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Alcohol Consumption in a Preclinical Model of Schizophrenia

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Alcohol Consumption in a Preclinical Model of Schizophrenia

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by

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ABSTRACT

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Schizophrenia is a debilitating psychiatric disorder that affects approximately 1% of the global population. Schizophrenia is highly comorbid with other psychiatric disorders such as Alcohol Use Disorder (AUD) with a prevalence rate of 27% - 65%, which is significantly higher than AUD exhibited by the general population (6%). Research indicates that a higher rate of AUD in individuals suffering from schizophrenia may be related to the common neuronal pathways that underlie the expression of both disorders. The present study will determine whether the neonatal quinpirole (NQ) rodent model of schizophrenia will approximate the human condition and exhibit increased EtOH consumption. Rats will be treated neonatally with quinpirole or saline. Following the treatment period, rats will be tested for EtOH consumption using a 24-hour two-bottle free-access paradigm. The proposed research will test the hypothesis that rats neonatally treated with quinpirole will consume significantly greater amounts of EtOH than their saline counterparts.

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CHAPTER 1

INTRODUCTION

Schizophrenia is a debilitating psychiatric disorder that affects approximately 1% of the global population (McGrath, Saha, Chant, & Welham, 2008; Khokhar, Dwiel, Henricks, Doucette, & Green, 2018). Schizophrenia carries the fourth highest psychiatric disease burden worldwide due to early age of onset, lifelong impairments (social, occupational, & cognitive), and premature mortality (Miettunen, Immonen, McGrath, Isohanni, & Jääskeläinen, 2018; Whiteford, Ferrari, Degenhardt, Feigin, & Vos, 2015). For instance, a recent meta-analysis indicated that individuals with schizophrenia die an average of 13-15 years earlier than non-schizophrenic individuals due to factors that include: somatic disorders (e.g. cardiovascular disease & diabetes), side effects from second-generation antipsychotics (e.g. olanzapine), poor lifestyle (e.g. sedentary behavior & poor dietary habits), reduction of health-seeking behavior, and increased frequency of illicit and licit drug use (e.g. tobacco, marijuana & alcohol (EtOH); Hjorthøj, Stürup, McGrath, & Nordentoft, 2017). However, since schizophrenia is a spectrum disorder without a single diagnosis, a wide range of severities as well as a complex etiology (e.g. genetic and environmental factors), there is limited understanding of this disorder and further research is needed (Horváth & Mirnics, 2015).

Schizophrenia is characterized by multiple symptom clusters that include positive, negative, and cognitive symptoms. Positive symptoms include delusions (believing in something that cannot be true), hallucinations (false sensory experiences), disorganized thought or speech, and disorganized or abnormal motor behavior (APA, 2014; NIMH, 2016). Negative symptoms include blunted affect, avolition (difficulty in initiating or sustaining activities), alogia (reduction in verbal communication), anhedonia (decreased enjoyment in pleasurable activities), and

asociality (lack of interest in socializing), with the DSM-5 classifying blunted affect and avolition as the most prevalent negative symptoms (APA, 2014). Cognitive symptoms are manifested as deficits in attention, memory (e.g. working memory and declarative memory), executive functioning (e.g. regulation of thoughts, behaviors, and emotions to attain a goal), and recognition of having a disorder (i.e. anosognosia). People with schizophrenia have reported difficulties in completing educational and vocational tasks due to decreased executive functioning (Nestler, Hyman, Holtzman, & Malenka, 2015).

Overall, the severity of positive and negative symptoms combined with poor social functioning is directly correlated with treatment outcome success for individuals suffering from schizophrenia (Di Michele & Bolino, 2004). Numerous treatment methods are used to manage symptoms, including psychosocial (e.g. psychotherapy, social skills training, and vocational rehabilitation) and pharmacological interventions (e.g. antipsychotics; Mayo Clinic, 2018). However, numerous factors such as delusion of paranoia, anosognosia, and/ or substance use disorders contribute to a failure to maintain an adequate treatment regimen in 50% of patients (Haddad, Brain, & Scott, 2014). This is of great concern as noncompliance is associated with several negative outcomes including hospitalization, reoccurring positive symptoms, enhanced negative symptoms, decreased quality of life, substance abuse, and self-harm (Haddad et al., 2014). Additionally, there is evidence that adolescent substance abuse (e.g. EtOH and cannabis use) is positively correlated with the onset of psychotic symptoms in people later diagnosed with schizophrenia, suggesting an important relationship between drug use and disorder progression (Hambrecht & Häfner, 1996; Semple, McIntosh, & Lawrie, 2005; van Nimwegen, de Haan, van Beveren, van den Brink, & Linszen, 2005).

Adolescent Period of Development

The adolescent period of development is indicative of the developmental stage that segregates childhood from adulthood. During this period of development, an abundance of alterations are occurring in the brain. Behaviorally, there is an increased tendency to explore and seek out euphoric experiences (such as sex and drug use; Walker et al., 2017). The promotion of exploration is most likely due to neuronal synaptic pruning and an underdeveloped reward circuit (Nimwegen, Haan, Beveren, Brink & Linszen, 2005). During the reorganization of this circuitry adolescents not only have an elevated risk and enhanced reward-sensitivity towards using drugs but also display a reduction in sensitivity toward the aversive effects of drugs (Doremus-Fitzwater & Spear, 2016).

Schizophrenia Comorbid with Alcohol Use Disorder

Research indicates that individuals diagnosed with schizophrenia have a significantly higher risk of developing an alcohol-use disorder (AUD; APA, 2014; Green, Drake, Brunette, & Noordsy, 2007; Khokhar et al., 2018) however, the literature differs drastically on the prevalence of comorbid schizophrenia and AUD, ranging from 27% (Thoma & Daum, 2013) to 65% (Volkow, 2009). Regardless of the specific prevalence, it is clear that individuals suffering from schizophrenia are at a much greater risk to develop a comorbid AUD than the general population (6.2%; NIAAA, 2018**).** Schizophrenia comorbid with AUD is typically exhibited by males that experienced an earlier onset of the disorder and leads to greater severity of extrapyramidal, positive symptoms (Thoma & Daum, 2013). Moreover, comorbid expression of schizophrenia and AUD is associated with an increased likelihood of several negative outcomes including; lower quality of life, increased treatment non-compliance rates, increased violent behavior, risk

of suicide, homelessness, and hospitalization (Green et al., 2007; Thoma & Daum, 2013; Khokhar et al., 2018).

There are two predominant hypotheses as to the high prevalence of comorbid schizophrenia and AUD. An initial theory, the self-medicating hypothesis (SMH**),** suggests that people abuse drugs deliberately based on the psychopharmacological effects that provide relief from the symptoms associated with schizophrenia (Chambers, Krystal, & Self, 2001; Goswami, Mattoo, Basu, & Singh, 2004; Khantzian, 1985). For instance, people with schizophrenia have reported that EtOH consumption alleviates positive and negative symptoms including, hallucinations, delusions, anhedonia, asociality, and anxiety (Addington & Duchak, 1997; Chambers, Krystal, & Self, 2001; Thoma & Daum, 2013). A second theory, the primary addiction hypothesis**,** postulates that individuals suffering from schizophrenia have a heightened risk of developing an AUD as both disorders affect common brain pathways (Volkow, 2009). Specifically, the atypical neuropathology of schizophrenia also produces alterations in the regulation of positive reinforcement, incentive salience, behavioral inhibition, and addictive behavior due to the dysregulation of the mesocorticolimbic circuitry (Chambers, Krystal, & Self, 2001). It is important to delineate the nature of the disruptions in the neuropathology pertaining to schizophrenia to further understand the enhanced comorbidity of SUDs in this population as well as to research novel treatment methods.

CHAPTER 2

LITERATURE REVIEW

Nestler and colleagues (2015) indicated that schizophrenia and AUD are independent disorders derived from abnormalities primarily in the mesocorticolimbic circuitry. The mesocorticolimbic dopamine (DA) pathway has been thoroughly established in both humans and nonhuman animals, to be involved in the manifestation of several symptoms associated with schizophrenia, as well as motivation and reward, (for review see Brisch et al., 2004; see also Fallon & Moore, 1978; Oleson & Roberts, 2018; Wise, 2004) and has been further divided into the mesolimbic and the mesocortical pathways (Chinta & Andersen, 2004). Both pathways are comprised predominantly of DA neurons in the ventral tegmental area (VTA) projecting to various regions of the brain including the nucleus accumbens (Acb), olfactory tubercles, amygdala, hippocampus, septum, prefrontal cortex (PFC), cingulate cortex, and perirhinal cortex (Adinoff, 2004; Chinta & Andersen,2004; Gardner, 2011; Olds, & Milner, 1954; Wise, & Bozarth, 1984). Research has found that DA neuronal activation in the mesolimbic pathway is primarily associated with pleasurable stimuli (e.g. food, sex, social interactions, or drugs; for review see Ikemoto, 2007). DA signaling within the mesocortical pathway has been linked to executive functions such as working memory, goal-directed behaviors, and attention (Siddiqui, Chatterjee, Kumar, Siddiqui, & Goyal, 2008). Thus, disruption of the mesocorticolimbic circuit has been implicated in numerous disorders, including schizophrenia and AUD (Nestler et al., 2015).

Mesocorticolimbic Circuitry and Schizophrenia

Malfunction within the mesolimbic pathway contributes to the positive symptoms of schizophrenia (e.g. hallucinations and delusions; Nestler et al., 2015). Evidence suggesting the

involvement of this pathway in schizophrenia was first reported when DA D_2 receptor (D_2-R) antagonist administration resulted in a significant reduction of psychoses in patients diagnosed with schizophrenia (Chambers et al., 2001; Crow, Deakin, & Longden, 1977). Additionally, psychostimulants have been shown to induce psychotic-like effects in human and animal subjects causing DA dysregulation (Chambers et al., 2001; Connell, 1957; Laviolette, 2007; Lodge & Grace, 2007; McCollum & Roberts, 2015). Using functional magnetic resonance imaging (fMRI), patients with schizophrenia were asked to perform a memory retrieval task, and individuals who did not display hippocampal activation during the task also exhibited psychosocial impairments (Weiss et al., 2003). Increased amygdala activation is prevalent in schizophrenia, causing abnormal classifications of aversive or threating stimuli (Kumakura et al., 2007). Similarly, an increase of amygdala activation in schizophrenia patients induces a heightened bias towards aversive processing by over-emphasizing emotions associated with a specific sensory stimulus leading to delusions (Laviolette, 2007; Pankow et al., 2013).

The mesocortical pathway has been implicated in both the negative and cognitive symptoms of schizophrenia. Aberrations in neural processing of the PFC contribute to decreased motivation, drive, and hygiene, as well as asociality and impairment of intuition and judgment (Knable & Weinberger, 1997). Evidence suggests that negative and cognitive symptoms are a result of hypoactivity of DA released from the VTA to the PFC, as well as dysfunction of the DA D_1 receptor, which primarily mediates DA transmission (Chambers et al., 2001; Knable & Weinberger, 1997; McCutcheon, Abi-Dargham, & Howes, 2019; Slistein et al., 2015; Thoma & Daum, 2013). Disruption in DA transmission observed in schizophrenia patients has been associated with abnormalities in “top-down processing” of the PFC ultimately affecting cognition (Lesh, Niendam, Minzenberg, & Carter, 2011). Specifically, researchers conducted

fMRI studies to indicate that the dorsolateral PFC (DLPFC), anterior cingulate cortex, and the mediodorsal thalamus are DA deficient possibly leading to cognitive deficits in schizophrenia patients (Minzenberg, Laird, Thelen, Carter, & Glahn, 2009).

Mesocorticolimbic Circuitry and AUD

The mesolimbic pathway is believed to mediate the reinforcing effects of EtOH, as well as play a key role in EtOH craving and relapse (For review see: Gilpin & Koob, 2008; see also Eisenhardt, Leixner, Luján, Spanagel, & Bilbao, 2015; Imperato & Di Chiara, 1986). EtOH has been shown to stimulate DA neurons that project from the VTA to the Acb and the amygdala (Di Chiara & Imperato, 1988; Engel & Jerlhag, 2014; Fadda, Mosca, Colombo, & Gessa, 1989; Yoshimoto et al., 2000). For instance, EtOH enhances the firing rate of VTA DA neurons stimulating DA release in the shell of the Acb (AcbSh; for review see Deehan, Brodie, & Rodd, 2013; see also Bassareo et al., 2003; Deehan et al., 2016; Engel & Jerlhag, 2014). EtOH consumption has also been found to enhance associative learning by stimulating DA transmission to the amygdala, thereby increasing the emotional salience of EtOH (Di Chiara et al., 1999). Furthermore, EtOH interacts with other neurotransmitters causing an indirect increase of extracellular DA (Engel & Jerlhag, 2014). Critically, co-infusion of compounds that inhibit DA signaling (e.g., DA D_2-receptor agonist, quinpirole) in this pathway produce reductions in the self-administration of EtOH into the posterior VTA suggesting that the reinforcing properties of EtOH in the mesolimbic DA pathway are dependent on DA neuronal activation (Rodd et al., 2004, 2005).

The mesocortical pathway has also been implicated in drug-seeking behaviors and drug dependence and has been shown to control compulsory behaviors directed toward obtaining EtOH, the suppression of thoughts associated with EtOH, and “hyper-responsiveness” to EtOH-

associated stimuli (Adinoff, 2004; Feltenstein & See, 2013). Acute EtOH administration results in a decrease in PFC functioning that contributes to deficits in planning and spatial recognition tasks (Abernathy, Chandler, & Woodward, 2010; Weissenborn & Duka, 2003). Data indicate that the rewarding effects of acute EtOH intake are, in part, mediated by DA release within the PFC (Lammel et al., 2008; Trantham-Davidson & Chandler, 2015). However, chronic EtOH intake is associated with a decrease in DA signaling from the VTA to the PFC producing anhedonia and blunted reward processing during withdrawal (Trantham-Davidson & Chandler, 2015). Researchers have found that AUD causes decreased grey matter in the DLPFC which results in a decrease in neuronal processing (Jernigan et al., 1991; Yang et al., 2016). Unfortunately, the research is lacking as to the biological underpinning of decreased DA transmission during chronic EtOH exposure (Trantham-Davidson & Chandler, 2015).

Modeling in Preclinical Research

Gestational Methylazoxymethanol Acetate Model (MAM)

The gestational MAM model has been extensively used as a developmental model of schizophrenia (Ratajczak, Woźniak, & Nowakowska, 2013). The model was developed in response to research suggesting that schizophrenia is attributed to significant gestational distress (e.g. influenza or malnutrition) to the fetus, during the second trimester of pregnancy (Jones, Watson, Fone, 2011). MAM is a neurotoxin that inhibits DNA synthesis, causing apoptosis in cells that are actively replicating DNA (Talamini, Koch, Ter Host, & Korf, 1998). Interestingly, MAM does not affect glial cells or peripheral organs making it a practical method for modeling schizophrenia (Jones et al., 2011; Ratajczak et al., 2013). Pregnant female rats are treated with MAM on gestational day (GD) 17 when the fetus has completed brain cortex proliferation, but subcortical regions are still undergoing development (Jones et al., 2011). The treatment causes

reductions in the size of several regions of the neocortical and limbic systems (medial prefrontal cortex, entorhinal cortex, hippocampus, and occipital cortex), which is consistent with the clinical histopathology observed in schizophrenia (Talamini et al., 1998; Lodge & Grace, 2009; Jones et al., 2011; Ratajczak et al., 2013). However, studies have not been able to exhibit an alleviation of symptoms caused by MAM when rodents are administered typical or atypical antipsychotics (For review see: Jones, 2011). There is a limited amount of research conducted on female rats exposed to MAM during GD 17 (Perez, Donegan, & Lodge, 2019), which is concerning given that schizophrenia affects males and females equally (Li, Ma, G. Wang, Yang, & C. Wang, 2016). Finally, MAM is a known carcinogen and exposure is potentially hazardous to laboratory personnel, thus extreme caution must be utilized when handling the compound (Lodge, 2013).

Neonatal Ventral Hippocampal Lesion Model (NVHL)

The NVHL model was developed to approximate abnormalities in the ventral hippocampus (VH) that have been reported in people suffering from schizophrenia (Lipska, Jaskiw, Chrapusta, Karoum, & Weinberger, 1992). On postnatal day (PND) 7 rats are bilaterally infused with ibotenic acid in the VH causing irreversible ablation and disruption of the hippocampal formation (For review see: Lipska & Weinberger, 2002; see also Lipska, Jaskiw, & Weinberger, 1993). The VH lesions progressively produce DA-related behavioral and molecular changes during late adolescence into early adulthood that approximate the clinical population with schizophrenia such as increases in mesolimbic DA activity and inhibition of cortical DA activity (Khokhar & Todd, 2018; Lipska & Weinberger, 1995; Tseng, Chambers, & Lipska, 2009). It has also been noted that mortality rates for the NVHL surgery are approximately 15%

(Richtand et al. 2005) and 30-33% of rodents show unilateral damage leading to failure to reach the histopathological criteria of schizophrenia (Jones et al., 2011).

Neonatal Quinpirole Model of Schizophrenia

Quinpirole is a DA D_2/D_3-receptor agonist that creates a lifelong enhanced sensitization, but not overall quantity, of D2 receptors (D_2-R) following chronic intraperitoneal (i.p.; 1mg/kg) injections during the neonatal period (PND 1-21; Kostrezewa, 1993; Peterson et al., 2017; Rodrigo et al., 2011). The enhanced sensitization of D_2 receptors is behaviorally manifested as stereotypy (i.e. clockwise lateral movement), and abnormalities in locomotion, learning, and memory (Kostrzewa, Nowak, Brus, & Brown, 2016; Rodrigo et al., 2011), which is also observed in the human population with schizophrenia (For review see: Weidenauer et al., 2017). The unchanged quantity of D_2-R is important because this aspect of the model is also consistent with findings in the clinical population (Kostrezewa et al., 2016). DA receptor sensitivity can be behaviorally measured in increases of locomotion, yawning, stereotypies, and vertical jumping, deficits can also be observed in cognitive tasks (Kostrezewa, 1993).

The neonatal quinpirole (NQ) model exhibits face validity concerning atypical behaviors. For example, D_2 supersensitization in rodents creates deficits in prepulse inhibition (PPI; sensorimotor gating; Kostrezewa et al., 2016; Maple, Smith, Perna, & Brown, 2015) which is indicative of deficits in information processing that are associated with schizophrenia (Brisch et al., 2014; Maple et al., 2015). In humans diagnosed with schizophrenia, PPI deficits are directly correlated with the severity of positive symptoms which are markedly reduced by antipsychotic drugs (Meincke et al., 2004). Similarly, PPI deficits in NQ rats can be attenuated by the administration of an antipsychotic (Maple et al., 2015).

Construct validity is demonstrated when a preclinical model and a human disorder share a common biological factor, such as a genetic mutation (Kostrezewa et al., 2016). In the NQ model, brain-derived neurotrophic factor (BDNF) is significantly reduced, similar to humans with schizophrenia (Maple et al., 2015). BDNF is imperative for CNS neurogenesis by increasing cell survival (Durany et al., 2001) and disruption in BDNF levels is believed to contribute to the neuropathology of schizophrenia in the affected brain regions (Favalli, Li, Belmonte-de-Abreu, Wong, & Daskalakis, 2012). The NQ model displays deficits in hippocampal BDNF expression resulting in cognitive aberrations (Brown, Gass, & Kostrzewa, 2002; Thacker et al., 2006). Coincidentally, Durany and colleagues (2001) observed hippocampal BDNF deficits in postmortem patients diagnosed with schizophrenia. In the NQ model, microdialysis studies have indicated significant increases in DA outflow of the Acb compared to control rats, which is similar to the observed increased accumbal DA levels in the clinical population (Cope et al., 2010).

Predictive validity is established when a preclinical model successfully responds to human treatment (Belzung & Lemoine, 2011). The common treatment for schizophrenia is the administration of antipsychotics, such as haloperidol (typical antipsychotic) or clozapine and olanzapine (atypical antipsychotic; Patel, Cherian, Gohil, & Atkinson, 2014). The function of typical antipsychotics is to block DA from binding to D2-R resulting in reductions of DA transmission to the Acb (Seeman, 2002). The administration of antipsychotics in NQ rats creates a marked reduction of cognitive symptoms demonstrated in Morris Water Maze (MWM) performance (Thacker et al., 2006). The MWM is a hippocampal spatial learning task for rodents, in which there is a platform submerged in water and rodents must use spatial navigation and reference memory to find the platform for a set number of trials (Morris, 1984; Vorhees &

Williams, 2006). When NQ rats were administered olanzapine in adulthood, they exhibit an alleviation of cognitive deficits demonstrated by an increased performance on the MWM (Thacker et al., 2006). Additionally, the conditioned place preference (CPP) task can demonstrate the associative properties formed nicotine and the context in which the rats received the drug (Brown et al., 2018; Perna, Henderson, Bruner, & Brown, 2011). The CPP paradigm implements the principles of classical conditioning to assess the associative properties of a stimulus by measuring the amount of time spent in a particular area that was paired with the stimulus (Tzschentke, 2007). Interestingly, the administration of haloperidol blocked the associative effects of nicotine in both the NQ rats and the saline rats, but clozapine only blocked associative effects of nicotine in NQ treated animals (Brown et al., 2018a).

Animal Models of Schizophrenia and AUD

Several studies investigating the comorbidity of SUDs using animal models of schizophrenia have provided mixed findings (For review see: Ng, McGirr, Wong, & Roder, 2013; see also Amitai & Markou, 2009; Rezvani, Kholdebarin, Dawson, & Lavin, 2008). Only two models have been studied relative to SUDs. Studies utilizing the NVHL model of schizophrenia have found that VH lesioned rats will self-administer multiple substances (e.g. cocaine, methamphetamine, nicotine, and EtOH) and become sensitized to the substances more quickly than control rats in a similar fashion to the human population exhibiting comorbid schizophrenia and SUD (Berg, Sentir, Bell, Engleman, & Chambers, 2015; Brady, McCallum, Glick, & O'Donnell, 2008; Chambers & Self, 2002; Khokar & Todd, 2018). Evidence also exists that adolescent EtOH consumption produces an increase in adult EtOH drinking in NVHL animals (Jeanblanc et al. 2014). This correlates with human schizophrenia research indicating that prodromal EtOH exposure in adolescence is associated with AUD in adulthood (Jeanblanc et

al. 2014; Khokar & Todd, 2018). To date, however, the majority of research on drug use in the NQ model has focused on the addictive properties of stimulants (e.g. nicotine and amphetamines; Cope et al., 2010; Peterson et al., 2017). Prior to the current study, there has not been any work to analyze whether EtOH consumption would be affected in the NQ model of schizophrenia.

Current Study

The prevalence of AUD in people diagnosed with schizophrenia is significantly higher than the general population, with rates reaching upwards of 65% (Volkow, 2009). The neuronal mechanisms associated with these disorders are not well understood, therefore further research is necessary. This project seeks to analyze ethanol drinking behavior in a preclinical model of schizophrenia as a preliminary step to potentially understand the underlying aberrations in neurotransmitter signaling that manifest in schizophrenia and AUD. The purpose of assessing EtOH consumption in this model is to produce supplementary information on the common neuronal pathways that intersect schizophrenia and AUD. Based on the literature review above the hypotheses of the proposal are as follows:

- H1: The neonatal quinpirole model will prove to be predictively valid in assessing EtOH consumption in a preclinical model of schizophrenia comorbid AUD.
- H2a: Rats neonatally treated with quinpirole during PND 1-21 will consume significantly more EtOH than their saline counterparts during both exposure periods (PND 28-42, PND 75-120).
- H2b: Rats neonatally treated with quinpirole during PND 1-21 will significantly consume more EtOH than their saline counterparts during the first exposure period (PND 28-42).

- H2c: Rats neonatally treated with quinpirole during PND 1-21 will significantly consume more EtOH than their saline counterparts during the second exposure period (PND 75-120).

CHAPTER 3

METHODS

Subjects

Adolescent NQ female Sprague Dawley rats were 22 days old when obtained from Brown Laboratory (Mountain Home, TN) and group housed until PND 28. Male and female adult Sprague Dawley breeders were ordered (Envigo Inc., Indianapolis, IN) and housed together until females are approximately at gestational day (GD) 17 at which point pregnant dams were singly housed. Rat pups were born at approximately GD 22 which represented post-natal day (PND) 0. The rat pups resided with the female dam until PND 21 when they were weaned, and group housed until PND 28. Animals were derived from four litters and group assignments were based on neonatal treatment and EtOH concentration exposure in adolescence and adulthood (Table 1). Animals were housed in a reverse 12-h light/dark cycle. Food and water were available *ad libitum* throughout the experiment. All procedures were approved by East Tennessee State University Animal Care and Use Committee prior to initiation.

Table 1.
Group Assignment Table

	Quinpirole (NQ 10-20) n = 10	**Quinpirole (NQ 10-10) n = 10**	**Saline n = 10**
Adolescent Ethanol Concentration	10% (v/v)	10% (v/v)	10% (v/v)
Adulthood Ethanol Concentration	20% (v/v)	10% (v/v)	20% (v/v)

Drugs and Solution

Quinpirole hydrochloride (Sigma Aldrich, St. Louis, MO) was diluted with 0.9% (w/v) isotonic saline (Ricca Chemical Company, Arlington, TX) to form a 1 mg/kg concentration. 190 proof EtOH (Pharmco by Greenfield Global, Inc., Shelbyville, KY) was diluted with deionized water to 10% (v/v) and 20% (v/v) EtOH concentrations.

Procedure

Rats were given single daily intraperitoneal (i.p.) injections of either quinpirole HCL (1 mg/kg) or 0.9% saline (1 mg/kg) based on body weight from PND 1-21. On PND 21 rats were weaned from the dam and group-housed (3-4 to a cage). On PND 28, all rats were singly housed in order to assess adolescent EtOH consumption.

Two-bottle Choice Task with Two Exposure Periods

Animals were tested for EtOH consumption using a 24-hour 2 bottle free-access paradigm. The timing of EtOH access approximated previous research examining EtOH consumption in animal models of schizophrenia (Jeanblanc et al., 2014). Rats were exposed to EtOH during two developmental periods. The first exposure occurred during adolescence (PND 28-42) and the second occurred during adulthood (PND 75-120). During both exposure periods, rats were provided with two Ancare (Bellmore, NY) screw top bottles on their home cage. In the first exposure period (PND 28-42) the bottles contained either 10% (v/v) EtOH or tap water. On PND 42 the EtOH bottles were removed and the rats had access only to tap water. The second exposure period (PND 75-120) the bottles contained either 10% EtOH (NQ 10-10), 20% EtOH (v/v; NQ 10-20 & Saline) or tap water. On PND 90 the EtOH bottles were removed and the rats had access to tap water only. During the two exposure periods, food and fluid intake and body weights were recorded daily.

Statistical Analysis

Daily readings of body weight and the consumption of EtOH, water, and food were recorded into a spreadsheet using Microsoft Excel (2019). Daily means and standard errors of consumption (EtOH, water, and food) were calculated for each group. To properly assess EtOH intake, ml of EtOH consumed was converted to grams of EtOH consumed by animal body weight in order to obtain the amount of intake relative to the animal's body weight. Daily intake graphs were created using GraphPad Prism 6 (2017). EtOH intake data was organized into JASP 0.9.2 (2019) to investigate the effect of EtOH consumption during two Exposure Periods (Adolescence vs. Adulthood) by Neonatal Treatment (NQ 10-20, NQ 10-10, & Saline) and a repeated-measures ANOVA with Neonatal Treatment as the between-subjects factor and Exposure Period as a within-subject factor was fitted to the data. Since the exposure period was a repeated measure of EtOH consumption (g/kg). The alpha criterion was set at $p < 0.05$ to further investigate significant interactions. Outliers were defined as data anomalies that were two standard deviations above or below the mean. When outliers were identified the datapoint was reverted to the mean. In order to determine the significance of body weights, food and water consumption on individual days of exposure, between the three groups, a one-way ANOVA was fitted to the data using *aov* function (stats package) and *PostHocTest* (DescTools; Signorell et al., 2019) in R 3.6.0 (2019). Since there were 28 days of exposure, *p*-values acquired from the one-way ANOVAs were adjusted using the R package *stats* (2019) with Benjamini – Hochberg corrections in order to decrease the false-discovery rate (Benjamini & Hochberg, 1995).

CHAPTER 4

RESULTS

The descriptive measurements for EtOH consumption are presented in Table 1. An ethanol bottle leaked causing an animal in the NQ 10-20 group to display larger than possible ethanol consumption, thus this data point was reverted to the group mean (Table 2). A two-way ANOVA (Days of EtOH Exposure by Neonatal Treatment Group) with repeated measures was fit to the data. Mauchly's test indicated that the data violated the sphericity assumption, therefore sphericity corrections using Greenhouse – Geisser were implemented and are shown in Table 3. The repeated measures ANOVA demonstrated an increase in EtOH consumption, as it revealed a significant between-subjects effect of Neonatal Treatment ($F_{(2,27)} = 4.259$, $p = 0.025$, $\eta^2 = 0.240$), a significant within-subjects effect of Days of EtOH Exposure ($F_{(8.926, 241.001)} = 7.717$, $p < 0.001$, $\eta^2 = 0.191$; Figure 1), and an interaction effect of Neonatal Treatment by Days of EtOH Exposure ($F_{(17.852, 241.001)} = 2.813$, $p < 0.001$, $\eta^2 = 0.139$). A Benjamini-Hochberg post hoc test revealed that the NQ 10-10 and Saline groups differed significantly at $p = 0.020$. Pairwise comparisons were fit to the data to assess group differences of EtOH consumption during individual days (Figure 2) indicating that NQ 10-10 group consumed more EtOH than NQ 10-20 and Saline groups on PND 83; 85-87; 89 (*p's* < 0.05, Fig. 2) and NQ 10-10 group had a greater intake of EtOH than the Saline group on PND 84 (*p's* < 0.05, Fig. 2). NQ 10-20 group consumed more EtOH than NQ 10-10 group on PND 77-78 (*p's* < 0.05, Fig 2).

Figure 1. Overall mean (± SEM) EtOH consumption between Exposure Period. * represents Adulthood mean EtOH consumption is significantly greater than Adolescent mean consumption, $p < 0.05$.

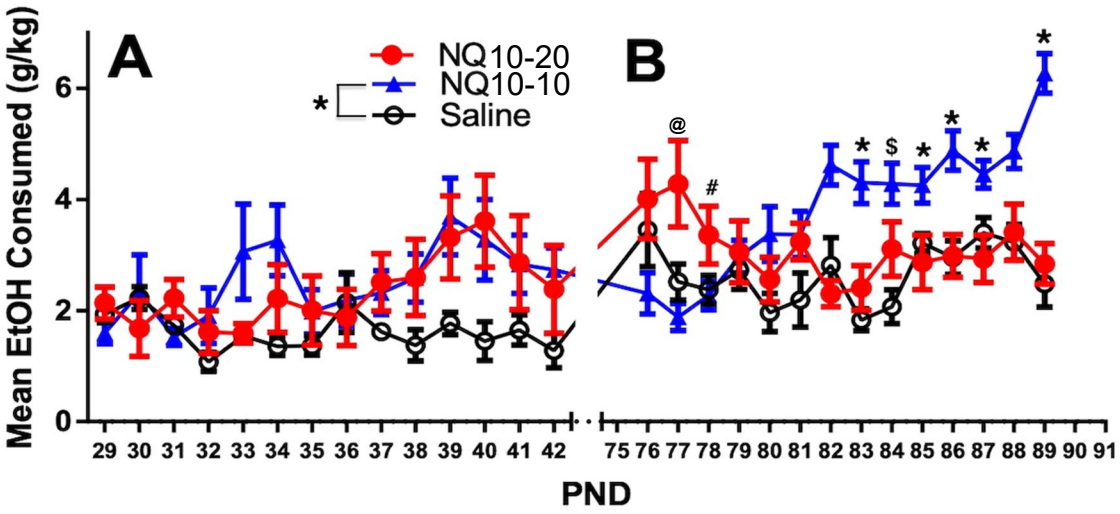

Figure 2. Treatment Group mean (± SEM) of EtOH consumption during each day of EtOH exposure. Figure A represents the Adolescent Exposure Period while Figure B denotes the Adulthood period. There was a significant interaction effect between the NQ #2 & Saline, denoted by * in the legend. @ represent NQ 10-20 being significantly higher than NQ 10-10 & Saline. # represent NQ 10-20 being significantly higher than NQ 10-10. * represent NQ 10-10 being significantly higher than NQ 10-20 and Saline and $ represent NQ 10-10 being significantly higher than Saline. Significance determined through pairwise comparisons using Benjamini-Hochberg corrections (p's < 0.05).

Body Weight and Food and Water Consumption

Bodyweight and food and water consumption (grams) during adolescence and adulthood were examined between Neonatal Treatment Groups (NQ 10-20 vs. NQ 10-10 vs. Saline). Means and standard deviations of Exposure Period between Treatment group are presented in Table 3.

Body Weights

A repeated-measures ANOVA (Days of EtOH Exposure by Neonatal Treatment Group) was fit to the data. Mauchly's test indicated that the data violated the sphericity assumption, therefore sphericity corrections using Greenhouse – Geisser were implemented. The repeated measures ANOVA demonstrated an increase in body weight, as it revealed a significant

between-subjects effect of Neonatal Treatment ($F_{(2,27)} = 7.261$, $p = 0.003$, $\eta^2 = 0.350$), a significant within-subjects effect of Days of EtOH Exposure ($F_{(1.448, 39.103)} = 2348.90$, $p < 0.001$, $\eta^2 = 0.980$), and an interaction effect of Neonatal Treatment by Days of EtOH Exposure ($F_{(2.897, 39.103)} = 10.01$, $p < 0.001$, $\eta^2 = 0.008$). A post hoc Benjamini-Hochberg test revealed that the NQ 10-20 and Saline groups differed significantly at $p = 0.003$.

Pairwise comparisons using one-way ANOVAs were fit to each day and the p values were adjusted using Benjamini-Hochberg corrections. The comparisons indicated that the NQ 10-20 group weighed significantly more than the Saline group during the Adolescent Exposure Period on PND 37 - 41 (*p*'s < 0.043, Fig. 3), with mean weight differences of 21.072 grams. During Adulthood and PND, 42 NQ 10-20 and NQ 10-10 groups weighed significantly more than Saline groups on PND 76 - 89 (*p*'s < 0.001, Fig. 3), with mean weight differences of 41.816 grams.

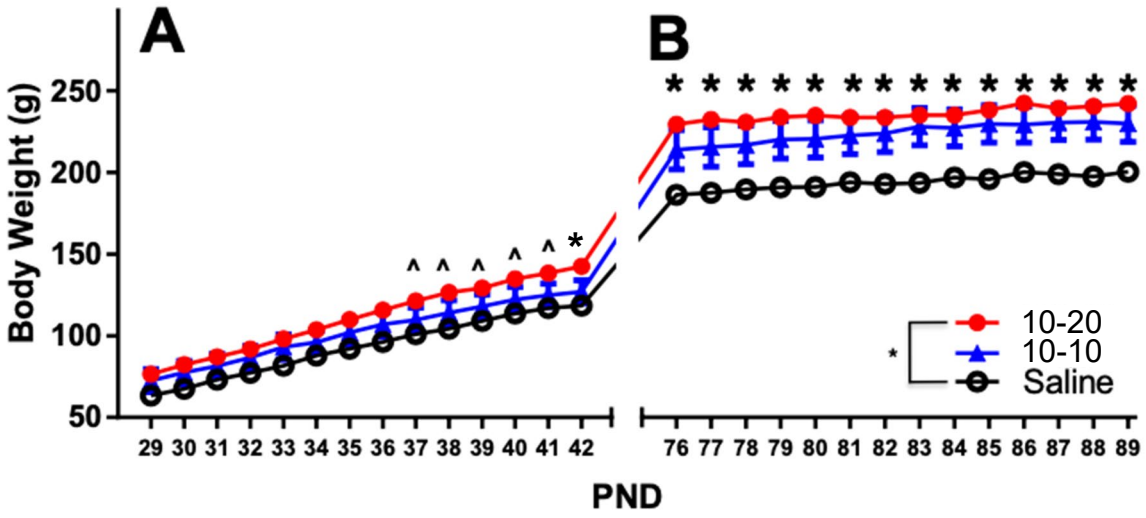

Figure 3. Treatment Group mean (± SEM) body weight during each day of EtOH exposure. Panel A is the Adolescent Exposure Period and Panel B is the Adulthood Exposure Period. There was a significant interaction effect between the NQ 10-20 & Saline, denoted by * in the legend. ^ represent NQ 10-20 being significantly higher than Saline. * represents NQ 10-20 & NQ #2 being significantly higher than Saline. Significance determined through pairwise comparisons using Benjamini-Hochberg corrections (*p's* < 0.05).

Food Intake

The analysis of food consumption commenced on PND 34 rather than PND 28 because the pups were recently weaned and separated from their siblings. To view whether food intake differed, a two-way ANOVA (Days of EtOH Exposure by Neonatal Treatment Group) with repeated measures was fit to the data. Mauchly's test indicated that the data violated the sphericity assumption, therefore sphericity corrections using Greenhouse – Geisser were implemented. The repeated measures ANOVA demonstrated a difference in food consumption, as it revealed a significant between-subjects effect of Neonatal Treatment ($F_{(2,27)} = 8.159$, $p = 0.002$, $\eta^2 = 0.377$), a significant within-subjects effect of Days of EtOH Exposure ($F_{(7.497, 202.427)} = 6.154$, $p < 0.001$, $\eta^2 = 0.145$), and an interaction effect of Neonatal Treatment by Days of

EtOH Exposure ($F_{(14.995, 202.427)} = 4.630$, $p < 0.001$, $\eta^2 = 0.218$). A post hoc Tukey's test revealed that the NQ 10-20 and NQ 10-10 groups differed significantly at $p = 0.006$ and that NQ 10-20 and Saline groups differed significantly at $p = 0.004$.

Pairwise comparisons were fit to the data to assess group differences of food consumption during individual days (Figure 4) indicating that the NQ 10-20 group consumed significantly more food than the NQ 10-10 and the Saline group during the Adolescent Exposure Period on PND 42 (p's < 0.05, Fig. 4). During Adulthood the NQ 10-20 group consumed significantly more food than the NQ 10-10 and Saline groups on PND 77, 80 and 88 (p's < 0.028, Fig. 4). NQ 10-20 and NQ 10-10 groups consumed significantly more than the Saline group on PND 83 ($p = 0.030$, Fig. 4). NQ 10-20 and Saline groups consumed significantly more than the NQ 10-10 group on PND 86 ($p < 0.001$, Fig. 4).

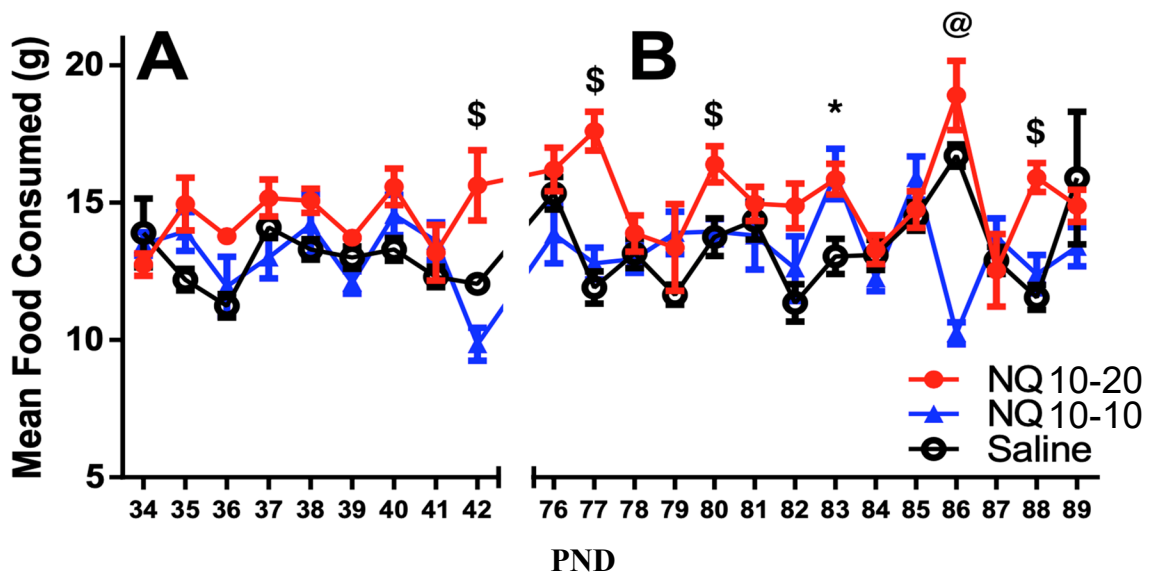

Figure 4. Treatment Group mean (± SEM) food intake during each day of EtOH exposure. Panel A is the Adolescent Exposure Period and Panel B is the Adulthood Exposure Period. There was a main effect of interaction in that NQ 10-20 > NQ 10-10 & Saline. $ represents NQ 10-20 being significantly higher than NQ 10-10 & Saline. * represent NQ 10-20 & NQ 10-10 being significantly higher than Saline. @ represent NQ#1 and Saline being significantly higher than NQ 10-10. Significance determined through pairwise comparisons using Benjamini-Hochberg corrections (*p's* < 0.05).

Water Consumption

To assess whether water intake differed, a two-way ANOVA (Days of EtOH Exposure by Neonatal Treatment Group) with repeated measures was fit to the data. Mauchly's test indicated that the data violated the sphericity assumption, therefore sphericity corrections using Greenhouse – Geisser were implemented. The repeated measures ANOVA demonstrated a difference in water consumption, as it revealed a significant between-subjects effect of Neonatal Treatment ($F_{(2,27)} = 4.459$, $p = 0.021$, $\eta^2 = 0.248$), a significant within-subjects effect of Days of EtOH Exposure ($F_{(9.671, 261.117)} = 15.322$, $p < 0.001$, $\eta^2 = 0.300$), and an interaction effect of Neonatal Treatment by Days of EtOH Exposure ($F_{(19.342, 261.117)} = 4.389$, $p < 0.001$, $\eta^2 = 0.172$).

A post hoc Tukey's test revealed that the NQ 10-20 and Saline groups differed significantly at p = 0.029. Pairwise comparisons were fit to the data to assess group differences of water consumption during individual days (Figure 5) indicating that the Saline group consumed significantly more water than the NQ 10-20 and/or NQ 10-10 groups during Adulthood on PND 76, 78, 81, 84, 85, 87, and 89 (*p*'s < 0.01, Fig. 5) with a mean consumption difference of 8.626 grams. NQ 10-20 and Saline groups consumed significantly more water than the NQ 10-10 group on PND 86 (p < 0.001, Fig. 5) with a mean consumption difference of 12.056 grams.

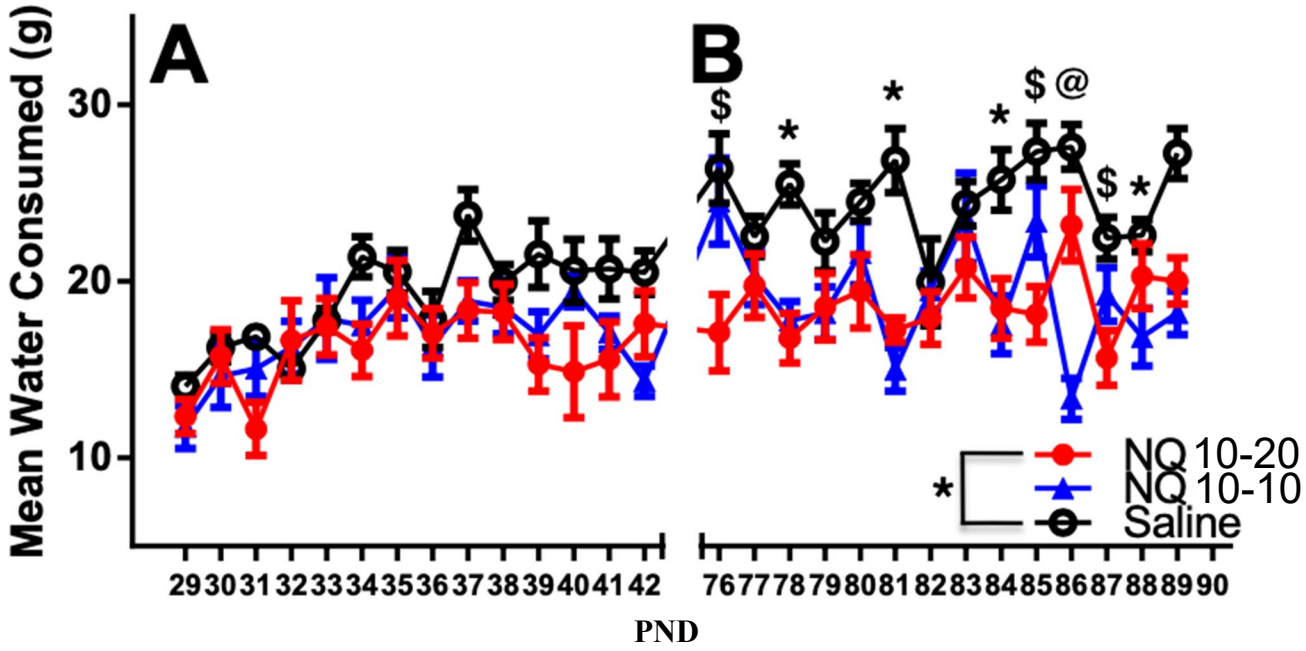

Figure 5. Treatment Group mean (± SEM) water consumption during each day of EtOH exposure. Panel A is the Adolescent Exposure Period and Panel B is the Adulthood Exposure Period. There was a main effect of interaction between the NQ10-20 & Saline, denoted by * in the legend. $ represent Saline being significantly higher than NQ 10-20. * represent Saline being significantly higher than NQ 10-20 & NQ 10-10. @ represent NQ#1 10-20 & Saline being significantly higher than NQ 10-10. Significance determined through pairwise comparisons using Benjamini-Hochberg corrections (*p's* < 0.05).

Table 2.
Descriptive statistics for EtOH consumption

Descriptive Statistics									
	Adolescent EtOH Consumption (with bottle leak)			Adolescent Adjusted EtOH Consumption (without bottle leak)			Adult EtOH Consumption		
	NQ 10-20	NQ 10-10	Saline	NQ 10-20	NQ 10-10	Saline	NQ 10-20	NQ 10-10	Saline
N	10	10	10	10	10	10	10	10	10
Mean	2.329	2.519	1.608	2.053	2.519	1.608	3.096	3.864	2.657
SD	1.242	1.024	0.3192	0.7833	1.024	0.3192	0.9942	0.5579	0.7492
Min	1.273	1.275	1.14	1.273	1.275	1.14	1.423	3.029	1.664
Max	5.084	4.213	2.21	3.553	4.213	2.21	4.249	4.734	4.133

Note. An outlier was found in the adolescent quinpirole group; thus, it was reverted to the group mean. Changes in the Quinpirole group mean before and after adjusting the outlier is indicated above, in red.

Table 3.
Repeated measures ANOVA for ETOH consumption

Between Subjects Effects

	Sum of Squares	df	Mean Square	F	p	η²
Neonatal Treatment	126.0	2	63.000	4.259	0.025	0.240
Residual	399.4	27	14.79			

Note. Type III Sum of Squares

Within Subjects Effects

	Sum of Squares	df	Mean Square	F	p	η²
EtOH Exposure	309.8	8.926 (26.000)	34.710 (11.916)	7.717	6.565e -10 (7.163e -25)	0.191
EtOH Exposure * Neonatal Treatment	225.9	17.852 (52.000)	12.653 (4.344)	2.813	1.900e -4 (1.186e -9)	0.139
Residual	1084.0	241.001 (702.000)	4.498 (1.544)			

Note. Type III Sum of Squares. Mauchly's test of sphericity indicates that the assumption of sphericity is violated ($p < 0.05$). Greenhouse – Geisser corrections are noted in the table with values prior to the corrections in parentheses.

Table 4.
Descriptive Statistics for Food, Water, and Body Weight

		Food Consumption (g)		Water Consumption (g)		Body Weight (g)	
		Ado	Adult	Ado	Adult	Ado	Adult
NQ 10-20 (n = 10)							
	Mean	13.335	15.223	16.149	18.926	111.236	235.712
	SD	1.170	1.010	4.224	4.195	9.431	12.022
	Min	11.5	13.827	10.664	14.400	96.329	213.014
	Max	15.457	16.700	23.750	28.233	124.764	251.357
NQ 10-10 (n = 10)							
	Mean	12.154	13.417	16.743	19.225	102.246	224.125
	SD	2.020	1.459	3.832	4.066	22.915	35.733
	Min	9.679	11.643	11.821	13.036	80.393	183.571
	Max	15.429	15.742	24.179	27.628	138.929	289.429
Saline (n = 10)							
	Mean	12.218	13.517	19.061	24.674	92.979	193.896
	SD	0.819	0.937	3.165	3.381	4.216	9.429
	Min	10.633	12.536	14.464	18.451	87.571	180.607
	Max	13.400	15.750	25.679	30.393	99.464	205.893

Note. Ado = adolescent exposure period; Adult = adult exposure period.

CHAPTER 5

DISCUSSION

The purpose of this experiment was to investigate EtOH consumption in the NQ model of schizophrenia using the two-bottle 24 hr access paradigm with adolescent and adulthood exposure periods. The data suggest an increased level of consumption in an animal model of schizophrenia. Specifically, the NQ 10-10 group consumed significantly larger amounts of EtOH than the Saline group. This significant increase in EtOH consumption occurred only in adulthood beginning at PND 82 and lasted throughout the remainder of the study. The late onset of increased consumption in the NQ 10-10 group could have been due to solution palatability towards EtOH (Kiefer, 1995; Kiefer, Bice, & Badia-Elder, 1994). Previous studies (Kiefer & Dopp, 1989) have demonstrated that rats may habituate to the taste of EtOH after a prolonged exposure, which suggests that the taste towards EtOH has become less aversive.

Taste reactivity tests are a way to measure the hedonic value an organism attributes to a gustatory stimulus (Kiefer & Dopp, 1989; for review see: Grill & Norgren, 1978). The palatability of a substance can have a great impact on future consummatory behaviors (Grill & Norgren, 1978). Specifically, concerning EtOH palatability in rats, EtOH concentrations exceeding 15% have been shown to result in a diminished interest towards the EtOH, which is represented as a lack of consumption (Kiefer et al., 1994). When conducting a two-bottle choice task (one bottle containing water, one bottle containing EtOH) diminished interest in the EtOH solution would result in an avoidance of the EtOH bottle and the subsequent consumption of mostly water (Kiefer, 1995; Kiefer & Dopp, 1989).

In the current study, palatability could have affected the EtOH consumption amount of the NQ 10-20 and Saline groups due to the increased EtOH concentration between adolescence

(10%) and adulthood (20%). During adulthood, the two groups could have experienced aversive reactions towards the 20% EtOH consequently causing the diminished intake levels seen in Figure 2. Alternatively, the NQ 10-20 and Saline group could have increased their palatability for the taste of EtOH but the increase in consumption did not occur due to the postingestional factors associated with EtOH (Deutsch, Walton, & Thiel, 1978; Kiefer et al., 1994). However, the prolonged exposure to the 10% EtOH concentration in the NQ 10-10 group seemed to increase the palatability and decreases the aversion towards EtOH (Kiefer, 1995). The habituation towards the solution took effect on PND 82, in which a significant increase of EtOH consumption was observed for the remainder of the experiment.

During the adolescent exposure period, all three treatment groups consumed similar amounts of EtOH. Even though one of the hypotheses of the present study suggested that NQ rats would consume more EtOH during adolescence the results of there not being a difference have been observed in previous research (Jeanblanc et al., 2014) as well. EtOH consumption in humans also suggest that adults consume more than adolescents, overall, but adolescents consume larger quantities of EtOH than adults on a single occasion (Spear, 2018). Since human adolescents exhibit a tendency to consume large amounts of EtOH over a small period of time, the assumption was that the adolescent rodents would show similar drinking behaviors.

During adulthood, beginning on PND 83, the NQ 10-10 group diverged from the other treatment groups and chronically consumed more EtOH for the remainder of the study. Unfortunately, there was not a Saline control group to compare NQ 10-10 group's EtOH consumption against. Since, there was not a control group for the NQ 10-10 group, the interpretations of the data must be limited. A study using a three-bottle (10% EtOH, 10% diluted white wine, & water) free-choice paradigm found that over a four-week period adult Sprague

Dawley females consumed on average 7.17 g/kg/week of combined white wine and 10% EtOH (Cacace, Plescia, Sardo, & Cannizzaro, 2012), which is significantly less than the amount of EtOH consumed by the NQ 10-10 group in the current study.

Interestingly, the NQ 10-10 group exhibited a late onset of increased EtOH consumption, commencing at PND 82. From a neurobiological perspective, the phenomena could be a byproduct of neuroadaptation, by the brain trying to adapt to the effects of EtOH (Fadda & Rossetti, 1998; Himmelsbach, 1941). Neuroadaptation can be triggered by chronic EtOH administration and allows an organism to gain an increased tolerance to the substance. Increased tolerance to EtOH would explain the delayed increase in EtOH consumption in the NQ 10-10 group (Fadda & Rossetti, 1998).

Unfortunately, the NQ 10-20 group did not significantly differ from the Saline group in their ethanol consumption. The hypothesis that quinpirole would enhance EtOH consumption is because EtOH has been shown to enhance dopaminergic transmission in the brain, specifically from the VTA to the Acb (Di Chiara, 1997). EtOH enhances DA transmission directly, by increasing DA firing rate from the VTA to the Acb (Deehan et al., 2013; Deehan et al., 2016; Gilpin & Koob, 2008), and quinpirole super sensitizes D_2-R in this pathway (Kostrezewa, 1993; Peterson et al., 2017) creating an enhanced response to the increased flow of DA due to EtOH consumption which would speculatively increase dependence to EtOH. Other factors namely, change of adulthood EtOH exposure, rat strain, and sex differences, could have also contributed to the insignificance in EtOH consumption between the NQ 10-20 group and the Saline group.

Change of Adulthood EtOH Exposure Period

The current study attempted to replicate a prior study (Jeanblanc et al., 2014) that increased the EtOH percentage from 10% to 20% from the adolescent exposure period to

adulthood. However, during the adulthood exposure period, the current study used an unrestricted free-choice paradigm while Jeanblanc et al. (2014) conducted an intermittent access two-bottle choice paradigm. The 20% intermittent access paradigm gives animals access to EtOH every other day for 24 hours (Jeanblanc, 2014; Simms et al., 2008, Wise, 1973). This method creates long-lasting high-EtOH preferencing by establishing an alcohol deprivation effect (ADE). The ADE is a transient increase in voluntary consumption compared to baseline due to the reinstatement of EtOH. The temporary increase in consumption allows rats to reach pharmacologically significant blood EtOH concentrations (BECs) (Simms et al., 2008; Sinclair, Hyytiä, & Nurmi, 1992). Thus, differing paradigms could be why different levels of consumption were seen between the two studies.

Alternatively, the intake differences between groups could have been attributed to a floor effect in EtOH consumption. During adulthood, NQ 10-20 and Saline rats consumed similar amounts of EtOH, but the NQ 10-10 rats consumed significantly more EtOH than both groups. The difference in EtOH concentration could contribute to why the NQ 10-10 rats consumed significantly greater quantities of EtOH than the NQ 10-20 and Saline groups. Similarly, studies have shown that rats prefer EtOH concentrations ranging from 5 to 15% (Myers & Eriksson, 1968). Although, a study assessing EtOH dose-response in Long-Evans rats, found that peak responding occurred during 10% and 20% EtOH concentrations indicating that these doses should exhibit similar reinforcing properties (Carnicella, Yowell, & Ron, 2011). Unless the reinforcing properties of EtOH are dependent on the strain of rat.

Strain of Rat and EtOH Intake

In the current study, the non-significance of EtOH consumption between the NQ 10-20 and Saline groups could be attributed to a floor effect due to the rat strain used in the present

study (Carnicella, Ron, & Barak, 2014). Sprague Dawley rats were utilized because all previous NQ research used this rat strain (e.g. Brown et al., 2012; 2018a & b). EtOH intake can vary tremendously depending on the strain of rat and even the supplier where that the rat was purchased (e.g. Hosová & Spear, 2018; Palm, Roman, & Nylander, 2011; Simms et al., 2008; for review see Carnicella et al., 2014). The most common outbred rat strain used for EtOH research is the Wistar rat and because of their superior EtOH intake capabilities, this strain has also been selectively bred to create lines of alcohol-preferring rats (e.g. Conte et al., 2019; Jadhav, Magistretti, Halfon, Augsburger & Boutrel, 2017; Momeni, Segerström & Roman, 2015; Palm et al., 2011; Priddy et al., 2017). However, some studies have used Long-Evans rats (e.g. Barak, Ahmadiantehrani, Kharazia, & Ron, 2011, Doherty, & Gonzales, 2015; Li, Bian, Dave, & Ye, 2011; Simms et al., 2008) or Sprague Dawley rats (e.g. Bito-Onon, Simms, Chatterjee, Holgate, & Bartlett, 2011; Hosová & Spear, 2019; Li et al., 2019; Martinetti et al., 2006) to assess EtOH consumption. Even though the Wistar strain is the most commonly used rat strain for EtOH studies, researchers have differing opinions on whether the Wistar strain is the best rat to use for assessing EtOH consumption (Carnicella et al., 2014). With one study indicating that Sprague Dawley rats voluntarily consumed the same amount of EtOH as Wistar rats and significantly more EtOH than Long Evans Rats, using a sucrose fading paradigm (Gauvin, Moore, & Holloway,1993). Contrarily, a systematic review (Carnicella et al., 2014) on the EtOH consumption paradigm, intermittent access to EtOH in 2-bottle choice, concluded that Long-Evans rats reached higher blood EtOH levels than other outbred rat strains. Other factors could result in outbred rat strains to consume different amounts of EtOH. The type of paradigm used to study EtOH consumption can greatly affect the amount consumed. For example, intermittent access to 20% EtOH in 2-bottle choice will result in higher levels of consumption than a

continuous access paradigm (Fu et al., 2015; Simms et al., 2008). Another factor that affects consummatory behaviors is if palatability enhancers, such as saccharin or sucrose, are added to the EtOH since it is known that rodents prefer sweet solutions (Boughter & Bachmanov, 2007; Crabbe, Phillips, & Belknap, 2010).

Sex Differences and Quinpirole

A potential issue in the current study could be that only female rats were used. Since sexual dimorphic behaviors are suggested in previous drug research utilizing the NQ model (Brown et al., 2011; Cope et al., 2010; Kostrzewa et al., 2016; Thacker et al., 2006), it will be important to further investigate whether sex differences are shown toward EtOH consumption behavior in the NQ model. Acute injections of quinpirole during adulthood revealed that rats injected with quinpirole yawn significantly more than those injected with saline, but male rats yawn significantly more than female rats injected with quinpirole (Cope et al., 2010; Kostrzewa et al., 2016; Thacker et al., 2006). This is important because yawning is a dopamine D_2 receptor-mediated event (Kostrzewa, Brus, Rykaczewska, & Plech, 1993; Kostrzewa et al., 2016). There are sex differences that reside in the development of the dopamine system, specifically in the Acb and striatum (Str). Male rats have been shown to have an increased level of D_1-R from adolescence into adulthood, while D_2-R levels in the Str seem to vary throughout adolescence until approximately P60 when D_2- R levels stabilize and are similar to female expression (Andersen & Teicher, 2000; Kostrzewa et al., 2016). Studies have assessed whether the differences in DA levels are great enough to cause any sexual dimorphic behaviors in NQ rats, with results suggesting female rats exhibit a reduced conditioned effect but an enhanced behavioral activation to nicotine compared to male rats (Sheppard, Lehmann, Cope, & Brown, 2009). Additionally, research demonstrated that female NQ rats acutely treated with

methylphenidate manifest significantly higher levels of locomotor activity, increased response, and sensitization as opposed to male NQ rats (Cope et al., 2010). Interestingly, past work has also revealed that adult female rats have been shown to consume more EtOH than adult male rats (Alemedia et al., 1998; Priddy et al., 2017; Vetter-O'Hagen, Varlinskaya, & Spear, 2009). Further investigations are required to assess the gender variations in NQ EtOH consummatory behaviors.

Body Weight, Food, and Water

Bodyweight, food consumption, and water intake were recorded daily and analyzed to view any variations between groups and the relationship between these variables and EtOH consumption. NQ 10-20 rats weighed significantly more than Saline rats. Additionally, both groups treated with quinpirole weighed significantly more than the Saline group throughout adulthood. This finding correlates with the clinical population of schizophrenia that suggests that the elevated risk of weight gain is perhaps due to dysfunction in anticipatory reward processing in the striatum (Grimm, Kaiser, Plichta, & Tobler, 2017). The NQ 10-20 Treatment group was also found to have consumed significantly more food than the NQ 10-10 and Saline Treatment Groups. Studies have examined the relationship between food intake and EtOH consumption finding that rats will decrease food consumption in direct proportion to EtOH intake (Larue-Achagiotis, Paussard, & Louis-Sylvestre, 1990; Richardson, Rumsey, & Read, 1990). NQ 10-10 rats were consuming increased quantities of EtOH compared to the NQ 10-20 group or Saline group, thus possibly reducing their food intake. Also, the differences in food consumption between groups could have been a byproduct of changing the manner of how the food was administered to the rats. For NQ 10-20 rats, the food was placed on top of the rats' cages but for the NQ 10-10 and Saline rats, the food pellets were placed in a hanging food hopper inside the

rats' cages. Intriguingly, Saline rats significantly consumed more water than the NQ 10-20 rats but not the NQ 10-10 rats. Perhaps the 20% EtOH was less appealing to the Saline rats than the NQ 10-20 rats. The current study's hypotheses were partially supported in that the NQ 10-10 group did significantly consume more EtOH than the Saline group; but only during adulthood and the EtOH concentrations were different, NQ 10-10 rats received 10% EtOH and the Saline rats received 20% EtOH.

Conclusion

Overall, the data partially support the proposed hypotheses and provides further evidence that EtOH consumption during adolescence significantly increases the amount of EtOH consumed during adulthood. The data from the NQ 10-10 group seems promising in providing partial evidence that NQ rats are a valid model for assessing EtOH consumption. Schizophrenia is a detrimental psychiatric disorder that has a high disease burden due to premature mortality (Hjorthøj et al., 2017). Several factors contribute to the elevated risk of mortality, namely the increased frequency of drug abuse (APA, 2014; Green et al., 2007). Specifically, AUD effects upwards to 65% of the schizophrenic population magnifying negative health outcomes (Volkow, 2009). Investigations have revealed that the elevated risk of AUD comorbid schizophrenia is due to similar neuronal pathways being affected in both disorders (Nestler et al., 2015). This is the first time the NQ model has been implemented to assess EtOH consumption using the two-bottle choice task with two-exposure periods. Future studies will be needed to provide an enhanced knowledge of AUD comorbid schizophrenia by using the NQ model of schizophrenia.

Future Directions

Future studies will aim to replicate the current study to increase the power and effect size in hopes that this will delineate EtOH consumption between the NQ rats and Saline rats, as well

as using male Sprague Dawley rats to examine the potential effect of sex differences on NQ drinking behavior. Furthermore, an additional saline neonatal treatment group in which the adulthood EtOH concentration is reduced from 20% to 10% needs to be implemented to extend the interpretation of the adulthood drinking data for the NQ 10-10 animals. Results from the NQ 10-10 rats consuming an EtOH concentration of 10% seem very promising (shown in Figure 1) but the evaluation of a control group must occur prior to any further inferences. A study examining the effect of EtOH consumption only during adulthood in the NQ model would provide valuable insight concerning whether the adolescent exposure period is a key factor for increased EtOH consumption later in life. Rodent model research results have shown mixed findings on the significance of EtOH consumption during adolescence. Some studies indicate that EtOH consumption during adolescence increases drinking behavior in adulthood (Amodeo, Kneiber, Wills, & Ehlers, 2017; Gilpin, Karanikas, & Richardson, 2012), while others have not found significant differences in rats that were exposed to EtOH in adolescence versus those that were not (Slawecki & Betancourt, 2002; Vetter, Doremus-Fitzwater, & Spear, 2007).

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