inactivation mean = 93.37 ± 31.80%, no treatment mean = 95.08 ± 1.63%, $t[6] = -0.71$, $p = 0.5$; single NAc: inactivation mean = 86.64 ± 6.80%, no treatment mean = 99.44 ± 0.56%, $t[4] = -1.98$, $p = 0.12$) or NoGo accuracy (Figure 5.5A & 5.5B: single mPFC: inactivation mean = 57.45 ± 7.30%, no treatment mean = 72.71 ± 6.64%, $t[6] = -2.03$, $p = 0.09$; single NAc: inactivation mean = 77.17 ± 6.20%, no treatment mean = 77.44 ± 8.15%, $t[4] = -0.03$, $p = 0.98$). Single, unilateral mPFC inactivation had no effects on RT. The comparison of RT following single, unilateral NAc inactivation depended on the treatment and trial type interaction ($F(1,912)=6.12$, $p<0.05$). In this condition, RT was slower for NoGo errors than Go corrects (Go RT = 532 ± 19ms, NoGo RT = 643 ± 75ms, $F(1,912)=4.98$, $p<0.05$) and slower in the single inactivation than the no treatment day (inactivation RT = 546 ± 27, no treatment RT = 535 ± 25, $F(1,912)=5.51$, $p<0.05$). Notably, though, in no condition did RT slow to the point of resulting in increased errors for Go trials or corrects for NoGo. That is, no average RT exceeded 1s, and RTs did not approach the 4s/4.5s limited availability of the Go/NoGo lever, respectively.

5.6 Discussion

Here, I used pharmacological inactivations in series of configurations to temporarily disrupt the functional connectivity between mPFC and NAc. I showed that both bilateral and ipsilateral disconnections resulted in reduced inhibitory control on NoGo trials. However, this reduction was not seen when only a single mPFC or NAc was inactivated. This reduction in NoGo accuracy was similar to what was seen when mPFC is bilaterally inactivated and implicates the functional communication between mPFC and NAc as critical for inhibitory control expressed on NoGo trials.

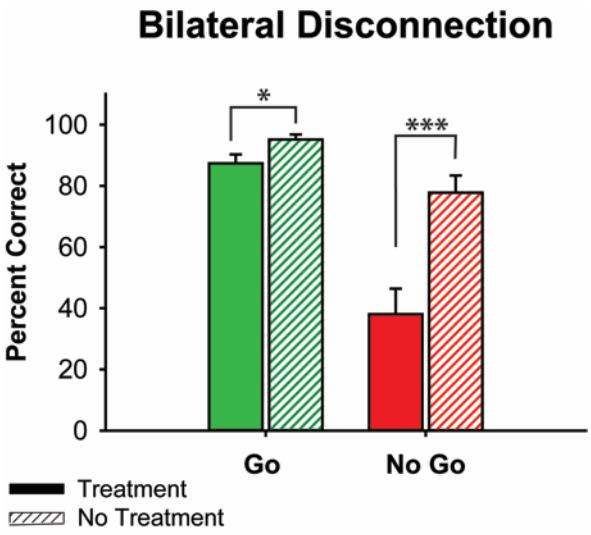

Figure 5.1. Functional communication between mPFC and NAc was disrupted bilaterally using muscimol/baclofen (hashed bars). Bilateral disconnection resulted in a small reduction in accuracy on Go trials and large reduction on NoGo trials, indicating that bilateral communication between mPFC and NAc is important for supporting inhibitory control.

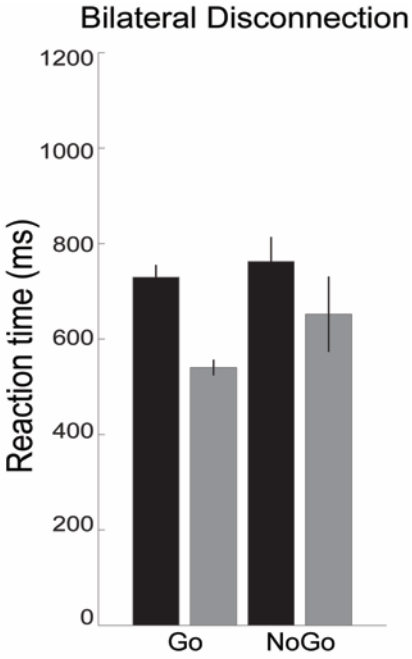

Figure 5.2. RT depended on condition (Treatment/NoTreatment). Bar shading indicates Treatment (black) or NoTreatment (gray), with average Go and NoGo RT shown separately (error bar = ± 1 s.e). After pharmacological treatment, RT was slower than the NoTreatment session in the bilateral disconnection treatment. Overall, average RT was faster than 1s, thus even small increases in RT did not result in a higher incidence of Go errors or improvement in NoGo accuracy.

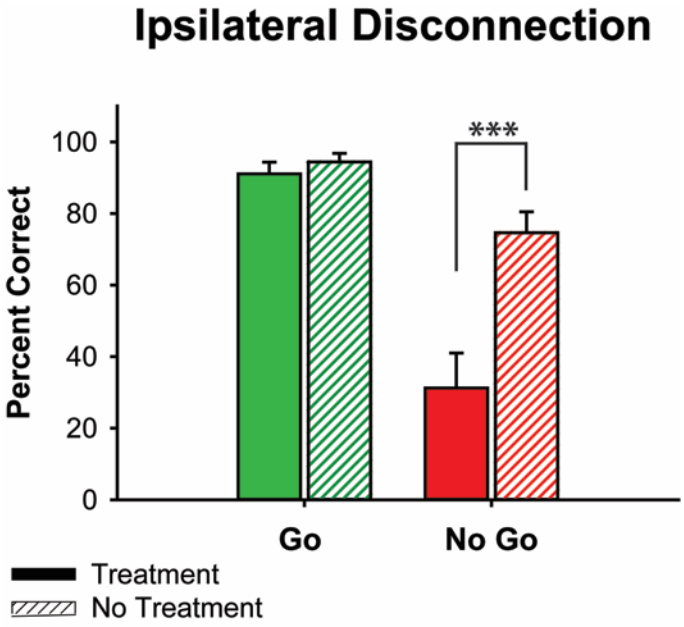

Figure 5.3. Functional communication between mPFC and NAc was disrupted ipsilaterally using muscimol/baclofen (hashed bars). Ipsilateral disconnection resulted in a large reduction in NoGo accuracy indicating that ipsilateral communication between mPFC and NAc is important for supporting inhibitory control.

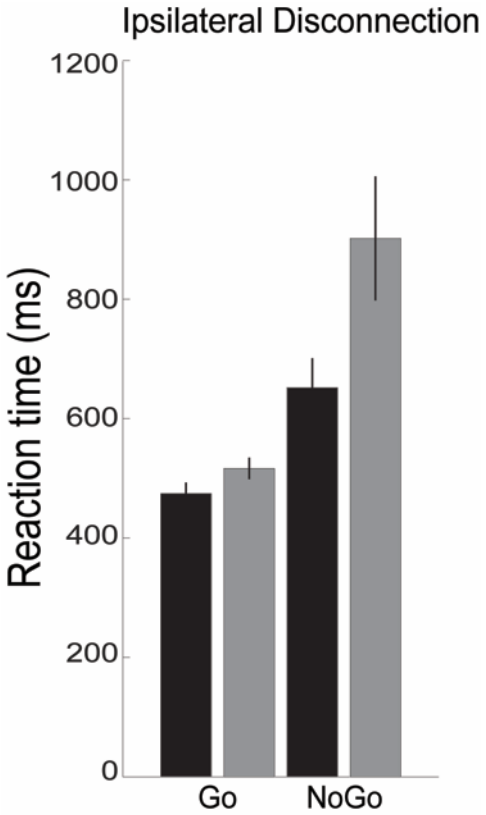

Figure 5.4. RT depended on trial type (Go/NoGo) and/or condition (Treatment/NoTreatment). Bar shading indicates Treatment (black) or NoTreatment (gray), with average Go and NoGo RT shown separately (error bar = ± 1 s.e). NoGo RT was significantly slower than Go RT in the ipsilateral disconnection. Overall, average RT was faster than 1s, thus even small increases in RT did not result in a higher incidence of Go errors or improvement in NoGo accuracy.

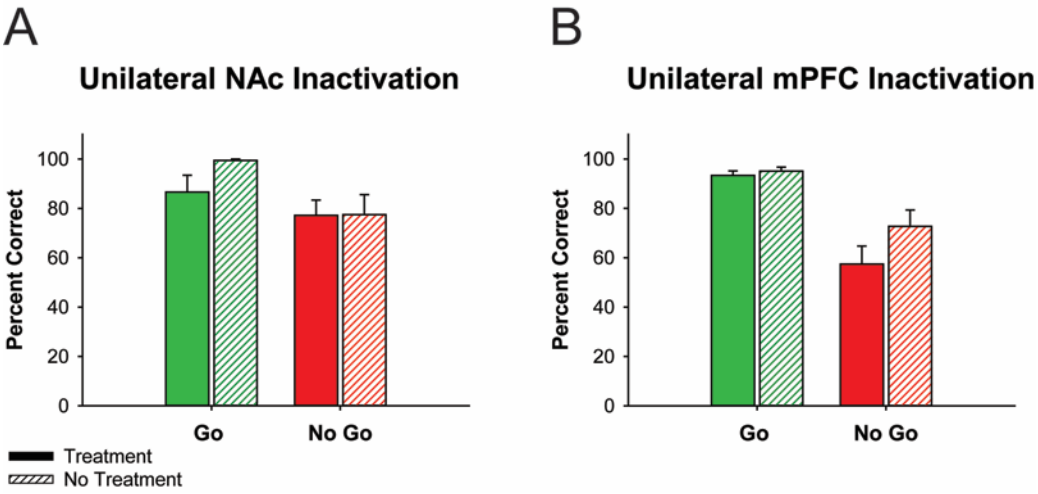

Figure 5.5. Unilateral NAc and mPFC were activated using a mixture of baclofen/muscimol. No differences were seen between treatment and no treatment conditions for either Go or NoGo behavior in either inactivation.

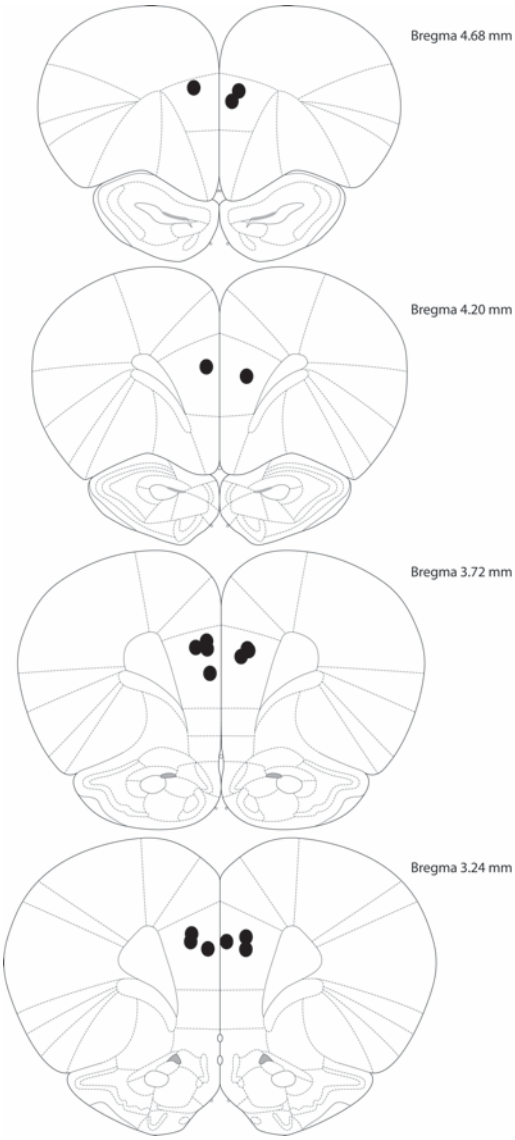

Figure 5.6. Histological verification of the cannula placement in mPFC for bilateral disconnection and ipsilateral disconnection.

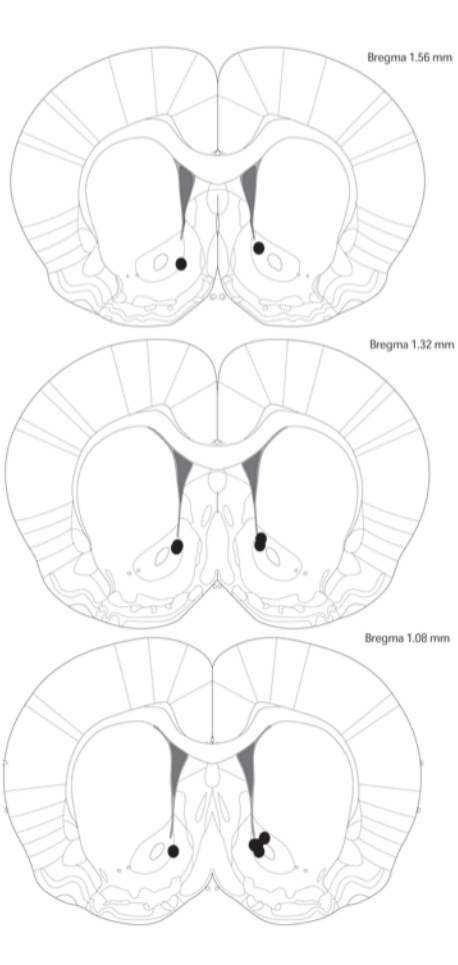

Figure 5.7. Histological verification of the cannula placement in NAC for bilateral disconnection and ipsilateral disconnection.

6. General Discussion

The mPFC has long been suggested to play a crucial role in executive control of behavior. However, the patterns of activity within mPFC and to where that signal is transmitted to support inhibitory control in response to appetitive cues is still unclear. Here we used a behavioral model in which animals were conditioned to develop a strongly biased approach/consummatory response to one reward-predictive cue (Go) and then instructed to periodically inhibit that approach response using a distinct reward-predictive cue (NoGo). Importantly, the consequences for correct and incorrect Go and NoGo behaviors resulted in the same consequences (reward/time-out). My findings provided evidence that subsets of mPFC neurons selectively encode Go cues and NoGo cues. An additional subset of mPFC neurons responded to both Go and NoGo cues and these neurons exhibited excitation that was higher when animals successfully withheld behavior on NoGo trials, a signal that mimics previous findings in NAc (Roitman and Loriaux 2014a). I also found that excitatory signaling in mPFC was both necessary and sufficient to support inhibitory control, and that functional connectivity between mPFC and NAc enabled animals to restrain approach appropriately.

6.1 NoGo behavior as an index of inhibitory control

Several paradigms have been used to test inhibitory control, but model different aspects of it according to task demands that likely rely on different neural substrates. For example, Stop Signal Tasks (SST) model action cancellation by cueing subjects to

initiate an approach response and then periodically present a distinct stop signal, at variable latencies, to determine how a planned action is cancelled (Logan and Cowan 1984). On the other hand, traditional Go/NoGo tasks model action restraint. These tasks often use two distinct cues to instruct approach (Go) or withhold (NoGo) separately with the NoGo cue instructing the subject to restraint their approach; that is, prevent approach from being initiated from the outset (Iversen and Mishkin 1970). Failure to inhibit the approach action on NoGo results in punishment. On both SST and the traditional Go/NoGo paradigm correct inhibition of action is not rewarded, but serves only to advance the animal to the next trial with no immediate appetitive consequence. Conversely, Five Choice Serial Reaction Time tasks (5-CSRTT) model a type of action inhibition by allowing animals to initiate a trial, then requires them to withhold responding until the port that will deliver a reward is cued, in essence rewarding their inhibitory control. Premature responding is indicative of the subjects' impulse control (A. Bari, Dalley, and Robbins 2008). Similarly, the Symmetric Go/NoGo task used here also rewards correct inhibition of action on NoGo trials. Therefore in the 5-CSRTT and Symmetric Go/NoGo paradigms, it is immediately beneficial to restrain approach (for reviews of action restraint paradigms see (Dalley, Everitt, and Robbins 2011a; Hamilton, Littlefield, et al. 2015; Winstanley 2011). Although all of these paradigms study inhibitory control, it likely that mPFC is recruited differentially due to the value of action inhibition. For example, lesions in mPFC (prelimbic and infralimbic) cortex decrease inhibitory control on 5-CSRTT, but have no effect on SST or standard Go/NoGo (Risterucci, Terramorsi, 2003; Chudasama et al., 2003; Roitman & Roitman, 2010; Eagle & Robbins, 2003a, 2003b; Ragozzino, Detrick, & Kesner, 2002). Prelimbic cortex,

specifically, has been shown to be necessary for goal-directed action (Tran-Tu-Yen et al. 2009). I found that this area was necessary for inhibitory control in our Symmetric Go/NoGo task and these findings were in contrast with previous lesion studies. This contradiction may be due to inherent differences between ablating this area versus pharmacologically inactivating it. However, my findings fit more closely with lesions during 5-CSRTT in which mPFC is necessary to support inhibition and thus I conjecture the contradiction is due to differences in the task contingencies. Furthermore, my findings may seem at odds with existing notions that prelimbic cortex influences “go” behavior while infralimbic cortex is more closely associated with “stopping” behavior (for review see Gourley & Taylor, 2016). One way to reconcile my findings is that there is not a strict dichotomy between the two structures (Gourley and Taylor 2016). Indeed, the small proportion of neurons I recorded in infralimbic cortex showed activity that was not distinguishable from the phasic activity to cues observed in prelimbic cortex neurons. Another way to reconcile the contradiction is to examine the withholding behavior on NoGo trials. I proposed that withholding in the Symmetric Go/NoGo paradigm is an active process that is positively reinforced when executed correctly on NoGo trials. Therefore, inhibiting the biased approach response may be thought of as its own goal-directed behavior that is supported by proper prelimbic functioning.

In general, I showed that animals maintained a high level of accuracy on Go trials irrespective of manipulation. However, in some drug treatment experiments there were small, but statistically significant reductions in Go performance and these reductions do not fit with out our hypothesis. These findings may be an artifact of the method of statistical analysis. Currently, we analyze Go and NoGo behavior separately, treating

Go and NoGo as independent variables. It could be, however, that performance on either trial type is related to the other and when this relationship is controlled for, the effects on Go trials is abolished or enhanced. Signal detection theory (SDT) may provide a more precise analytical approach that would take into account changes in Go behavior to provide indices of overall performance. Under SDT, latent decision variables are thought to underpin animals' actions in the Go/NoGo task and these variables are influenced by two factors: How well the animal can discriminate between the Go and NoGo signals (sensitivity) and the animal's underlying general penchant to approach or withhold (bias). The latter is contingent on the value-based criterion set by the animal such that for any perceived signal value that equals or exceeds the criterion, the animal will perform one action and for any signal value that falls below, the animal will perform the opposite action. To calculate sensitivity and bias measures (d' and C, respectively), SDT relates the rate at which the animal correctly approached on Go ('hit rate') to the rate at which it incorrectly approached on NoGo ('false alarm rate'). Together, these two indices provide insight into how well the animal was able to distinguish between the Go and NoGo trials, as well as whether the animal exhibited a behavioral bias to press or hold that might prejudice behavior. Such bias would obscure the interpretation of their performance when only straightforward "percent correct" measurements used. Future behavioral analysis of Go/NoGo performance would do well to integrate these analytical methods.

6.2 Role of mPFC and functional circuitry in inhibitory control

My findings suggest that an excitatory signal transmitted by glutamatergic,

pyramidal neurons in mPFC play a key role in inhibitory control. I showed that neurons responding to both Go and NoGo cues had higher levels of activity when animals correctly inhibit approach behavior. I also showed that inhibitory control in response to appetitive cues was enhanced when I facilitated the excitability of pyramidal cells within mPFC. These findings are consistent with previous work that showed reduced impulsivity on a 3-choice serial reaction time task when mPFC pyramidal cell firing was facilitated in mice (Warthen et al. 2016). It is important to note that I observe multiple subtypes of increasing and decreasing responses, which are indicative of the complex microcircuitry of the cortex. Inhibitory interneurons play a role in coordinating pyramidal cell firing and pyramidal cells make intracortical connections to facilitate firing (for review see (Tremblay, Lee, and Rudy 2016)). How this micro-circuitry within mPFC supports inhibitory control is still unclear. Pinto and Dan (2015) found that pyramidal cells as well as different interneuron subtypes (parvalbumin, somatostatin, vasoactive intestinal peptide) within mouse mPFC track distinct task related components in a Go/NoGo paradigm. In this task NoGo behavior was not rewarded, and so it is still unclear how these different neuron types would contribute under conditions in which NoGo cues were reward-predictive (Pinto et al. 2016). A limitation of extracellular electrophysiological recording is that is it difficult to disentangle the contribution of different neuron types (Fuentealba et al. 2008; Vigneswaran, Kraskov, and Lemon 2011), even though some studies have found success using the biophysical properties of the action potential waveforms (Csicsvari et al. 1999; Gutman and Taha 2016). Unlike the latter studies, I did not observe distinct clusters according to waveform characteristics (data not shown).

My findings showed that the excitatory functional connection from mPFC to NAc allowed for inhibitory control of approach action in response to cues. NAc is proposed to integrate incoming excitatory signals from cortex and mesolimbic structures to promote and direct actions through communication with down-stream basal ganglia structures (for reviews, see (Floresco, 2015)). Roitman and Loriaux (2014) observed phasic increases in firing rates of NAc medium spiny neurons (MSNs) in response to both Go and NoGo cues in this Symmetric Go/NoGo task, and these phasic increases were higher when rats correctly withheld pressing on NoGo trials. These findings suggested that NAc receives an excitatory afferent signal at the time of the NoGo cue that biases behavior towards inhibition of the approach action. NAc MSNs receive excitatory input from both mPFC and limbic structures with multiple inputs often synapsing on the same MSN (O'Donnell 2010). Previous work from our lab also found that blocking excitatory signaling at AMPA receptors reduces rats' ability to inhibit approach (S.R. Ebner, dissertation). This excitatory signal necessary for inhibition of action on NoGo trials may originate, at least in part, in the mPFC. mPFC sends a dense glutamatergic projection to the ipsilateral, and a less dense projection to the contralateral, NAc (Sesack et al. 1989; Vertes 2004). I showed that both bilateral and ipsilateral pharmacological disconnection of the functional communication between mPFC and NAc impaired performance on NoGo trials, suggesting that one full circuit between mPFC and NAc is needed to support inhibitory control. My findings, though, dovetail nicely with recent work (Liu et al. 2016) showing that reduced glutamatergic signaling directly from mPFC to NAc results in enhanced reward-seeking, measured by consumption of sucrose, in sleep deprived mice that cannot be attributed to other limbic excitatory afferents. Indeed, loss of

inhibitory control can be thought of as inability to keep reward seeking in check (James David Jentsch and Pennington 2014). Moreover, Lui et al. (2016) were able to return mice to non-sleep-deprived levels of reward-seeking with optogenetic stimulation of mPFC-NAc glutamate signaling to MSNs. With these findings in mind, we speculate that the direct projection from mPFC to NAc is critical for supporting behavioral control in the Symmetric Go/NoGo task.

An alternative explanation may be that the reduced inhibitory control is supported through mPFC communication with subcortical structures (for discussion, see (Bossert et al. 2012)); indeed my result showing impaired NoGo accuracy during the ipsilateral disconnection may suggest such an alternative explanation. In addition to direct projections to NAc, mPFC projections via mesolimbic structures that in turn project to the NAc may have been affected, disrupting the chain of communication through these structures, resulting in a loss of inhibitory control. However, in order for the ipsilateral disconnection result to be explained by subcortical relays, either the mPFC must bilaterally project to the structure or the structure must bilaterally project to NAc. One such structure is ventral tegmental area (VTA). mPFC sends dense bilateral glutamatergic projections the VTA, which in turn projects to NAc (Beckstead 1979; Sesack et al. 1989). However this pathway does not seem to be a viable alternative explanation for our findings as reduced glutamatergic signaling from mPFC to VTA would reduce dopamine transmission in NAc. Previous work from our lab showed that blocking either dopamine D1 or D2 receptors in NAc during performance of the Symmetric Go/NoGo task reduced motivation and accuracy on Go trials (although it did not impair motor movement as assayed by latency to retrieve reward) while leaving

NoGo accuracy intact (S.R. Ebner, dissertation). It is possible that the mPFC to NAc signal is relayed through other structures. However, such an explanation does not detract from the main point: whether through direct projection or through subcortical relays, the excitatory signal exhibited in mPFC eventually affects NAc and this signal is necessary to support inhibitory control of the biased approach responding.

Interfering with the communication between mPFC and NAc did not result in an overall disruption of behavior, as animals were able to maintain high level of pressing on Go trials. This may be due to overtraining on Go trials to establish the biased approach response to the cue which may establish a more habit-like approach response that is governed by different (or additional) neural circuitry, such as through dorsal striatum (see (Balleine and O'Doherty 2010) for review). Indeed, my findings may suggest that behavioral responses toward appetitive cues are not strictly habitual *or* goal-directed. In fact, there may be an interplay between the two processes wherein the fundamental response is habit-like, and governed by neural circuits associated with stimulus-response behavior, that is then tempered to be goal-directed through mPFC-NAc communication when there is a shift in the behavioral contingencies leading to reward.

In the functional disconnection studies, I showed that ipsilateral disconnection between mPFC and NAc resulted in animals' reduced accuracy on NoGo trials, but maintain this finding does not detract from our argument that mPFC-NAc communication is necessary. Again, these findings appear at odds with the logic of this type of pharmacological disconnection protocol and thus only tell us that an mPFC excitatory signal reaches NAc. But, it is unable to definitively ascertain if the signal is transmitted directly to NAc through mPFC-NAc projections or whether the signal

reaches NAc through additional subcortical relays. One way to address the direct mPFC-NAc connectivity is to use a more precise chemogenetic manipulation. Here, I used an excitatory DREADD in mPFC to address the structure's sufficiency in supporting inhibitory control. I accomplished this by administering CNO peripherally. To test the direct excitatory connection between mPFC and NAc, one could also centrally administer the CNO to NAc that would then bind to only the axon terminals of neurons that originated in mPFC and facilitate transmitter release. Alternatively, one could to test for the necessity of this connection by transfecting cells in mPFC with an *inhibitory* DREADD and then centrally administering CNO in NAc. This manipulation would prevent vesicle docking at axon terminals and therefore reduce excitatory neurotransmitter release in NAc (for example, Mahler et al., 2014; Stachniak, Ghosh, & Sternson, 2014). If this manipulation also resulted in reduced accuracy on NoGo trials, it would strongly implicate the mPFC-NAc connection as necessary for inhibitory control. A word of caution, though: a positive result would bolster the argument that the mPFC-NAc connection is necessary for inhibitory control. However, a null result would not necessarily diminish the argument. Viral vectors that transfect cells with the genes for DREADD receptors do not transfect cells ubiquitously across the tissue (see Wirtshafter & Stratford, 2016). Moreover, mPFC cells that project directly to NAc are not tightly localized within mPFC. Therefore, one would have to achieve just the right spread of transfection in mPFC to inhibit enough of the descending fibers to sufficiently prevent transmitter release in NAc. If this were achieved, it would be confirmatory evidence for the role of the connection. However, if it was not achieved and the behavioral effect was not expressed, the latter could be due to inhibition of too few neurons and the

unaffected neurons remain sufficient to support the behavior. Because of such inconsistencies, pharmacological manipulations at doses high enough to saturate receptors in the area, may be a more reliable approach.

In my disconnection studies, I used a mixture of baclofen and muscimol to temporarily inactivate areas in mPFC and NAc to show reduced accuracy on NoGo trials, but I executed our disconnection based on previous studies that used CNQX to show that reduced excitatory signaling via AMPA receptors in NAc reduced accuracy on NoGo trials. At first blush, this logic may seem incongruent. However, the NAc is complex both anatomically and through afferent connectivity with other brain regions. NAc is made up primarily of GABAergic MSNs that project out of NAc. But, these neurons' activity is gated by a much smaller proportion of GABAergic interneurons and even smaller proportion of cholinergic (Ach) interneurons. Together, the neurons form microcircuits that complexly influence MSN excitation and efferent signals. All of these neurons posses AMPA receptors, but play different roles in the consequent efferent NAc signals. For example, mPFC projection neurons collateralize on both MSN and GABAergic interneurons and so mPFC glutamate signaling produces competing effects on the efferent NAc signal: glutamate will excite MSN and GABAergic interneurons, but the interneurons will fire to inhibit the activity of the MSNs, creating an intricate balance of excitation through AMPA receptor activation. Moreover, increased activity in in Ach neurons via AMPA receptor activation also results in inhibition of MSNs (Mark et al. 1999). With such intricacies in mind, I sought to circumvent the complex influence of specific AMPA receptor driven microcircuits in NAc excitation by taking a broad inactivation approach; reducing the activity of the microcircuits ubiquitously. It would be

beneficial to our understanding, though, for future research to hone in on exactly what role AMPA receptors, and their corresponding microcircuitry, play in the augmented excitation in NAc that corresponds with inhibitory control.

These findings are important to our larger understanding of the biological basis of impulsivity, particularly impulsivity that is rooted in inhibitory control. Inhibitory in is a pertinent feature to our daily lives, but it is especially important to understand it as it is a germane to the development, maintenance, and treatment of many psychiatric and addiction disorders. These findings imply that to combat these disorders, further emphasis should be placed on providing incentives to inhibit approach behavior. In cases where incentivizing behavior is not relevant, though, these findings provide a potential biological target to develop therapeutics to combat impulsiveness, such as those treatments that would increase mPFC activity while subjects were learning to inhibit their approach and consummatory behavior. Moreover, treatments that strengthen the communication between mPFC and NAc may prove beneficial in combatting impulsiveness.

6.3 Summary

Appetitive cues often elicit approach and consummatory that can be hard to override. I used a task that provided rats with cues to approach (Go) to receive a reward and cues to inhibit (NoGo) in order to receive a reward. I showed that mPFC in the rat responds to Go and NoGo cues associated with approach behavior towards food and its inhibition. I also showed that this excitatory signal was both necessary and sufficient to support inhibitory control and that mPFC's communication with NAc is necessary to

support goal-directed stopping behavior.

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8. ACC Approval

All experiment were approved as part of ACC protocols 14-034 &15-029

9. Curriculum vitae

Kirk F. Manson M.A.

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EDUCATION

2015 **University of Illinois at Chicago**, *Doctoral Candidate,* Program in Behavioral Neuroscience, Psychology, Chicago IL

2013 **University of Illinois at Chicago**, Program in Behavioral Neuroscience, Psychology Chicago IL

2008 **The University of Chicago***, M.A*., Masters of Arts Program in the Social Sciences, Comparative Human Development Section, Chicago IL

2005 **The Ohio State University**, *B.S.,* Psychology, Columbus OH

RESEARCH EXPERIENCE

2013-Present **PhD Program in Behavioral Neuroscience,** Psychology, University of Illinois at Chicago, Chicago IL
PI: Jamie D. Roitman PhD

Focus: the role of medial prefrontal cortex and its communication with subcortical structures in inhibitory control of behavior.

Techniques: electrophysiological recording of ensembles of single neurons, chemogenetic (DREADD) manipulations of neuronal circuits, behavioral pharmacology, survival animal surgery (stereotaxic; intraoral), operant conditioning

Software: PlexControl, Plexon Offline Sorter, Neuro Explorer, SPSS, Sigma Plot, Office, Adobe Illustrator and Photoshop;
Programming: Matlab, R, Med PC

2009-2013 **Laboratory Manager,** Decision Neuroscience Laboratory, Section of Comparative Medicine, Yale School of Medicine, New Haven, CT
PI: Ifat Levy PhD

Focus: the neural and psychophysiological correlates of value-based learning and decision-making in normal individuals, obese individuals, and PTSD patients.

Techniques: fMRI, galvanic skin response, eye-tracking, behavioral and psychiatric testing

Software: Brain Voyager, SPM/GSRalyze, Biopac & Acknowledge (psychophysiology), Tobii Studio (eyetracking);
Programming: Matlab, E-prime

2009-2012 **Research Affiliate,** Comparative Cognition Laboratory, Psychology, Yale University
New Haven, CT
PI: Laurie Santos PhD

Focus: the influence of automatic evaluation of environmental cues on approach and withdrawal responses in brown tufted capuchin monkeys *Cebus appella*

Techniques: Observational quantification (focal-animal sampling of behavior), ethogram construction, behavioral shaping, behavioral apparatus design

2008-2009 **Research Consultant,** NBBJ, Columbus, OH
Supervisor: Liz Sanders PhD

Focus: latent cognitive needs of stakeholders to inform design of the wayfinding system at Miami Valley Hospital

2007-2008 **Masters of Arts Program in the Social Sciences,** Comparative Human Development, The University of Chicago, Chicago IL
PI: Susan Margulis PhD

Focus/Thesis: Tool-use in white-cheeked gibbons (or lack thereof).

Techniques: Observational quantification (focal-animal sampling of behavior), ethogram construction, behavioral shaping, behavioral apparatus design

2002-2005 **Student Volunteer,** The Ohio State University Chimpanzee Center, Psychology, The Ohio State University, Columbus, OH
PI: Sarah Boysen PhD

Focus: Tool-use in brown tufted capuchin monkeys *Cebus appella* and Chimpanzees *Pan troglodytes*

Techniques: Observational quantification, behavioral shaping, behavioral apparatus design

AWARDS

Society for the Study of Ingestive Behavior New Investigator Travel Award: $1,000

2016 *Society for the Study of Ingestive behavior, Porto, Portugal*, 2016

UIC Provost's Graduate Research Award: $1,500

2015 *Funded purchase of equipment to develop novel cost-benefit, decision-making task*

UIC Chancellor's Supplemental Graduate Research Fellowship: $8,000

2013 *Funded research project on role of mPFC on inhibitory control*

UIC Behavioral Neuroscience Summer Research Award: $5,400

2014 *Provided stipend support for summer research*

UIC LAS Travel Award: $500

2014 *Society for Neuroscience, Washington DC*

UIC Department of Psychology Travel Award: $1,600

2014 *Society for Neuroscience, Washington DC*

2016 *Society for Neuroscience, San Diego CA*

2016 *Society of Society for the Study of Ingestive behavior, Porto, Portugal*

UIC Graduate College Travel Award, $550

2014 *Society for Neuroscience, Washington DC*

2016 *Society for Neuroscience, San Diego CA*

UIC Student Council Travel Award: $400

2014 *Society for Neuroscience, Washington DC*

PUBLICATIONS

In Preparation

Manson K. F., & Roitman, J. D. Differential encoding of impulsive action ad reward in medial prefrontal cortex and nucleus accumbens. *Invited to Physiology & Behavior*.

Jacobs-Brichford, E., **Manson, K. F.,** & Roitman, J.D. Adolescent cannabinoid exposure impairs risky decision-making and alters mPFC firing patterns in adult rats. *In Preparation.*

Corwin, S. D., **Manson, K. F.,** & Roitman, J.D. The effects of adolescent alcohol exposure on risky decision-making and orbital frontal cortex signal. *In Preparation.*

Submitted

Manson, K. F., Ebner, S.E., & Roitman, J. D. Prefrontal-striatal control of restraint in response to environmental cues.

Published

Zhang, Z., Mendelsohn, A**., Manson K. F**., Schiller, D., & Levy, I. Functional heterogeneity of the ventromedial prefrontal cortex: value representation and affective response update. 2015. *ENuero*. DOI: 10.1523/ENEURO.0072-15.2015

Manson, K. & Levy, I. 'Selling' Value: the Influence of Language on Willingness-to-Accept. 2015*. PLoS ONE* 10(3): e0120292. doi: 10.1371/journal.pone.0120292

Zhang, Z., **Manson, K**., Schiller, D., & Levy, I. Impaired learning of food predictive cues in obese women. 2014. *Current Biology*, 24:15, p1731–1736. DOI: http://dx.doi.org/10.1016/j.cub.2014.05.075

Tymula, A., Rosenberg-Belmaker, L., Ruderman, L., Roy, A., **Manson, K**., Glimcher,P., & Levy, I. Adolescents risk-taking behavior is driven by tolerance to ambiguity and not a taste for risk. 2012. *PNAS* 17135–17140, doi: 10.1073/pnas.1207144109

Levy, I., Rosenberg-Belmaker,L., **Manson, K.,** Tymula, A., & Glimcher, P. Measuring the subjective value of risky and ambiguous options using experimental economics and functional MRI methods. 2012. *J. Vis. Exp.* (67), e3724, doi:10.3791/3724

ACADEMIC POSTERS AND PRESENTATIONS

Manson, KF, Ebner, S., Amodeo-Horn, L., Jamal, B., & Roitman, JD. "Medial prefrontal cortex event-related cue signaling is necessary for inhibitory control". Society for Neuroscience Annual Meeting, San Diego CA, 2016

Manson, KF, Ebner, S., Amodeo-Horn, L., Jamal, B., & Roitman, JD. "Response of Medial Prefrontal Cortex to Cues for Behavioral Restraint" Society for the Study of Ingestive Behavior, Porto, Portugal. 2016

Manson, KF, & Roitman, JD. "Response of Medial Prefrontal Cortex to Cues for Behavioral Restraint" Brain Research Foundation, Chicago IL. 2016

Manson, K. & Roitman, JD. "Connectivity between medial prefrontal cortex and nucleus accumbens is necessary for restraint of impulsive reward-directed behavior" Society for Neuroscience Annual Meeting, Washington DC, 2014

Zhang, Z., Mendelsohn, A., **Manson, K.,** Schiller, D., & Levy, I. " Functional heterogeneity of the ventromedial prefrontal cortex: value representation and affective response" Society for Neuroscience Annual Meeting, Washington DC, 2014

Manson, K. & Roitman, JD. "Connectivity between medial prefrontal cortex and nucleus accumbens is necessary for restraint of impulsive reward-directed behavior" Chicago Society of Neuroscience Annual Meeting, Chicago IL 2014

Manson, K. & Levy, I. "Selling a Reference Point: the Influence of Language on the Endowment Effect" Society for Neuroeconomics Annual Meeting, Key Biscayn FL, 2012

Manson, K., Jackson, E., Hull, L., Pusharskaya, H., and Levy, I. "Fear of the Unknown? Using GSR to Study Decision-Making under Risk and Ambiguity" Society for Neuroeconomics Annual Meeting, Key Biscayn FL, 2012

* Zhang, Z., ***Manson, K.,** Schiller, D., and Levy, I. "Impaired Reversal Learning of Food Reward in Obesity" Society for Neuroscience Meeting, New Orleans LA, 2012 * Contributed equally to this work

Schiller, D., **Manson,K.,** Reddan, M., Jackson, E., Levy, I., and Harpaz-Rotem, I. "Reversal of fear and safety in PTSD patients" Society for Neuroscience Meeting, New Orleans LA 2012

Tymula, A., Rosenberg-Belmaker, L., Ruderman, L., Roy, A., **Manson, K.,** Glimcher, P., and Levy, I. "Effect of age on human preferences and decision-making processes under risk and ambiguity" Society for Neuroscience Meeting, New Orleans LA, 2012

Tymula A., Rosenberg- Belmaker, L., **Manson K.,** Levy I., and Glimcher P "Examination of decision-making under risk and ambiguity across the life span". AWI Workshop on Behavioural Economics and Life-span Changes in Decision Making, Heidelberg, Germany, 2011

Rosenberg- Belmaker, L., Tymula A., **Manson K.,** Glimcher P., and Levy I. "Human decision-making under conditions of risk and ambiguity across the life span" Society for Neuroscience Meeting, Washington DC, 2011

Tymula A., Rosenberg- Belmaker, L., **Manson K.,** Levy I., and Glimcher P. "Examination of decision-making under risk and ambiguity across the life span" Society for Neuroeconomics Meeting, Chicago IL, 2011

Rosenberg-Belmaker, L., **Manson, K.,** & Levy, I. "Ambiguity aversion is abolished in decision-making under losses" Israeli Society for Neuroscience Meeting, Eilat Isreal, 2010

Margulis, S., Manson**, K.,** Weischelbaum, C. "Tool-use in white-cheeked gibbons (or lack thereof)" *Animal Behavior Society 46th Annual Meeting*, 2009

INVITED TALKS

"Decision-Making and Pharmaceuticals" Science in the News, Yale Science Diplomats, Yale University, New Haven CT, 2013

"Correlating Visual Attention with Food Consumption: an Eye-Tracking Study" Works in Progress, Yale Integrative Cell Signaling and Neurobiology of Metabolism, Yale University, New Haven CT, 2012

"Cognition in Non-Human Animals" Guest Lecture, University of Illinois School of Veterinary Medicine. Champaign IL, 2008

"Tool-use in White-Cheeked Gibbons (or Lack There-of)" Conservation & Science Lecture Series, Lincoln Park Zoo, Chicago IL, 2008

TEACHING EXPERIENCE

Teaching Assistant, University of Illinois at Chicago, Chicago IL
Cognitive Neuroscience: Fall 2013, Spring 2014, Spring 2015
Lab in Learning and Conditioning: Fall 2015
Introduction to Behavioral Neuroscience: Fall 2015
Lab in Cognitive Neuroscience: Fall 2016
Neuroanatomy: Spring 2015, Spring 2016

Guest Lecturer, Introduction to Psychology, The Ohio State University, Columbus OH, January 2009

MENTORING

Honors Capstone Supervisor

2015-2016 Baasit Jamal, University of Illinois at Chicago, Chicago IL
- Capstone: Influence of pyramidal cells on medial prefrontal cortex mediated behavioral restraint
- Nancy Hirschberg Memorial Prize for Undergraduate Excellence in Psychology
- Currently enrolled in the MA in Physiology & Biophysics program at UIC

Direct Supervisor of Undergraduate Student Researchers

2013-2016 University of Illinois at Chicago, 6 students
2010-2013 Yale School of Medicine, 13 students
2009-2011 Yale Psychology Department, 4 students

Trainer of Research Technicians and Graduate Students

2010-2013 Yale School of Medicine

SERVICE (Professional)

2016-2017 **Chair, Cross Program Conference Organization Committee,** University of Illinois at Chicago, Chicago IL
- Coordinated programmatic details: set deadlines, tracked budget, and liaised with department supervisor

2015-2016 **Member, Cross Program Conference Organization Committee,** University of Illinois at Chicago, Chicago IL

- Contributed to selection of speaker, decisions on program, and advertising

2014-2015 **Inaugural Member, Cross Program Conference Organization Committee,** University of Illinois at Chicago, Chicago IL
- Invited speaker, worked with other committee member to design the structure of the program to be used henceforth, designed advertisement materials

2013-2014 **Behavioral Neuroscience Division Assistant,** University of Illinois at Chicago,
2016-2017 Chicago IL
- Liaised with program chair regarding communication with the program, organized prospective student interviews and interview activities

SERVICE (Community)

2015-present **Adult Education Tutor,** The Center on Halsted, Chicago IL
- Tutor homeless and marginalized adults in preparation for the GED and other placement testing

2002-2003 **Hot-Line Volunteer,** Suicide Prevention Services, North Central Mental Health Center, Columbus, OH
- Completed 120 hours of crisis intervention training, conditioning for organization and focus during stressful situations.
- Provided callers with counsel and resources preventing immediate suicide and other crisis situations.

M.A. THESIS

Tool-use in Gibbons (or Lack Thereof)

The University of Chicago, Academic Advisor: Dr. Susan Margulis 2008

Many animals have shown a propensity to use tools, though the most proficient tool-users appear to be monkeys and the great apes. However a gap exists in our knowledge of how primate understanding of tool-use has progressed evolutionarily from monkeys to the great apes. This gap is due to a lack of cognitive research with gibbons (*Hylobatidae*), the primate evolutionarily positioned between monkeys and the great apes. To investigate gibbon understanding of tool-use, we designed a project that provided a dipping apparatus to four white-cheeked gibbons *Nomascus leucogenys* at the Lincoln Park Zoo. The gibbons did not show a proclivity to tool-use. Instead, their interest waned over time resulting in an almost total abandonment of the task. These findings lie in contrast to previous observations and experimental findings and suggest perhaps we may not be able to group all genera of the *Hylobatidae* into the same tool-using category.