AN INVESTIGATION OF THE NEURAL CIRCUITRY OF CUED ALCOHOL BEHAVIORS IN P AND WISTAR RATS

by

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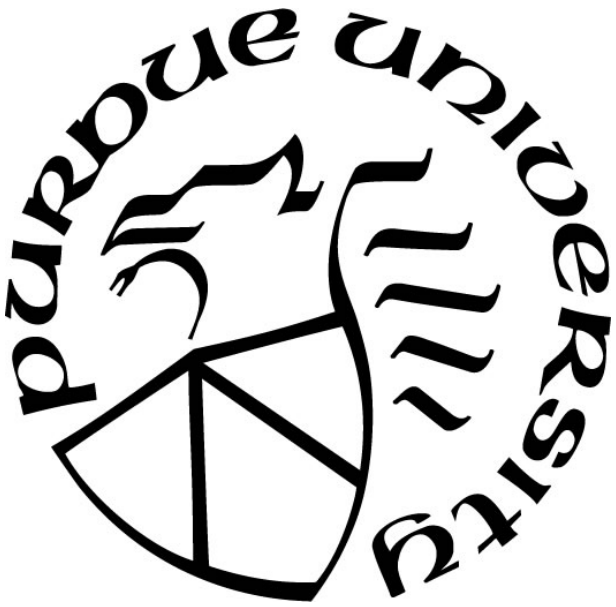

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This work is dedicated, with love,

To the two four-legged adventurers, Vega and Loki who now and forever are playing in the eternal green fields

To my husband, Michael, whose tireless love helped me to endure the years of graduate school

To my sisters, Asiya and Fatimah, whose sleepovers and encouraging texts recharged both my body and heart

To my parents, Laquila and Yahya who have encouraged and supported me since birth to become the best person that I could

To my mother-in-law, Karen, who welcomed me into her family and home and has always treated me with love and kindness

Lastly, to Hannibal who gave me a name which supersedes all others, "Mother" and has brought untold joy into my life

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ABSTRACT

Author: McCane, Aqilah, Maryam. Ph.D.
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Alcohol-paired cues invigorate alcohol-seeking and drinking behaviors in both rodents and individuals with alcohol use disorder (AUD). Additionally, genetic susceptibility plays a key role in alcohol addiction behaviors. Alcohol preferring (P) rats model both genetic vulnerability and symptoms of AUD. The basolateral amygdala (BLA), prefrontal cortex (PFC), hippocampus (HC) and nucleus accumbens (NA) are important brain regions involved in cued alcohol seeking. These regions are interconnected and their functional connections are hypothesized to be critical in the expression of motivated behaviors. Electrophysiological recordings in these four regions were collected in P rats engaged in a cued alcohol task. Data were filtered in the theta band (5-11 Hz) and segregated by behavioral epoch. The phase locking index γ was computed and used to measure strength of phase locking between signals from any two brain regions. The cross correlation between the amplitude of two signals was used to determine directionality. PFC-NA synchrony increased after stimuli presentation and remained elevated, relative to baseline synchrony. PFC-NA synchrony was also stronger for trials in which the animal made three or more lever presses (rewarded; R), compared to trials in which the animal responded fewer than three times (not-rewarded; NR). During lever pressing, PFC-BLA, NA-HC and PFC-HC synchrony was stronger after presentation of the DS+, in R compared to NR trials. NA-HC and PFC-BLA synchrony was stronger when responses were withheld in

extinction, relative to conditioning. These data inform our knowledge of how corticolimbic connections are involved in cued ethanol seeking behaviors.

CHAPTER 1. INTRODUCTION

1.1 Clinical significance

Alcohol-paired cues invigorate alcohol-seeking and drinking behaviors in both rodents (Reid et al., 2006; Remedios et al., 2014) and individuals with alcohol dependence (Grusser et al., 2004; Reid et al., 2006; Vollstadt-Klein et al., 2012). An attentional bias to stimuli paired with alcohol has been observed in individuals with alcohol dependence (Bauer and Cox, 1998). Importantly, individuals with a greater attentional bias to alcohol related stimuli exhibited more difficulty remaining abstinent following treatment (Cox et al., 2002), suggesting that cue reactivity is correlated with treatment outcomes. Additionally, drugs which reduce responsivity to alcohol-paired cues in rats have also shown moderate efficacy in treating alcohol dependence in clinical populations (Bachteler et al., 2005; Heilig and Egli, 2006). These data underscore the importance of ethanol-paired cues in persistent ethanol use and suggest that treatments which affect cued ethanol seeking may possess clinical utility.

Understanding the neural mechanisms by which environmental stimuli induce relapse is of great importance in treatment of alcohol use disorder (AUD). Current AUD pharmacotherapies target specific neurotransmitter systems and show moderate efficacy in their ability to prevent relapse (Heilig and Egli, 2006; Spanagel and Kiefer, 2008). Importantly, enhancing or reducing levels of neurotransmitters can have varied effects in different brain regions. An inability of current pharmacotherapies to target the brain with regional specificity might partially explain their modest ability to treat AUD. A better understanding of the neural substrates which underlie relapse may therefore complement neurobiological research and facilitate the development of novel, improved therapies.

1.2 Genetic vulnerability factors and ethanol seeking phenotypes

Genetic susceptibility factors, which are present in many individuals who abuse alcohol (Goldman et al., 2005), are hypothesized to be critical for both initiation and dependence of alcohol use in at-risk populations (Heilig and Egli, 2006). Environmental stimuli paired with alcohol become capable of inducing craving and triggering relapse (Perry et al., 2014). Alcohol-paired stimuli play a role in relapse and provide clinically relevant and measurable therapy targets (Heilig and Egli, 2006). A model which incorporates genetic susceptibility factors, a history of alcohol use and mechanisms known to induce relapse will facilitate the development of novel AUD treatments (Heilig and Egli, 2006).

Genetically mediated alterations in brain regions identified as critical for reinstatement have been reported. Individuals family history positive (FH+) for AUD show increased activity in the prefrontal cortex (PFC) in the presence of stimuli associated with alcohol (Kareken et al., 2012; Kareken et al., 2010). FH+ individuals also showed deficits in inhibitory processing, resting state cortico-striatal connectivity and impaired resting state connectivity in the right and left amygdala (Cservenka et al., 2014a; Cservenka et al., 2014b). Family history mediated differences in brain volume in the amygdala and striatum have also been reported and are hypothesized to be associated with genetic risk for AUD (Cservenka et al., 2015; Dager et al., 2015). However, it remains unclear how physiological differences between individuals with a family history and those without contributes to expression of behaviors observed in AUD. Utilization of animal models can therefore elucidate the influence of genetic vulnerability on alcohol-seeking behaviors.

1.3 Preclinical models of alcoholism

Alcoholism is a disorder with complex etiology. Preclinical models have provided a useful tool to explore the etiology of this disease as they are not bound by some of the ethical and experimental limitations present when working with clinical populations. Another strength of these models is the experimenters' ability to exert compete control over the environment and conduct environmental manipulations (Grahame, 2000). Additionally, preclinical models can dissect complex disorders into behavioral and physiological components, facilitating an investigation of disorder features (Tabakoff and Hoffman, 2000). Importantly, while animal models can mimic features of a disorder, they are merely models and are themselves not capable of being diagnosed with a specific disorder (Tabakoff and Hoffman, 2000). Thus, while such models hold distinct advantages over clinical models, they are also subject to disadvantages to be discussed below.

Tolerance and withdrawal are defining features of AUD (Association, 2013) which can be observed in preclinical models. Alcohol vapor exposure is commonly used to induce both tolerance (Lopez et al., 2012) and symptoms of withdrawal in preclinical models (Becker, 2000). In these paradigms, animals are exposed to chronic intermittent ethanol vapor. This technique is useful in that it can assess how alcohol exposure induces neural adaptations. Importantly, in this paradigm, ethanol delivery is non-contingent and the animal cannot control how much ethanol they are exposed to (Tabakoff and Hoffman, 2000). Additionally, inhalation of ethanol vapor, and the pharmacokinetics of such exposure are different from oral consumption of ethanol. Moreover, the subjects of vapor inhalation are unable to increase or decrease ethanol exposure, making it difficult to ascertain ethanol's motivational properties in this task. Lastly, volumes of alcohol

administered in this task often surpass amounts an animal would voluntarily consume, weakening the validity of such models.

Alcohol preference models, where an animal chooses between alcohol and water, have allowed for the selection of animals who exhibit a preference for alcohol (Spanagel, 2000). Models of home-cage drinking are useful in that they can characterize genetic differences in alcohol consumption between rodent strains as well as be used as a selection criteria for the creation of rodent strains which model alcohol-related phenotypes (Cunningham et al., 2000). Importantly, preference for alcohol does not necessarily suggest addictive behavior since animals may consume large quantities of alcohol but not exhibit loss of control over drinking, or other clinical symptoms of alcohol dependence (Spanagel, 2000). Animal models of self-administration are further limited in that they cannot determine why an animal choses to drink or abstain from drinking (Tabakoff and Hoffman, 2000). These models have utility in determining molecular and neurochemical pathways involved in alcohol use but cannot fully model alcoholism in clinical populations (Tabakoff and Hoffman, 2000). Similarly, models which utilize free access to alcohol are not suited to answer questions regarding motivation to consume alcohol (Tabakoff and Hoffman, 2000). These criticisms highlight how preclinical models can model features of a disorder, but not the disorder in totality.

An inability to abstain from alcohol use, or relapse into alcohol seeking is another core feature of AUD which can be modeled in preclinical models (Spanagel, 2000). The reinstatement model attempts to measure craving and alcohol relapse in rodents (Spanagel, 2000). In this model, rodents are trained to make an operant response for a reinforcer, followed by a period of time where such responses no longer result in reward delivery

(extinction). Lastly, the animal is presented with stimuli and their ability to reinstate drug-seeking behavior is assessed. Reinstatement stimuli can take the form of a drug prime, stress or presentation of previously conditioned stimuli (Bossert et al., 2013). These paradigms are beneficial in that they can be used to test pharmacological compounds which seek to remediate craving or relapse (Spanagel, 2000). Additionally, these paradigms can inform our understanding of how stimuli elicit craving and drug seeking behaviors. However, before reinstatement can be assessed, operant responding must be extinguished. In clinical populations, relapse may occur after an individual has made a voluntary attempt to cease alcohol consumption. Individuals with a desire to stop problem drinking may avoid alcohol-paired stimuli and contexts. In contrast, preclinical models impose abstinence by removing access to reinforcers during extinction procedures. Next, the animal is presented with reinstatement stimuli. Such procedures do not reflect the experience of alcohol dependent individuals (Spanagel, 2000). Thus, paradigms which attempt to model alcohol relapse show utility in their ability to elucidate how reward-paired stimuli may elicit craving or relapse but are lacking in their ability to emulate clinical populations.

A rodent paradigm which attempts to model compulsive, uncontrolled alcohol seeking is the alcohol deprivation model. In this paradigm, animals have several months of alcohol access followed by several days of deprivation from alcohol. This cycle is repeated monthly and results in an increase in alcohol intake and preference following periods of deprivation (Spanagel, 2000). In operant settings, this deprivation routine can result in increases in motivated responding which has been likened to craving (Spanagel, 2000). Animals in this paradigm will also consume adulterated alcohol, thought to model uncontrolled alcohol seeking (Spanagel, 2000). Similar to previous models, this model

cannot answer questions of why an animal drinks. Moreover, the experimenter imposed alcohol deprivation may not accurately model the variability observed when clinical populations with AUD are deprived of alcohol either by choice or by force.

Genes play an important role in AUD and animal models allow for the manipulation of genetic components to test hypotheses regarding their function in AUD (Tabakoff and Hoffman, 2000). Selected breeding is the breeding of an organism in order to enhance desired phenotypes. This occurs over multiple generations and results in different variants of genes related to a target behavior but similar genes for other characteristics. Free-choice drinking is commonly used as a phenotype of interest in rodent lines selected for alcohol phenotypes (Grahame, 2000). Generation of selected lines is useful in that it allows for the identification of neurobiological mechanisms which may be associated with alcohol consumption, apart from effects induced by alcohol exposure (Grahame, 2000). This ability of preclinical models to control for alcohol drinking history is an advantage over clinical models where alcohol history cannot be precisely controlled for (Grahame, 2000). However, through repeated inbreeding, it is possible that, in addition to alleles of interest, alleles irrelevant to the behavior of interest may become fixed (Grahame, 2000). Therefore, in order to correlate traits with genetic markers, one must run large numbers of rodents which can be cost and labor intensive but yield only moderate genetic correlations (Grahame, 2000).

A reverse genetics approach can be employed to investigate candidate genes for alcoholism (Bowers, 2000). Genetic influence on a given trait or set of traits can also be assessed by using transgenic and knock out (KO) models. Transgenic lines involved the insertion of altered genes where KOs involve the inactivation of genes of interest (Bowers,

2000). Using these techniques, one can assess the function of specific proteins in alcohol dependence (Bowers, 2000). However, both transgenic and KO models can be influenced by compensatory responses to gene manipulation (Bowers, 2000). Moreover, removal of some genes negatively impact development or can lead to sterility, making it difficult to determine the role of the candidate gene (Bowers, 2000).

Overall, preclinical genetic models of alcoholism have improved upon our understanding of neurobiological differences which influence the likelihood of one to develop alcohol dependence. Importantly, these models can mimic symptoms or features of AUD but cannot replicate the disorder in its entirety. As such, care must be taken when interpreting findings from studies which utilize these models.

There are currently a multitude of rodent models of alcohol addiction. Importantly, each is subject to both strengths and weaknesses, as discussed previously. Alcohol preferring (P) rats are selectively bred for excessive ethanol consumption (Murphy et al., 2002). Although this selected line is subject to the caveats discussed previously, it reliably models features of individuals with a genetic risk to develop AUD (Froehlich, 2010). The translational nature of this organism, coupled with its ability to voluntarily seek and drink unadulterated ethanol make it an ideal candidate to employ in conditioning tasks for oral reinforcers.

The validity of the P rat as a model for symptoms of AUD has been tested extensively. Cicero (1979) posited that animals which were characterized as rodent models of alcoholism should orally self-administer ethanol at pharmacologically meaningful levels, demonstrate willingness to work for ethanol, exhibit dependence and tolerance and consume ethanol for its pharmacological effects rather than caloric value. The P rat meets

these criteria. In free choice drinking paradigms, P rats exhibit a 2:1 preference for ethanol over water (Murphy et al., 2002). Furthermore, P rats will voluntarily consume large quantities of ethanol in both free choice (McCane et al., 2014; Simms et al., 2008) and operant settings (Czachowski and Samson, 2002). Moreover, P rats maintain high ethanol intakes even in the presence of other palatable solutions (Lankford et al., 1991). P rats exhibit ethanol tolerance (Gatto et al., 1987a; Gatto et al., 1987b) dependence and withdrawal (Waller et al., 1982). Lastly, P rats are hypothesized to be more aroused after ethanol administration relative to alcohol non-preferring (NP) rats (Ehlers et al., 1991), suggesting this genetic model may be more sensitive to the hedonic effects of alcohol. Importantly, enhanced hedonic responses to rewards are associated with alcohol abuse vulnerability in preclinical populations (Kampov-Polevoy et al., 2001; Kampov-Polevoy et al., 2003). These data further highlight the similarities between the P rat and individuals with genetic susceptibility for AUD.

In addition to a behavioral phenotype congruent with AUD, P rats exhibit biological alterations similar to those observed in AUD. Reduced metabotropic glutamate receptor 2 (mGluR2) function contributes to elevated alcohol consumption (Zhou et al., 2013). Importantly, a loss of this receptor is observed in P rats (Zhou et al., 2013). Agonism of mGluR2 is shown to attenuate both alcohol self-administration and cue-induced reinstatement in rats (Bäckström and Hyytiä, 2005), demonstrating its functional importance in alcohol-related behaviors. Alterations in mGluR2 are also observed in clinical populations where expression of the gene which encodes mGluR2 was reduced in individuals with AUD relative to controls (Meinhardt et al., 2013). Importantly this was in postmortem tissue where a reduction in prefrontal volume has previously been observed

(Miguel-Hidalgo et al., 2006). P rats also exhibit lower basal concentrations of dopamine (DA) in the PFC relative to their progenitor strain, Wistar rats (Engleman et al., 2006). Similar results have been observed in human populations where abstinent alcoholics were reported to have decreased DA transmission in the cortex, relative to healthy controls (Narendran et al., 2014). P rats have greater theta power and P300 amplitude in the parietal cortex relative to NP rats (Ehlers et al., 1999). Importantly, P300 amplitude is reduced in FH+ individuals (Hesselbrock et al., 2001; O'Connor et al., 1986; Porjesz and Begleiter, 1990; Ramachandran et al., 1996), suggesting a link between this physiological measurement and vulnerability to consume alcohol. Moreover, pharmacological therapies which reduce alcohol consumption in clinical populations are also efficacious in P rats (Froehlich et al., 2016; Rasmussen et al., 2015; Verplaetse et al., 2012; Weiss et al., 1990), further advocating for both their efficacy as a model of AUD features as well as their translational nature.

While P rats show promise as models of AUD features, it should be noted that they exhibit a more broad addiction phenotype. P rats will excessively seek and consume sucrose (Eiler et al., 2005; Le et al., 2006; McCane et al., 2014). P rats will also self-administer nicotine to a greater level than NP rats (Le et al., 2006). Additionally, P rats are hypothesized to have greater sensitivity to rewarding substances, relative to other rodent strains (Katner et al., 2011). P rats will self-administer a range of concentrations of cocaine into their nucleus accumbens (100-80 pm/100nl; NA), whereas Wistars administered only the highest concentrations (400 and 800 pmol; Katner et al., 2011), suggesting P rats may be more sensitive to cocaine than their progenitor strain. P rats also exhibited greater resistance to extinction and more robust reinstatement for cocaine, relative to NP rats (Le

et al., 2006). Collectively, these data highlight a tendency of P rats to consume rewarding substances, and experience greater sensitivity to the hedonic effects of rewards. Importantly, the generalized nature of reward seeking is both a strength and weakness of this model. Co-morbid nicotine use is frequently observed in AUD (Dani and Harris, 2005). Additionally, FH+ individuals exhibit a greater preference for sweet tastes, relative to subjects with no history of AUD (Kampov-Polevoy et al., 2001; Kampov-Polevoy et al., 2003). However, non-specific reward seeking may suggest that P rats do not model alcoholism per se, but rather symptoms of addiction more globally, of which AUD symptoms are encompassed.

1.4 Neural substrates of reward seeking

The amygdala, hippocampus (HC), PFC and ventral striatum (VS) are implicated in reward-paired cue reactivity (Dayas et al., 2007; Jupp et al., 2011; Schacht et al., 2013), drug craving (Myrick et al., 2004; Park et al., 2007; Reid et al., 2006) and relapse (Beck et al., 2012; Chaudhri et al., 2010; Grusser et al., 2004; Willcocks and McNally, 2013). However, the exact mechanisms by which these regions are associated with these behaviors remains to be elucidated. Despite the knowledge that these regions are reciprocally connected (Anton, 1999; Chiba et al., 2001; McDonald et al., 1996), it is unknown how these regions interact with one another to encode information about cues which induce alcohol seeking. Understanding the contribution of each region necessitates an examination of neural substrates both in isolation and as neural networks. While a wealth of literature examines the former, there is a scarcity of studies which seek to assess the latter.

1.5 Basolateral amygdala and reward seeking

The amygdala can be functionally divided into several sub-regions (LeDoux, 2007), of these, the basolateral amygdala (BLA) is hypothesized to be critical in assigning value to motivational stimuli (Jenison et al., 2011). Inactivation of the BLA attenuates expression of conditioned place preference for heroin (Cummins et al., 2014), sucrose (Everitt et al., 1991) and cocaine (Fuchs et al., 2002). Additionally, both heroin primed and cue induced reinstatement of heroin seeking is impaired after inactivation of the BLA (Fuchs and See, 2002). Both reinstatement and conditioned place preference assess whether environmental stimuli paired with rewarding substances promote drug seeking. Thus, the BLA is believed to encode motivational information about reward-paired stimuli. This is further supported by the observation that BLA inactivation has no effect on operant responding which is not contingent on presentation of conditioned stimuli (Meil and See, 1997; Simmons and Neill, 2009). In addition, suppression of reinstatement and conditioned place preference following BLA inactivation may reflect a change in the motivational properties of the rewarding substances. Importantly, micro-infusions of cocaine or amphetamine into the BLA do not elicit conditioned place preference (O'Dell et al., 1999), further suggesting the manner by which BLA inactivation attenuates reward seeking is cue-dependent. BLA lesions block devaluation and acquisition of second order conditioning (Hatfield et al., 1996). Importantly, both of these behaviors involve attribution of motivational value to conditioned stimuli. Additionally, inactivation of the BLA impaired stimulus discrimination (Burns et al., 1993). Both individual neuron firing rates and local field potential (LFP) power in the BLA are increased in the presence of conditioned stimuli after discrimination learning (Fenton et al., 2013). Moreover, lesioning the BLA disrupts rodents' ability to bias responding to an aversive relative to neutral conditioned stimulus (Killcross

et al., 1997). Elevated c-fos expression in the BLA was associated with presentation of ethanol-related stimuli (Dayas et al., 2007; Radwanska et al., 2007). Collectively, these data suggest the BLA plays a role in cued reward seeking. More specifically, the BLA is hypothesized to assign value to conditioned stimuli. Therefore, alterations in BLA functioning may be associated with maladaptive processing of environmental stimuli paired with rewarding substances.

The role of the BLA in reward-related behaviors has been further elucidated by studies which investigate how functional interactions between the BLA and other brain regions are associated with behavior. These connections and their behavioral consequences will be discussed below.

The amygdala has strong bidirectional connections with the PFC (Ghashghaei et al., 2007), which are important for assessing the value of conditioned stimuli as it relates to behavioral output (Likhtik et al., 2014). PFC to BLA inputs are glutamatergic (Pape and Pare, 2010; Rosenkranz et al., 2003) and it has been hypothesized that the mPFC exerts excitatory influences over the BLA (Floresco and Maric, 2007; Pape and Pare, 2010). PFC inputs excite BLA inhibitory interneurons (Hübner et al., 2014; Rosenkranz and Grace, 2001, 2002), a mechanism by which the PFC may inhibit BLA output, thereby suppressing BLA-mediated behaviors (Rosenkranz and Grace, 2002). The PFC is hypothesized to suppress BLA mediated responses when enhanced emotional responses to stimuli may be inappropriate (Grace and Rosenkranz, 2002). In such cases, activation of the PFC prior to the BLA would attenuate the BLA's ability to respond to sensory inputs, preventing the expression of behaviorally inappropriate or irrelevant responses to stimuli (Grace and Rosenkranz, 2002). As such, in fear conditioning, synchrony between the PFC and BLA

is associated with cued fear and safety responses (Likhtik et al., 2014). Importantly, activity in the PFC precedes activity in the BLA (Likhtik et al., 2014), further suggesting that appropriate cued responding may be associated with PFC input to the BLA. However, the manner in which the PFC and the BLA respond during maladaptive cued reward seeking remains to be elucidated. Thus, whether activity of the PFC precedes or proceeds activity of the BLA may determine the emotional valance an organism assigns to conditioned stimuli and the subsequent conditioned responses elicited. With regards to addiction, it remains unclear how interactions between the PFC and BLA may be associated with cue-evoked drug-seeking behaviors.

DA transmission in the NA is important for goal-seeking behaviors (Goto and Grace, 2005a).The influence of the BLA on NA DA transmission (Floresco et al., 1998) is a hypothesized mechanism by which the BLA may influence NA-mediated behaviors. In anesthetized rats, stimulation of glutamatergic afferents from the BLA resulted in time-locked changes to the DA oxidation currents in the NA (Floresco et al., 1998). Furthermore, unilateral inactivation of the BLA coupled with contralateral DA receptor antagonism of the NA were as efficacious as bilateral inactivation of the BLA or antagonism of DA receptors in the NA when assessing changes in instrumental responding (Simmons and Neill, 2009). These findings further implicate BLA-mediated modulation of NA DA transmission in BLA-NA interactions pertaining to motivated responding. Inactivation of the BLA reduced stimuli-evoked approach and concomitant stimuli-evoked DA release in the NA (Jones et al., 2010). However, instrumental responding, once initiated, was not altered by BLA inactivation (Jones et al., 2010), suggesting that BLA input to the NA may play a role in stimuli value representations which guide behavior.

The BLA and ventral (v)HC share reciprocal connections (O'Donnell and Grace, 1995; Pitkänen et al., 2000) and interactions between the BLA and HC are involved in memory processes. Inhibition of BLA neurons projecting to the vHC impairs retention of foot-shock learning while BLA activation enhances learning (Huff et al., 2016). Both inactivation and stimulation of the BLA influenced the generation of long-term potentiation (LTP) in the HC (Ikegaya et al., 1995a, b). As such, BLA-HC interactions are hypothesized to play a role in affect or arousal-mediated changes to memory consolidation. Inhibition of BLA axons terminating in the vHC reduced behavioral measures of anxiety while activation of these projections increased anxiety-like behaviors (Felix-Ortiz et al., 2013). Given the high level of arousal associated with anxiety-like behaviors in animals (Lang et al., 2000), these findings may represent BLA-mediated modulation of contextual memories. Alterations in the amygdala are observed in both individuals with AUD and those with a family history. FH+ individuals exhibit reduced activation of the amygdala in response to emotional stimuli which may be associated with greater attraction to hedonic experiences such as excessive alcohol intake (Glahn et al., 2007). Relative to healthy controls, reduced amygdala volume has been observed in individuals with AUD and those at high risk for AUD and is hypothesized to be associated with vulnerability to drug dependence (Benegal et al., 2007; Dager et al., 2015; Hill et al., 2001; Makris et al., 2008). Additionally, decreased amygdala volume in individuals with alcohol dependence correlates with measures of craving and response to emotional stimuli (Wrase et al., 2008). Importantly, it remains unclear to what degree reduced brain volumes are associated with the neurotoxic effects of alcohol. However, differences in brain volumes in alcohol naïve, addiction-vulnerable individuals implicates alterations in the physiology of these structures with

susceptibility to abuse alcohol. These physiological alterations suggest that activity within these brain regions may be associated with an addiction phenotype. Lastly, drug-paired cue-induced activation (Schneider et al., 2001) as well as cued-evoked DA release (Fotros et al., 2013) in the amygdala is observed in drug-dependent individuals, further suggesting that this region is involved in the processing of salient reward-related stimuli.

1.6 Hippocampus and reward seeking

The HC is a three layered structure made up of a pyramidal layer sandwiched between two plexiform layers (Anand and Dhikav, 2012). The HC, curls into an S-shaped structure which has been likened to the horn of a ram (Cornu Ammonis) and can be divided into subfields with the abbreviation CA preceding numbers one through four (Wright and al., 2017). CA1 pyramidal neurons project along the longitudinal axis of the HC (Yang et al., 2014). Rodent hippocampi on either lobe of the brain are connected via the commissure of fornix (Wright and al., 2017). HC neurons are primarily pyramidal and granule cells (Wright and al., 2017). Additionally, cortical and subcortical inputs to the HC arise via the perforant path (Wright and al., 2017). Lastly, the HC receives projections from several different neuron types, of which cholinergic and GABAergic projections are integral for maintenance of the theta rhythm (Bentley et al., 2011).

The HC shares connections with the NA, PFC and BLA. HC afferents are carried to the NA via the fimbria fornix (Goto and O'Donnell, 2001). HC connections are hypothesized to shift medium spiny neurons in the striatum to a depolarized state, which may gate neural ensembles to be active dependent on the context (Goto and O'Donnell, 2001). Moreover, HC afferents contact cell bodies or proximal dendrites in the NA, in contrast to PFC projections which contact distal dendrites (Meredith et al., 1990), resulting

in stronger HC to NA input, relative to PFC-NA input (Goto and Grace, 2005b). The HC and amygdala share reciprocal connections and can also influence each other. The vHC CA1 region shares bi-directional connectivity with amygdalar nuclei and mPFC regions (Fanselow and Dong, 2010). Specifically, pyramidal neuron axons in the vHC project via the fornix to the BLA and mPFC (Cenquizca and Swanson, 2007).

Altered neurophysiology in the HC has been observed in addiction. In drug-dependent individuals, hippocampal neurodegeneration and cell loss are observed (Anderson et al., 2012; Obernier et al., 2002; Walker et al., 1980). Moreover, diminished hippocampal volumes are consistently observed in individuals with alcohol dependence (Agartz et al., 1999; Bleich et al., 2003; Harper, 1998; Kühn et al., 2014; Nagel et al., 2005; Oscar-Berman and Song, 2011; Sullivan et al., 1995) as well as those with a family history of AUD (Hanson et al., 2010). Importantly, hippocampal volume was observed to increase following abstinence from alcohol in clinical (Kühn et al., 2014) and preclinical populations (Nixon and Crews, 2004). Furthermore, hippocampal volume was negatively correlated with withdrawal symptoms and severity (Kühn et al., 2014), further implicating an association between reduced hippocampal volumes and addiction-related behaviors.

Drug-related cue-induced activation of the HC has been observed in clinical populations (Childress et al., 1999; Grant et al., 1996; Wexler et al., 2001). Moreover, DA which is implicated in attribution of salience to drug-paired cues (Berridge and Robinson, 1998) is released in the HC following the presentation of drug-paired stimuli in substance-dependent individuals and is correlated with drug craving (Fotros et al., 2013). Additionally, activity in the HC is associated with drug euphoria (Sell et al., 2000) and craving in preclinical populations (Schneider et al., 2001; Wexler et al., 2001).

The HC can be divided into sub-regions (Bannerman et al., 1999). Among the HC sub-regions, the ventral section is involved in regulation of drug-seeking behaviors. Stimulation of the vHC can elicit reinstatement of drug-seeking (Taepavarapruk and Phillips, 2003; Vorel et al., 2001). In some cases (Lasseter et al., 2010; Rogers and See, 2007; Sun and Rebec, 2003), but not all (Atkins et al., 2008; Black et al., 2004), inactivation of the vHC can impair cued drug-seeking behaviors. The HC is hypothesized to play a role in modulating associations of salient memories such as those related to reward-paired cues (Shohamy and Adcock, 2010). Inactivation of the HC impaired acquisition of conditioned approach and cued responding (Burns et al., 1993). Physiological alterations in the HC may therefore convey risk for addiction-related behaviors via modulation of drug-related memories.

1.7 Nucleus accumbens and reward seeking

The NA is comprised of medium spiny projection neurons which make up 90% of its neuronal population (Floresco, 2015). These output neurons are GABAergic, project to the basal ganglia and fire phasically (Nicola, 2007). Medium spiny neurons are less excitable than pyramidal cells and are not capable of spontaneous firing, thus changes in NA activity are attributed to excitatory glutamatergic inputs from cortical and limbic regions (Floresco, 2015). Importantly, the NA receives glutamatergic input from the PFC, amygdala and HC (Floresco, 2015).

Firing of NA neurons is hypothesized to be critical for behavioral inhibition with inhibition lessening when NA neurons are inhibited (Nicola, 2007). Inhibition of NA neurons during reward consumption (Janak et al., 1999; Taha and Fields, 2005) but excitation of NA neurons during reward-paired stimulus presentation (Nicola et al., 2004a,

b) suggests that neural activity in the NA is associated with transitions between appetitive and consummatory behaviors (Nicola, 2007). Conversely, NA neuronal firing has been hypothesized by some to be associated more generally with locomotion (Taha and Fields, 2005).

The NA has also been extensively investigated as a critical substrate in goal-directed behaviors. Increased NA activity is associated with Pavlovian stimuli-evoked instrumental responding (Lewis et al., 2013; Talmi et al., 2008). Importantly, the NA, while involved in expression of conditioned behaviors, is itself not a site of Pavlovian association but rather is hypothesized to form an interface between limbic and motor substrates (Mogenson et al., 1980). The NA has also been demonstrated to be critical to conditioned alcohol seeking where inactivation of this region suppresses cued responding for alcohol (Chaudhri et al., 2010). Furthermore, neural alterations within the NA are posited to play a role in a compulsive drive to seek reward (Kalivas and Volkow, 2005; Volkow et al., 2005). Bilateral inactivation of the NA abolished expression of conditioned place preference (Everitt et al., 1991), further suggesting involvement of the NA in reward-seeking behaviors.

In clinical populations, activation of the VS is associated with symptoms of AUD. Individuals who are at risk to develop an AUD show greater activation to alcohol cues in the VS compared to low-risk individuals (Kareken et al., 2004). Similarly, individuals with an AUD exhibited an enhanced response to alcohol-paired cues in the VS relative to social drinkers (Myrick et al., 2004; Myrick et al., 2008). Importantly, cue-induced activation of the NA is correlated with craving and impaired control over drinking (Myrick et al., 2004; Schacht et al., 2013). In rodents, presentation of drug-paired stimuli after a period of

abstinence induced both robust drug seeking as well as neural adaptations within the NA (Gipson et al., 2013). Lastly, striatal volume was associated with a family history of AUD (Cservenka et al., 2015), collectively suggesting physiological alterations in the VS are associated with AUD.

The NA can be divided into the core (NAc) and the shell (NAs; Heimer et al., 1990; Voorn et al., 1989; Zaborszky et al., 1985). These regions have distinct afferent and efferent connections as well as behaviorally differentiated roles (Chaudhri et al., 2010; Corbit and Balleine, 2011). Phasic DA release is hypothesized to be integral to the attribution of salience to conditioned stimuli (Flagel et al., 2011; Saunders and Robinson, 2012) and presentation of a conditioned stimulus evoked an increase in phasic DA in the NAc but not NAs (Brown and Barlow, 2009). The NAc has also been implicated in conditioned responding (Di Ciano et al., 2008; Saunders and Robinson, 2012). Inactivation of the NAc but not NAs was observed to block cue-induced reinstatement (Chaudhri et al., 2010; Di Ciano et al., 2008; See, 2005). Additionally, inactivation of the NAc but not NAs disrupted expression of ethanol conditioned place preference (Gremel and Cunningham, 2008) as well as ethanol consumption in a limited access paradigm (Cassataro et al., 2014). Corbit and Balleine (2011) investigated the NA sub-regions and their ability to invigorate responding to general or specific rewards using a Pavlovian to instrumental transfer procedure. Inactivation of the NAc but not NAs impaired expression of outcome general Pavlovian to instrumental transfer while NAs but not NAc inactivation impaired expression of outcome specific Pavlovian to instrumental transfer suggesting that the NAc is essential for the arousing impact of conditioned stimuli while the NAs may play a more direct role in conditioned stimulus induced reward expectancy (Corbit and Balleine, 2011).

1.8 Prefrontal cortex and reward seeking

Approximately 85% of neurons in the PFC are of glutamatergic pyramidal cells with GABAergic neurons comprising the remaining 15% (Ding et al., 2001). Thus, the PFC is comprised primarily of glutamatergic pyramidal cells, of which, subpopulations support the maintenance of intrinsic recurrent activity (Wang et al., 2006). More specifically, neurons in this region, via recurrent synapses among other PFC neurons can sustain excitation in the absence of external stimulation (Floresco, 2015; Wang et al., 2006). This persistent intrinsic activity is hypothesized to be associated with the PFC's ability to execute attentional processes (Miller, 2000).

The PFC may influence activity in the NA via modulation of striatal DA. Different populations of DA neurons are hypothesized to innervate the PFC, relative to the NA. The PFC is innervated by DA neurons in the mesocortical division of the VTA while the NA is innervated by the mesolimbic division (Gorelova and Yang, 1996). These VTA sub-regions can be delineated by their efferent projection pathways, with mesolimbic neurons projecting from the VTA to the striatum while mesocortical VTA projections innervate the cortex (Düzel et al., 2009). PFC terminals synapse onto GABA cells that project to the NA and DA cells that project to the PFC (Carr et al., 1999; Carr and Sesack, 2000a, b) and in this way can regulate NA DA levels (Carr and Sesack, 2000a; Karreman and Moghaddam, 1996).

Physiological alterations in PFC activity are consistently observed in individuals with AUD, a family history of AUD or alcohol dependence (Moselhy et al., 2001). Alterations in glucose metabolism as well as reductions in cortical tissue are both observed in individuals with AUD (Cardenas et al., 2007; Fein et al., 2002; Moselhy et al., 2001). Additionally, individuals with AUD as well as those with a family history of AUD show

increased activity in the PFC in the presence of stimuli associated with alcohol (Cservenka and Nagel, 2012; George et al., 2001; Kareken et al., 2012; Kareken et al., 2010; Kim et al., 2014; Myrick et al., 2004; Park et al., 2007).

In addition to physiological alterations, deficits in PFC-mediated behaviors have been reported in both individuals with AUD and those with a family history (Davies et al., 2005; Gierski et al., 2013). Response inhibition is strongly mediated by PFC activity (Jentsch and Taylor, 1999) and is impaired in individuals with AUD (Kamarajan et al., 2004; Noel et al., 2007). The severity of alcohol misuse is correlated with reduced frontal activity during response inhibition (Claus et al., 2013). Moreover, individuals with AUD as well as those with a family history of AUD show frontal deficits in signal processing during response inhibition (Kamarajan et al., 2006; Kamarajan et al., 2004). Attentional deficits are also observed in AUD where alcohol dependent individuals show a bias towards stimuli paired with alcohol relative to non-alcohol stimuli (Noel et al., 2007). Similarly, an alcohol stimuli bias is also observed in individuals with a family history of AUD (Kareken et al., 2010).

Alterations in PFC activity associated with vulnerability to alcohol abuse are also observed in preclinical models. Inactivation of the PFC in rodents impairs behavioral flexibility or the ability to inhibit an unproductive behavioral response (Birrell and Brown, 2000; Floresco et al., 2008; Ragozzino, 2007). Presentation of an ethanol-paired cue increased activity in the mPFC and this effect was reduced after extinction (Groblewski et al., 2012). Cortical differences in rodent models of addiction have also been reported where P rats exhibit reduced PFC DA tone (Engleman et al., 2006), and higher PFC firing rate (Linsenbardt and Lapish, 2015), relative to their progenitor strain, Wistar rats. Moreover,

manipulations of cortical DA reduced drinking in P rats but not Wistars (McCane et al., 2014). Collectively, these data suggest that alterations in the PFC may be associated with expression of an addiction phenotype.

The mPFC is composed of the cingulate, prelimbic (PL) and infralimbic (IL) cortices. The PL and IL sub regions are hypothesized to have distinct roles in drug-seeking behaviors (Perry et al., 2011; Senn et al., 2014). The IL has been shown to have a more pronounced role in inhibition of previous learned response or extinction (Peters et al., 2008; Rhodes and Killcross, 2007) while the PL is implicated in reinstatement of drug seeking (McLaughlin and See, 2003; Willcocks and McNally, 2013). Inactivation of the PL attenuated cue-induced responding, an effect not observed in the presence of IL inactivation (McLaughlin and See, 2003). Importantly, the PL projects primarily to BLA, (Peters et al., 2009). Additionally, the mPFC projects to NA but different mPFC sub regions project to different NA sub regions. Specifically, the PL sends input to NAc while the IL preferentially sends input to NAs (Ding et al., 2001; Peters et al., 2009). Importantly, PL connections to the NAc are hypothesized to enhance cue-evoked drug-seeking behaviors following a period of drug abstinence (West et al., 2014).

Disrupted function in the PFC is hypothesized to be associated with impairments in response inhibition and salience attribution (Goldstein and Volkow, 2002). The clinical and preclinical findings mentioned previously support this hypothesis. Thus, it would seem that one of the primary roles of the PFC in addiction-related behaviors is maladaptive cue processing and subsequent impaired decision making. Moreover, the fact that deficits in PFC functioning are observed in both individuals with alcohol dependence and those with a family history suggest that impaired PFC functioning may be associated with

vulnerability to abuse alcohol. Preclinical studies support this hypothesis where alterations in PFC DA were observed in a rodent model of addiction prior to exposure to alcohol (Engleman et al., 2006). Sub-regions of the PFC appear to differentially modulate behavior where the PL cortex plays a significant role in drug-seeking behaviors. Collectively, these data highlight significant involvement of the PFC, specifically the PL sub-region, in addiction-related behaviors.

1.9 Cortico-striatal-limbic interactions and reward seeking

It is well accepted that cognitive processes require coordinated activity across neural networks (Uhlhaas et al., 2008). Functional connections between the BLA, HC, NA, and PFC are hypothesized to be critical for expression of motivated behaviors (McGinty and Grace, 2008). Studies which functionally disconnect brain pairs in this circuit have demonstrated that these regions interact during expression of reinstatement (Chaudhri et al., 2013; Fuchs et al., 2007). Additionally, both clinical and preclinical models suggest activity within these structures are implicated in relapse of ethanol seeking behaviors. Human imaging studies consistently report cue-induced activation of these brain regions in alcohol dependent individuals (Myrick et al., 2004; Schacht et al., 2013; Vollstadt-Klein et al., 2012). Immunohistochemistry studies have also demonstrated involvement of these regions in reinstatement (Dayas et al., 2007; Jupp et al., 2011). Lastly, preclinical models have shown these regions are important for expression of reinstatement of cocaine (Fuchs et al., 2007; Fuchs et al., 2005; McLaughlin and See, 2003), heroin (Fuchs and See, 2002; Rogers et al., 2008) and ethanol seeking (Chandra et al., 2013; Chaudhri et al., 2010), indicating these regions may be a common neural substrate across addictive substances.

Currently, few studies have assessed the involvement of neural networks in cued alcohol-seeking behaviors, choosing instead to focus on brain regions in isolation. A systems level approach will to facilitate the ultimate goal of understanding the neural circuity of cued-alcohol seeking. Understanding the neural mechanisms by which conditioned stimuli induce alcohol-seeking behaviors is essential for the development and improvement of therapies for AUD.

1.10 Neural oscillations

Electrical currents in the brain can originate from any excitable membrane (Buzsáki et al., 2012). For example, synaptic activity, action potentials and calcium spikes are some of several physiological occurrences which can generate extracellular current (Buzsáki et al., 2012). The summation of current flux, induced by coordinated excitation of neurons, gives rise to neural oscillations.

Oscillations can be characterized by three primary attributes: phase, frequency and amplitude. Frequency refers to the speed of the oscillation and is measured in hertz (Hz) or cycles per second (Cohen, 2014). Amplitude refers to the strength of the signal and can be visualized in a raw voltage trace or measured in power, or the squared amplitude of an oscillation, segregated by frequency bins (Cohen, 2014). Amplitude reflects the strength, size and depth of an electrode's source (Freeman and van Dijk, 1987). Lastly, phase refers to the position along the sine wave at a given point and is measured in radians or degrees (Cohen, 2014). Power and phase are independent of one another except when power is small, at which time phase becomes difficult to measure (Cohen, 2014).

Oscillations are generated by synchronization of inhibitory interneurons which gate excitation in neural ensembles via modulation of excitatory neuron firing in a rhythmic

manner. More specifically, a population of pyramidal cells activated from inputs of other neural networks may excite one another resulting in increasing excitation. These pyramidal cells in turn may activate inhibitory interneurons and as activity in the interneuron population increases, activity in the pyramidal cells may become inhibited. Inhibition of pyramidal cells may dampen excitatory input onto interneurons, resulting in a state of excitation. Oscillations occur when states fluctuate between excitation and inhibition (Cohen, 2014).

Different interneuron populations play a role in generation of frequency specific oscillations. For example, optogenetic inhibition of fast spiking parvalbumin interneurons attenuated power in the gamma frequency band (Sohal et al., 2009) while stimulation of these neurons resulted in generation of gamma oscillations (Cardin et al., 2009; Sohal et al., 2009). In contrast, oscillations in the theta band arise from interactions between slow stellate cell inhibitory interneurons and excitatory principle neurons (Dickson et al., 2000; Rotstein et al., 2005).

Oscillations can be measured via LFP recordings. LFPs cannot disambiguate the contributions of individual neurons but instead can reflect their common action (Gray et al., 1989). LFPs have both good temporal (< 100 ms) and spatial (~1mm) resolution (Gray et al., 1992), which makes possible a temporally and spatially precise investigation of functional brain dynamics during behavioral processes. However, when recording electrodes are distal from their sources, LFP measurements become less informative (Buzsáki et al., 2012). Because LFPs can be influenced by multiple sources, the various generators of electrical current should be considered when interpreting LFP data. Additionally, volume conduction can be problematic when interpreting LFP data. Volume

conduction occurs when signals generated from a distinct source are detected by multiple recording electrodes (Cohen, 2014). When this occurs, it cannot be ascertained whether one is measuring connectivity between two different sources or two electrodes are detecting the same activity from one source (Cohen, 2014). Volume conductance can be assessed by several different strategies. Firstly, if volume conduction is occurring then a zero-phase lag will be observed (Cohen, 2014). However, a zero phase lag can be observed under natural circumstances (Roelfsema et al., 1997) and may occur via modulatory reciprocal connections of a third region to a pair of coupled regions (Chawla et al., 2001; Viriyopase et al., 2012), complicating interpretations of this measure (Cohen, 2014). Volume conduction can also be determined by correlating connectivity and power, where significant correlations indicate volume conduction is occurring (Cohen, 2014). Given the potential complications and confounds which can arise should volume conduction occur, one should carefully test LFP data in order to decrease the likelihood that volume conductance is occurring.

1.11 Neural synchrony

Single neurons can oscillate with one another at multiple frequencies, collectively comprising brain rhythms (Llinás, 1988). These network oscillations give rise to synchrony (Buzsáki et al., 2012). Synchronous oscillations have been hypothesized to play several roles in animal behavior.

There are several hypotheses regarding the functional consequences of neural synchrony. One hypothesized role of synchrony is that it facilitates the encoding of information about the features of stimuli. In accordance with this hypothesis, neural synchrony is a mechanism by which neurons which represent related information are bound

(Singer, 1999; Singer and Gray, 1995). For example, stimuli-evoked synchrony has been correlated with neural processing of stimuli features, where the strength of synchrony is modulated by the similarity of object features and spatial orientation of these objects (Gray et al., 1989). This may occur through the summation of inputs from multiple axons onto a single neuron which integrates the various features of an object (Singer, 1999). Gray et al. (1989) observed the orientation and direction of movement of a light-bar stimulus was associated with different patterns of oscillations which led to the hypothesis that neural synchrony binds features of an object. This was further supported by the observation that synchrony occurs when neurons which respond to specific features of an object fire at the same time while neurons which respond to different features do not (Gray et al., 1989; Singer and Gray, 1995). Additionally, differences in neural synchrony are observed for one perceptual object relative to another (Gray and Singer, 1989; Singer and Gray, 1995). Importantly, this may be one of many functions of synchrony. Synchrony in the middle temporal visual area, a brain region sensitive to motion, failed to differentiate moving patterns which could be perceived as coherently or not coherently moving (Thiele and Stoner, 2003). Furthermore, Roelfsema et al. (2004) observed synchronization in the visual cortex which was unrelated to the grouping objects in contour grouping task, where monkeys had to group together contour segments of a target curve. Collectively, these studies suggest that synchrony may have roles beyond encoding perceptual features of stimuli. For example, synchrony is a hypothesized mechanism by which the saliency of some items is increased above others (Roelfsema et al., 2004; Uhlhaas et al., 2009). In support of this hypothesis, synchrony can be modulated by the properties of stimuli (Biederlack et al., 2006). Synchronized oscillations were also observed during sustained

attention in cats (Roelfsema et al., 1997), suggesting synchrony plays a role in attention and behavioral processes beyond stimulus perception. Additionally, response enhancement is correlated with attentional processes, which themselves are associated with enhanced synchrony (Roelfsema et al., 2004), suggesting a larger role of synchrony in mediating behavioral responses.

Synchrony may serve to integrate and coordinate activity between neurons in various brain regions (Roelfsema et al., 1997). Signal-to-noise ratio is enhanced by the phase locking of neural oscillations (Rangaswamy and Porjesz, 2014), suggesting synchrony may be a mechanism by which relevant information is propagated to neural systems. Additionally, action potentials which occur synchronously with one another were more effective at eliciting a postsynaptic response than those with asynchronous activity (Alonso et al., 1996) indicating synchronous activity has a greater influence on neurons than spontaneous activity. Furthermore, synchrony between spatially spread out brain regions is observed (Brecht et al., 1998; Roelfsema et al., 1997), suggesting neural synchrony may also be a mechanism by which distal brain regions exchange information (König et al., 1995). Weak or absent synchrony results in impaired communication (Barry et al., 2016), further implicating neural synchrony in communication between neuronal groups. Moreover, coordinated activity between neurons may be a mechanism by which neural assemblies are grouped to efficiently engage in neural processes (Barry et al., 2016). Collectively, these data highlight a role for neural synchrony in facilitating communication between neuron populations.

Synchronized neural oscillations are critical for the tuning of action potential timing which is necessary for synaptic plasticity. Synaptic connections can be strengthened or

weakened by the degree of neural synchrony (Hebb, 1949; Magee and Johnston, 1997). Moreover, the temporal order of action potentials is important and determines whether a synapse becomes potentiated or depressed (Bi and Poo, 1998; Markram et al., 1997; Zhang et al., 1998). More specifically, in cases where postsynaptic action potentials are preceded by presynaptic action potentials then a synapse is potentiated where the opposite scenario results in synaptic depression (Bi and Poo, 1998; Zhang et al., 1998). Importantly, changes in neural plasticity are one way in which neural oscillations are critical for expression of behavior.

Synchronous oscillations are hypothesized to link single neuron activity with complex behavior (Hasselmo et al., 2002; Somers and Kopell, 1993; Steriade, 2001). Coordinated activity of neurons is important for normal cognitive functioning, where temporal discoordination of neurons is associated with learning deficits (Barry et al., 2016). Synchrony has been implicated in perception of stimulus features (Singer, 1999; Singer and Gray, 1995), integration of sensory information (Roelfsema et al., 1997) and transfer of information between neural assemblies (Roelfsema et al., 1997), collectively suggesting that synchronization of neural oscillations may be critical for expression of complex behaviors (Barry et al., 2016). Given the numerous roles oscillations play in normal functioning, it is not surprising that alterations in neural oscillations are observed in mental illness (Kwon et al., 1999; Light et al., 2006; Park et al., 2017). Oscillations can tell us how neuronal communication is altered at a systems level (Ahn et al., 2013), making them a clinically relevant measure.

1.12 Neural oscillations and alcohol dependence

Alterations in neural oscillations have been observed in alcohol addiction. Importantly, alcohol exposure alters neural oscillations. Alcohol is hypothesized to disorganize neural oscillations (Rangaswamy and Porjesz, 2014). More specifically, alcohol is hypothesized to disrupt the structure of EEG oscillations, making them asynchronous (Ehlers et al., 1998). Alcohol exposure shifted hippocampal theta activity to a lower frequency in addition to decreasing the prevalence of theta oscillations (Givens, 1995) and theta power (Ehlers et al., 1992). Importantly, hippocampal theta has been linked to memory formation and retrieval, behaviors which are also impaired by alcohol exposure (Gál and Bárdos, 1994; Walker and Hunter, 1978).

Neural oscillations can be sensitive to acute effects of alcohol and can be used to measure sensitization or tolerance, thus differentiating individuals at risk for AUD (Rangaswamy and Porjesz, 2014). Furthermore, electrophysiological measures of stimulus processing may discriminate populations susceptible for AUD from populations with no such risk (Andrew and Fein, 2010). As such, alterations in neural oscillations between genetically at-risk individuals have been proposed as endophenotypes (Porjesz et al., 2005). AUD patients have increased interhemispheric coherence relative to non-dependent subjects (Kaplan et al., 1985; Park et al., 2017). Importantly, increased interhemispheric theta activity was correlated with alcohol use severity in AUD patients (Park et al., 2017). Neural oscillations can also predict subjective response to alcohol or intoxication index in social drinkers (Gevins et al., 2012).

The P300, sometimes referred to as the P3 component of the event-related potential is a positive wave that occurs 300 milliseconds (ms) after an informative event and is associated with information processing (Sutton et al., 1965). Importantly, P300 amplitude

has been proposed as a biomarker for addiction vulnerability (Berman et al., 1993). The P300 component is hypothesized to be generated from several brain rhythms, including theta oscillations in frontal central regions (Harper et al., 2014; Karakaş et al., 2000a; Karakaş et al., 2000b). The amplitude of the P300 component is related to significance of stimuli with larger signals being associated with inhibitory processes (Birbaumer et al., 1990). Alcohol administration affects the P300 component but also individuals with a family history have alterations in this component (Elmasian et al., 1982; Porjesz and Begleiter, 1990; Schuckit, 1988; Schuckit and Gold, 1988). Importantly, alterations in the P300 component persist in alcoholics, even after prolonged abstinence from alcohol use (Glenn et al., 1994; Porjesz and Begleiter, 1985). P300 amplitude is correlated with the number of first degree alcoholic relatives but not the drinking history of an alcoholic (Pfefferbaum et al., 1991; Porjesz et al., 1998). Low P300 amplitude is observed in individuals with AUD (Hill and Steinhauer, 1993; Prabhu et al., 2001; Suresh et al., 2003) and is correlated with increased impulsivity and decreased activity in frontal regions (Chen et al., 2007). Lastly, decreased P300 amplitude has been observed in individuals with AUD (Emmerson et al., 1987; Parsons et al., 1990) and alcohol naïve FH+ children (Hill et al., 1995; Whipple et al., 1991). In addition to identifying novel therapy targets, comparisons of neural dynamics between genetically vulnerable and wild type models may be useful in the identification of novel endophenotypes of addiction.

In addition to the P300 response, other physiological markers linked to alcohol dependence have been identified. P100 amplitudes are associated with detection of motivationally relevant stimuli and binge drinkers were observed to exhibit increased cortical P100 amplitudes relative to controls (Petit et al., 2012). Interestingly, alcohol

intoxication attenuated P100 amplitude (Krull et al., 1994). Moreover, individuals predisposed to alcoholism exhibited changes in the P100 latency not observed in controls (Pollock et al., 1988).

Neural oscillations are a translational tool which can predict addiction phenotypes. Electrophysiological measures can serves as endophenotypes for alcoholism (Rangaswamy and Porjesz, 2014). Currently, these endophenotypes are used to look for genes associated with AUD and AUD symptoms (Porjesz and Rangaswamy, 2007; Rangaswamy and Porjesz, 2008a, b; Zlojutro et al., 2011). For example, EEG coherence is heritable (Chorlian et al., 2007; Stassen et al., 1988; Van Baal et al., 1996), further arguing for the use of electrophysiological measurements as endophenotypes for AUD. Moreover, dysfunctional connectivity in cortical regions is hypothesized to be linked with behaviors observed in addiction and may serve as an endophenotypes for AUD (Park et al., 2017).

While alcohol exposure can alter neural oscillations, alterations in neural oscillations have also been hypothesized to be associated with vulnerability to develop an AUD. Whether alcohol use induces alterations in neural oscillations or is a consequence of dysfunctional neural oscillations remains to be elucidated. Regardless, alterations in neural oscillations are associated with addiction vulnerability. Importantly, these measures are translational and can be assessed in both clinical and preclinical populations, but rodent models of oscillatory activity in alcohol addiction are scarce.

1.13 Generation of theta oscillations

Neural oscillations occur at different frequencies and these different frequency domains, though their distinct properties, are believed to sub serve different functions (Canolty and Knight, 2010). Theta oscillations (5-11 Hz) are observed in several cortical

and limbic regions, including the amygdala (Popa et al., 2010), PFC (Jones and Wilson, 2005; Popa et al., 2010), HC (Green and Arduini, 1954; Jones and Wilson, 2005) and VS (van der Meer and Redish, 2011).

Theta oscillations are most prominent in the HC (Buzsáki, 2002) but it remains unclear how the theta rhythm is generated. Previous attempts to elucidate the mechanisms by which theta is generated have concentrated efforts on regions which share connections with the HC and influence HC theta oscillations. Several subcortical nuclei are hypothesized to contribute to generation of the theta oscillation. The medial septum (Petsche et al., 1962; Rawlins et al., 1979; Vinogradova, 1995) and supramammillary nucleus (Kirk and McNaughton, 1991; Kocsis and Vertes, 1994; Kocsis and Vertes, 1997) are both hypothesized to contribute to the theta rhythm. The hypothesized roles of each of these regions in generation of theta will be discussed below.

Inactivation of the medial septum abolishes HC theta rhythms (Petsche et al., 1962; Rawlins et al., 1979; Vinogradova, 1995) while stimulation of this region is reported to drive theta activity (Kramis and Vanderwolf, 1980; McNaughton et al., 1980; McNaughton et al., 1977). Importantly, the medial septum is not the sole generator of HC theta. Optogenetic stimulation of the medial septum in the theta frequency altered HC theta, an effect mediated by the animals' locomotor activity (Blumberg et al., 2016). This suggests that the medial septum is not the only influence on HC theta and that other regions, possibly those with strong implications in motor output, play a role in generation of HC theta oscillations. This hypothesis is further supported by the observation that theta rhythms can occur without the inputs of the medial septum in vitro in HC slices (Goutagny et al., 2009).

The medial septum has been hypothesized by some to serve as a "pacemaker" for theta oscillations in the HC (Kocsis and Vertes, 1997; Vinogradova, 1995). Medial septum neurons are diverse, innervating the HC via cholinergic, GABAergic and glutamatergic projections (Apartis et al., 1998; Gritti et al., 2006; Kiss et al., 1990). Importantly, only a subpopulation of medial septum neurons entrain HC theta oscillations while others exhibit slow-firing non-theta rhythmic activity (Stewart and Fox, 1989; Zhang et al., 2011). Pace-making of theta in the HC is hypothesized to occur when GABAergic neurons of the medial septum disinhibit HC pyramidal cells in a rhythmic manner (Freund and Antal, 1988), resulting in rhythmic inhibitory activity on pyramidal cells. Cholinergic inputs to the HC from the septum also modulate theta where they suppress other spurious rhythms which are asynchronous with theta (Lee et al., 1994; Vandecasteele et al., 2014), suggesting that theta rhythm, in addition to GABAergic activity, can be influenced by cholinergic activity (Lee et al., 1994). Additionally, lesioning cholinergic medial septum neurons but not GABAergic neurons reduced theta oscillation amplitude with no effect on frequency (Apartis et al., 1998; Lee et al., 1994). However, using an information theory approach, Hangya et al. (2009) reported that a high amount of information was shared between medial septum GABAergic neurons and HC theta oscillations. Lastly, infusions of glutamate in the medial septum resulted in generation of HC theta (Bland et al., 2007; Carre and Harley, 2000) while administration of the glutamate receptor antagonist MK801 decreased power and frequency of theta oscillations (Bland et al., 2007). Collectively these data suggest involvement of multiple medial septum neurons in generation of HC theta. However, the manner in which coordinated activity from glutamatergic, GABAergic and cholinergic projections from the medial septum influences HC theta remains to be elucidated.

The supramammillary nucleus projects to the HC and septum (Vertes, 1992) and cells within this region fire rhythmically with theta oscillations in the HC (Kirk and McNaughton, 1991). Furthermore, inactivation of the supramammillary nucleus results in a decrease in HC theta power (Bland et al., 1994; Oddie et al., 1994; Żakowski et al., 2017) while stimulation of the supramammillary nucleus drives theta (Bland et al., 1994; Oddie et al., 1994). Importantly, inactivation of the medial septum which abolished HC theta did not influence the firing of neurons in supramammillary nucleus (Kirk and McNaughton, 1991), suggesting that the medial septum and supramammillary nucleus independently contribute to HC theta. Moreover, silencing activity in the medial septum attenuated but did not abolish theta power in the supramammillary nucleus, further indicating the involvement of additional sources in contributing to theta rhythm (Ruan et al., 2017). Inactivation of the medial septum attenuated the frequency of theta while inactivation of the supramammillary nucleus reduced the amplitude but not frequency of theta, generating the hypothesis that the supramammillary nucleus encodes the amplitude while the medial septum encodes the frequency of theta oscillations (Kirk and McNaughton, 1993; Kirk and McNaughton, 1991; Woodnorth et al., 2003). Stimulation of the reticularis pontis oralis, which densely innervates the supramammillary nucleus (Vertes, 1988) results in phasic bursts in the theta rhythm in the HC (Kirk and McNaughton, 1991). Importantly, rhythmic firing of these cells was immune to inactivation of the medial septum (Kirk and McNaughton, 1991). Kirk and McNaughton (1993) also observed that inactivation of connections between the reticularis pontis oralis and supramammillary nucleus reduced theta frequency but not amplitude, whereas inactivating connections between the medial septum and supramammillary nucleus resulted in a reduction in both frequency and

amplitude of theta oscillations. Additionally, inhibition of supramammillary nucleus cells reduced the mean frequency of theta oscillations (McNaughton et al., 1995). Collectively, these data suggest that the supramammillary nucleus is important for encoding theta frequency. Lastly, although the supramammillary nucleus contributes to the establishment of theta frequency, other brain regions also play a role in maintaining theta frequency since movement-evoked theta oscillations are not affected by supramammillary nucleus lesions (Thinschmidt et al., 1995).

Several lines of evidence suggest the presence of multiple generators of theta in the brain. Moreover, within a given substrate, different types of projections can have different roles in influencing the theta rhythm. However, while researchers have identified several neural substrates thought to contribute to generation of the theta rhythm, the exact mechanisms of theta generation remain poorly understood.

1.14 Theta oscillations and reward seeking

Theta oscillations are hypothesized to modulate neuronal activity by coordinating activity across networks (Steriade et al., 2001) and may also be important for organizing brain activity during behavior (Siapas et al., 2005). The phasic and temporal relationship of neuronal firing in the theta range is important in encoding and retrieval of neural information (Hasselmo et al., 2002; Siegle and Wilson, 2014). Siegle and Wilson (2014) stimulated peak and trough of theta in the HC during different phases of a spatial navigation task and found that the HC encodes and retrieves information at different stages of theta, dependent on behavioral demands of the task. Phase specific effects on LTP have also been observed. Stimulation of the theta peak causes LTP while trough stimulation results in long-term depression (LTD) in vitro (Huerta and Lisman, 1996a; Huerta and Lisman, 1995).

Collectively, these data suggest a mechanism by which theta oscillations encode behavioral information.

Alterations in theta oscillations are observed in alcoholics (Rangaswamy et al., 2003) and have been associated with alcohol use. Alcohol use (De Bruin et al., 2004; Jones et al., 2006; Kamarajan et al., 2004; Kamarajan et al., 2012), exposure (Krause et al., 2002) and genetic vulnerability to alcohol dependence (Andrew and Fein, 2010; Kamarajan et al., 2006; Rangaswamy et al., 2007) are all associated with alterations in theta oscillations. Moreover, alcoholics show deficits in the P300 response (Cohen et al., 2002), which is evoked by salient stimuli (Jones et al., 2006) and hypothesized to be the outcome of oscillatory changes in delta and theta rhythms during stimulus processing (Jones et al., 2006). Theta oscillations are associated with stimulus evaluation (Başar and Güntekin, 2008) and are reduced in the frontal cortex in individuals with AUD compared to healthy controls (Kamarajan et al., 2004). Low doses of alcohol alter oscillations in the 8-12 Hz range (Ehlers et al., 2004). Specifically, alcohol acutely increases theta activity in healthy subjects (Lei et al., 2014), an effect which is amplified in chronic alcoholics (Rangaswamy and Porjesz, 2014), and in individuals sensitive to the euphoric effects of alcohol (Lei et al., 2014). Reduced EEG power between 8-12 Hz was observed in FH+ individuals (Finn and Justus, 1999). Additionally, decreases in theta power were observed in abstinent alcoholics (Coutin-Churchman et al., 2006). Theta power was increased after treatment mediated abstinence in alcoholics while patients who relapsed exhibited reduced theta power in frontal regions (Saletu-Zyhlarz et al., 2004). Reduced theta event related oscillation amplitudes are observed during the visual oddball paradigm in alcoholics during the processing of target stimuli (Jones et al., 2006). Neural activity between 8 and 12 Hz is

positively correlated with drinking desire in FH+ individuals (Kaplan et al., 1988). Moreover, oscillations in this frequency range are more prevalent in FH+ versus FH- individuals (Cohen et al., 1993; Pollock et al., 1983). Alterations in phase-locked theta oscillations were observed in long term abstinent alcoholics (Andrew and Fein, 2010), further suggesting neural oscillations may represent translational biomarkers for alcohol dependence.

Neural oscillations are a translational tool which may have promise in predicting alcohol-addiction phenotypes. Importantly, electrophysiological measures can serve as endophenotypes for alcoholism (Rangaswamy and Porjesz, 2014). Currently, these endophenotypes are used to look for genes associated with AUD and AUD symptoms (Rangaswamy et al., 2007; Rangaswamy and Porjesz, 2014; Zlojutro et al., 2011). More specifically, theta oscillations have been used to identify candidate genes for alcoholism (Chen et al., 2009; Jones et al., 2004). Along with EEG coherence (Chorlian et al., 2007; Stassen et al., 1988; Van Baal et al., 1996), theta power (Van Beijsterveldt and Boomsma, 1994; Van Beijsterveldt et al., 1996; Van Beijsterveldt and Van Baal, 2002) is also heritable, suggesting clinical utility of electrophysiological biomarkers for AUD.

While alcohol exposure can alter neural oscillations, alterations in neural oscillations have also been hypothesized to be associated with vulnerability to develop an AUD (Rangaswamy and Porjesz, 2014). Whether alcohol use induces alterations in neural oscillations or is a consequence of dysfunctional neural oscillations remains to be elucidated. However, several studies suggest that alterations in neural oscillations are associated with addiction vulnerability (Hill et al., 1995; Pfefferbaum et al., 1991; Porjesz et al., 1998; Whipple et al., 1991). Alterations in theta oscillations are linked to AUD

symptoms. Individuals with an AUD exhibit decreased theta power during reward processing as well as increased impulsivity and risk taking (Kamarajan et al., 2012). Non-phase locked theta oscillations observed in alcoholics are hypothesized to be a marker of chronic alcohol use (Gilmore and Fein, 2012). Importantly, these measures are translational and can be assessed in both clinical and preclinical populations, but rodent models of oscillatory activity in alcohol addiction are scarce. Such models can test hypotheses generated in clinical studies which may be unethical or hold great risk for subjects. For example, using preclinical models, one can investigate the influence alcohol exposure has on neural oscillations in a controlled environment. Family history, subject drug history and alcohol exposure can all be systemically manipulated and controlled. Preclinical models can therefore bridge the gaps in clinical literature and inform our understanding of how neural activity is associated with addiction-related behaviors.

1.15 Summary

Alcohol-paired cues are associated with craving and relapse in alcohol dependent individuals. The neural mechanisms which underlie aberrant cue reactivity in AUD remain poorly understood. The PFC, NA, BLA and HC have been studied extensively and each region has been observed to contribute to maladaptive behaviors present in alcohol addiction. While, these regions are interconnected, few studies have looked at how neural activity between these regions is altered in AUD. While electrophysiological studies in clinical populations have elucidated how these networks contribute to cue reactivity, these studies are confounded by their inability to control the environment and histories of their participants. Moreover, these techniques show reduced temporal and spatial precision relative to preclinical models. Currently, there are several preclinical models of alcoholism.

Each model has both utility and short comings. Of these models, the P rat exhibits a robust alcohol-seeking and alcohol-drinking phenotype while modeling the genetic component of AUD, making it one of the better models in which to investigate both genetic vulnerability and physiological markers of alcohol-seeking behaviors. Given the heritability and translational nature of neural oscillations, especially those in the theta Hz range, the P rat represents a suitable model to investigate the neural mechanisms of alcohol addiction.

1.16 Overall Aims

Behavioral and cognitive processes do not occur in one brain region in isolation but instead require coordinated exchange of information between neural networks (Bressler and Menon, 2010). Several lines of evidence suggest that the BLA, HC, NA and PFC and are important brain regions involved in cued reward seeking. Moreover, genetic vulnerability is strongly linked to phenotypes associated with excessive alcohol seeking and drinking. Behavioral differences observed between P and Wistar rats during cued alcohol seeking, extinction and reinstatement suggest these strains may exhibit physiological differences in the brain regions which process alcohol-paired cues. The experiments outlined below seek to investigate the physiological differences between P and Wistar rats during cued alcohol-seeking behaviors with the purpose of elucidating the way in which genetic vulnerability mediates the physiological processes underlying these behaviors as well as inform our understanding of how discrete brain regions work together to encode information about stimuli paired with alcohol to influence alcohol-seeking behaviors. An operant model was employed in order to investigate goal-directed decision making. Whereas in classical conditioning an animal can sometimes receive a reward just by being in the right place at the right time, in operant conditioning, in order to acquire a

reward, an animal must make a response. Moreover, in operant conditioning, responses are reinforced and not merely a reward. This distinction is important since much literature supports involvement of the above mentioned brain regions in drug reinforcement.

CHAPTER 2. MATERIALS AND METHODS

2.1 Subjects

Alcohol naïve male Wistar (Harlan, Indianapolis, IN) and P rats (Indiana University, IN) were used for all experiments. Animals weighed approximately 250-300 grams (g) upon arrival and were individually housed in a climate-controlled room on a 12-hour reversed light/dark cycle. All animals were handled a minimum of one week prior to experimental testing and were approximately 12 weeks of age at the start of testing. All procedures were approved by the IUPUI School of Science Institutional Animal Care and Use Committee and were in accordance with the National Institutes of Health guide for the care and use of laboratory animals.

2.2 Behavior

2.2.1 Ethanol acquisition

All animals had four weeks of intermittent free choice access to 20% ethanol in their home cages to induce alcohol consumption. One hour into the start of the dark cycle, all water bottles were replaced with two bottles, one containing tap water and the other 20% ethanol. Twenty-four hours after bottle placement, bottlers were removed, replaced with one water bottle and fluid intake of both bottles was measured. Animal weights taken prior to bottle placement were used in conjunction with fluid intake to determine grams (g) per kilograms (kg) of ethanol consumed. Using this method of ethanol exposure, animals exhibit escalated alcohol intake over days to pharmacologically relevant levels in the absence of added sweeteners (McCane et al., 2014; Simms et al., 2008).

2.2.2 Lever press training

Following home cage drinking, animals progressed to operant training. All operant conditioning sessions were conducted in modular operant chambers (30 x 30 x 24.5 cm; Med Associates, St. Albans, VT) equipped with a house light, retractable lever, auditory tone generator and a retractable graduated cylinder tube fitted with stainless steel spouts containing two double ball bearings to reduce leakage. Within the operant boxes, the retractable lever and retractable sipper were located on the same side of the box beside each other with the tone generator located directly above the retractable lever. Animals were initially fluid restricted and trained to lever press for a water reinforcer on a fixed ratio (FR) one schedule which was gradually increased to an FR3 over days. An FR3 was chosen to reduce the likelihood of accidental presses. Thus, the higher schedule was employed to increase the likelihood that lever-press responses would be deliberate and reflect reinforcer seeking. Following stable responding on this schedule, water was given ad libitum and animals were trained to respond for a 10% ethanol reinforcer. Ethanol was reduced from 20% (home cage access) to 10% in order to increase the number of trials an animal would perform. We have previously observed using 20% alcohol results in reduced performance and increased sleeping bouts in P rats (data not published). After responding for ethanol was established, animals transitioned into the conditioning phase of the experiment.

2.2.3 Conditioning

During the conditioning phase, animals were trained to discriminate between two different auditory stimuli (3,500 or 1,000 Hz tone; counterbalanced) using a modified version of the procedure used by Brown et al. (2011) and Jones et al. (2010). Food restricted

rats can learn to discriminate between 2,750 and 1,000 Hz for sucrose reinforcers (Brown et al., 2011; Jones et al., 2010). The auditory stimuli parameters were therefore chosen based on previous discrimination studies. Each trial consisted of presentation of a ten second discriminative stimulus (DS) and either ten seconds' access to a lever that will be reinforced (10% ethanol; DS+) or a ten-second omission trial (DS-) where lever presses had no consequences (Figure 1A). For reinforced levers, an FR3 schedule was employed and animals had ten seconds to respond before the lever was retracted. Conditioning sessions consisted of 60 trials (30 DS+, 30 DS-) in a randomized order. Animals were considered to have reached criterion when 70% of all lever presses were for the DS+ for at least two consecutive days. Animals who failed to reach criterion within 40 days were not used for electrophysiological recordings. Because progressing from one phase to another was dependent on individual behavior, the amount of conditioning days experienced varied by animal. P rats on average took between 20 to 25 days to acquire discrimination whereas Wistars took closer to 30 days to learn discrimination.

2.2.4 Extinction

Following conditioning, animals entered the extinction phase. During extinction, animals experienced 60 ten second lever extensions. During this phase DS stimuli were absent and no lever presses were reinforced. However, the retractable sipper contained 10% alcohol to control for scent cues. Animals experienced multiple extinction sessions to ensure responding was consistently reduced, relative to conditioning sessions. Extinction of both reinforcer and stimuli was conducted in the manner outlined in order to facilitate the assessment of cue-induced reinstatement, where the stimuli, but not the reinforcers

would be reintroduced. Because of methodological issues, reinstatement testing could not be conducted. Thus, an explanation of reinstatement methodologies has been omitted.

2.3 Electrophysiology

Animals which reached discrimination criterion (Wistar, N=10; P rat, N=11) underwent surgery for electrophysiological recordings.

2.3.1 Electrophysiology probes

Each electrophysiology probe, which would later be surgically implanted, was custom made (Figure 2). Probes were assembled using 32 (eight per brain region) 20 µm tungsten wires (California Fine wires, Grover Beach, CA), approximately 10 cm in length, fed through silica capillary tubing (Polymicro Technologies, Phoenix, AZ). The outer diameter of the silica tubing was 170 µm and the inner diameter was 100 µm (Figure 2X). For the BLA and vHC, silica tubing was cut using a razor blade into 2 cm pieces. For the mPFC and NAc, silica tubing was cut into 1.5 cm pieces. Silica tubing was arranged in a 1 × 4 array and superglued. Next, two 1 × 4 arrays were sandwiched together and glued, forming a 2 × 4 matrix. The tungsten wires were then fed into the silica tubing with approximately 5-10 mm extending from one end of the probe. The tungsten wires were secured to the matrix using liquid super glue. The minimum and maximal distance between wires within this matrix was 85 µm and 340 µm, respectively. The wires extending from 2 × 4 matrix, opposite the 10 mm tip were thread through a plastic connector piece and pinned with gold wires. Two copper wires were stripped at the both of the ends using a razor blade. A stripped end of each wire was soldered to a gold pin fed through the plastic connector piece. These wires were then soldered to each other, such that there was only one end point

connecting the two gold pins. Animals were next implanted with the two custom made probes.

2.3.2 Surgery

Animals were anesthetized with isoflurane for implantation of the custom-made electrophysiology probes described previously. The rat was first placed in the induction chamber and isoflurane vaporizer was turned to five. When the animal was non-responsive, it was removed from the chamber and secured in the ear bars. At this time, the vaporizer was adjusted to three. The rat's head was then cleaned with betadine. The animal was next checked for a pain response, in order to ascertain that they were deeply enough anesthetized. Dura tears were applied to the eyes to prevent drying. Next, the scalp was removed using a pair of sharp scissors. The skull was made visible be removing additional skin and membranes. Bregma was measured using the stereotaxic arms and probes were implanted over the PFC (AP: 3.0, ML: 0.5, DV:-3.2), NA (AP: 1.6, ML: 1.5, DV:-6.7), BLA (AP -2.8, ML +5.0, DV -8.4) and vHC (AP -5.6, ML +6.3, DV -6.8), all relative to bregma. The ground wires were externally referenced to stainless steel skull screws over the cerebellum. Lastly, the custom-made head caps were secured to the skull with dental cement. Following surgery, animals had one week of recovery before electrophysiological recordings were conducted. During the recovery week, animals were fed a high caloric breeder chow and weighed daily.

2.3.3 Electrophysiological recordings

Of the 21 animals implanted, eight (Wistar, N=3; P rat, N=5) reacquired consistent lever press behavior. Animals were run in conditioning behavior over approximately eight days yielding a total of 23 data sets for Wistars and 39 data sets for P rats, where each day

for each animal was an individual data set (Table 1). For extinction, animals were run for three to four days, yielding 8 data sets for Wistars and 16 data sets for P rats. Electrophysiological recordings were conducted in a custom made operant box (10 x 10 x 21 inches). LFPs were acquired with a 32 channel Neuralynx Cheetah recording system. LFPs were sampled at 32,556 Hz, amplified 2000 times, initially filtered between 0.01 and 1000 Hz and then down sampled to 1017 Hz for analyses. Behavioral events were synced with Neuralynx, time locking them to neural recordings. Locomotion activity was tracked using recording software and synched to neural recordings (Any-Maze, Wood Dale, IL).

2.4 Histology

Following data collection, animals were anesthetized with urethane (1 to 1.5 ml per rat, intraperitoneally) and transcardially perfused with phosphate buffered saline (PBS) followed by 10% formalin. Afterwards, brains were removed from the skull, soaked in 30% sucrose mixed in PBS, rinsed with milli-Q water and stored in a -80˚ freezer. Frozen brains were then cut into 30µm sections using a cryostat, mounted and stained with cresyl violet to determine probe placement (Paxinos and Watson, 2007). Brain regions were excluded if probe placement was outside of the four target regions (Figure 3). Hit rate for the PFC was 100%, NA, 88%, BLA 75% and vHC 60%.

2.5 Data analysis

All data was analyzed using MATLAB (Mathworks, Nautick, MA) and R (http://www.r-project.org). For electrophysiological recordings, data were first imported using custom written software. Data were then segregated into behavioral epochs (Figure

1B). Next a power spectrum density (PSD) was computed using a fast Fourier transform (fft; Welch, 1967) for each behavioral epoch in each task for each strain, yielding 14 PSDs for each of the four brain regions. Data were further segregated by whether the animal responded on the lever at least three times (response) or fewer than three times (no response), resulting in a total of 28 PSDs per brain region. The mean and standard deviation (SD) were calculated for a population of wires within each of the PSDs. Wires which were within three SD away from the mean were considered "noisy" and were excluded from all analyses. All remaining wires within a given brain region were averaged for each dataset, yielding a maximum of four signals per trial per dataset. Next, the signals were filtered in the theta band (5-11Hz) and the phase and amplitude were extracted using the Hilbert transform (Hurtado et al., 2004; Pikovsky et al., 2001). To investigate neural synchrony between brain region pairs, the phase locking index γ was computed by taking the complex value of the average of all points (1/N) where $\varphi_1(t)$ and $\varphi_2(t)$ are two phases from the filtered signals, the phase difference $\theta(t_j) = \varphi_1(t_j) - \varphi_2(t_j)$, t_j are the times of data points, and N is the number of all data points during the given time interval (Hurtado et al., 2004, Lachaux et al., 1999, Pikovsky et al., 2001, Figure 4). The range of γ values is 0 (no phase locking) to 1 (perfect phase locking). For analyses of neural synchrony, analysis of variance (ANOVA) testing was used for all comparisons followed by Bonferroni post hoc. To investigate directionality, the cross correlation between the amplitude of two signals was computed (Adhikari et al., 2010a). This yielded a distribution of lags (distance between peak amplitude and zero) which indicated whether one signal led another. Poor signals resulted in aberrant cross correlations. These cross correlations were excluded by two criteria. Firstly, the amplitude of one signal was scrambled, and cross correlated with a

non-scrambled signal, yielding a surrogate data set. All cross correlations were then tested against the surrogate cross correlations with a two-sample t-test to determine whether or not their distribution was significantly different from those of the surrogate data. Next, a histogram of the mean peak lags was generated to determine whether the distribution was bimodal. Collectively, these analyses generated an exclusion criteria of cross correlations peak lags which were + 50 milliseconds (ms) in length. Cross correlations which reached exclusion criteria were removed from statistical analyses. Cross correlations that survived exclusion were averaged, yielding a single cross correlation peak lag for each behavioral epoch. This mean peak lag was tested using an independent one sampled t-test to determine whether or not it was significantly different from zero.

CHAPTER 3. RESULTS

3.1 Aim 1 analysis

A preliminary group of male P (N=12) and Wistar rats (N=11) were trained to discriminate between two auditory stimuli. Both P and Wistar rats increase their intake over days [main effect of day: $F(1,19)= 4.75$, $p=0.04$; Figure 5A]. Additionally, both strains learn to discriminate between stimuli which predict access to ethanol [criterion=70% of all lever presses for DS+; Figure 5 B1). However, P rats exhibit a faster rate of learning [$t(27.5)=3.3$, $p=0.003$], acquiring stimuli discrimination approximately ten days sooner than Wistars (Figure 5 B2). Both strains extinguish responding over days [main effect of day: $F(1,21)=51.6$,$p<0.001$;Figure 5 C1] but P rats extinguish alcohol-seeking behavior sooner than Wistars [$t(13.4)=4.7$,$p=0.0004$; Figure 5 C2].

3.2 Behavioral analyses

3.2.1 All animals increase free choice ethanol intake in the IAP

A significant main effect of group, (surgery or no surgery) [$F(1,493)=68.852$,$p<0.001$; Figure 6] was observed, indicating that overall animals which were implanted showed differences in free choice ethanol consumption, compared to animals which did not undergo surgery. Significant interactions between strain and group [$F(1,493)=34.270$,$p<0.001$] and day and group [$F(1,493)=12.326$,$p=0.000488$] were also observed. Follow-up analyses revealed that animals that were not implanted increased their ethanol intake over days [main effect of day: $F(1,21)=14.745$, $p=0.000952$] and P rats consumed more ethanol than Wistars [main effect of strain: $F(1,20)=50.243$,$p<0.001$, Figure 6A]. Animals which were implanted did not show different ethanol intake between

the two strains, although a trend was observed [main effect of strain: $F(1,14)=3.486, p=0.083$]. Additionally, in animals which were later implanted, intake increased over days across both strains [main effect of day: $F(1,16)=47.134, p<0.001$; Figure 6B].

3.2.2 A subset of rats learn to discriminate between the two stimuli

Intake during conditioning was influenced by rodent strain [main effect of strain: $F(1,32)=13.982$, $p=0.000724$], group [main effect of group: $F(1,32)=12.168, p=0.001438$] and day [main effect of day: $F(1,32)=13.999, p=0.000720$; Figure 7A].

Percentage of total lever presses for the DS+ differed by group [main effect of group: $F(1,32)=12.516, p=0.00126$] and strain [main effect of strain: $F(1,32)=9.428, p=0.00433$; Figure 7B]. Interactions between group and day [$F(1,34)=36.513, p<0.001$] and strain and day [$F(1,34)=11.750, p=0.00161$] were also observed. Follow-up analyses indicated that in the surgery group, P rats did not differ from Wistars in their overall percentage of lever presses for the DS+ [main effect of strain: $F(1.634)=2.633, p=0.105$; Figure 7 B2]. However, in animals which were not implanted, P rats exhibited greater lever pressing for the DS+ than Wistars [main effect of strain: $F(1,701)=19.517, p<0.001$; Figure 7 B1]. Additionally, animals in the surgery group increased their discriminated lever pressing over days [main effect of day: $F(1,634)=230.804, p<0.001$] while non-implanted animals did not differ in their behavior over days [main effect of day: $F(1,701)=0.406, p=0.5241$].

3.2.3 Strain differences in behaviors are absent during electrophysiological recordings

During electrophysiological recordings, there were no differences in ethanol intake between Wistar and P rats [main effect of strain: $F(1,59)=0.11, p=0.736$; Figure 8A].

Similarly, the strains did not differ in their ability to discriminate between the two stimuli types [main effect of strain: $F(1,59)=0.27, p=0.606$; Figure 8B].

3.2.4 Responding decreases in extinction during electrophysiological recordings

While there was no difference between strains in total lever presses during all recordings [main effect of strain: $F(1,82)=2.434, p=0.122$], overall rats pressed fewer times during extinction, relative to conditioning [main effect of task: $F(1,82)=15.139, p=0.000202$; Figure 9A]. Moreover, during extinction, lever pressing decreased over day for both strains [main effect of day: $F(1,16)=10.154, p=0.00055$; Figure 9B].

3.3 Synchrony analyses

3.3.1 Baseline synchrony is modulated by strain and brain region

To determine whether changes in synchrony were associated with preselected epochs, a period of five seconds prior to onset of the DS+ was used as a measure of baseline. Data were first collapsed across strain and analyzed using ANOVA testing to assess how brain region and trial influenced neural synchrony. A main effect of brain [$F(5,6556)=272.785, p<0.001$] indicated synchrony differed between brain region pairs. However, a main effect of trial [$F(1,6556)=0.148, p=0.70$], and a trial × brain interaction [$F(5,6556)=1302, p=0.26$] were both not significant (Figure 10). Baseline data were therefore collapsed over trials. Next, the influence of strain was assessed. A significant main effect of strain [$F(1,6556)=318.3$, $p<0.001$] as well as a strain × brain interaction [$F(5,6556)=264.4, p<0.001$] were observed (Figure 11). Given the small group size for

Wistars and the significant influence of strain, Wistars were removed from all future analyses.

3.3.2 Synchrony changes over behavior

To assess whether changes in synchrony were behaviorally relevant, synchrony over behavior was compared to baseline synchrony (Table 3). Behavioral epochs were DS+ trials in which P rats responded three or more times. Similar to baseline, behavioral data did not differ by trial [main effect of trial: $F(19,1040)=0.679, p=0.843$; Figure 12]. Data were therefore collapsed across trials. When synchrony across behaviors and brain region pairs was assessed, a significant main effect of brain [$F(5,93)=9.883, p<0.001$] and brain × behavior interaction [$F(15,222)=2.209$, $p=0.00692$; Figure 13] were observed. Data were therefore next stratified by brain to better understand how synchrony changes across behavior (Figure 14). Overall, there was no effect of behavioral epoch for BLA-HC synchrony [main effect of behavior: $F(3,1474)=0.22, p=0.881$; Figure 14 A]. Synchrony between the NA and BLA did significantly change over behavioral epoch [main effect of behavior: $F(3,990)=4.504, p=0.0038$; Figure 14 B] where synchrony during drinking was lower than synchrony during baseline ($p=0.007$, Bonferroni post hoc). A non-significant trend was also observed for lever synchrony compared to baseline ($p=0.095$). Similarly, synchrony between the NA and HC changed over behavioral epoch [main effect of behavior: $F(3,990)=10.28, p<0.001$, Figure 14 C], where synchrony increased during lever pressing relative to baseline ($p<0.001$, Bonferroni post hoc). PFC-BLA synchrony was also modulated by behavioral epoch [main effect of behavior: $F(3,1402)=5.398, p=0.00108$; Figure 14 D] where synchrony was increased during lever pressing, relative to baseline ($p=0.0013$, Bonferroni post hoc). Significant changes in synchrony were also observed

between the PFC and HC [main effect of behavior: $F(3,7675)=6.27, p=0.000302$; Figure 14 E] where synchrony increased during lever pressing ($p<0.001$, Bonferroni post hoc). Lastly, synchrony between the PFC and NA was also influenced by behavioral epoch [main effect of behavior: $F(3,1397)=10.38, p<0.001$; Figure 14 F) where, relative to baseline, synchrony was increased during presentation of the DS+ tone ($p=0.00472$, Bonferroni post hoc), lever pressing ($p=0.00042$, Bonferroni post hoc) and alcohol consumption ($p=0.00028$, Bonferroni post hoc).

3.3.3 Synchrony changes by discriminative stimulus and responding

To understand the consequence of discriminative stimuli and animal response on synchrony, synchrony was next compared between DS+ and DS- trials and trials in which animals responded three or more times (response) or fewer than three times (non-response) in brain regions and behaviors which were different from baseline.

3.3.4 Tone epoch

During presentation of the tone, PFC-NA synchrony was higher for response trials, compared to non-response [main effect of response: $F(1,1312)=46.946, p<0.001$; Figure 15]. PFC-NA synchrony was not altered by stimulus type [main effect of group: $F(1,1312)=0.070, p=0.792$] or an interaction between stimulus type and response [group × response interaction: $F(1,1312)=0.095, p=0.758$].

To better understand how synchrony was modulated by behavior, data were stratified by whether or not the animal behaved at or above criteria on a given day (70% or greater overall lever presses for the DS+) and analyzed during the tone epoch. As done previously, data were first compared to baseline to determine which brain pairings were

behaviorally relevant (Figure 16 A). Days in which the animal discriminated and subsequently responded were compared to baseline.

For DS- trials, there was a significant main effect of brain [$F(1,4159)=141.629, p<0.001$]. When data were next separated by brain region, only synchrony between the PFC and NA was different from baseline ($p=0.049$, Bonferroni post hoc). Similarly, for DS+ trials, there was a significant brain by group (baseline or behavior) interaction [$F(5,4727)=2.404, p=0.0347$]. When data were further stratified by brain, only synchrony between the PFC and NA ($p=0.036$, Bonferroni post hoc) and NA and HC ($p=0.0011$, Bonferroni post hoc), differed from baseline.

Next, animal response was assessed as a factor for differences in synchrony. Whether or not an animal discriminated between the two stimuli had no effect on synchrony between the PFC and NA [main effect of discrimination: $F(1,1368)=2.60, p=0.1071$; Figure 16 B1] but was influenced by whether or not an animal made a response [main effect of response: $F(1,1368)=38.230, p<0.001$]. However, synchrony between the NA and HC was significantly affected by an animal's ability to discriminate between the two stimuli [main effect of discrimination: $F(1,890)=102.748, p<0.001$]. Specifically, NA-HC synchrony was stronger when the animal exhibited stimuli discrimination, compared to periods where discrimination was not apparent (Figure 16 B2).

3.3.5 Lever pressing epoch

There was a trend towards significance when comparing synchrony between the NA and HC for DS+ and DS- trials [main effect of group: $F(1,894)=3.112, p=0.078$]. However, whether or not an animal responded significantly influenced synchrony [main

effect of response; F(1,894)=13.495,p=0.000253] and this effect was modulated by stimuli type [group × response interaction: F(1,894)=10.511,p=0.001230, Figure 17 A]. Furthermore, synchrony during non-response trials was significantly lower than response trials following presentation of the DS+ tone (Bonferroni post hoc, p<0.001). However, this effect was not observed in DS- trials (Bonferroni post hoc, p=0.54). Synchrony between the PFC and BLA was influenced by animal response [main effect of response: F(1,1194)=9.945,p=0.00165] and this effect was modulated by stimuli type [group × response interaction: F(1,1194)=7.076,p=0.0079, Figure 17 B). In DS+ trials, synchrony was greater when the animal responded relative to non-response trials (p<0.001, Bonferroni post hoc). This effect was not observed in DS- trials where there was no difference between response and non-response trials (p=0.7, Bonferroni post hoc). A significant group × response interaction [F(1,1194)=4.258,p=0.0393] was observed for PFC-HC synchrony where synchrony was greater during responding relative to non-responding in DS+ trials (Bonferroni post hoc, p<0.001;Figure 17 C). This effect was not observed in DS- trials (p=0.19, Bonferroni post hoc). PFC-HC synchrony was also influenced overall by response [main effect of response: F(1,1194)=27.812,p<0.001]. Lastly, PFC-NA synchrony was greater overall for response trials, relative non-response trials [main effect of response: F(1,1312)=50.023,p<0.001; Figure 17 D]. However, synchrony did not differ by group [main effect of group: F(1,1312)=0,p=0.99] and a group × response interaction was also not significant [F(1,1312)=1.075,p=0.30].

3.3.6 Drink epoch

NA-BLA synchrony was greater during trials where animals responded fewer than three times [main effect of response: F(1,934)=15.837,p<0.001; Figure 18 A], but was not

influenced by stimuli type [main effect of group: F(1:934)=0.858,p=0.355] or an interaction between stimuli type and response [response × group interaction: F(1,934)=0.027,p=0.869]. Conversely, PFC-NA synchrony was stronger during trials in which animals pressed three or more times [main effect of response: F(1,1362)=49.507,p<0.001; Figure 18 B]. However, PFC-NA synchrony did not differ by stimuli type [main effect of group: F(1,1362)=2.256,p=0.1333] but a non-significant trend between group and response was observed [F(1,1362)=3.056,p=0.0806]. Importantly, only DS+ trials in which the animal responded resulted in alcohol availability.

3.3.7 Synchrony changes by brain region

Synchrony was next compared between brain regions in behavioral epochs and brain regions which differed from baseline (Figure 15). During DS+ trial lever pressing epochs in which the animals responded three or more times, a main effect of brain was observed [F(3,775)=75.84,p<0.001; Figure 19 A]. All brain region pairs were significantly different from each other (Bonferroni post hoc, p<0.05) except PFC-NA compared to NA-HC (p=0.6). During drinking epochs, PFC-NA synchrony was significantly greater than NA-BLA synchrony [two-sampled t-test: t(390.28)=-7.7623, p<0.001; Figure 19 B].

3.3.8 Synchrony during extinction is modulated by brain region, response and epoch

To investigate neural synchrony changes during extinction, synchrony over trials was assessed. Synchrony during lever pressing in the extinction phase was not altered by trial [main effect of trial: F(59,2721)=1.115,p=0.256; Figure 20]. Extinction data were therefore collapsed over trial. Next, the influence of group (response, no response or baseline) and brain region pair was assessed. Synchrony differed by brain region pair [main

effect of brain: F(5,7128)=282.12, p<0.001; Figure 21]. With the exception of BLA-HC versus PFC-HC (p=1; Bonferroni post hoc), synchrony between all brain region pairs was significantly different from one another (Bonferroni post hoc, p<0.007; Figure 21 C). Synchrony during extinction was also influenced by group [main effect of group: F(1,7128)=32.25,p<0.001; Figure 21 A]. Additionally, a significant brain × group interaction was also observed [F(5,7128)=25.64, p<0.001]. Next, each brain region pair was isolated and synchrony during extinction for both responses and non-responses was compared to baseline to determine whether changes in neural synchrony were behaviorally relevant (Figure 21 B). A significant main effect of group was observed in BLA-HC [F(2,1213)=3.598,p=0.0277], NA-BLA[F(2,1025)=9.189, p=0.000111], NA-HC [F(2,1025)=75.11,p<0.001], PFC-BLA [F(2,1420)=9.51,p<0.001], PFC-HC [F(2,1181)= 14.42. p<0.001] and PFC-NA[F(2,1501)=144.1,p<0.001]. With the exception of PFC-NA (p=0.079), synchrony during trials in which the animal did not respond significantly differed from baseline in all brain region pairs (p<0.001; Bonferroni post hoc; Figure 21 B). Synchrony between the PFC- HC and NA-HC for trials in which the animal responded was observed to also differ from baseline (p<0.0054; Bonferroni post hoc).

3.3.9 Synchrony differs by task

To determine how synchrony changes by task (conditioning or extinction), data were stratified by brain region pair during lever pressing for regions previously identified to differ from baseline. BLA-HC synchrony was lower during extinction [main effect of task: F(1,1105)=6.047,p=0.0141; Figure 22 A]. However, BLA-HC synchrony was not significantly influenced by response [main effect of response: F(1,1105)=1.680,p=0.1951], nor was an interaction between response and task observed [response × task interaction:

F(1,1105)=.311,p=0.5773]. For NA-BLA synchrony, a significant task × response interaction was observed [F(1,925)=6.888,p=0.00882; Figure 22 B]. Bonferroni post hoc indicated that conditioning differs from extinction only for non-response trials (p=0.00035). Synchrony between the NA and HC was greater during extinction, relative to conditioning [main effect of task: F(1,925)=100.339,p<0.001; Figure 22 C]. A significant interaction between response and task was also observed [F(1,925)=9.369,p=0.00227]. Post hoc tests indicated that synchrony was higher during extinction, compared to conditioning in non-response trials (Bonferroni post hoc, p<0.001). For PFC-BLA synchrony, there was a task × response interaction [F(1,1314)=9.373,p=0.00225; Fig 22 D] where synchrony during extinction is stronger than synchrony during conditioning in non-response trials (Bonferroni post hoc, p<0.001). Greater PFC-HC synchrony was observed for response compared to non-response [F(1,1075)=10.464,p=0.00125] and extinction compared to conditioning [main effect of task: F(1,1075)=37.582,p<0.001] but the interaction between the two factors failed to reach significance [response × task interaction: F(1,1075)=1.129,p=0.28824; Figure 22 E].

3.4 Directionality analyses

3.4.1 Baseline directionality

To better understand the neural dynamics of cued alcohol-seeking behavior, directionality between brain regions during behavioral epochs was determined (Table 4). During the baseline epoch, the PFC is led by both the NA [t(395)=-6.0405, p<0.001] and BLA[t(104)=2.20406,p=0.0438; Figure 23]. The BLA also leads both the NA [t(269)=4.4850, p<0.001] and HC [t(398)=-4.4092,p<0.001]. PFC-HC [t(279)=1.4885,p=0.1377] and NA-HC [t(373)=0.8996,p=0.3689] lags were not

significantly different from zero so directionality between these brain regions could not be determined.

3.4.2 DS+ Tone directionality

During DS+ tone presentation, in trials in which the animal responded three or more times, the NA leads the PFC [t(120)=-4.8643,p<0.001; Figure 24].

3.4.3 DS+ lever pressing directionality

During lever pressing in DS+ trials in which the animal responded three or more times, both the BLA [t(51)=2.8166,p=0.0069] and the NA lead the PFC [t(105)=-3.0195,p=0.0032; Figure 25]. Directionality between the PFC and HC [t(101)=1.5914,p=0.1147] and NA and HC [t(122)=0.1871,p=0.8519] could not be determined.

3.4.4 DS+ Drink directionality

During drinking, the NA leads the PFC [t(155)=-6.9268,p<0.001; Figure 26] but directionality between the NA and BLA could not be determined [t(92)=0.9636,p=0.3378].

3.4.5 Extinction no-response trials directionality

During extinction trials where the animal did not make a response, the BLA leads the NA [t(148)=2.4444,p=0.0157] and PFC [t(134)=1.9946,p=0.0481] while the HC leads the NA [t(372)=3.2232,p=0.0014; Figure 27]. However, directionality between the BLA and HC [t(200)=0.7184,p=0.4733] and PFC and HC [t(234)=0.9658,p=0.3352] could not be determined.

3.4.6 Extinction response trials

Directionality between the HC and NA [t(32)=-0.2984,p=0.7673] or [PFC t(26)=0.7352,p=0.4688] during extinction trials in which the animal responded could not be determined (Figure 28).

CHAPTER 4. DISCUSSION

4.1 Strain differences in behavior and physiology

Only animals which reached discrimination criteria were implanted for electrophysiological recordings. While strain differences in stimuli discrimination and intake were absent prior to implantation (Figure 8), pronounced strain differences in neural synchrony were observed (Figure 11). Wistar synchrony between the BLA and HC, NA and BLA and PFC and BLA were virtually absent. Overall, there were fewer Wistar animals, and fewer Wistar data sets (Table 1). Additionally, within Wistars, BLA and HC misses reduced the number of statistical comparisons that could be made. Visually, the comparison of PFC-NA synchrony between strains seems to suggest that strain differences in synchrony between these two regions may exist. Stronger PFC-NA synchrony in Wistars relative to P rats has been previously observed (McCane et al., in preparation), suggesting that at least in this brain region, differences observed are not likely a statistical anomaly. Interestingly, Wistars chosen for implantation did not differ from P rats in motivated behavior. Given that Wistars are the progenitor strain for P rats, it remains unclear, how physiologically similar implanted Wistars were to P rats. In the current data, behavioral differences between the two strains were absent in animals which electrophysiological recordings were obtained. However, strain differences in neural activity suggests that the overall network dynamics between the two strains are innately different. The fact that these differences are evident in Wistars that are motivated in a similar fashion as P rats supports this hypothesis. Several physiological differences between P rats and Wistars have been reported. Firstly, P rats exhibit reduced PFC DA tone relative to Wistars (Engleman et al., 2006). Additionally, mGluR2, a receptor associated with alcohol-seeking behaviors

(Bäckström and Hyytiä, 2005; Zhou et al., 2013) and AUD (Meinhardt et al., 2013) is absent in P rats (Zhou et al., 2013). Both glutamate and DA transmission play critical roles in alcohol-related behaviors. Additionally, both neurotransmitter systems are strongly impacted by ethanol exposure. Acute ethanol exposure inhibits NMDA receptor function (Hoffman et al., 1989; Lovinger et al., 1989; White et al., 1990). After repeated chronic exposure, various NMDA receptor subunits are upregulated (Hu et al., 1996; Kalluri et al., 1998; Trevisan et al., 1994), hypothesized to be a neural adaptation to ethanol's depressant effects (Gulya et al., 1991). Additionally, chronic ethanol results in increases the AMPA receptor function, resulting in a shift in the AMPA/NMDA ratio (Stuber et al., 2008a; Stuber et al., 2008b). Alterations in glutamate signaling are therapeutically relevant for cued ethanol-seeking behaviors. Glutamate antagonists attenuate ethanol cue-induced reinstatement (Bäckström and Hyytiä, 2004). Moreover, acamprosate, one of the few prescribed pharmacotherapies for alcohol dependence is believed to exert its effects via alterations in glutamate transmission (Bachteler et al., 2005). With regards to DA, chronic ethanol vapor exposure was associated with reduced DA release and increased DA reuptake in the NAc (Budygin et al., 2007; Karkhanis et al., 2015). Similar results were obtained in non-human primates who orally consumed alcohol where ethanol exposure increased striatal DA reuptake (Budygin et al., 2003). P rats may therefore exhibit altered reward-seeking neural circuitry as well as a sensitivity to neural adaptions induced by alcohol exposure. Importantly, the current work is unable to determine how ethanol exposure may interact with rodent strain to influence neurophysiology. Future studies which utilize exposure and testing with a non-psychoactive reinforcer such as sucrose may

elucidate the differences between these strains, informing our understanding of genetic and physiological contributions to an alcohol addiction phenotype.

4.2 Impaired stimuli discrimination

Only animals which reached discrimination criteria were implanted but following implantation, discrimination behavior became inconsistent, with only a subset of all data sets exhibiting stimulus criteria (Figure 8B). The anesthetic isoflurane has been observed to alter auditory processing in rats (Ruebhausen et al., 2012; Santarelli et al., 2003). Isoflurane-induced alterations in hippocampal dependent cognition have also been reported. Isoflurane exposure was associated with deficits in spatial learning (Lin and Zuo, 2011) and memory (Callaway et al., 2012). Isoflurane-associated impairments in conditioned responding were also observed (Lin and Zuo, 2011). Isoflurane-induced cognitive impairments may therefore be associated with impaired stimuli discrimination which occurred following implantation surgery.

The present experiments sought to investigate network dynamics during cued alcohol seeking. Poor discrimination, coupled with increased post-operative lever-press training, occluded the ability to assess cued reinstatement. Importantly, in the behavioral task employed, several salient cues are present. The operant box itself sets the context that alcohol may be available. Moreover, the retractable lever itself may represent a salient cue that alcohol is available. Importantly, changes in synchrony during the tone presentations were observed between the PFC and NA and synchrony between these regions seemed to be influenced by whether or not the animal responded on the lever sufficiently to acquire a reinforcer (Figure 16). Thus, while discrimination behavior was inconsistent, information regarding the cue was likely encoded by the NA and PFC. Additionally, differences in

synchrony during lever pressing following presentation of the DS+ or DS- were observed in several brain region pairs (Figure 18). This suggests that the stimuli, although not sufficient to influence consistent behavior throughout a session, still maintained some incentive motivational properties. Given the overlap in stimuli presentation (Figure 1), it is also possible that the tone and lever become a compound stimulus more salient than either stimulus alone. Synchrony observed only during lever pressing may therefore be associated with a carryover of increased synchrony during both stimuli. If this is the case, one may still conclude that behavior in the discriminative stimulus task presented here was cue-induced.

4.3 Change in basal neural synchrony

Synchronous neural activity is necessary for information exchange between neural networks. Neuron assemblies are networks of neurons linked to other neurons by reciprocal connections (Lumer et al., 1997a, b). Synchrony emerges when two neural assemblies oscillate with the same frequency and neurons with these networks fire within the same phase of the oscillation, at which time the signals are "phase locked" (Lachaux et al., 1999). Coupling of oscillations is necessary for sending and receiving information via phase synchronization (Fries, 2005). The temporal order of action potentials can influence the strength of synchrony which in turn affects whether synaptic connections are strengthened or weakened (Magee and Johnston, 1997). Thus, impaired synchrony can result in altered communication between neural networks.

In the experiments described previously, we observed that synchrony between several brain regions changed as a function of behavior (Table 3). During DS+ tone presentation, PFC-NA synchrony increases. During reinforced lever presses, NA-HC,

PFC-BLA, PFC-HC and PFC-NA synchrony are all increased, relative to basal levels. During alcohol consumption, NA-BLA synchrony is reduced while PFC-NA synchrony is increased. Because synchronized excitation between neuronal groups is necessary for information transfer, synchronized neural firing may provide a mechanism to differentiate relevant neural processing (synchronized activity) from irrelevant asynchronous neural activity or noise (Fries, 2005). Significant increases or decreases may suggest that connectivity between these regions is strengthened or weakened. Increased synchrony between two regions may suggest that their interactions contribute significantly to correlated behaviors. Conversely, weakened synchrony may indicate that the contribution of interactions between two regions becomes less important for output of the behavior observed. Importantly, disruptions in synchrony are associated with functional abnormalities result in aberrant psychopathology. For example individuals with schizophrenia exhibit impairments in stimulus-evoked neural responses relative to controls, hypothesized to be the result of aberrant synchronization between brain regions (Krishnan et al., 2005; Kwon et al., 1999). Additionally impaired synchrony has been observed in individuals with alcohol dependence and is hypothesized to be associated with addiction vulnerability (Cservenka et al., 2014a). The manner in which synchrony changes as a function of behavior, may therefore be associated with aberrant or adaptive behavioral processes.

Time-locked coordinated activity between neurons is necessary for optimal functioning of neural processes (Lumer et al., 1997b). For example, a target neuron may only become excited when it receives an adequate level of input from other neurons. If a group of input neurons fire sporadically, then the electrical summation necessary for the

target neuron to fire may never occur. In this case, the target neuron cannot be activated. Synchrony is a mechanism by which the timing of action potentials for a group of neurons can be organized in order to efficiently transfer neural signals between assemblies. As such, coordinated synchronous spiking of several input neurons may be sufficient to activate a target neuron.

If synchrony is necessary for optimal communication between neural assemblies, it follows that changes in synchrony strength may be associated with correlated behavioral observances. Differences in synchrony strength, relative to baseline may indicate exchange of information induced by behavior. Behaviorally relevant changes in synchrony between different brain regions may be associated with a myriad of influences both within and beyond the networks assessed. The behavioral consequences of alterations within discrete brain regions associated with reward have been extensively researched. An assessment of brain region pairs first in isolation and then subsequently as complex neural networks will therefore facilitate the interpretation of changes in synchrony between these networks.

4.4 Sources of synchrony and directionality

Historically, studies which inactivate a brain region and subsequently assess behavior have been used to elucidate the neural substrates of behavior. However, because these brain regions often share reciprocal connections, it is unclear if/how these regions work in concert. Moreover, such techniques make it difficult to discern what kind of information may be encoded by the inactivated regions or what compensatory mechanisms may be involved in expression of behavior following inactivation. Investigating network connectivity in vivo attempts to overcome these shortcomings. The strength of this technique is that temporal dynamics of neural activity can be assessed. Recording

simultaneous brain rhythms during behaviors allows one to infer with better precision the type of information encoded by a given circuits during behaviors. Moreover, assessing directionality can inform our understanding of how brain regions influence each other to guide behaviors. However, currently it is not feasible to record from every brain region which may be involved in a behavior, a shortcoming of the techniques employed here. Thus, while two brain regions may be entrained to one another, it remains possible that inputs from one or more brain regions onto the entrained pair drives neural synchrony. Thus, activity in two regions may be driven by a third unknown brain region and in actuality be unrelated to one another.

In the current data, lag of the peak amplitude cross correlation between two signals was used to assess directionality (Adhikari et al., 2010a). Importantly, suboptimal lags are associated with impaired efficacy of inputs from one region to another (Hermans et al., 2014). In some cases, directionality could not be determined (Table 5). This could result from several possibilities. Firstly, high variation in the peak lags could result in a mean close to zero. Additionally, too few or too weak signals could diminish power, making it difficult to detect oscillation lead between two brain regions. Lastly, an inability to determine directionality may indicate the one brain region does not lead another but instead both brain regions are entrained by substrates not recorded from. Lags near zero can be the result of common drive from a single source (Fischer et al., 2006).

DA inputs from the VTA can modulate NA activity. Tonic DA in the NA may modulate neural inputs presynaptically (Floresco, 2015). Nicola (2007) proposes a model in which NA neurons encode associations between stimuli and behavioral responses with DA facilitating action selection by increasing the firing of neurons which represent the

optimal stimulus-action association. DA can inhibit or activate NA activity depending on receptor subtype (Neve et al., 2004). Additionally, DA can also influence firing of the cortico-limbic inputs, indirectly influencing activity within the NA (Floresco, 2015).

Differences in DA activity in the striatum are associated with alcohol-seeking behaviors in both clinical and preclinical populations. DA levels in the NA are hypothesized to play a role in ethanol preference (Quintanilla et al., 2007). In rodents, alcohol-paired cues increase DA release in the NA (Katner et al., 1999). Naltrexone, a Food and Drug Administration (FDA) approved pharmacotherapy for treatment of AUD (Anton et al., 2004; O'Malley et al., 1995) reduce alcohol stimulated DA release in the NA (Benjamin et al., 1993; Gonzales and Weiss, 1998) and decreased alcohol cue-induced activation of the ventral striatum (Myrick et al., 2008). Lastly, DA D2 receptor availability in the striatum is associated with alcohol craving severity (Heinz et al., 2004) and individuals with AUD exhibited lower striatal DA release (Volkow et al., 2007) and DA D2 receptor availability (Heinz et al., 2004) relative to controls.

All of the brain regions recorded from are innervated by neurons originating in the VTA (Swanson, 1982). Moreover, DA activity is heavily implicated in expression of reward seeking behaviors (Baik, 2013; Hyman et al., 2006). While the VTA was not recorded from in the current experiments, future experiments may investigate how activity within the VTA is associated with activity in the circuits discussed here.

The thalamus shares connections with the both cortical and subcortical substrates (Haber and Calzavara, 2009; Palmer et al., 2001). Importantly, the thalamus is positioned to modulate zero phase coupling (Sherman and Guillery, 2002; Viriyopase et al., 2012). When two populations of neurons are bidirectionally linked, a third may redistribute

common activity of the two resulting in a phase lag of zero (Vicente et al., 2008). Importantly, the thalamus is hypothesized to induce and stabilize zero phase lag synchronization between coupled neural assemblies (Llinas et al., 1998; Sherman and Guillery, 2002). Disruption in thalamo-circuits connecting is hypothesized to be associated with craving and loss of control in alcoholism (Modell et al., 1990). Additionally, the thalamus is active by alcohol paired stimuli in alcohol dependent subjects (George et al 2001), further suggesting that connections with this region may play a role in cue-elicited alcohol-seeking behaviors. Future studies may explore how thalamic nuclei influence oscillations between cortical and subcortical regions.

4.5 BLA-HC synchrony

Overall, synchrony between the BLA and HC was not behaviorally relevant during conditioning but was observed to weaken during inhibition of responding in extinction, relative to basal (Figure 21) and conditioning levels (Figure 22). In isolation, the BLA is hypothesized to play a role in assigning value to conditioned stimuli (Killcross et al., 1997) while the HC is important for modulating salient memories (Sanders et al., 2003). Furthermore, interactions between these two regions are hypothesized to be important for memory formation (Cahill and McGaugh, 1998). If BLA-HC connections are necessary for memory processes regarding the value of conditioned stimuli, an association between poor stimuli discrimination and weak BLA-HC synchrony is unsurprising. Given the inability of animals to consistently discriminate between stimuli, low BLA-HC synchrony may reflect deficits in memories regarding the conditioned stimuli.

In the context of learning, extinction is not the erasure of the original memory but instead the generation of new inhibitory memory which can attenuate conditioned

responding (Quirk and Mueller, 2007). During extinction, activity within the BLA is hypothesized to be associated with inhibition of expression of conditioned responses while HC activity may be associated with contextual modulation of that inhibition (Quirk and Mueller, 2007). Importantly, the BLA is observed to also play a role in extinction of both fear and appetitive-linked stimuli (Everitt et al., 2003; Lindgren et al., 2003; Quirk and Mueller, 2007). Regardless, attenuation of BLA-HC synchrony during extinction, relative to conditioning may therefore reflect information transfer related to the establishment of a new inhibitory memory (extinction). Synaptic plasticity in the HC is reduced by amygdala lesions (Ikegaya et al., 1995b) and facilitated by BLA stimulation (Ikegaya et al., 1995a). Seidenbecher et al. (2003) hypothesized that amygdala-hippocampal theta activity promotes or stabilizes synaptic plasticity related to conditioned memories. In support of this hypothesis, functional disconnection of the BLA and vHC blocked renewal of fear (Orsini et al., 2011). Furthermore, inactivation of the BLA or vHC before extinction training attenuated conditioned responding while inactivation of these regions during extinction training impaired extinction memory, indicating that both the vHC and BLA are necessary for extinction memory and expression of conditioned behaviors (Sierra-Mercado et al., 2011). Collectively, these data suggests connections between these brain regions convey information about conditioned memories. During extinction, if a new inhibitory memory is formed, one might expect an increase in BLA-HC synchrony, relative to conditioning, which was not observed. Moreover the effect of behavioral task on BLA-HC synchrony was visually unimpressive. During baseline, the BLA leads the HC but directionality between these regions during extinction could not be determined. This may suggest impaired connectivity between these regions in extinction. Given the importance

of BLA-HC interactions in extinction, weak effects observed here may be associated with compensatory inputs to either the HC, the BLA or both. Lastly, differences in BLA-HC synchrony were observed only during lever pressing epochs. Differences in synchrony during tone presentation may have yielded more convincing evidence of involvement of these regions in the current behavioral task. Importantly, after implantation, discrimination between stimuli was attenuated. BLA-HC synchrony which did not differ from basal synchrony may indirectly suggest that BLA-HC connections are important in memories of salient appetitive stimuli. It is possible that stronger BLA-HC synchrony may have been observed if animals had performed at pre-surgery levels.

Context can be a strong modulator of behavior. Moreover, hippocampal-amygdala connections are important for contextual modulation of neural activity during reward seeking (Wells et al., 2011) and extinction (Maren and Hobin, 2007; Orsini et al., 2011). Here we report that synchrony between the BLA and vHC was relatively weak overall. In the current behavioral paradigm, outcomes are strongly mediated by presentation of discrete auditory cues. More specifically, the reinforcers could only be attained if a sufficient operant response was made following one of the two stimuli. While context may represent an integrated summation of discrete cues (Maren et al., 1998; Nadel and Willner, 1980), contextual learning is hypothesized to differ from learning associated with discrete cues (Holland and Bouton, 1999). Moreover, HC activity is hypothesized to be essential for contextual learning, but not necessarily discrete cue learning (Holland and Bouton, 1999). Additionally, hippocampal lesions modulate context dependent behaviors (Maren et al., 1998; Winocur and Olds, 1978), suggesting that HC activity is associated with contextual manipulations. Inactivation of the vHC blocks context induced drug seeking

(Lasseter et al., 2010). In the experiments described herein, discrete auditory cues signal that alcohol may be made available. Thus, under conditions where context was manipulated to predict availability of alcohol, stronger synchrony between the vHC and BLA may have been observed.

4.6 NA-BLA synchrony

At both baseline (Figure 23) and during extinction (Figure 27), the BLA leads the NA, consistent with previous findings that the amygdala modulates activity in the NA (Ambroggi et al., 2008; Jones et al., 2010; Jones et al., 2008).

In isolation, the NA is implicated in motivated responses where the BLA is associated with stimulus-reward associations (Baxter et al., 2000; Everitt et al., 1991). Connections between these two regions are hypothesized to play a role in limbic activity mediated control over behavioral output (Everitt et al., 1991). Functional disconnection of the BLA from the NA abolishes conditioned place preference, suggesting that interactions between these two regions are important for incentive cue elicited approach behaviors (Everitt et al., 1991; Simmons and Neill, 2009). Moreover, functional disconnection of the NA and BLA blocked acquisition of second order conditioning, further suggesting that information about the motivational value of conditioned stimuli is mediated, at least in part, by BLA-NA connections (Setlow et al., 2002). Additionally, context-induced renewal is blocked by disrupting communication between the BLA and NA (Chaudhri et al., 2013). Disconnecting the BLA from the NA also impaired rats' ability to reduce responding for a devalued reward (Shiflett and Balleine, 2010).

While BLA-NA connections are hypothesized to modulate stimulus value associations linked to instrumental behaviors (Baxter et al., 2000), the current data suggest

that in P rats, BLA-NA connections are more generally involved in post-responding processes. Specifically, BLA-NA synchrony did not differ from baseline during lever pressing in the conditioning phase (Figure 13). However, whether or not an animal chose to make a response had a significant effect on NA-BLA synchrony during the post-lever availability time where a reinforcer might be expected (Figure 18). If an animal chose to make a response, NA-BLA synchrony was markedly lower, compared to inhibition of responding during the same epoch.

Dysfunctional activity within the BLA of P rats may be associated with response-driven changes in synchrony observed during conditioning. In the present experiments, DS+ induced changes in BLA-NA synchrony are not evident. However, BLA-NA synchrony may have a more pronounced role in processing information pertaining to the lever. Specifically, P rats may attribute preferential salience to the presentation of the lever over the tones and this effect may be associated with dysfunctional activity within the BLA. BLA-NA connections may therefore drive responding, regardless of discriminative stimulus type. Differences in BLA-NA synchrony are observed after the lever is no longer available but not during lever pressing or tone presentation, (Figure 18) further suggesting processes between the NA and BLA may be impaired. Additionally, BLA to NA directionality is evident prior to stimuli presentation but could not be determined during behavioral conditions, a deficit which may be linked to impaired BLA-NA processing.

BLA-NA synchrony is lower in extinction, relative to conditioning during inhibition of responding. It is possible that BLA-NA connections are behaviorally associated with inhibition of responding, with reduced connectivity between these regions resulting in greater inhibition. However, since blocking BLA-NA information exchange

results in a reduction of cued responding (Chaudhri et al., 2013) this is unlikely. Another potential explanation is that input from the BLA to the NA is associated with a drive to respond but competes with input to the NA from other brain regions. Relative to BLA input, the NA, receives stronger HC input during response inhibition (See discussion NA-HC) which may convey information which drives reward-seeking activity. Stronger competing input from the HC could also explain low BLA-NA synchrony. Low BLA-NA synchrony during response inhibition may also be associated with processes related to discriminative stimulus presentation. In the present experiments, NA-BLA synchrony is not associated with differences in stimuli discrimination. Given previous findings that BLA-NA connections are important for encoding information about the incentive value of stimuli (Setlow et al., 2002), these data may suggest a neural mechanism associated with poor overall stimuli discrimination observed after surgery. Therefore, another byproduct of weak NA-BLA synchrony may be diminished value assigned to the auditory stimuli.

Several lines of study suggest that theta oscillations are implicated in rewarding processes (Gruber et al., 2013; van Wingerden et al., 2010). However, gamma oscillations in the BLA may be important to modulating BLA projections. BLA-striatal coupling may preferentially occur in the gamma frequency band (Popescu et al., 2009). Additionally, increased BLA LFP power in the gamma frequency range was observed following presentation of a conditioned stimulus compared to an unconditioned stimulus (Fenton et al., 2013). Inactivation of the BLA alters gamma oscillations in the NA (Popescu et al., 2009). Moreover, gamma oscillation strength is associated with learning and is hypothesized to induce synaptic plasticity (Bauer et al., 2007; Popescu et al., 2009). Optogenetic stimulation of the BLA in the gamma frequency range was also observed to

modulate memory consolidation (Huff et al., 2013). Increased gamma synchrony between the BLA and the striatum was associated with learning and memory (Popescu et al., 2009). Null behavioral effects on BLA-NA synchrony during stimuli presentation in the current data may therefore suggest synchrony between these brain regions occurs in a different frequency band.

Collectively, these findings suggest that impaired connectivity between the BLA and NA may be associated with aberrant response strategies. Because of group sizes, the current experiments did not compare strain differences in synchrony and correlated behavior. Future studies may employ a Wistar control group to better understand how activity between the BLA and NA may differ in a non-addiction-vulnerable model.

4.7 NA-HC synchrony

Hippocampal modulation of NA activity has been reported (Goto and O'Donnell, 2001) and is hypothesized to be associated with goal-directed actions. The NA can be modulated by hippocampal input via glutamatergic projections, influencing both NA DA transmission (Blaha et al., 1997; Floresco et al., 2001) and regulation of locomotor activity (Brudzynski and Gibson, 1997). Hippocampal pharmacological manipulations which induced locomotor activity were blocked by antagonizing glutamate receptors in the NA (Mogenson and Nielsen, 1984). Moreover, inactivation of the HC enhances amphetamine induced locomotor activity (Everitt et al., 2001), which is dependent on NA DA tone (Whishaw and Mittleman, 1991). Additionally, HC lesions potentiate amphetamine-induced locomotor activity and extracellular NA DA (Wilkinson et al., 1993). Importantly, DA plays a critical role in motor function (Pijnenburg et al., 1976) and accumbal DA is associated with goal directed actions (Owesson-White et al., 2016). In the current data,

synchrony between the NA and HC was stronger than synchrony between all other brain regions during lever pressing (Figure 19 A). This may indicate that in motivated subjects, synchrony between these two brain regions exerts the greatest influence on instrumental responding during the conditioning phase.

Synchrony between the NA and HC may reflect learning related to goal directed actions. Increased striatal-hippocampal theta synchrony was observed during decision making in rats which learned a maze task, relative to those which did not (DeCoteau et al., 2007). Greater synchrony is observed during extinction, relative to conditioning (Figure 22). Additionally, synchrony most notably differs by task (conditioning or extinction) when an animal inhibits a response in the lever pressing epoch. Cognitive impairments following isoflurane exposure were observed to mediate the retrieval of conditioned memories (Callaway et al., 2012; Lin and Zuo, 2011). During extinction, a new inhibitory relationship between the lever pressing and reinforcement acquisition must be learned. Greater NA-HC synchrony may therefore be associated with new learned behavioral responses during extinction. This finding would support the hypothesis that NA-HC connections are be important for relapse (Kalivas and Volkow, 2005). Induced theta stimulation in the HC elicited reinstatement of cocaine seeking, an effect hypothesized to be associated with hippocampal modulation of NA DA tone (Vorel et al., 2001).

While it is hypothesized that HC modulation of NA activity reflects goal directed learning, the role of NA-HC synchrony in the P rats is less clear. In the present data, NA-HC synchrony during tone presentation is stronger on days where the animal shows correct discrimination compared to days where the animal behaves below criteria (Figure 16 B2). Synchrony between the NA and HC during lever pressing also seems to be influenced by

the discriminative stimuli which preceded lever availability (Figure 17 A). Interactions between the NA and HC are hypothesized to be critical for learning behavioral strategies (Belujon and Grace, 2015). Moreover these learned strategies may be cue dependent. Animals that exhibit preferential conditioned approach to conditioned stimuli are known as sign trackers while animals which preferentially attend to unconditioned stimuli are known as goal trackers. Sign trackers release more DA in the NA relative to goal trackers (Flagel et al., 2011; Saunders and Robinson, 2012). This difference in DA transmission is hypothesized to reflect an enhanced attribution of incentive to reward-paired cues in sign trackers (Fitzpatrick et al., 2016). Lesioning the vHC during acquisition of conditioned approach decreased sign tracking behavior and increased goal tracking (Fitzpatrick et al., 2016). Dampening vHC input to NA may disrupt NA signals associated with conditioned approach to reward-related stimuli (Fitzpatrick et al., 2016). If this is the case the strengthening HC input to NA may result in enhanced conditioned responding. Thus, in the P rat, synchrony between the HC and NA may play a role in cued responding for rewards.

Theta oscillations are found throughout the brain but are most prominent in the HC, a brain region which modulates striatal firing (Lansink et al., 2009; Lansink et al., 2016; van der Meer and Redish, 2011). Theta oscillation power in the vHC was higher during cued, compared to non-cued approach to reward locations (Lansink et al., 2016). Importantly, Lansink et al. (2016) observed that theta activity was highest when the animal had already initiated its approach action and not during cue presentation. However, in the present data, synchrony between the NA and HC is influenced by discriminative stimulus type, albeit not necessary during presentation of the auditory stimuli. NA-HC theta

synchrony may be associated with maintenance or cessation of goal directed action but not initiation. Information about the stimuli which precede the action may be the result of input from other brain regions such as the BLA to the HC. Thus, while theta oscillation synchrony between the HC and NA may encode information about behavioral responses, these regions may also, in some part, encode information about the stimuli which precede the action.

4.8 PFC-BLA synchrony

BLA input to the PFC is important for encoding of conditioned stimuli (Laviolette et al., 2005) (John et al., 2013). Functional disconnection of the BLA and mPFC impaired expression of fear conditioning (Stevenson, 2011). Moreover, increased activity evoked by presentation of conditioned stimuli occurs in mPFC neurons which receive BLA input and this response is attenuated by inactivation of the BLA (Fenton et al., 2013), further suggesting that BLA-mPFC interplay is critical for associative learning. Importantly, synchrony between the BLA and PFC during reinforced lever pressing trials following presentation of the DS+ was weaker than all other brain region pairs during this epoch. Additionally, BLA-PFC synchrony during DS+ tone presentation does not differ from basal activity. The mPFC is hypothesized to be integral for encoding information related to action execution (Simon et al., 2015). If the role of the BLA in conditioned responding is to assign value to stimuli, the PFC may integrate this information, together with other sensory inputs, to mediate instrumental responding. John et al. (2013) posit that the amygdala may integrate sensory information and segregate this information by salience before conveying information regarding salience to the PFC which in turn integrates information to inform executive function. The interactions between the mPFC and BLA

are therefore hypothesized to link assignment of incentive value to instrumental contingencies (Baxter et al., 2000; John et al., 2013). An absence of a DS+-evoked change in synchrony coupled with observed weak synchrony during lever pressing may be associated with inconsistent discrimination observed after surgery. This hypothesis is supported by the observation that synchrony between the PFC and BLA doesn't differ from basal levels during tone presentation in contrast with previous observations that coordinated activity between the BLA and PFC is necessary for conditioned auditory (Sotres-Bayon et al., 2012) and olfactory (Laviolette et al., 2005) responses. An effect of stimulus type for reinforced trials was observed during lever pressing where synchrony was higher during conditioning lever pressing relative to lever pressing which occurred during extinction. Changes in synchrony during lever pressing but not DS+ presentation may suggest attribution of salience to the lever over the DS+ tone. However, it is possible that the DS still has some influence over neural activity between the BLA and PFC because greater synchrony during lever pressing was observed following the DS+ compared to the DS-.

During lever availability, when P rats inhibited their responding, synchrony was higher during the extinction phase relative to the conditioning phase (Figure 22 D). Connectivity between the BLA and PFC has been shown to be critical for flexible behavioral responses to reward (Baxter et al., 2000). In isolation, the BLA is hypothesized to form associations between environmental stimuli paired with reward and incentive value (Baxter and Murray, 2002). In contrast, the PFC plays a role in representation of these environmental stimuli (Baxter and Murray, 2002), which may in part be influenced by BLA input, but also, other limbic structures. If BLA input encodes information regarding

stimulus value, increased synchrony in extinction relative to conditioning may be associated with updated representation of the value of the lever. P rats are consistently observed to exhibit behavioral impulsivity and disinhibition (Beckwith and Czachowski, 2014; Beckwith and Czachowski, 2016; Linsenbardt et al., 2016). Given the poor level of discrimination, responding behaviors may reflect compulsive pathology. This compulsive responding, regardless of outcome may explain a lack of difference between PFC-BLA synchrony during active lever pressing in extinction and conditioning. Inhibition of responding may be a cognitively and physiologically more demanding task, necessitating activation of the PFC-BLA. Differences in conditioning and extinction during inhibition of responding in the presence of the lever may therefore reflect an updated stimulus value association in P rats.

4.9 PFC-HC synchrony

Phase locking of PFC neurons to HC theta oscillations have been observed on multiple occasions (Hyman et al., 2005; Jones and Wilson, 2005; Siapas et al., 2005) and are associated with completion of memory tasks (Hyman et al., 2005), and exchange of spatial information (Jones and Wilson, 2005). In the context of reward seeking, HC input to the PFC is hypothesized to occur during the encodings of a memory associated with a goal directed behavior (Colgin, 2011). Greater PFC -HC entrainment was observed after learning a behavioral task (Benchenane et al., 2010), further illustrating a role for information transfer between these two regions in acquisition of learned behaviors. It is therefore possible that stronger HC-PFC synchrony may have been observed during the initial learning of the conditioning task. However, greater overall synchrony during extinction, compared to conditioning was observed (Figure 22 E). This increase in

synchrony during extinction might be explained by the learning of a new stimulus-outcome association or memory, supporting the hypothesis that HC-PFC synchrony is important for reward seeking learning and memories.

PFC-HC synchrony is stronger during responding compared to non-response (Figure 22 E), with response differences observed following DS+ but not DS- presentation during the conditioning phase (Figure 17 C). Hippocampal theta oscillations have been shown to be associated with locomotor activity (Sławińska and Kasicki, 1998) and behavioral responses (Hasselmo, 2005). HC theta involvement in behavioral response and connections with the NA, suggest increased HC-PFC synchrony in the P rat may be associated with compulsive responding (see discussion, NA-HC synchrony). In fear conditioning, hippocampal-mPFC theta synchrony was increase during recall of extinction (Lesting et al., 2011). Similarly, in the appetitive task employed here, HC-PFC was stronger during extinction (Figure 22). Theta synchrony between the PFC and HC may therefore play an important role mediating extinction behaviors.

4.10 PFC-NA synchrony

MPFC connections to the NA are hypothesized to play a role in drug craving (Koya et al., 2009). More specifically, PFC-NA connections are hypothesized to underlie alterations in incentive motivation to reward-paired stimuli which may lead to craving. Connectivity between the ventral striatum and PFC have been linked to craving, with poorer connectivity correlating with stronger measures of craving in alcohol-dependent subjects (Park et al., 2010). Additionally, dysfunctional connectivity between these two regions has been associated with dependence severity (Courtney et al., 2013). Frontal-striatal dysfunctional connectivity has also been documented in both FH+ and alcohol-

dependent individuals (Courtney et al., 2013; Heitzeg et al., 2010; Park et al., 2010). Biased approach to alcohol stimuli in alcohol-dependent subjects was associated with an increased BOLD response in the NA and mPFC (Wiers et al., 2013). Lastly, adaptations that specifically occur between the PFC and NA are hypothesized to be strongly linked to enhanced cue reactivity to drug-paired stimuli (Kalivas and Volkow, 2005; Kalivas et al., 2005). In the current data, only PFC-NA synchrony was different from baseline during presentation of the discriminative stimuli (Figure 14).

The current data support the aforementioned role of PFC-NA connectivity in stimuli-evoked reward seeking. During DS+ presentation, only synchrony between the PFC and NA was statistically distinguishable from baseline (Figure 13). DS-evoked changes in PFC-NA synchrony appear to have lasting effects on synchrony cross behavioral epoch. For conditioning trials, PFC-NA synchrony remains moderately elevated from baseline during lever availability (Figure 18) and following lever pressing where a reward may be available (Figure 19). In extinction, where the DS is absent, PFC-NA synchrony is not different from baseline (Figure 21). These data support previous findings that activity between the PFC and NA is important for encoding information about conditioned stimuli which influences behavior.

Relapse is hypothesized to be mediated by an interaction between neural changes induced by drug use and conditioned cues (Yalachkov et al., 2012). In preclinical models, reinstatement is hypothesized to model cue-induced relapse of drug-seeking behaviors. Optogenetic inhibition of the PL fibers projecting to the NAc reduced reinstatement responding (Stefanik et al., 2013). Similar results have been obtained elsewhere where functional disconnection of the PFC and NA impairs expression of cocaine cue-induced

reinstatement (McGlinchey et al., 2016). Inputs from several substrates are hypothesized to converge on the PFC which in turn drives reinstatement behavior (Rebec and Sun, 2005). Cue-evoked activation of PFC neurons during drug self-administration has been observed and PFC to NA projections are hypothesized to be necessary for expression of reinstatement (Rebec and Sun, 2005). While reinstatement was not assessed in the current experiments, one might hypothesize that PFC-NA synchrony would be enhanced relative to baseline and extinction. These data would strengthen the hypothesized role of PFC-NA connections in stimuli driven reward-seeking responses. Moreover, aberrations between these regions may represent addiction and relapse vulnerability. A direct comparison with Wistar rats or other outbred species may elucidate the manner in which activity between these regions is associated with cued reward seeking.

While synchrony between the PFC and NA is hypothesized to be associated with a neural representation of the discriminative stimuli which drives behaviors, PFC-NA synchrony does not appear to be influenced by stimuli type. Rather, synchrony between these regions is stronger for trials in which an animal response (Figure 16 B1). However, lack of PFC-NA synchrony in extinction lever pressing indicates that these regions are not merely driving response behavior but rather are under the influence of the discriminative stimuli in some capacity. Input to the PFC from other regions, such as the BLA may play a more notable role in stimuli discrimination (see discussion, BLA-PFC). Importantly, the presence of either DS tone is sufficient to evoke changes in PFC-NA synchrony and may be the impetus which determines whether or not an animal will later make a response. Increased synchrony evoked by the DS tone, and remains high during lever pressing and after the lever is no longer available (Figure 14 F), supporting this hypothesis.

4.11 Network interactions across behaviors

During presentation of the DS, only synchrony between the PFC and NA is different from baseline levels with stronger synchrony observed in trials in which the animal made a response, relative to those in which a response was inhibited. Interestingly, the PFC was led by the NA. To date, anatomical and physiological studies investigating PFC-NA connections have failed to report evidence that the NA inputs to the PFC. However, the NA can influence activity in the PFC indirectly. The PFC receives information from the striatum via thalamic nuclei and in this way, striatal modulation of the cortex may occur (Albin et al., 1989; Barbas and Zikopoulos, 2007; Oldenburg and Sabatini, 2015). However, the indirect influence of the NA over the PFC is not likely to occur within the span of three to four milliseconds. Given that both regions are innervated by VTA neurons, it is possible that stronger VTA to NA inputs compared to VTA to PFC inputs resulted in the appearance that the NA is driving PFC activity. It is also possible that PFC inputs to the NA compete with VTA inputs to the NA, obscuring PFC signals which precede NA signals.

The PFC is hypothesized to integrate and disseminate information necessary for cognitive and executive function (Miller, 2000). Importantly, the PFC is believed to exert "top down" control over other brain regions (Miller, 2000). PFC projections to the NA are involved in cued reward seeking (Stefanik et al., 2013) but these data suggest NA activity may precede PFC activity, especially during neural processing of salient stimuli. The PFC is integral for executive function (Aron et al., 2003; Floresco et al., 2008) where the NA is involved in goal directed actions (Cardinal et al., 2002; Ito et al., 2004; Parkinson et al., 1999). In conjunction with these observations, the current data, suggests that in P rats,

synchrony between the PFC and NA may be associated with decision to respond or response initiation (Figure 29).

During lever pressing DS+ but not DS-, synchrony was stronger between the NA and HC, PFC and HC and PFC and BLA. Additionally BLA and NA inputs to the PFC were evident during the DS+ lever pressing epoch, further implicating limbic input to the PFC in guiding reward-related responses. Thus, in the present work, BLA and NA inputs to the PFC may convey information related to the maintenance of responding. During extinction when an animal inhibits a response, synchrony between the NA and HC and BLA and PFC is elevated, compared to during inhibition of response during conditioning. Conversely, NA-BLA synchrony is reduced when a response is inhibited during extinction, relative to conditioning. For both the NA and HC and the PFC and HC, synchrony is stronger overall during extinction, relative to conditioning, suggesting hippocampal inputs to the NA and PFC are involved in expression of behaviors during extinction. More specifically, BLA and NA inputs to the PFC which may promote response maintenance in conditioning, in extinction may be necessary for response inhibition.

Given the association between HC activity and contextual processing (Quirk and Mueller, 2007), it is not surprising that HC activity during extinction is increased relative to during conditioning. In the absence of both tone and reinforcer, the neural representation of the lever and its perceived value may change. These data suggest the mechanism by which this stimuli value update occurs is via hippocampal inputs to the PFC and NA. Lastly, in the current data, differences in synchrony were observed when an animal responded or did not respond but not perceivable differences in the availability or absence of an ethanol reward were no present. Following lever availability, NA-BLA and PFC-NA

synchrony was not influenced by reward consumption but instead by whether or not a P rat made a response. Interestingly, synchrony is stronger between the PFC and NA in trials where the animal made a response while NA-BLA synchrony was stronger in trials where P rats inhibited responding. This may suggest that connections between the PFC and NA and BLA and PFC are associated with response cessation. More specifically, BLA inputs to the NA may convey information about the value of stimuli linked with reward seeking where the NA conveys information about response strategy.

The current data suggest the NA may influence instrumental response through connections with the PFC, HC and BLA. Moreover, these data suggest that NA inputs and likely HC inputs to the PFC are also involved in initiation and maintenance of reward-seeking responses (Figure 29). Stimulation of the BLA results in an increase in extracellular glutamate and DA in the PFC and to a smaller and delayed increase in glutamate and DA respectively, in the NA (Jackson and Moghaddam, 2001). Differences in evoked glutamate and DA transmission within these regions are hypothesized to reflect strong PFC-BLA connections and a modulatory role of the PFC over NA output (Jackson and Moghaddam, 2001). Moreover, BLA activity has been observed to induce mPFC to NA neuronal activity (McGinty and Grace, 2008) and influence cued reward seeking (Stefanik and Kalivas, 2013), further implicating coordinated activity between these regions in reward seeking behaviors. Directionality analyses in the current work support this hypothesis. Goto and O'Donnell (2001) hypothesized that HC afferents gate PFC-NA information flow, while (Belujon and Grace, 2008) posit that the PFC exerts control over NA-HC activity. In the present data, HC to NA inputs may be modulated by PFC to NA inputs whose activity follows that of NA-HC (Figure 29). The HC is hypothesized to be

important for the forming and retrieving of memories where the PFC encodes features of these memories and operates with flexibility to initiate behavioral output (Preston and Eichenbaum, 2013) , likely via projections to the NA. The PFC receives input from the HC and BLA. BLA input to the PFC is mostly excitatory during conditioning responding where the vHC input to the PFC is inhibitory (Sotres-Bayon et al., 2012). An inability to determine directionality between the HC and PFC may suggest maladaptive alterations within this circuit in the P rat, although the control necessary to test this hypothesis is absent in the current data.

4.12 Caveats and future directions

4.12.1 Caveats and shortcomings of the behavioral model

Animals were trained to discriminate between two stimuli for access to ethanol. Relative to lever-pressing following the DS+, lever-press activity for the DS- was limited. For DS+ pressing, alcohol would become available after three presses, thereby halting future lever presses. In contrast, an animal could make DS- lever presses for 10 seconds, with no consequences following three presses. As such, it was easier for animals to acquire more presses for the DS- than the DS+. Thus, the criteria which compares lever pressing for the DS+ with lever pressing for the DS- may have been inaccurate. A more balanced design may have included retraction of the lever after three presses, regardless of stimuli type. However, while this would equalize the total number of lever presses allowed for the discriminative stimuli, the movement of the lever itself may become distracting during alcohol exposure. Moreover, if the lever itself acquires salience, lever movement prior to alcohol exposure may complicate interpretations of neural activity during drinking. However, this could be solved by implementation of an inter-stimulus interval.

The current model chose to extinguish the operant response by removing both the DS and the reinforcer. This was done for the purpose of reintroducing the DS to assess cue-induced reinstatement. Reinstatement can also be induced via drug prime or stress. Importantly, different neural substrates are associated with these different forms of reinstatement (Bossert et al., 2013). A weakness of this model is its inability to extinguish stimuli. In the current data, it is unclear how the neural representation of the cue changes when it is no longer paired with alcohol. If reinstatement is not the primary behavioral outcome, future studies may instead, present the auditory tones in the absence of reinforcers to better understand how cues are processed in alcohol-seeking populations.

4.12.2 Alternative approaches

The current experiments assessed connectivity by measuring phase-locking of two signals and directionality by computing cross correlation peak lags between the amplitudes of two signals. Alternative approaches may have yielded different results and should be considered by future studies.

To determine both directionality and synchrony, bivariate analyses were conducted where brain regions were assessed in pairs. This is a common technique because bivariate connectivity analyses are easier to conceptualize, interpret and test (Cohen, 2014). However, most brain connectivity is hypothesized to be multivariate (Cohen, 2014). For example, a temporal lag between two brain regions may be detected but each may be entrained by a third region to different degrees. This would result in a false sense of directionality between the first two brain regions. A technique which can be applied to multivariate networks is granger causality. Granger causality tests the predictability of one signal from another at a given time (Cohen, 2014). This technique ignores simultaneous

connectivity and is less sensitive to volume conductance (Cohen, 2014). Granger causality has been criticized by some for its mathematically complex nature which may obscure an individual's ability to understand what they are computing (Adhikari et al., 2010a). Moreover, granger causality analyses do not generate an estimate of the time lag between signals (Adhikari et al., 2010a). This is important because time lags can be compared to conduction velocities to determine the feasibility of observed directionality.

Another technique to investigate network dynamics is mutual information analyses. Mutual information detects the shared information between two variables. Mutual information can detect both linear and nonlinear relationships, but it cannot determine whether a relationship is linear, nonlinear, positive or negative (Cohen, 2014). Mutual information is also sensitive to the amount of data points as too few can inflate your estimates of mutual information due to the fact that you cannot have negative mutual information (Cohen, 2014). Not surprisingly, noisy signals decrease estimates of mutual information (Cohen, 2014), another factor to be considered when employing this analysis. Importantly, this technique has been employed to assess functional connectivity in the brain (Chen et al., 2008).

The current analyses used amplitude to assess directionality, however, phase based and power based analyses have the potential to yield different results (Cohen, 2014). Importantly, power-associated measures of connectivity are frequently employed in clinical populations (Cohen, 2014), and as such, preclinical models which use these techniques can be translational. The techniques discussed previously have both strengths and weakness. Regardless, these techniques should be considered for future analyses to better understand and interpret the current data set.

14.12.3 Alcohol exposure induces neural alterations

Chronic ethanol exposure is hypothesized to induce long lasting neural alterations which influence ethanol seeking and taking behaviors (Breese et al., 2011). In rodents, chronic ethanol exposure increases ethanol preference (Hölter et al., 1998) and consumption (Hölter et al., 1998; Roberts et al., 2000; Schulteis et al., 1996; Valdez et al., 2002). Additionally, rodents with chronic ethanol exposure maintain high levels of ethanol intake despite the addition of an aversive tastant or the option of a highly palatable solution (Spanagel et al., 1996). This suggests that a history of ethanol exposure may decrease flexibility of ethanol drinking behaviors or induce a loss of behavioral control (Spanagel et al., 1996), which are hallmark features of addiction (Goldstein and Volkow, 2002). Moreover, chronic alcohol exposure induces alterations in glutamate signaling (Clapp et al., 2008; Floyd et al., 2003), which is hypothesized to enhance alcohol-paired cue responsivity (Wackernah et al., 2014). In addition to identifying the critical neural substrates for cue-evoked alcohol seeking, it is necessary to determine if and how exposure to alcohol may alter neural processes within these regions in future studies.

An interaction between conditioned drug cues and drug-induced neural adaptations is hypothesized to mediate relapse (Wackernah et al., 2014; Yalachkov et al., 2012). The ability of cues to invigorate ethanol seeking (Gilman et al., 2008) behaviors persists even after extended abstinence of ethanol use (Bienkowski et al., 2004). Persistent alterations induced by ethanol exposure may account for these lasting effects. Chronic ethanol use results in an upregulation of glutamatergic NMDA receptors (Gass and Olive, 2008; Kroener et al., 2012), and glutamate receptor antagonists attenuate cue-induced reinstatement of alcohol seeking (Bäckström and Hyytiä, 2004). Additionally, cue-induced

ethanol seeking was correlated with an increase in extracellular glutamate in limbic and striatal regions (Gass et al., 2011), suggesting an association between prolonged exposure to ethanol and cue-evoked motivated behaviors.

Current attempts to determine the role of ethanol exposure on cue-modulated behaviors has yielded mixed effects. Alcohol exposure is reported to induce deficits in reversal learning, behavioral flexibility and fear extinction (Badanich et al., 2011; Borde and Beracochea, 1999; Holmes et al., 2012; Kroener et al., 2012; Trantham-Davidson et al., 2014). Additionally, chronic ethanol exposure was reported to enhance conditioned place preference and inhibit extinction of conditioned place preference (Moreira-Silva et al., 2014). Lastly, null effects of ethanol exposure on reinstatement have been reported (Ciccocioppo et al., 2003; Rodd-Henricks et al., 2002). Importantly, while ethanol exposure failed to enhance reinstatement, pharmacological attenuation of reinstatement was more efficacious in animals with a history of ethanol exposure (Ciccocioppo et al., 2003), suggesting ethanol exposure induced clinically relevant neural alterations.

Collectively these data suggest that exposure to alcohol can have behavioral and physiological ramifications. Future studies should therefore utilize control groups to determine how ethanol exposure both chronically and acutely impacts neural circuitry of cued reward seeking.

4.12.3 Genetic vulnerability influences neural activity

AUD is highly heritable (Cloninger et al., 1981) and genetic susceptibility factors are thought to significantly contribute to development of alcohol dependence (Froehlich, 2010). In the current experiments, lack of statistical power precluded an ability to determine whether or not changes in synchrony observed in P rats were maladaptive or

associated with the P rat phenotype. This comparison is important given that the P rat is a model of AUD, hypothesized to be the result of genetic induced aberrant neural pathology. It is of increasing importance that future studies utilize a control organism such as a Wistar or other outbred rodent in order to better understand how physiological changes are associated with behavior.

4.12.4 Gamma and theta oscillations modulate each other

In the experiments described previously, neural signals were all filtered in the theta frequency band. There are a myriad of reasons why theta was selected over other frequencies. Firstly, a primary goal of the experiments conducted was to determine how information was exchanged between the neural networks investigated. Slower rhythms such as theta oscillations are better suited for long-range communication between neural networks. Gloveli et al. (2005) reported that gamma coherence between two signals was high when the signals were in close proximity. However, as the distance between the two signals increased, the coherence of gamma oscillations also decreased and a slow shift in the phase of the oscillations was observed (Gloveli et al., 2005). In contrast, theta oscillations remained coherent as the distance between signals was increased and a low phase shift was not observed (Gloveli et al., 2005). Oscillation frequencies can vary by interneuron population because of their respective properties (Dickson et al., 2000; Rotstein et al., 2005; Sohal, 2012; Sohal et al., 2009). For example, differences in the arborization of parvalbumin containing interneurons versus oriens lacunosum-moleculare (O-LM) class cells were observed and hypothesized to be linked to differences in the ability of oscillations to persist between distal signals (Gloveli et al., 2005). Specifically, greater longitudinal axonal spread in O-LM cells may generate stronger output of theta oscillations

to distal pyramidal cells and interneurons (Gloveli et al., 2005). Interneurons influence oscillations where longer inhibition is associated with slower frequencies (Moran and Hong, 2011). More specifically, greater inhibition retards the activity of excitatory cells longer, reducing the frequency of the oscillation (Kopell et al., 2000). As stated above, this suggests the type of interneuron has profound effects on the frequency of the oscillation. Also, lower frequency oscillations can support synchronization between networks at longer conduction delays than faster oscillations (Kopell et al., 2000). This is due, in part, to the recruitment of more inhibitory cells during long-distance synchrony, resulting in extra inhibition (Kopell et al., 2000). Lastly, as power increases frequency decreases such that slower oscillations require less energy (Pfurtscheller and Da Silva, 1999). Thus, slower oscillations like theta are more suited than faster oscillations like gamma for long-range synchrony.

A secondary reason for the selection of theta was its translational implications. Aberrations in theta oscillations are observed in reward-seeking behaviors in clinical populations (Ehlers et al., 1992; Givens, 1995; Park et al., 2017), strengthening the notion that preclinical assessments of theta oscillations may have a translational impact. Additionally, oscillations in the theta frequency range produce temporal dynamics which efficiently potentiate or depress synapses (Huerta and Lisman, 1996a; Huerta and Lisman, 1996b), suggesting this frequency can modulate synaptic plasticity. Theta-mediated alterations of synaptic plasticity are hypothesized to underlie the expression of conditioned memories (Seidenbecher et al., 2003). Importantly, selection of theta in the current analyses does not preclude the investigation of other frequency ranges in the future, nor

does it assume that significant differences will not be observed in faster oscillations, such as gamma.

Low frequency theta oscillations have been observed to modulate higher frequency gamma (30-100Hz) oscillations (Bragin et al., 1995; Canolty et al., 2006; Jensen and Colgin, 2007). Gamma oscillations are nested within theta cycles and are largest when theta oscillations are present (Bragin et al., 1995).Co-occurrence and interaction between oscillations of different frequency bands suggests that coupling between these signals may reflect higher order processing (Tort et al., 2009). Moreover, coordination of theta and gamma oscillations may be necessary for neural processes underlying learning and memory processing (Tort et al., 2009).

Different frequency bands may have different relationships with behavior. Terada et al. (2013) observed that gamma coherence was associated with high but not low probability reward expectation whereas theta coherence was associated with reward expectation under both contingencies. Gamma band oscillations are important for cognitive processes and coordination of PFC networks that sub serve cognitive control (Cho et al., 2006). In the current experiments, it is unclear what role gamma oscillations may play in the maintenance and expression of conditioned behaviors. Theta-gamma coupling may be observed in several behavioral epochs. Differences in gamma and theta synchrony during behavioral epochs may therefore inform our understanding of how neural representations of reward-paired stimuli are generated as well as how stimuli-evoked responses are encoded in cortical-limbic networks.

Slow oscillations such as theta rhythms may synchronize distal brain regions while fast oscillations are capable of synchronizing proximal neural assemblies (Buzsáki and

Draguhn, 2004). As such, gamma rhythms are more prevalent in short range connections, contrast with long range connections of theta rhythms (Fries, 2005). If theta oscillations are associated with modulating activity over large spatial regions and are more prevalent in long range connections (Canolty and Knight, 2010; Gloveli et al., 2005), one might expect involvement of gamma oscillations between close range brain regions. Gamma oscillations can be isolated in the current data set. Therefore, future analyses should include an investigation of the involvement of gamma oscillations in conditioned responding as well of theta-gamma coupling across the brain regions surveyed to better understand the network dynamics of reward seeking.

4.13 Summary and conclusions

Theta oscillations are hypothesized to facilitate information transfer concerning behaviorally relevant occurrences across brain regions (Gordon, 2011). The present experiments sought to characterize the neural circuits of cued alcohol seeking in a genetically vulnerable rat model. Specifically, analyses of theta synchrony between the BLA, HC, NA and PFC and directionality were performed. Differences in theta band synchrony across behaviors, tasks and rodent strain were observed.

These data underscore the importance and necessity of a systems approach in elucidating the neural mechanisms of circuits which are integral for reward seeking. Moreover, while previous studies have demonstrated relationships between substrates necessary for cued behaviors (Fuchs et al., 2007; Fuchs et al., 2005; Keistler et al., 2017; Lasseter et al., 2011; Wells et al., 2011), for the first time directionality between these structures was determined for alcohol-seeking behaviors. Importantly, these data demonstrate that ablation between structures, while sufficient for impairing expression of

behavior, fails to adequately capture the temporal relationship of information transfer between these regions. In vivo electrophysiological recordings can, and do address this limitation. The data here propose a neural system of cued alcohol seeking in addiction vulnerable populations (Figure 29). Future studies may address how this system differs in non-addiction vulnerable populations as well as the neurotransmitter systems involved in expression of the behaviors observed here.

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TABLES

Table 1. Group Sizes

Animal numbers used for electrophysiological recordings. Each animal had approximately eight conditioning days and three or four extinction days.

	Conditioning	Extinction
Wistar	23	8
P rat	39	16
Total	62	24

Table 2. Histological placements

Histological placements by rodent strain in Wistar (W) and P rats. Hits (✓) and misses(X)

	PFC	NA	BLA	vHC
W1	✓	✓	✓	✓
W2	✓	✓	✓	✓
W3	✓	✓	X	X
P1	✓	✓	✓	✓
P2	✓	X	✓	X
P3	✓	✓	X	X
P4	✓	✓	✓	✓
P5	✓	✓	✓	✓

Table 3. Change in Baseline

Summary of changes in baseline by behavioral epoch. Direction of arrow indicates direction of change in baseline. R=trials in which an animal made a response, NR= trials in which no response was made.

	Tone	Lever pressing	Drink	Extinction (NR)	Extinction (R)
BLA-HC				↑	
NA-BLA			↓	↑	
NA-HC			↑	↓	↓
PFC-BLA		↑		↓	
PFC-HC		↑		↓	
PFC-NA	↑	↑	↑	↑	↑

Table 4. Directionality

Directionality between brain regions across behavioral epoch. Letters correspond to behavioral epoch and indicate top column leads bottom rows. During baseline (A), the BLA leads the PFC, NA and HC. Additionally, the NA leads the PFC during baseline. During DS+ tone presentation (B) the NA leads the PFC. In DS+ reinforced trials during lever pressing (C), the BLA and the NA both leads the PFC. During drinking (D), the NA leads the PFC. During extinction, in trials in which the animal did not make a response (E), the BLA leads the PFC and NA, which is also led by the HC.

	BLA	HC	NA	PFC
BLA				
HC	A			
NA	A,E	E		C
PFC	A,C, E		B, C, D	

Table 5. Peak Lags

Peak mean lags between brain regions. * indicate significant directionality between brain region pairs.

Epoch	Brain	Lag
Baseline	BLA-HC	3 ms*
Baseline	NA-BLA	4 ms*
Baseline	PFC-BLA	4 ms*
Baseline	PFC-HC	1 ms
Baseline	PFC-NA	4 ms*
Tone	PFC-NA	3 ms*
Lever	PFC-BLA	7 ms*
Lever	PFC-NA	3ms*
Lever	PFC-HC	1 ms
Drink	NA-BLA	1 ms
Drink	PFC-NA	4 ms*
Extinction (NR)	PFC-BLA	3 ms*
Extinction (NR)	NA-BLA	3 ms*
Extinction (NR)	NA-HC	1 ms*
Extinction (NR)	PFC-NA	1 ms*
Extinction (NR)	BLA-HC	1 ms
Extinction (NR)	PFC-HC	1 ms
Extinction (R)	PFC-HC	2 ms
Extinction (R)	NA-HC	1 ms

FIGURES

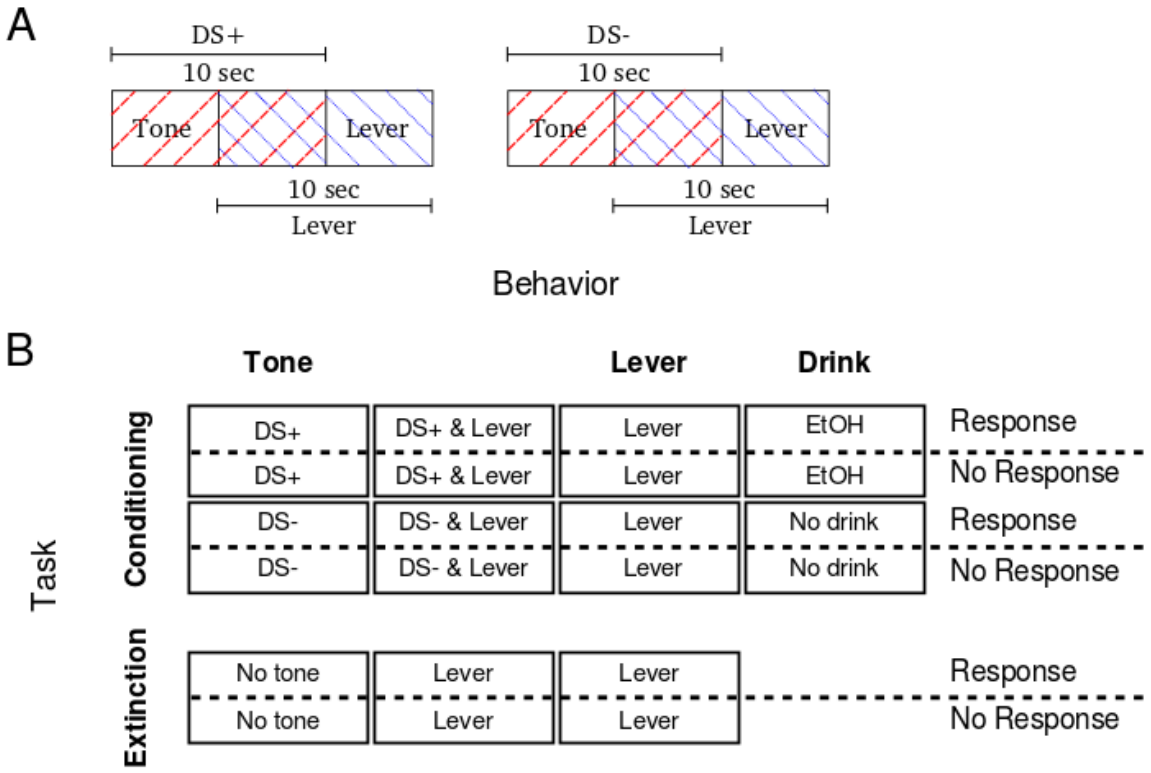

Figure 1. Experimental design and behavioral epochs.

Each trial consisted of 10 seconds of an auditory discriminative stimuli (DS) and ten seconds of lever access (A). Behavioral epochs were stratified by task, behavior, response and stimuli type (B).

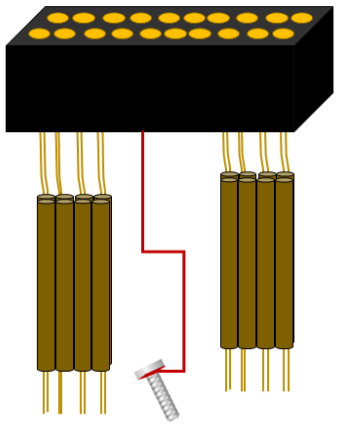

Figure 2. Cartoon of probe

Two probes were used for each animal. Each probe contains two 4 × 2 arrays and an insulated copper wire wrapped around a ground screw and implanted over the cerebellum to ground the signal.

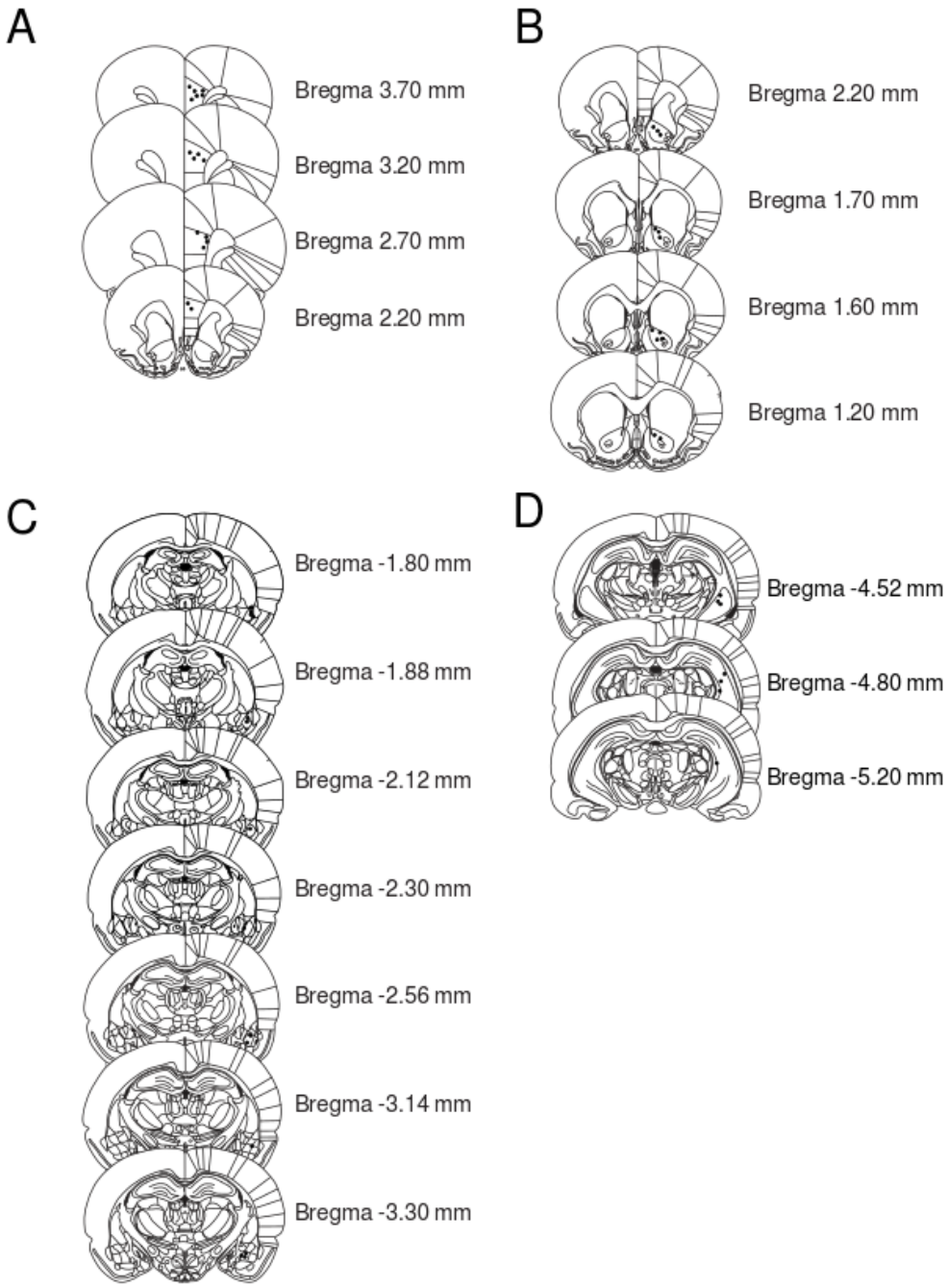

Figure 3. Histology

Histological placements of probes in the PL sub-region of the PFC (A), NAc (B), BLA(C) and vHC (D).

$$\gamma = \left\| \frac{1}{N} \sum_{j=1}^{N} e^{i\theta(t_j)} \right\|$$

Figure 4. Phase locking formula

The phase locking index (γ) was computed by taking the difference of the phase of two filtered signals $\theta(t_j)$ across tine t_j for N data points.

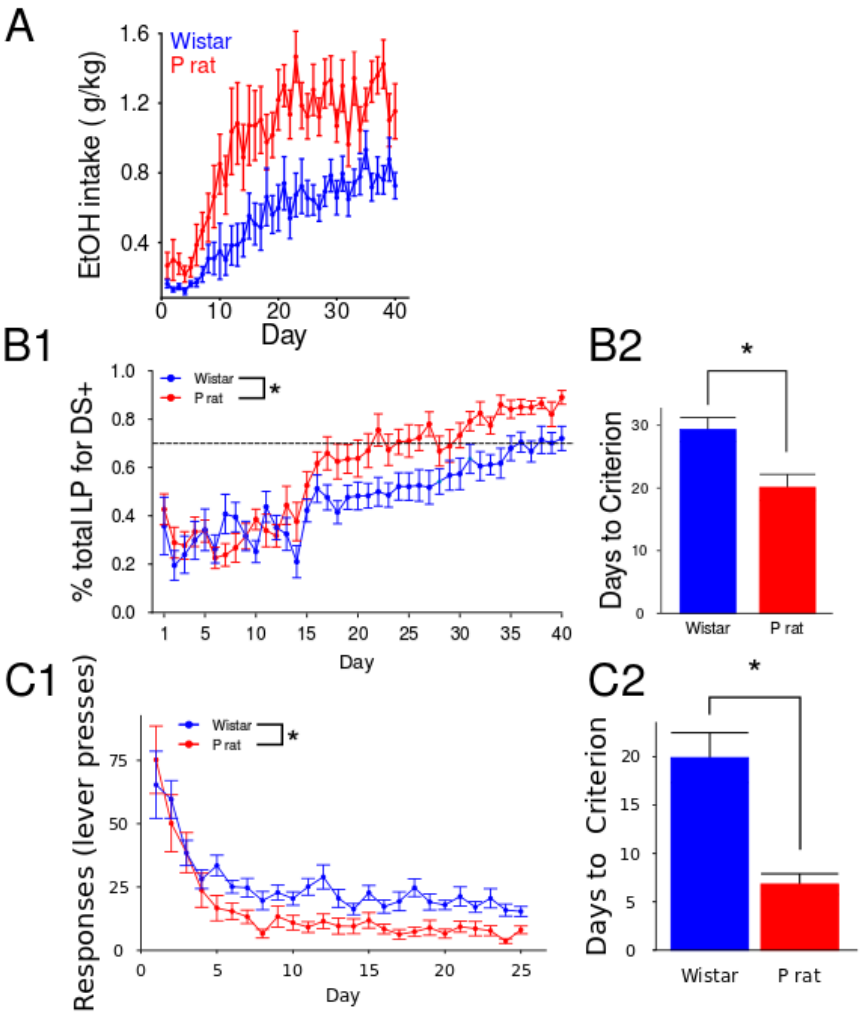

Figure 5. Aim one behavior results

P rats drink more than Wistars (A). Both Wistar and P rats learn to discriminate between the two stimuli (B1) but P rats acquire the task sooner (B2). Similarly, both strains extinguish responding over days (C1), with P rats extinguishing responding sooner (C2). All values are mean ± standard error of the mean (SEM).

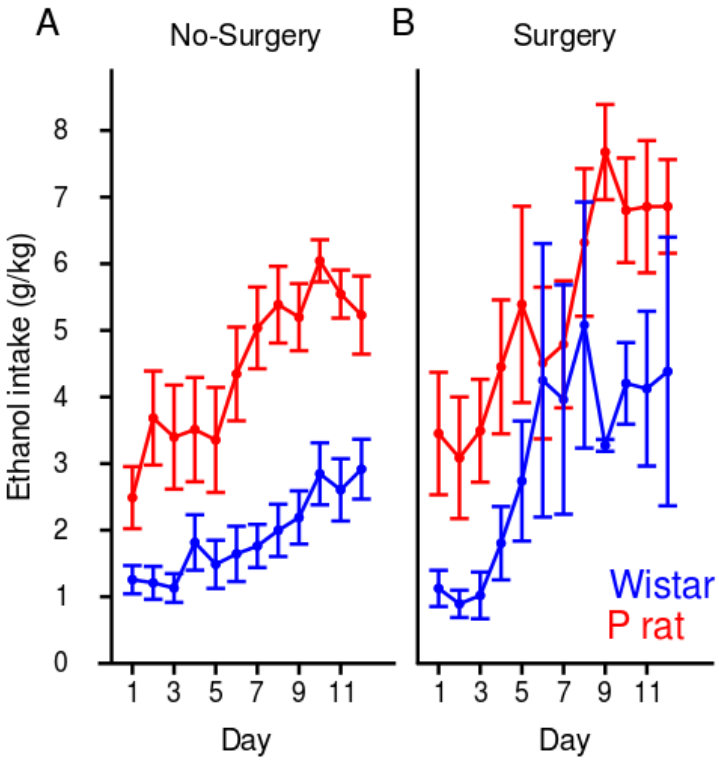

Figure 6. Home cage drinking

Home cage drinking data for Wistar (blue) and P rats (red). Panels represent animals which did not experience surgical implantation for electrophysiology (A) and animals which were later implanted (B). In the no-surgery group (A), both strains increase their intake over days but P rats drink more than Wistars. There is no effect of strain on intake in the surgery group but both strains increase their intake over days (B). All values are mean $\pm$ SEM.

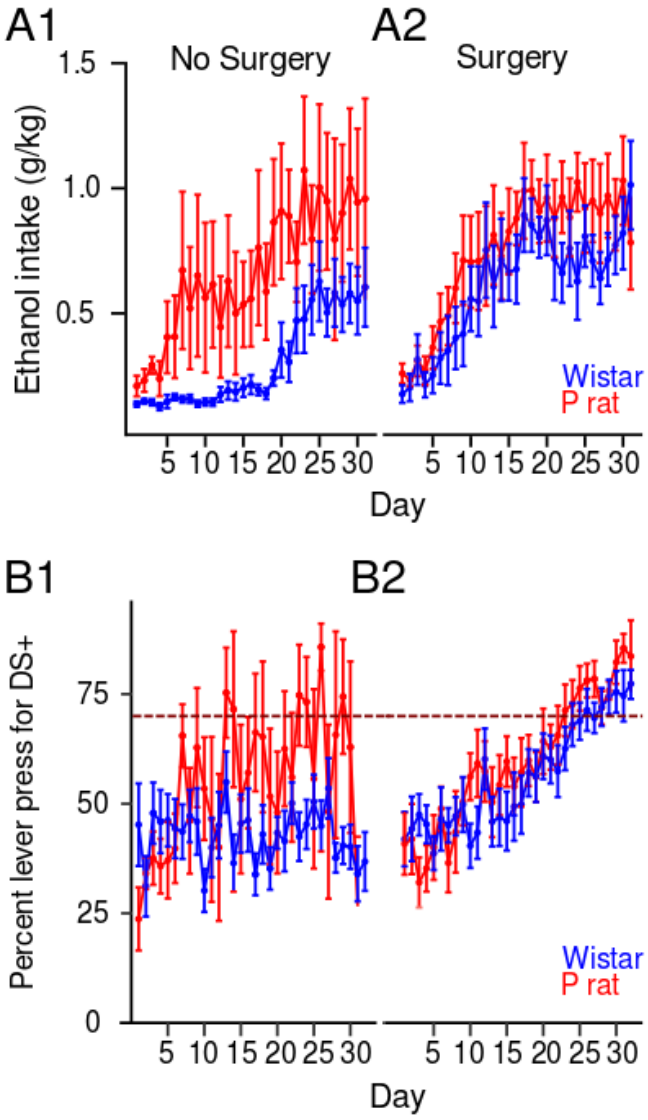

Figure 7. Aim two behavior

Intakes (A) and percent lever presses for the DS+ (B) during conditioning training for P (red) and Wistar (blue) rats which were later implanted (2) or only experienced behavior (1). Animals used for electrophysiological experiments increase stimuli discrimination over days, regardless of strain (B2), an effect no observed in animals who did not experience surgery (B1). All values are mean ± SEM.

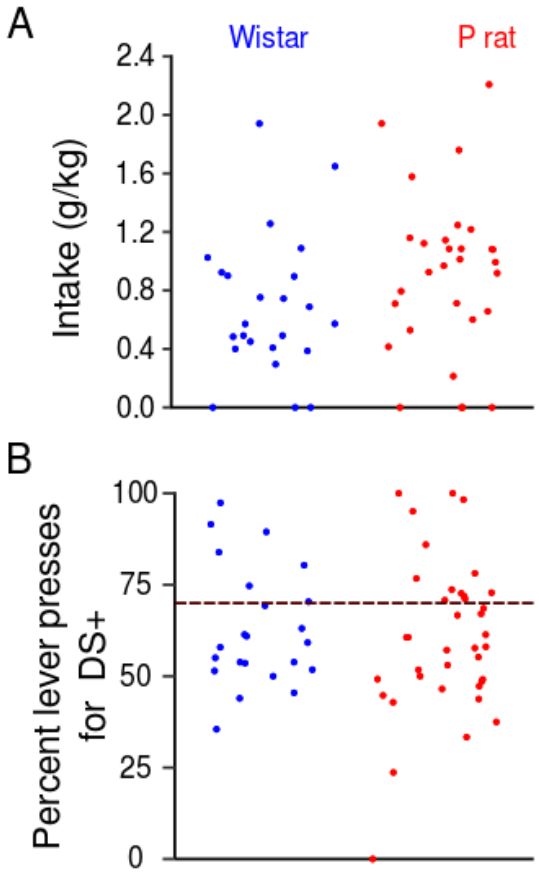

Figure 8. Behavior during recordings

Ethanol intakes (A) and percentage of lever presses for the DS+ (B) in Wistar (blue) and P (red) rats during electrophysiological recordings. Red line represents discrimination criteria by which animals were selected for electrophysiological experiments. There is no difference between the strains in intake or stimuli discrimination.

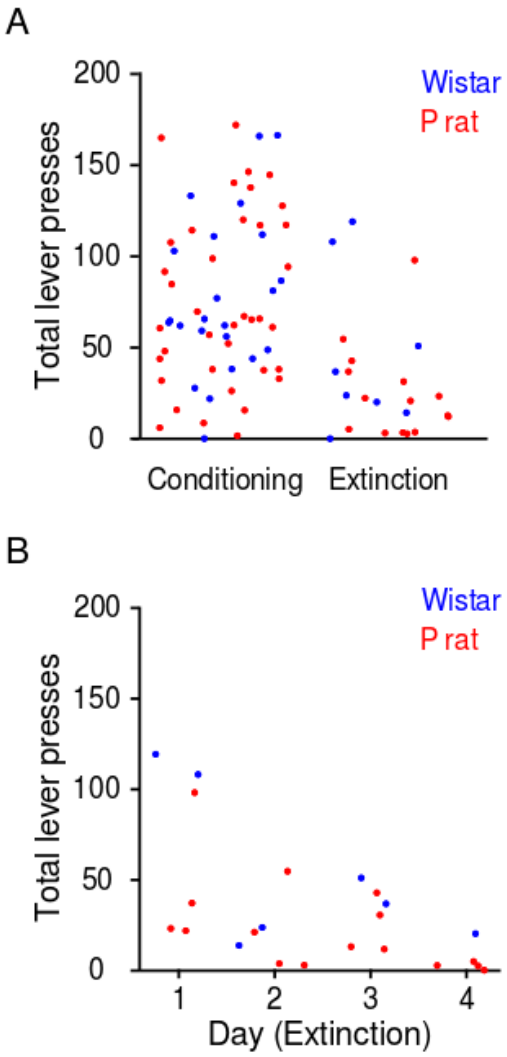

Figure 9. Extinction behavior

Lever pressing activity during extinction and conditioning in Wistar (blue) and P (red) rats. During extinction, overall lever pressing decreases, relative to conditioning (A). Lever pressing during extinction also decreases over day (B).

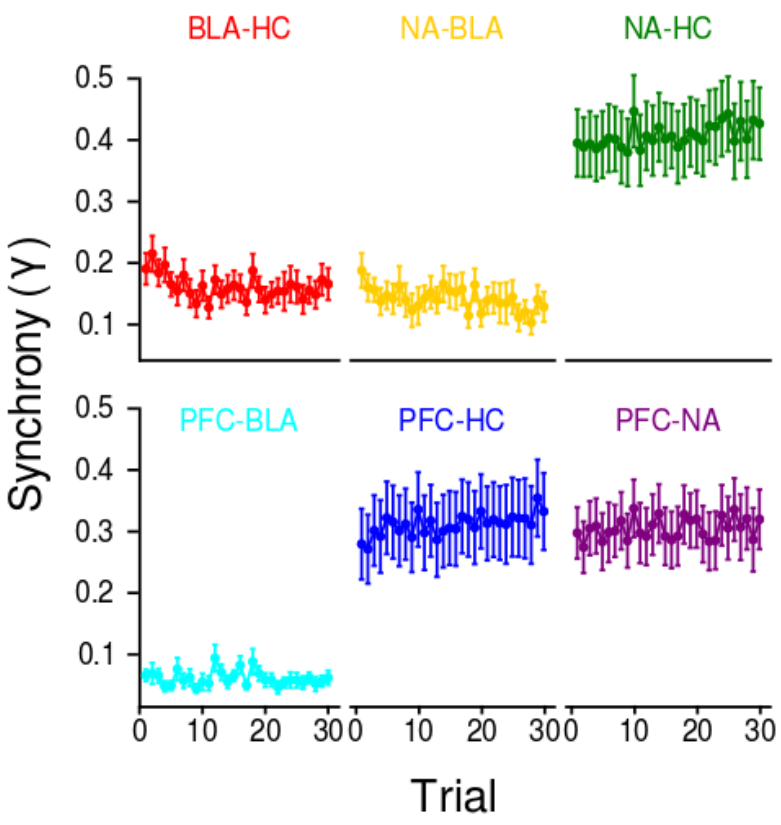

Figure 10. Baseline synchrony

Baseline (five seconds before DS presentation) synchrony between brain regions across trials. Baseline synchrony between the brain regions is different but does not significantly change over trial. All values are mean ± SEM.

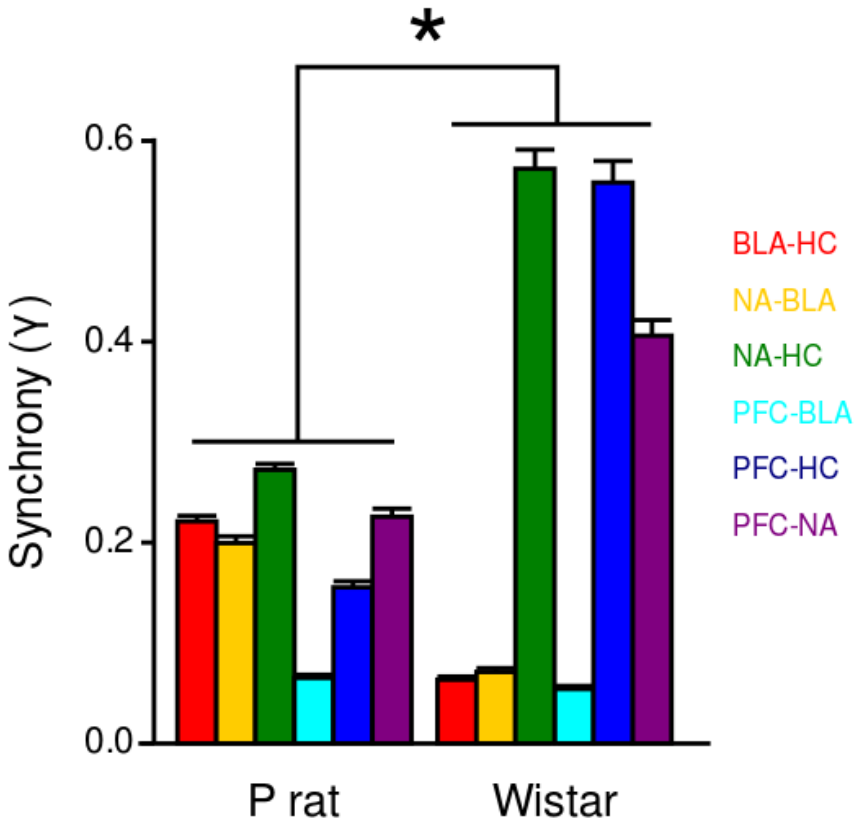

Figure 11. Baseline synchrony by strain

Figure 11. Baseline synchrony by rodent strain, collapsed across trials. Overall, synchrony, collapsed across brain, significantly differed by rodent strain. All values are mean ± SEM.

*p<0.05

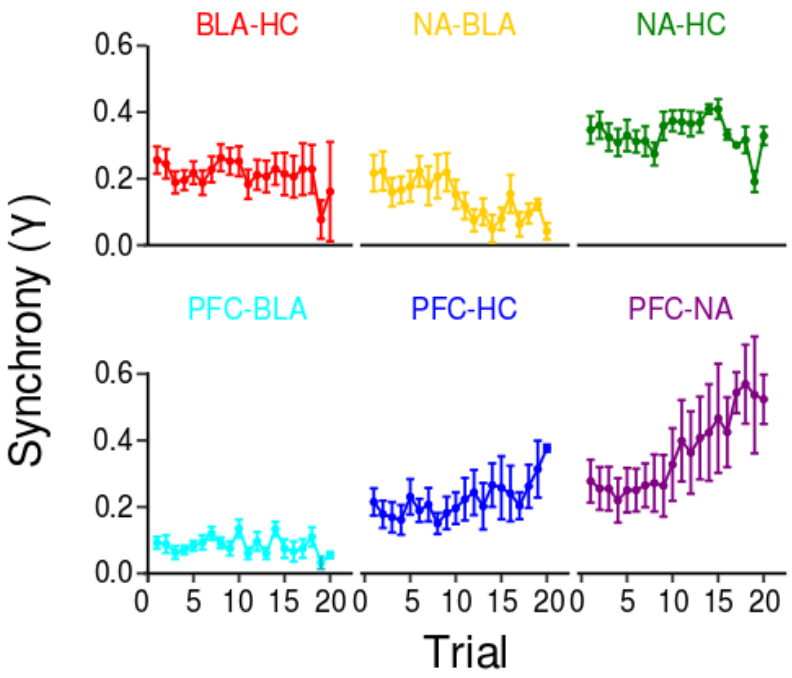

Figure 12. Synchrony across trials

Representative behavioral epoch across trials. Synchrony does not change over trial in P rats in DS+ trials during lever pressing when P animals respond three or more times. All values are mean ± SEM.

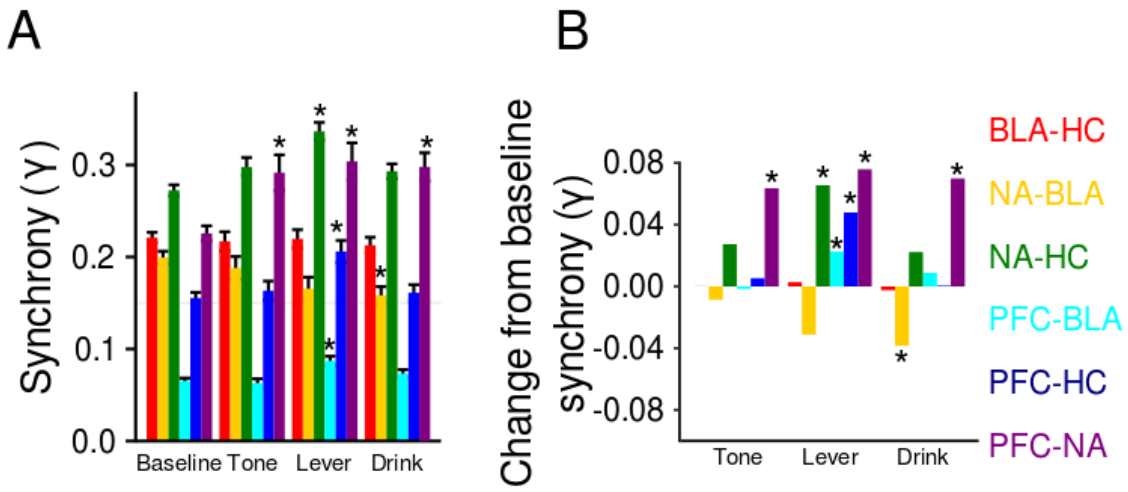

Figure 13. Change in baseline synchrony

Synchrony differs by behavioral epoch. Synchrony by behavioral epoch for each brain region pair in DS+ trials in which the animal responded (A). Change in synchrony from baseline for all brain region pairs (B). All values are mean ± SEM. * $p<0.05$, Bonferroni post hoc (Brain region is different from baseline).

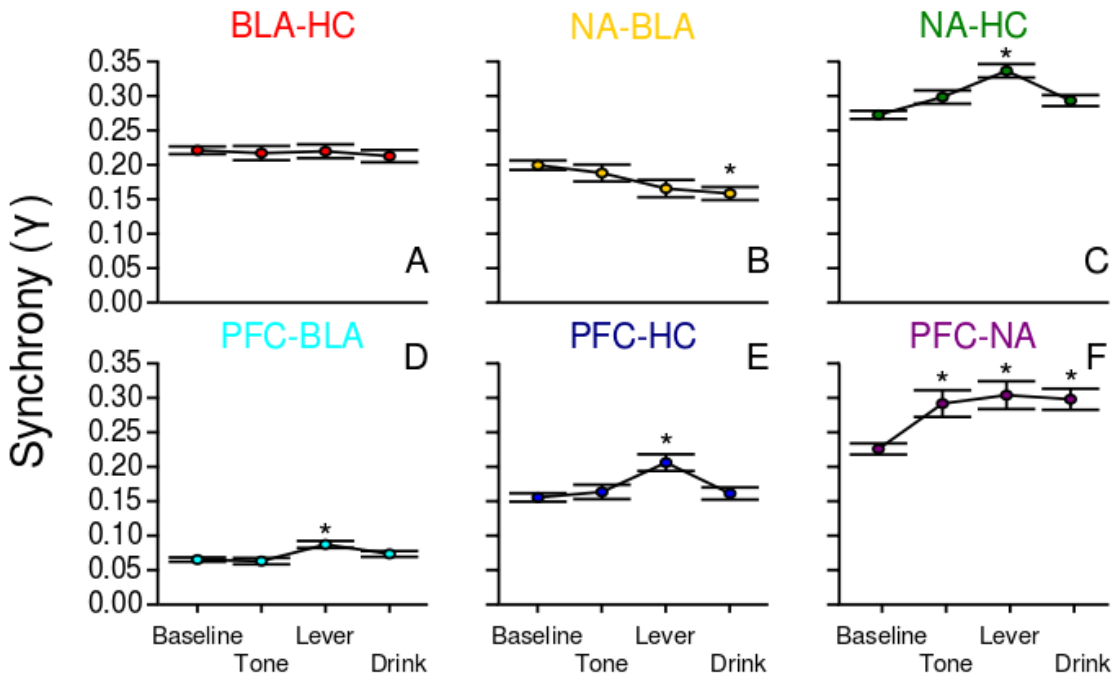

Figure 14. Synchrony across epoch

BLA-HC(A), NA-BLA(B), NA-HC(C), PFC-BLA(D),PFC-HC(E), and PFC-NA (F) neural synchrony by across behavior epoch in DS+ trials in which the animal responded. There was no significant effect of behavior on synchrony between the BLA-HC (A). However, synchrony was significantly reduced during drinking for NA-BLA (B) and lever pressing for PFC-BLA signals. Additionally, synchrony increased during lever pressing for NA-HC(C) and PFC-HC(E) and PFC-NA(F). Increased synchrony between the PFC and NA was also observed during tone presentation and drinking (F). All values are mean $\pm$ SEM. *$p<0.05$, Bonferroni post hoc, epoch different from baseline.

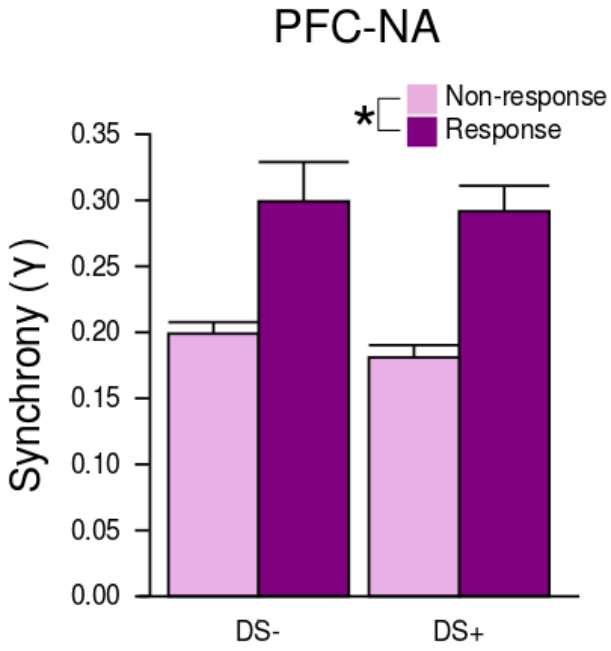

Figure 15. Synchrony during tone epoch

PFC-NA synchrony during tone presentation for DS+ and DS- trials in which an animal made a response or did not make a response. Bars are mean + sem. Overall, synchrony was greater for reinforced trials and was not influenced by stimuli type. All values are mean ± standard error of the mean (SEM).

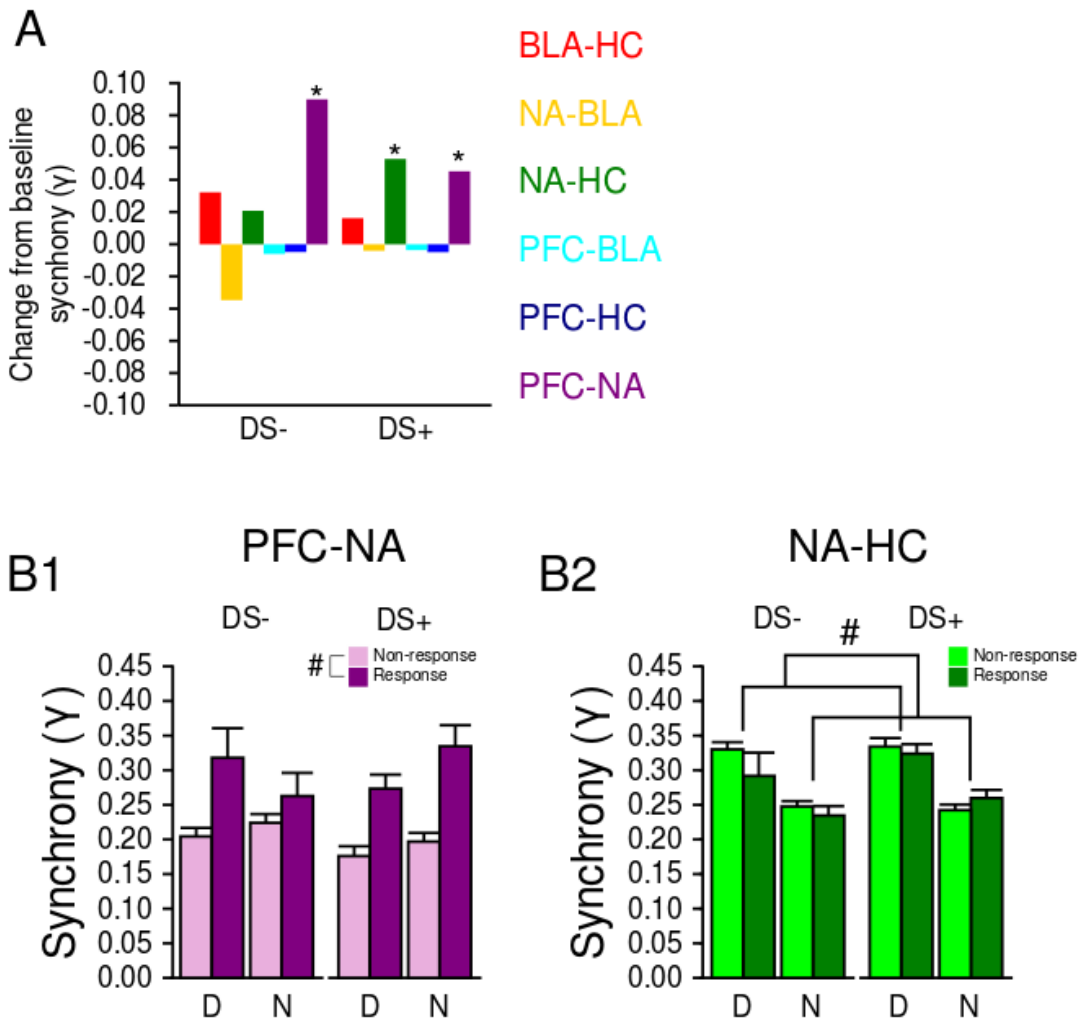

Figure 16. Synchrony by discrimination

Synchrony by discrimination (D) or no discrimination (N) during tone presentation. (A) Bars are change in synchrony from baseline for trials occurring on days in which the animals discriminated between the two stimuli and made operant responses. * $p<0.05$, Bonferroni post hoc (different from baseline). In brain regions different from baseline, response, but not discrimination influenced PFC-NA synchrony (B1). However, NA-HC synchrony was influenced by whether an animal discriminated at criteria throughout the session (B2). All values are mean $\pm$ SEM. #$p<0.05$, main effect.

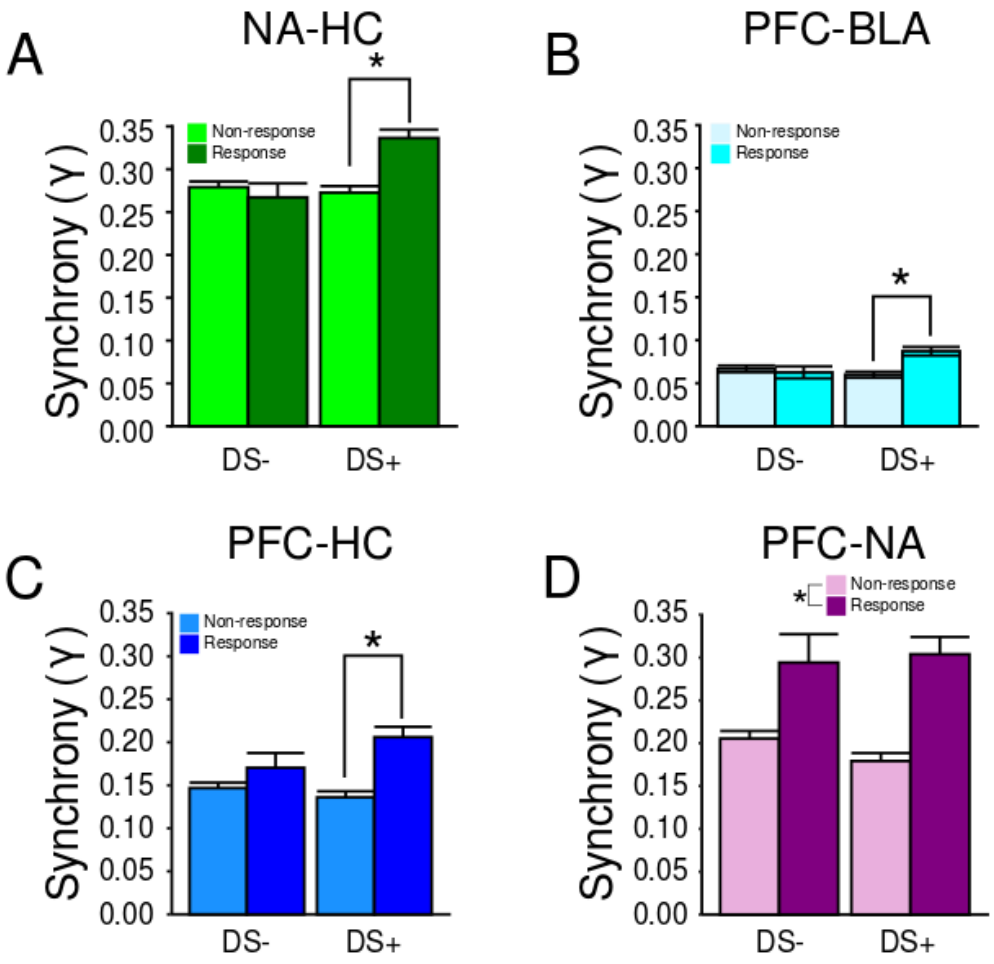

Figure 17. Synchrony during lever availability epoch

Synchrony between NA-HC (A), PFC-BLA (B), PFC-HC (C) and PFC-NA (D) during the lever pressing epoch. Bars are trials in which the animal responded or did not respond following presentation of the DS+ or DS-. For DS+ trials, synchrony between NA-HC (A), PFC-BLA (B), and PFC-HC (C) was greater during response versus non-response trials). Additionally, regardless of trial type, PFC-NA synchrony, was greater for response trials compared to non-response trials (D). All values are mean $\pm$ SEM. *$p<0.05$, Bonferroni post hoc

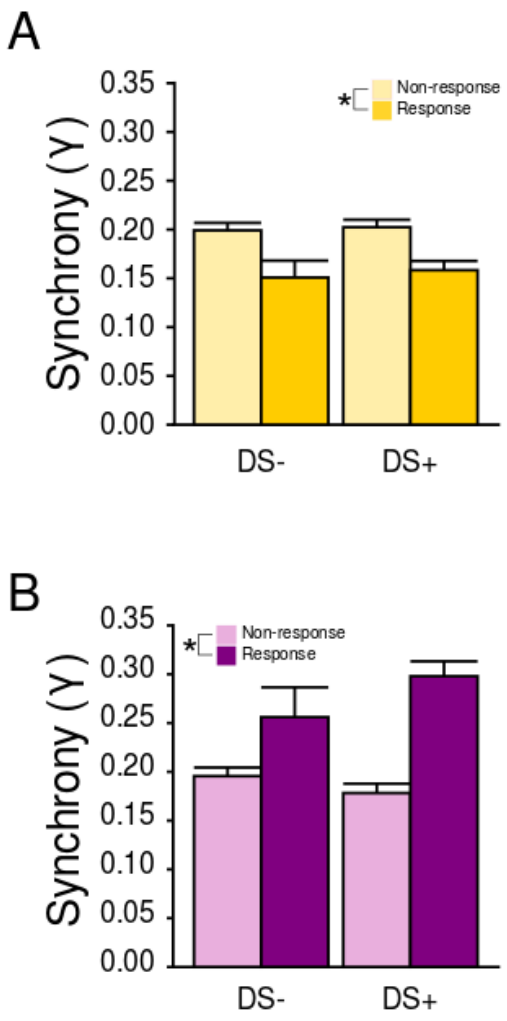

Figure 18. Synchrony during drink epoch

Figure 18. NA-BLA (A) and PFC-NA (B) synchrony during the drink epoch. Bars are DS+ or DS- trials in which the animal made a response or did not make a response. Only response DS+ trials resulted in alcohol availability. Synchrony between the NA and BLA (A) was significantly lower for trials in which the animal responded three or more times. Conversely, synchrony between the PFC and NA (B) was significantly higher during response trials. All values are mean $\pm$ SEM. *$p<0.05$, main effect

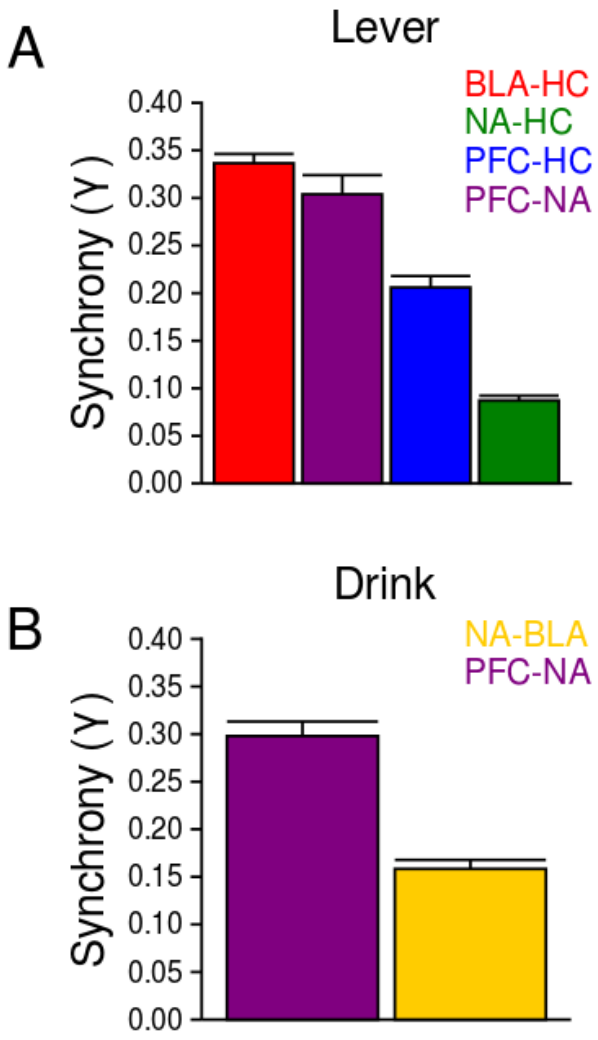

Figure 19. Synchrony by brain region

Synchrony strength differs by brain region pairs during lever pressing (A) and drinking (B). For lever pressing trials (A), synchrony between all brain region pairs were different with PFC-NA compared to NA-HC being the exception (p= 0.6, Bonferroni post hoc). During drinking epochs, greater synchrony was observed between the PFC and NA compared to the NA and BLA. All values are mean ± SEM.

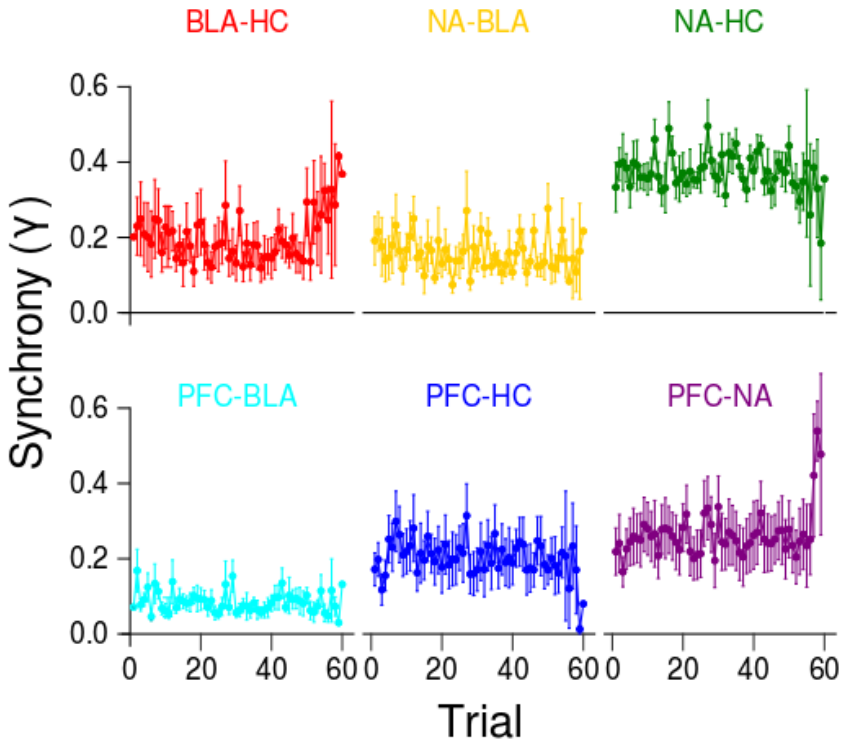

Figure 20. Synchrony during extinction

Synchrony during extinction (collapsed across days) for all brain region pairs is not influenced by trial. All values are mean ± SEM.

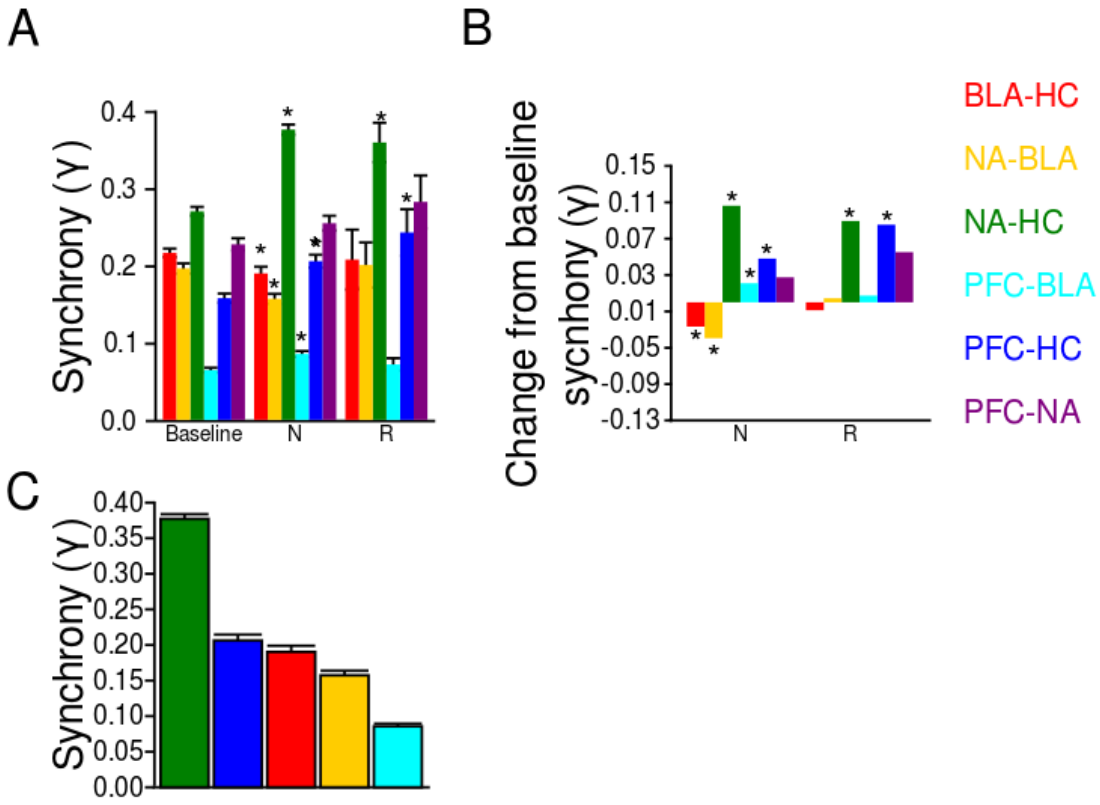

Figure 21. Change in baseline synchrony during extinction

Synchrony between brain region pairs during lever availability in extinction for trials in which the animal responded (R), did not respond (N) or baseline, where no stimuli were present (A). When an animal does not make a response, there are significant changes in synchrony between the BLA and HC, NA and BLA, NA and HC, PFC and BLA and PFC and HC. Conversely, when an animal makes a response in extinction, there are changes in synchrony between the NA and HC and the PFC and HC (B). Synchrony between all brain region pairs are different from one another (C). All values are mean $\pm$ SEM. *$p<0.05$, Bonferroni post hoc, different from baseline.

Figure 22. Extinction compared to conditioning synchrony

BLA-HC (A), NA-BLA (B), NA-HC (C), PFC-BLA (D) and PFC-HC (E) synchrony during lever availability for trials in which the animal responded (R) or did not respond (N) in extinction and conditioning. BLA-HC (A) and NA-BLA (B) synchronies are greater during conditioning, relative to extinction, during non-response trials (B). Conversely, NA-HC (C) and PFC-BLA (D) synchrony is greater during extinction for non-response trials. Lastly, synchrony between the PFC and HC is greater during extinction, compared to conditioning and response trials, compared to non-response trials (E). All values are mean $\pm$ SEM.

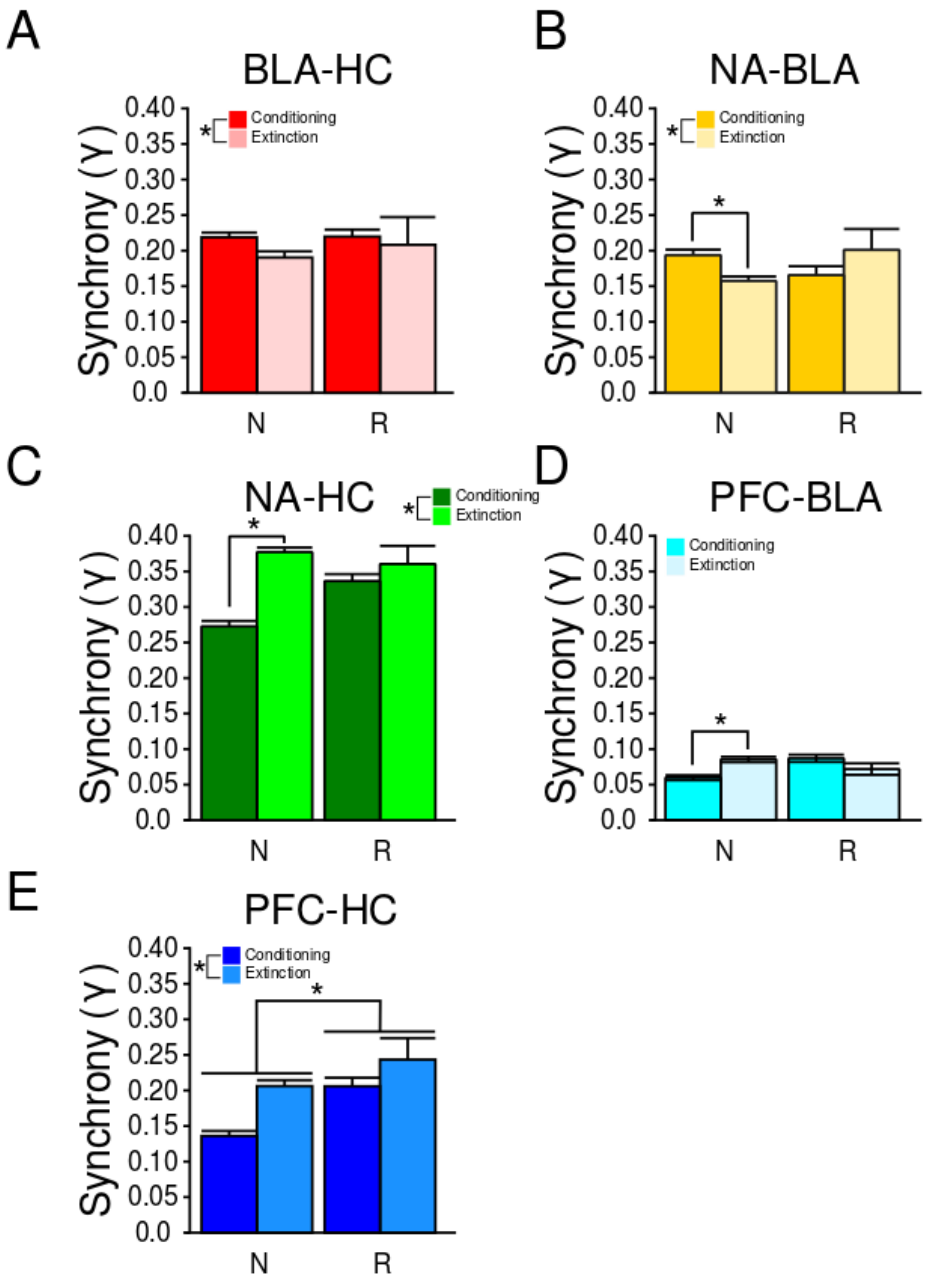

Figure 22. Extinction compared to conditioning synchrony

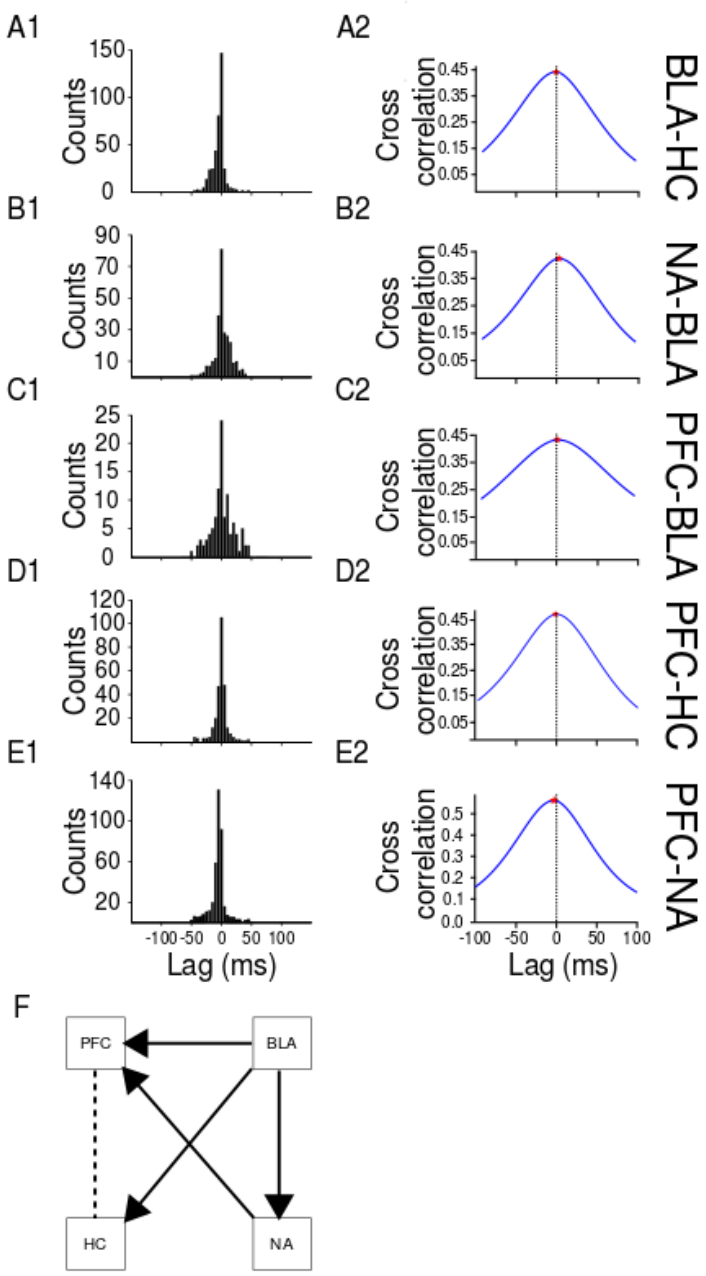

Figure 23. Baseline directionality

BLA-HC (A), NA-BLA (B), PFC-BLA (C), PFC-HC (D), and PFC-NA (E) baseline directionality histograms (1) and cross correlation peaks (2). Summary schematic (F) indicating the BLA leads the PFC, NA and HC, while the NA leads the PFC. Directionality between the PFC and HC could not be determined at baseline.

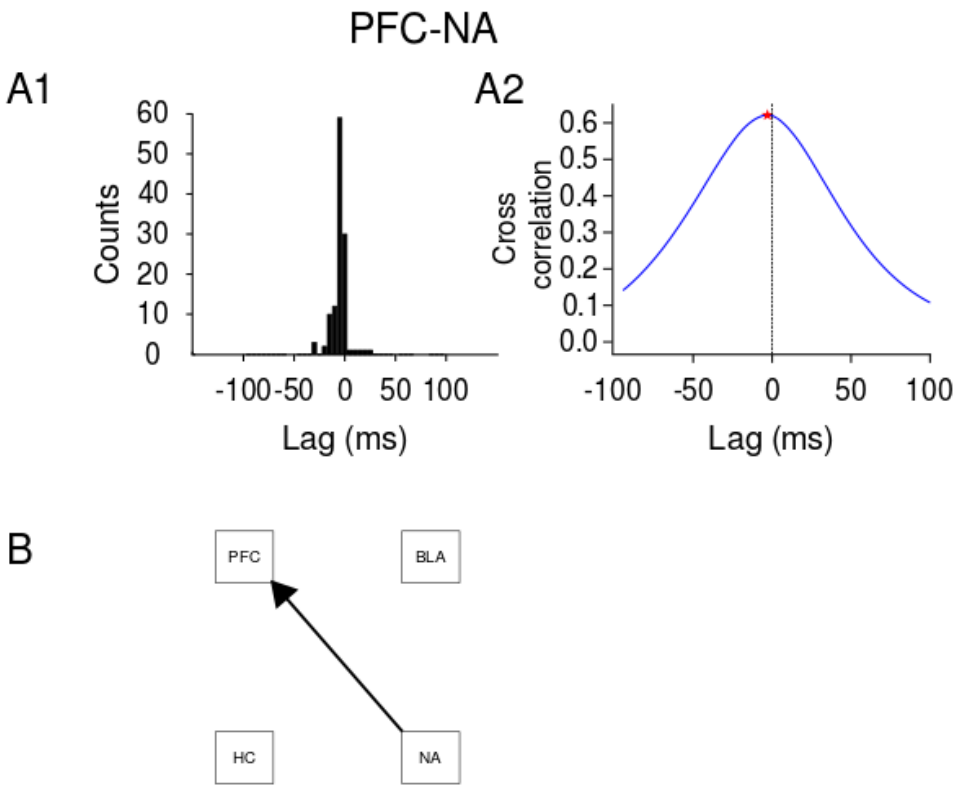

Figure 24. Directionality during tone epoch

PFC-NA (A) DS+ tone directionality histogram (1) and cross correlation peak (2). Summary schematic (B) indicating the NA leads the PFC during DS+ tone presentation in response trials.

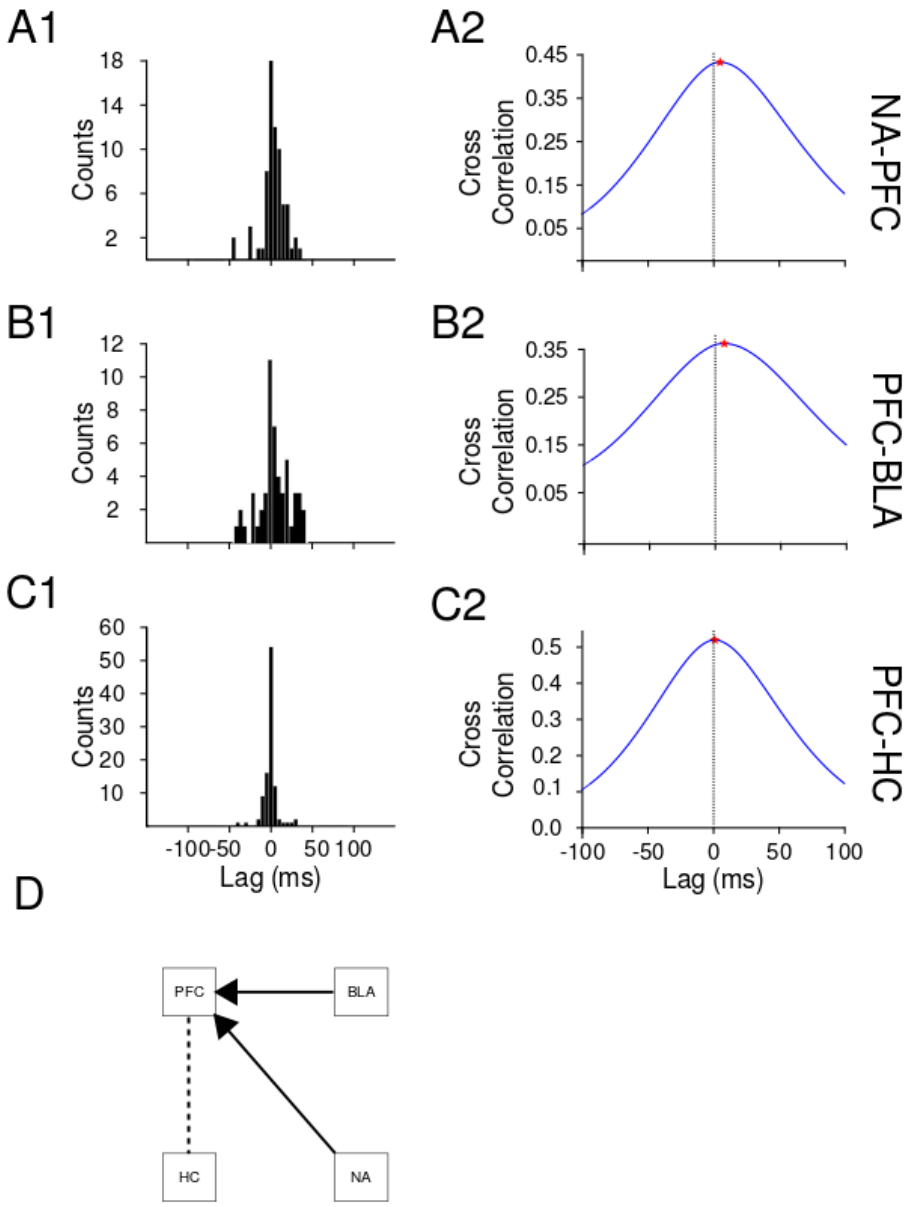

Figure 25. Directionality during lever epoch

NA-PFC (A), PFC-BLA (B) and PFC-HC (C) DS+ lever pressing directionality histograms (1) and cross correlation peaks (2). Summary schematic (D) indicating both the BLA and NA lead the PFC while directionality between the PFC and HC could not be determined during lever pressing following DS+ presentation.

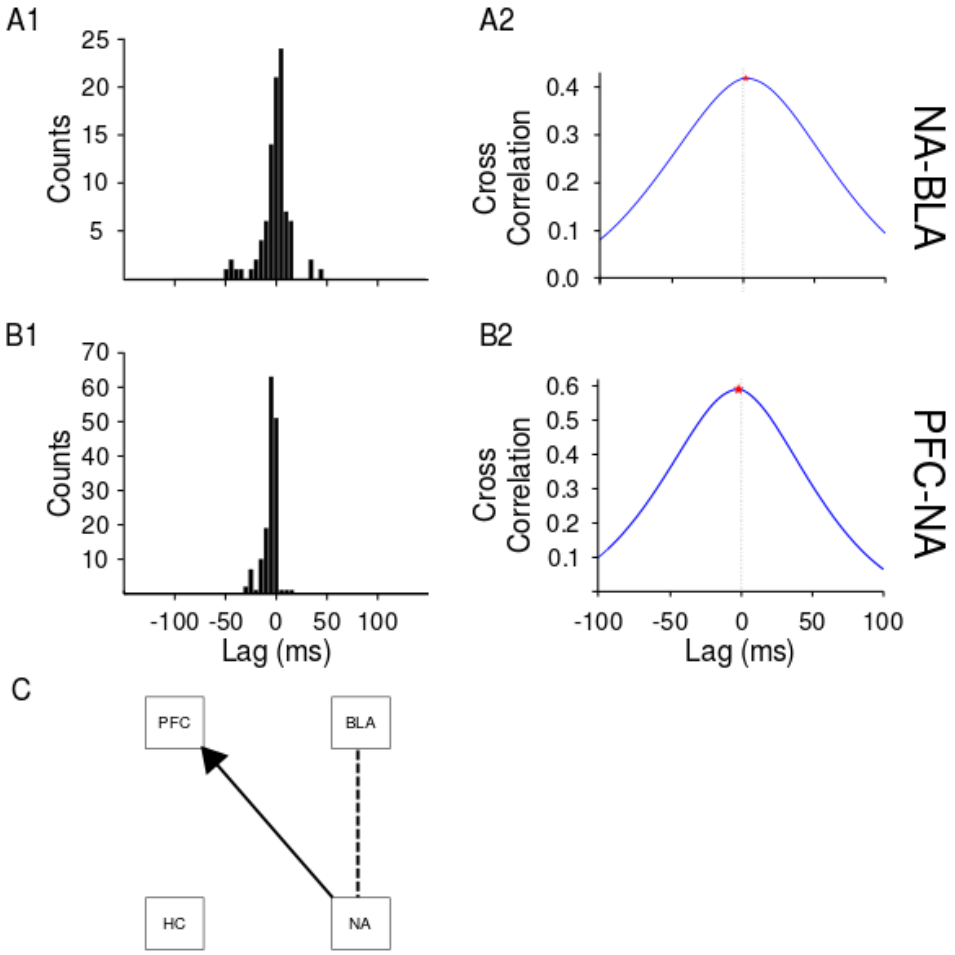

Figure 26. Directionality during drinking epoch

NA-BLA (A) and PFC-NA (B) drinking directionality histograms (1) and cross correlation peaks (2). Summary schematic (C) indicating the NA leads the PFC during drinking epochs while directionality between the BLA and NA could not be determined.

Figure 27. Directionality during extinction non-response

BLA-HC (A), NA-BLA (B), NA-HC (C), PFC-BLA (D) and PFC-HC (E) non-response extinction directionality histograms (1) and cross correlation peaks (2). Summary schematic (F) indicating the BLA leads the PFC and NA, and the HC leads the NA during extinction when an animal inhibits a response. Directionality between the PFC and HC and PFC and BLA could not be determine

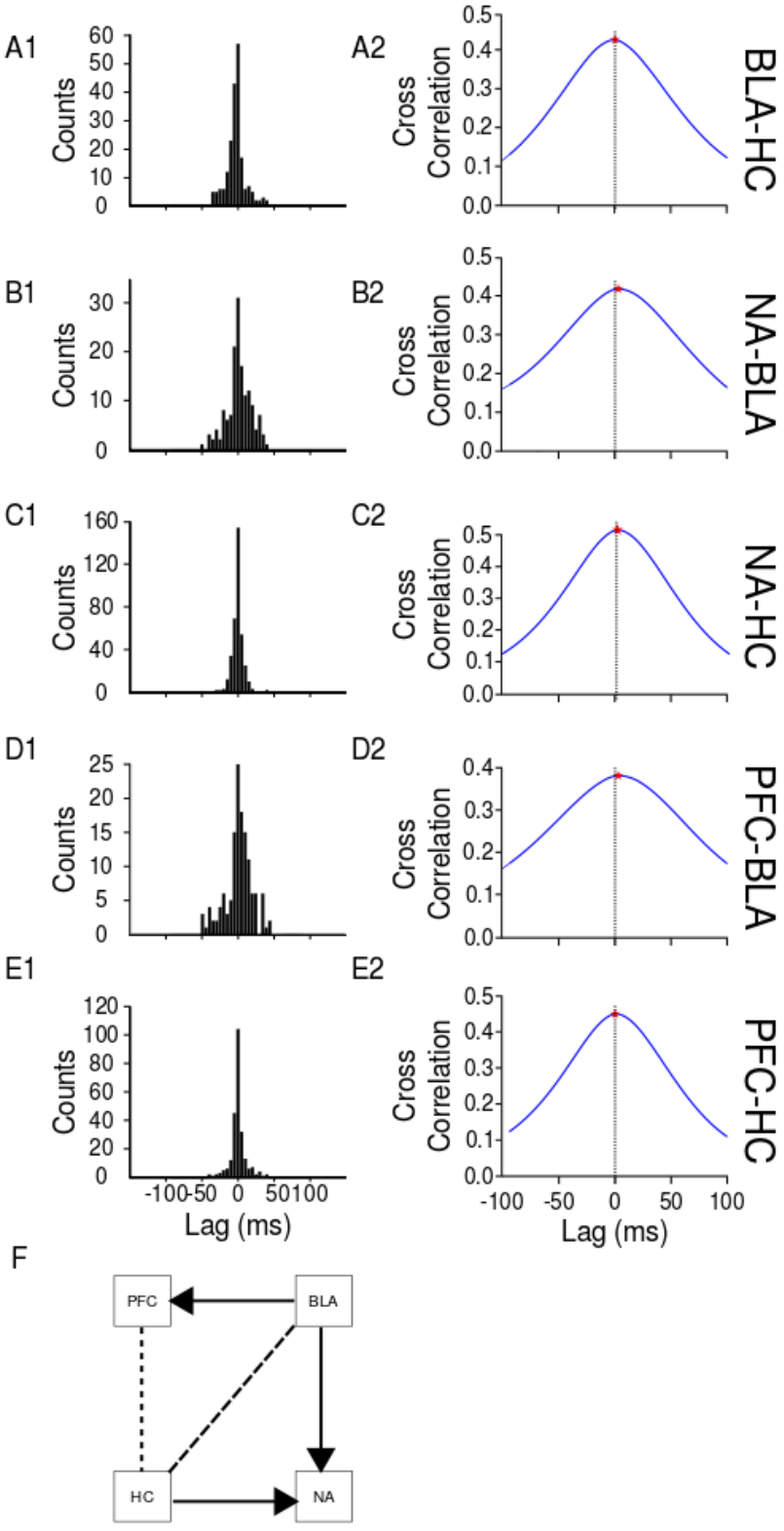

Figure 27. Directionality during extinction non-response

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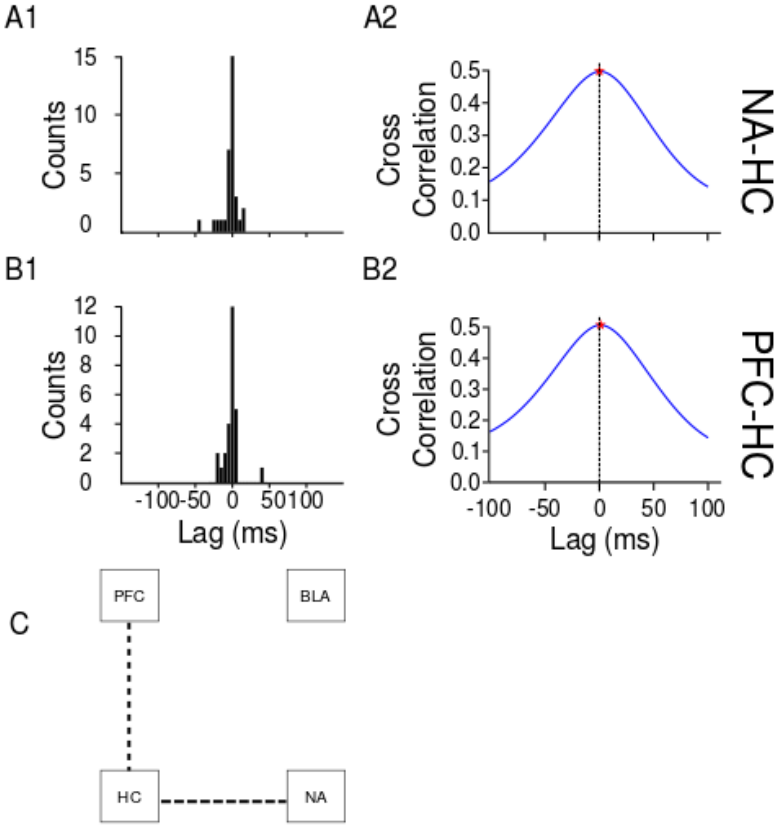

Figure 28. Directionality during extinction responding

NA-HC (A) and PFC-HC (B) extinction response directionality histograms (1) and cross correlation peaks (2). Summary schematic (C) indicating that directionality between the PFC and HC and HC and NA could not be determined during lever pressing in extinction.

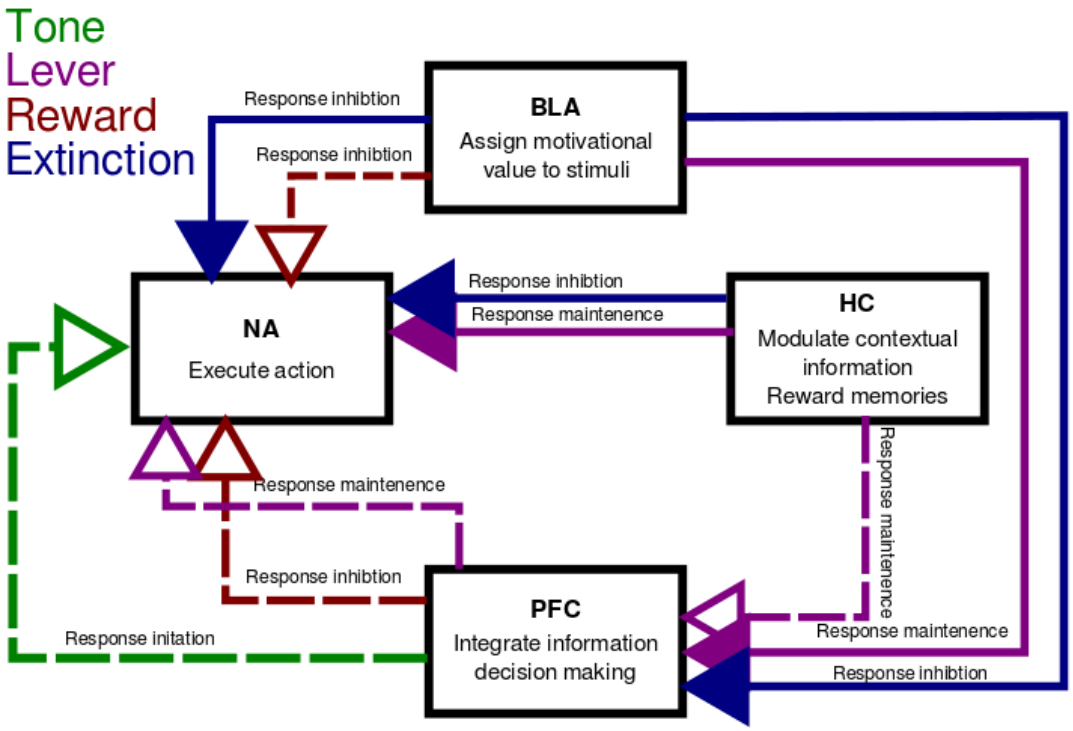

Figure 29. Hypothesized model of addiction circuitry

Model of proposed reward seeking circuitry in P rats. Arrows indicate hypothesized directionality of activity. Dotted lines indicated hypothesized projections. During tone presentation, synchrony between the NA and PFC may be involved in response initiation. During lever availability, activity between the HC and NA, NA and PFC, BLA and PFC and HC and PFC may be involved with maintenance of responding, which is modulated by environmental stimuli. During reward availability, synchrony between the BLA and NA and NA and PFC may be implicated in response inhibition. Lastly, during extinction, synchrony between the BLA and NA, HC and NA and BLA and PFC.