EARLY-LIFE TRAUMA ALTERS HIPPOCAMPAL FUNCTION DURING AN EPISODIC MEMORY TASK IN ADULTHOOD

by

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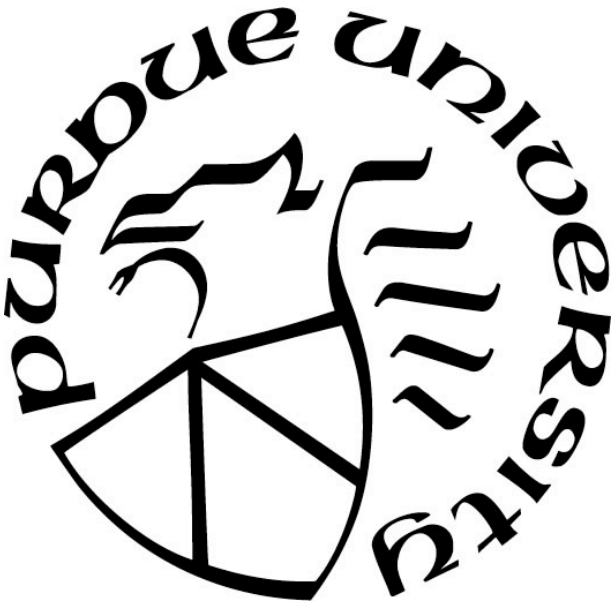
A Dissertation

Submitted to the Faculty of Purdue University

In Partial Fulfillment of the Requirements for the degree of

Doctor of Philosophy



Department of Psychology

Indianapolis, Indiana

August 2017

THE PURDUE UNIVERSITY GRADUATE SCHOOL
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ACKNOWLEDGMENTS

Firstly, I would like to thank my dear parents, Sarkis and Bettyna Janetsian, for their undivided love and support throughout my education. I know that it was incredibly difficult letting me move to another state during my undergraduate studies for one year, given that Armenian daughters are traditionally not allowed to move out of the house until they are married. I cannot even imagine the pain and uncertainty you both felt when I accepted my position as a graduate research assistant at IUPUI. Dad, I remember you told mom that you admire women who leave their household for education and that everything would be okay. Through the strength of your marriage, you both came to accept my decision. Without your encouragement and support, I would not be the independent Armenian woman that I am today. I owe this all to both of you.

To my husband, Brandon: You picked me up from the airport when I was interviewing for graduate school and I am so thankful that we decided to pursue a relationship one year later. You have played an integral role in my graduate career. You were always there for me when I thought I was failing and helped me to keep things in perspective. In graduate school we planned a wedding, you graduated with a Ph.D., you started a new job, we travelled often, and we bought a house. I never thought I would meet anyone like you. Your curiosity, motivation, love, intelligence, knowledge, level-headedness, and kindness surprises me every day. You are by far the greatest gift and I am endlessly thankful to call you my husband. I'm so glad to have you by my side for the rest of our lives.

To my sister, Talar Dufresne: You are my best friend and the greatest sister I could have ever imagined having. Although we have been in a long-distance sister relationship for the past six years, we have talked almost every single day. I appreciate all your support during my graduate career. You were always so proud of my accomplishments and made sure that I was aware of it. You have taught me the importance of sisterhood and I hope that one day, if I have kids, that their relationship will be as strong as ours is.

To my mentor, Christopher Lapish: You took me in as a graduate student when I had no background in Neuroscience. You pushed me to the limit, and then pushed me 10 times harder. You taught me behavior, electrophysiology, and computer programming. You taught me most the science I know. I would not be a successful scientist if it weren't for your mentorship and patience. Thank you for believing in me from the start. I am honored to be a former student of the Lapish Lab and I am truly grateful for this unforgettable experience.

I would like to thank my mother- and father-in-law, Dr. Vince and Barb Fritz, my brothers-in-law, Deven Dufresne and Ben Fritz, and my nephew, Nico Dufresne. All your support and love throughout this process has allowed me to flourish as an individual and young scientist. I am grateful to have such an encouraging and loving family and I cannot wait to see what the future holds for all of us.

Finally, I would like to thank each of my committee members, Dr.'s Charles Goodlett, Bethany Neal-Beliveau, and Susan Sangha, for guiding me through this process and for the excellent critiques and contributions to my Dissertation project. I would like to thank each of you for the time you invested into my education and experimental design.

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ABSTRACT

Author: Janetsian-Fritz, Sarine S. Ph.D.
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Degree Received: August 2017
Title: Early-life Trauma Alters Hippocampal Function During an Episodic Memory Task in Adulthood
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Early life trauma is a risk factor for a number of neuropsychiatric disorders, including schizophrenia (SZ) and depression. Animal models have played a critical role in understanding how early-life trauma may evoke changes in behavior and biomarkers of altered brain function that resemble these neuropsychiatric disorders. However, since SZ is a complex condition with multifactorial etiology, it is difficult to model the breadth of this condition in a single animal model. Considering this, it is necessary to develop rodent models with clearly defined subsets of pathologies observed in the human condition and their developmental trajectory. Episodic memory is among the cognitive deficits observed in SZ. Theta (6-10 Hz), low gamma (30-50 Hz), and high gamma (50-100 Hz) frequencies in the hippocampus (HC) are critical for encoding and retrieval of memory. Also, theta-gamma comodulation, defined as correlated fluctuations in power between these frequencies, may provide a mechanism for coding episodic sequences by coordinating neuronal activity at timescales required for memory encoding and retrieval. Given that patients with SZ have impaired recognition memory, the overall objectives of these experiments were to assess local field potential (LFP) recordings in the theta and gamma range from the dorsal HC during a recognition memory task in an animal model that exhibits a subclass of symptoms that resemble SZ. In Aim 1, LFPs were recorded from the HC to assess theta and gamma power to determine whether rats that were maternally deprived (MD) for 24-hrs on postnatal day (PND 9), had altered theta and high/low gamma power compared to sham rats during novel object recognition (NOR). Brain activity was recorded while animals underwent NOR on PND 70, 74, and 78. In Aim 2, the effects of theta-low gamma comodulation and theta-high gamma comodulation in the HC were assessed during NOR between sham and MD animals.

Furthermore, measures of maternal care were taken to assess if high or low licking/grooming behaviors influenced recognition memory. It was hypothesized that MD animals would have impaired recognition memory and lower theta and low/high gamma power during interaction with both objects compared to sham animals. Furthermore, it was hypothesized that sham animals would have higher theta-gamma comodulation during novel object exploration compared to the familiar object, which would be higher than the MD group. Measures of weight, locomotor activity, and thigmotaxis were also assessed. MD animals were impaired on the NOR task and had no change in theta or low/high gamma power or theta-gamma comodulation when interacting with the novel or familiar object during trials where they performed unsuccessfully or successfully. However, higher theta and gamma power and theta-gamma comodulation was observed in sham animals depending on the object they were exploring or whether it was a successful or unsuccessful trial. These data indicate altered functioning of the HC following MD and a dissociation between brain activity and behavior in this group, providing support that early life trauma can induce cognitive and physiological impairments that are long-lasting. In conclusion, these data identify a model of early life stress with a translational potential, given that there are points of contact between human studies and the MD model. Furthermore, these data provide a set of tools that could be used to further explore how these altered neural mechanisms may influence cognition and behavior.

INTRODUCTION

General Introduction

Early life traumatic experiences or exposure to stressful environments may predispose an individual to develop a mental disorder or health problems later in life, including schizophrenia (SZ) (Bale et al., 2010; Beydoun & Saftlas, 2008; Fatemi & Folsom, 2009; Lambás-Señas et al., 2009; Llorente et al., 2010). The prenatal period is critical for normal brain development and can be influenced by environmental factors (Marco et al., 2015). As such, early life adverse events such as malnutrition, maternal separation, viral infection, or genetic deficits (Bayer, Falkai, & Maier, 1999; Bowlby, 1982, 1988; Cannon et al., 2003; Murray & Fearon, 1999), may disrupt brain development and maturation (Pino et al., 2014), possibly leading to psychopathology later in life (Andersen et al., 2008; Meyer & Feldon, 2010).

Currently, one of the most widely used animal models of early life trauma used to induce SZ-like symptoms is the maternal deprivation (MD) model, which typically utilizes exposure to a stressful event in the early postnatal period (Ellenbroek, van den Kroonenberg, & Cools, 1998). Although there are other animal models used to study this complex mental disorder (see Jones, Watson, & Fone, 2011 for review), including drug-induced models (e.g. amphetamine or PCP administration), models that use genetic manipulation (e.g. DISC-1 knockout or Reelin knock-out), or lesion models (e.g. neonatal ventral HC lesion), the MD model utilizes an early-life traumatic event, which allows the long-term neurodevelopmental effects associated with early-life trauma to be assessed.

MD has been shown to cause disturbances in cognitive functions including recognition memory and spatial learning and memory (Llorente et al., 2011; Marco, Valero, de la Serna, et al., 2013; Oitzl, Workel, Fluttert, Frösch, & De Kloet, 2000). MD also alters basic forms of information processing in rodents, including sensorimotor gating measured by prepulse inhibition (PPI) (Ellenbroek et al., 1998; Ellenbroek & Cools, 2002; Ellenbroek, de Bruin, van Den Kroonenburg, van Luijtelaar, & Cools, 2004). Deficits in information processing are thought to contribute to impairments in cognitive function (Geyer, 1998). Since the most effective animal models of SZ are

currently those that model deficits in sensorimotor gating (Ratajczak, Wozniak, & Nowakowska, 2013), the MD model lends some level of translational validity to the condition being studied.

Individuals with SZ have deficits in recognition memory (Huron et al., 1995; Jessen et al., 2003; Kayser et al., 2010; Satterthwaite et al., 2010). Novel object recognition (NOR), a task to measure recognition memory in rodents, is suggested by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) to be a translational preclinical model to assess deficits in this cognitive domain (Young, Powell, Risbrough, Marston, & Geyer, 2009). NOR has also been compared to the three-dimensional object recognition task in humans (Heckers et al., 2000), and patients with SZ show an impairment on this task (Heckers et al., 2000). In this task, participants are shown 48 three-dimensional novel objects twice. Five minutes later, participants are shown the previously seen objects along with novel objects. During this task, patients with SZ had significantly lower recognition rates for previously seen objects compared to healthy controls. Collectively, these studies support that NOR has face validity and is a useful tool to assess cognitive function in the MD model. Furthermore, it is shown that the hippocampus (HC) and perirhinal cortex are important for successful recognition memory on the NOR task based on lesion studies (Ainge et al., 2006; Reger, Hovda, & Giza, 2009; Winters & Bussey, 2005). Since patients with SZ have decreased hippocampal and perirhinal cortex volume (Koolschijn et al., 2010; Narr et al., 2004; Turetsky, Moberg, Roalf, Arnold, & Gur, 2003), and these two regions are important for successful memory performance on the NOR task, NOR could be used to explore the function of these brain regions in this neurodevelopmental rodent model of SZ.

Theta (6-10 Hz in animals; 4-8 Hz in humans) (Jacobs, 2014) and gamma (30-100 Hz) frequencies in the HC are thought to be involved during encoding and retrieval of memories (Trimper, Stefanescu, & Manns, 2014b) by facilitating synaptic plasticity (Buzsáki & Draguhn, 2004b). However, it is unclear whether theta and gamma power are altered by MD and if the two frequencies are decoupled during NOR. Determining how MD alters TGC will be important for understanding impairments in encoding or retrieval during NOR. Therefore, electrophysiological methods were employed to assess

correlations between theta and gamma frequencies during recognition memory to provide novel information regarding pathophysiological function of the HC in this animal model.

Maternal Deprivation as a Model of Early Life Trauma

Currently, one of the most widely used neurodevelopmental rodent models of early life trauma is the MD model. MD is based on exposure to stress in early postnatal life in rats (an acute 24-hour deprivation period on postnatal day (PND) 9) (Ellenbroek et al., 1998). MD can induce deficits in adulthood due to many factors including 1) lack of maternal care during the 24-hour period (Llorente et al., 2011b) 2) lack of nutrition which can cause decreases in leptin levels and hypoglycemia during the 24-hour period (Viveros, Díaz, Mateos, Rodríguez, & Chowen, 2010), and 3) hypothermia due to a lack of mature thermal regulatory system in the 24-hour deprivation period (Zimmerberg & Shartrand, 1992).

MD on PND 9 alters body weight compared to controls that persists into adulthood (Llorente-Berzal et al., 2011; Mela et al., 2012, 2016). It is not surprising that MD animals weighed less compared to controls in some studies because it is shown that deprived animals eat less food during the dark phase of the light/dark cycle following deprivation (Wertheimer, Girardi, de Oliveira, Monteiro Longo, & Suchecki, 2016). Furthermore, in the same study, decreased body weight in the MD group was accompanied by decreased production of Neuropeptide Y (NPY), which is implicated in feeding behavior. Therefore, in these studies, MD animals ate less and weighed less compared to controls.

Interestingly, malnutrition can affect myelination during the second week of postnatal development in rats and in the third trimester in humans (Chertoff, 2015; Wiggens, 1982). Myelin forms around cells to increase the speed at which action potentials are conducted and allows the cell to store an electrical charge (or ions) inside the cell so that the cell could maintain at its resting state or become depolarized or hyperpolarized. Given that MD causes a lack of nutrition in the rat on PND 9-10, it is possible that malnutrition is altering developmental processes in the brain such as myelination.

As in humans, the brain of the rat undergoes a significant amount of development after birth. PND 8-9 in rats is equivalent to the early third trimester in humans (Bayer et al., 1999). During the late gestational period until the first few weeks of the postnatal period, the rat brain undergoes proliferation (i.e. rapid increase in the number of brain cells), migration (i.e. movement of cells to specific locations including different layers of the neocortex), differentiation (i.e. expression of neuronal or glial characteristics including shape, size, and polarity), and synaptogenesis (i.e. morphological and biochemical changes of presynaptic and postsynaptic elements of the neurons) (Jacobson, 1991; O'Rourke, Dailey, Smith, & McConnell, 1992; Rice & Barone, 2000). During the third trimester in humans, the fetal brain undergoes similar processes including cell proliferation, differentiation, and synaptogenesis (Herschkowitz, Kagan, & Zilles, 1997).

More specifically, the rat has a spurt in brain growth starting on PND 7 (Dobbing & Sands, 1979), which is measured by total weight gain of the brain as a percentage of the adult weight. Brain weight reaches 90% of its potential adult weight by PND 20. In the HC, the granular cell layer also continues to develop around PND 9, and any insult to this region will disrupt growth (Qiu et al., 2007). Furthermore, studies have shown that if brain injury occurs in the second postnatal week (~PND 11), volume of the cortex and HC decreases and there is greater tissue loss in the brain in general (Raghupathi & Huh, 2007). Also, in the first few post-natal weeks, changes in neurotransmitter systems are reported, such as increased NMDA receptor density and increased post-synaptic glutamate receptors (Sanderson & Murphy, 1981). Furthermore, the number of astrocytes increases in the HC, which are important for neurogenesis, neurotransmission and defending the immune system (Catalani et al., 2002). Lastly, myelination around cells begins to develop around PND 10-14 (Wiggins, 1986). In conclusion, the rat brain undergoes a significant amount of brain development in the first few postnatal weeks, especially around PND 9 (see review: Semple, Blomgren, Gimlin, Ferriero, & Noble-Haeusslein, 2013), and injury during this time period can alter or slow brain growth.

Behavioral, Neurochemical, and Neurophysiological Alterations Induced by MD

MD on PND 9 causes behavioral disturbances during adolescence and adulthood. For example, MD animals have altered recognition memory on the NOR task compared to controls when tested during adolescence (Marco, Valero, de la Serna, et al., 2013) or in adulthood (Llorente-Berzal et al., 2012; R. Llorente et al., 2011; Janetsian-Fritz et al., *in progress*). These findings are similar to clinical studies showing that patients with SZ have impairments in recognition memory in adulthood (Huron et al., 1995).

During the first two weeks of life, basal activity in the hypothalamic-pituitary-adrenal (HPA) axis is shown to be blunted in the MD model (Schmidt et al., 2003), possibly due to increases in serotonin (5-HT) in the prefrontal cortex (PFC), HC, striatum, and mesencephalon-regions (Llorente et al., 2010). Furthermore, during the second week, (also known as the 'stress hyporesponsive period'), infection, stress, or malnutrition increases the risk for rat offspring to develop psychiatric disorders later in life (Dent, Choi, Herman, & Levine, 2007). Some of these deficits induced by early stress may be due to neurochemical changes in the brain (Harrison, 1999), along with stress-induced increases in corticosterone levels (Ellenbroek & Cools, 2002) accompanied by hippocampal alterations (Llorente et al., 2008). Other studies show a rise in basal corticosterone levels, and decreased levels of glucose, insulin and leptin in rats (Viveros et al., 2010). These chemicals are shown to be important in the developing brain (Ahima, Bjorbæk, Osei, & Flier, 1999; Bouret, 2010). Collectively, MD alters normal development in the early stages of life, which in turn may result in various impairments in adulthood.

MD during this period has been shown to impair HC structure and function. For example, animals that underwent MD on PND 9 showed changes in NMDA receptor subunit expression in the HC (Roceri, Hendriks, Racagni, Ellenbroek, & Riva, 2002). NMDA plays an important role in brain plasticity and learning and memory (Lu & Chow, 1999; Mizuno, Yamada, He, Nakajima, & Nabeshima, 2003), and therefore changes in the glutamatergic system could alter cognitive function. Another study demonstrated that MD decreases the expression of brain derived neurotrophic factor (BDNF) in the HC, which is thought to be involved with neuronal survival, differentiation and plasticity of the brain (Das et al., 2001; Kuma et al., 2004). These changes in normal brain maturation

in the HC could ultimately alter cognitive function. Lastly, another study demonstrated that volume of the HC, specifically in areas that are abundant with granular cells (dentate gyrus) and pyramidal cells (CA1 and CA3) were significantly decreased in animals when measured on PND 60 that underwent a 24-hour MD period (Aksić et al., 2014). Considering that the HC plays a role in recognition memory, similar alterations may be involved in the etiology of this mental illness. Interestingly, post-mortem studies have observed changes in the cytoarchitecture in the entorhinal cortex of the hippocampal formation, including scarce neurons as well as displacement of neurons (Arnold, Hyman, Van Hoesen, & Damasio, 1991).

MD alters basic forms of information processing, including sensorimotor gating measured by PPI and latent inhibition (LI) (Ellenbroek et al., 1998; Ellenbroek & Cools, 2002; Ellenbroek et al., 2004). Sensorimotor gating is a process that enables an individual to filter out or "gate" unnecessary or redundant information (Freedman et al., 1987), and patients with SZ have difficulty gating out stimuli, suggesting that they may have an altered auditory system or altered regions that influence inhibitory processes. Deficits in information processing, including PPI and a reduction in the speed of habituation of the acoustic startle response (ASR), are also observed in patients with SZ (Braff, 1993; V. Carr & Wale, 1986). Interestingly, these deficits are thought to contribute to impairments in cognitive function (Geyer, 1998).

Patients with SZ also have neurophysiological alterations (Uhlhaas et al., 2006) (see later section on 'Aberrant Neural Synchrony in Individuals with SZ' for details). Although there are currently no studies that have assessed single unit activity using an identical MD procedure, one study assessed basal firing and local field potentials (LFP) using a maternal stress paradigm (Stevenson, Halliday, Marsden, & Mason, 2008). LFPs are electrical potentials that synchronize in extracellular space recorded around neurons and are a result of excitatory and inhibitory post-synaptic potentials that can be simultaneously collected from several brain regions (Buzsáki, Anastassiou, & Koch, 2012). This study observed the effects of maternal separation (separation 6 hr/day on PND 2-14) in the mPFC when animals were under anesthesia. Separated animals had decreased basal single unit activity in the right mPFC and decreased PFC LFP power in a range of frequencies (0-30 Hz) compared to controls. Lastly, separated animals had

attenuated LFP hemispheric synchronization at lower frequencies. These findings suggest alterations in neurophysiology are induced by maternal stress in early neurodevelopment. However, no study to date has assessed the MD model used herein (24-hr) and its long-term effects on neurophysiology.

Novel Object Recognition as a Measure of Recognition Memory

The NOR task is used to measure recognition memory and is suggested by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) to be a translational preclinical model to assess deficits in recognition memory (Young et al., 2009). It can be utilized as a tool to assess the effects of pharmacological treatments or the effects of brain damage during performance (Goulart et al., 2010). This task requires no external motivation, reward, or punishment. The main goal of NOR is to evaluate the ability of a rodent to recognize a novel object or remember a familiar object in the environment.

There are typically three phases to this task: habituation, familiarization, and the test phase. During habituation, an animal can freely explore an open-field chamber with no objects present. After an inter-trial interval (ITI), the animal is placed back into the chamber with two identical objects (familiarization phase). After another ITI, the animal is returned to the same chamber with an object from the familiarization phase along with a novel object (test phase). Exploration is usually considered when an animal directs its nose to an object at a distance of 2 cm or less (A Ennaceur & Delacour, 1988). Objects are usually located in opposite corners of the chamber (Hammond, Tull, & Stackman, 2004). Depending on the ITI, this task can be useful to assess short-term or long-term memory (Taglialatela, Hogan, Zhang, & Dineley, 2009).

There have been many variations to the NOR task (Antunes & Biala, 2012). The number of objects could be manipulated during the familiarization phase such that there are three objects instead of two. Then, during the test phase, the third object is replaced with a novel object. The locations of the objects could also be manipulated such that the objects could be the same but the location of the object changes (object in place) (Hale &

Good, 2005). Furthermore, the ITI could be decreased or increased between the familiarization and test phase to reflect short-term, immediate, or long-term memory.

It is shown numerous times that healthy animals will naturally explore the novel object more than the familiar (Baxter, 2010; A. Ennaceur, 2010). Successful recognition memory on the NOR task involves memory encoding, consolidation, and retrieval of the objects (Winters & Bussey, 2005). Memory encoding is the ability for a perceived object to be processed (i.e. acquired) and stored for later retrieval. Encoding occurs during the familiarization phase because animals are seeing two identical objects for the first time. However, to measure if animals successfully encoded objects in the familiarization trial, interaction time is expected to be higher with the novel object on the subsequent trial (testing). Memory consolidation follows encoding, and is the process of continual strengthening of the memory trace. Induction of long-term potentiation (LTP) is an important mechanism for memory consolidation (Tronson & Taylor, 2007). Lastly, retrieval is the ability to re-access the memory trace after it has been encoded. Memory retrieval is measured during the test phase. If an animal prefers the novel object, then this can possibly imply that the animal remembers (i.e. and is retrieving) the memory of the familiar object (Ennaceur & Meliani, 1992). Collectively, NOR is a useful tool to assess successful encoding and retrieval of short-term or long-term recognition memory, and was used as a measure of cognitive function in the current set of experiments.

Brain Regions Implicated in NOR

Recognition memory is impaired following transient inactivation of the HC (Broadbent, Gaskin, Squire, & Clark, 2010) and the perirhinal cortex (Hannesson, Howland, & Phillips, 2004), specifically during memory encoding, consolidation, and retrieval (Winters & Bussey, 2005). For example, one study used Lidocaine to inactivate the CA1 region of the HC 5-minutes before training on NOR (Hammond et al., 2004). Inactivating the HC did not alter the amount of time animals explored objects during the familiarization phase, indicating that the HC does not interfere with exploring objects (i.e. motivation to explore). However, animals exhibited impaired object recognition

when tested 24 hours after the familiarization phase, suggesting that the HC plays a critical role during this task.

Studies using lesions also implicate the HC, frontal cortex, and perirhinal cortex to be necessary for the expression of NOR. For example, recognition memory is decreased when lesions are made in the HC and frontal cortex (Buckmaster, Eichenbaum, Amaral, Suzuki, & Rapp, 2004; Clark, Zola, & Squire, 2000). The perirhinal cortex is also critical, because lesions of this brain region are correlated with poorer recognition, such that greater damage induces poorer recognition memory (Albasser, Davies, Futter, & Aggleton, 2009).

The HC and perirhinal cortex are brain structures that are implicated in normal brain function (Baxter, 2010). Although these structures are highly integrated, it is hypothesized that the HC is possibly involved in object recognition during longer ITIs and the perirhinal cortex is involved during shorter ITIs (Hammond et al., 2004; Reger, Hovda, & Giza, 2009). It is important to note that the perirhinal cortex, which sends inputs to the HC, is also important for processing visual, olfactory and somatosensory stimuli, which are all involved during object memory (Clark et al., 2000). However, when spatial or contextual information is involved, the dorsal HC is important during NOR (Goulart et al., 2010). Collectively, the HC and perirhinal cortex are brain regions implicated in this task; however, these sets of experiments specifically recorded from the dorsal HC during the NOR task because this region is shown to be involved with the generation and/or maintenance of theta and gamma oscillations (see 'Gamma Oscillations' for more detail) (Buzsáki & Wang, 2012; Csicsvari, Jamieson, Wise, & Buzsáki, 2003; Steward 1976; Hangya et al. 2009; Tóth et al. 1997). Furthermore, the HC is one region highly implicated during spike-timing dependent plasticity, LTP, and theta-phase precession, phenomena that are involved with learning and memory (see 'Theta Oscillations' for more detail) (Grover, Kim, Cooke, & Holmes, 2009; Mizuseki, Royer, Diba, & Buzsáki, 2012).

Hippocampal Structure

In the current set of experiments, neural recordings were collected from the CA1 region of the HC, so it is important to understand the structure, layers, and pathways of this region. The HC consists of three main subfields, including the CA1, CA2, and CA3 (Lorente De Nó, 1934). These regions are densely packed with pyramidal cells and inhibitory interneurons that are primarily glutamatergic or GABAergic, respectively (Kosaka, Katsumaru, Hama, Wu, & Heizmann, 1987; Mizuseki, Diba, Pastalkova, & Buzsáki, 2011; Pettit & Augustine, 2000). The hippocampal formation is an extension of the HC and includes the dentate gyrus, subiculum, pre and para subiculum, and the entorhinal cortex (David & Pierre, 2009). The CA1 and CA2 regions have four layers, which include the lacunosum-moleculare, radiatum, pyramidal, and orients. The CA3 region also includes these four layers in addition to the lucidum layer. The dentate gyrus consists of the molecular, inner molecular, and granular layers (Amaral, Scharfman, & Lavenex, 2007).

There are four major afferents projecting to the HC. The first is the perforant pathway which originates in the entorhinal cortex (from layers II and III) and projects to the dentate gyrus, subiculum, and CA1-CA3 (Witter, 2007). Pyramidal neurons and stellate cells in layers II project through the subiculum and terminate in the granular layer of the dentate gyrus and CA3. The temporoammonic branch of the perforant pathway consists of pyramidal cells that project to CA1 and subiculum from layer III and layer V (Bliss & Lømo, 1973). The alvear pathway has a similar origin as the perforant pathway, but fibers from the entorhinal cortex reach Ammon's horn (i.e. hippocampal proper) then to the CA1 after projecting through the subiculum (Deller, Adelmann, Nitsch, & Frotscher, 1996).

Another major afferent to the HC is via the septal-hippocampal pathway. From the medial septum, there are cholinergic and GABAergic fibers that project to the HC (Mamad, McNamara, Reilly, & Tsanov, 2015), which are shown to be important for generation of the theta rhythm (Hangya, Borhegyi, Szilágyi, Freund, & Varga, 2009), which will be discussed in detail below. Lastly, the hippocampal commissure connects the CA1 to the CA3 (Gloor, Salanova, Olivier, & Quesney, 1993). These pyramidal cells

carry information through nerve impulses. This pathway crosses the rostral splenium and corpus callosum before it reaches the contralateral HC.

There are also efferent pathways that project from the HC to many areas. For example, neurons in the HC project through the fornix to the septal nuclei (Unal, Joshi, Viney, Kis, & Somogyi, 2015) via the precommissural branch and to the mammillary bodies via the postcommissural branch (Raisman, Cowan, & Powell, 1966). Other areas that the HC projects to include: nucleus accumbens (Bagot et al., 2015), prelimbic cortex (Jay, Glowinski, & Thierry, 1989), anterior cingulate cortex (Rajasethupathy et al., 2015), amygdala (Phelps, 2004), ventral tegmental area (Gasbarri, Packard, Campana, & Pacitti, 1994), locus coeruleus (Segal & Bloom, 1976), thalamus (Aggleton et al., 2010), raphe nucleus (Aggleton et al., 2010), ventral striatum (van der Meer, Ito, Lansink, & Pennartz, 2014), and orbital cortex (Wikenheiser & Schoenbaum, 2016).

The trisynaptic loop or circuit (Andersen, 1975) relays synaptic transmission within the hippocampal structures. This loop consists of granule cells, pyramidal cells from the CA3, and pyramidal cells from the CA1 region. The first projection is the projection discussed above (perforant pathway), which projects from the entorhinal cortex to the dentate gyrus. From the dentate gyrus, mossy cell fibers synapse on pyramidal cells in CA3. The last projection is from the CA3 to CA1 region via Schaffer collaterals. There are also glutamatergic projections directly from the entorhinal cortex (layers II/III) to the distal region of the CA1 (Basu & Siegelbaum, 2015) (Tamminga, Southcott, Sacco, Wagner, & Ghose, 2012). Projections to the CA1 also project to local GABA interneurons, which provide feed-forward inhibition (Price, Scott, Rusakov, & Capogna, 2008).

Chandelier and basket inhibitory interneurons (Parvalbumin-expressing) are also found in the HC. Basket cells are shown to form recurrent inhibition loops with pyramidal neurons. In other words, a basket cell will receive excitatory input form pyramidal neurons, and then the basket cell will project back to the excitatory pyramidal cell and create an inhibitory feedback, which dampens the excitatory response (Freund & Buzsáki, 1996). In conclusion, the HC receives input from and projects to multiple brain regions, which is a reason why it is implicated in many cognitive behaviors as well as emotion (Engin & Treit, 2007; Squire, 1992).

Aberrant Neural Synchrony in Individuals with SZ

Neural synchrony is the simultaneous activity of a large number of neurons in a given brain region which gives rise to brain oscillations (Gray & McCormick, 1996; Uhlhaas et al., 2009). Brain oscillations are rhythmic neural activity that can be recorded at the surface of the scalp via EEG or in brain tissue via LFP. These recording methods show a variety of frequencies from the recorded oscillations that are thought to underlie various aspects of neural function. Using power spectral density (PSD), LFPs could be analyzed by breaking down the raw signal into power (i.e., energy per unit time, amplitude squared, or peak-to-peak voltage), phase (i.e. location (degree) on oscillation that is 360º), and frequency (i.e. number of cycles per unit time, measured from start of phase to end of phase) components to assess the influence of a frequency on neural function and behavior.

Neural synchrony allows for information to be integrated across widespread brain regions (Buzsáki & Draguhn, 2004a). It is hypothesized that synchronization is aberrant or disrupted in patients with SZ when recorded with EEG (Uhlhaas et al., 2006). For example, aberrant synchrony is associated with positive (e.g. hallucinations, delusions, thought disorder), negative (e.g. anhedonia, alogia, depressed mood), and cognitive (e.g. impairments in attention, working memory, declarative memory, executive function) symptoms of SZ and is observed in non-medicated first episode patients and high-risk individuals including first-degree relatives (Pachou et al., 2008; Spencer, Niznikiewicz, Nestor, Shenton, & McCarley, 2009; Uhlhaas & Singer, 2010). It is hypothesized that since gamma-aminobutyric acid (GABA) interneurons play a prominent role in synchronous oscillatory activity, then alterations in the GABA system may be associated with altered neural synchrony in these patients (Bartos, Vida, & Jonas, 2007). In conclusion, alterations in synchronization may cause changes in the way information is integrated, and this may be associated with deficits in cognition.

Gamma Oscillations

Generation and the ING/PING Mechanisms

One oscillation highly implicated in cognitive function is the gamma oscillation. Gamma oscillations have been observed in the cortex (Gonzalez-Burgos & Lewis, 2012), HC (Buzsáki & Wang, 2012), amygdala (Courtin, Karalis, Gonzalez-Campo, Wurtz, & Herry, 2014), striatum (Popescu, Popa, & Paré, 2009), and thalamus (Minlebaev, Colonnese, Tsintsadze, Sirota, & Khazipov, 2011), among other regions. These oscillations are generated by interactions between inhibitory interneurons and pyramidal cells. More specifically, the cortex receives input to layer IV excitatory (regular spiking) neurons as well as inhibitory (Parvalbumin-positive fast-spiking basket) neurons from the thalamus (feedforward pathway) (Douglas & Martin, 2004). These excitatory neurons from layer IV project to regular spiking excitatory and Parvalbumin-positive inhibitory neurons in layer II/III. There is also a feedback pathway where other cortical areas send inputs to regular spiking excitatory and Parvalbumin-positive inhibitory neurons in layer II and III (Douglas & Martin, 2004). Furthermore, in these layers, there are two networks: reciprocally connected excitatory and inhibitory neurons and mutually connected inhibitory neurons (Tiesinga & Sejnowski, 2009). These two separate mechanisms are thought to generate gamma oscillations that work by altering the synchronization of synaptic inputs. The first is the activation of inhibitory networks via the interneuron gamma (ING) and the second is the activation of pyramidal-interneuron gamma (PING) networks, where the neurons are reciprocally connected (Whittington, Traub, Kopell, Ermentrout, & Buhl, 2000). Each mechanism is described below.

In the ING mechanism, synaptic inputs arrive at approximately the same time (i.e. in volleys). The closer the synaptic inputs are in time, the more synchronous gamma oscillations will become (Azouz & Gray, 2000). The close proximity of the volleys allows inputs arriving initially to stop firing via inhibition. The intrinsic properties (e.g. ionic balance) of the inhibitory neuron also contribute to this mechanism. For example, an inhibitory neuron could fire but will have a refractory period due to ionic imbalance where no input will cause further stimulation of the neuron. After the ionic balance is restored, the inhibitory neuron could fire again. Collectively, the timing and pattern of

this cycle will cause an overall increase in gamma power (Brunel & Hakim, 1999; Tiesinga, Fellous, Salinas, José, & Sejnowski, 2004).

In the PING mechanism, when external drive projects to excitatory neurons, excitatory neurons will fire. Excitatory neurons that stimulate inhibitory neurons will cause the inhibitory neurons to increase firing. Increased stimulation of inhibitory neurons, in turn, will decrease the firing rate of the excitatory neurons that they project to. This period of inhibitory firing is thought to increase synchronous activity of volleys (Tiesinga, Fellous, & Sejnowski, 2002; P. Tiesinga & Sejnowski, 2009). Gamma oscillations are also generated locally in the hippocampal formation (Buzsáki & Wang, 2012), specifically in the entorhinal cortex and CA3 (Bragin et al., 1995; Csicsvari et al., 2003) by interactions between excitatory and inhibitory neurons (Banks, White, & Pearce, 2000; Bartos et al., 2007; Buzsáki & Wang, 2012; Mann & Paulsen, 2005) via the ING and PING mechanisms (ter Wal & Tiesinga, 2013). Based on these studies, it is hypothesized that changes in the neural mechanisms underlying ING and PING (e.g. altered number of inhibitory or excitatory neurons), can affect the generation of gamma oscillations, and may be involved in aberrant cognitive function.

Cognitive Function and Spike-Timing Dependent Plasticity

Some of the cognitive processes gamma mediates includes working memory (John Lisman, 2010) and storage and recall of information (Lisman & Idiart, 1995). Furthermore, its activity plays an important role in various aspects of information processing, including object recognition (Martinovic, Gruber, & Müller, 2007; Trimper et al., 2014b) and object perception (Castelhano, Rebola, Leitão, Rodriguez, & Castelo-Branco, 2013). Gamma rhythms in the HC are also associated with memory recall (Colgin et al., 2009). Taken together, gamma activity plays a critical role in a number of cognitive functions.

Gamma is thought to be important for cognitive function because it provides the precise timing of action potentials that leads to spike-timing dependent plasticity (Nyhus & Curran, 2010). Spike-timing dependent plasticity is the ability for LTP, or strengthening of synapses, to occur based on the timing of the presynaptic neuronal firing

relative to postsynaptic neuronal firing (Skaggs, McNaughton, Wilson, & Barnes, 1996). LTP is necessary because it is one of the cellular mechanisms that underlies learning and memory (Bliss & Collingridge, 1993; Cooke & Bliss, 2006). For spike-timing dependent plasticity to occur, the first mechanism is that glutamate released from the presynaptic neuron binds to N-methyl-$_D$-aspartic acid (NMDA) receptors on the postsynaptic neuron. Then depolarization of the postsynaptic neuron will cause a magnesium plug to be removed from the NMDA receptor. Back-propagating action potentials also contribute to depolarization (Shouval, Wang, & Wittenberg, 2010). It has been hypothesized that neural firing in the range of gamma oscillations occurs at a specific frequency that provides the exact timing parameters for spike-timing dependent plasticity to occur as it increases calcium in the neuron (Skaggs et al., 1996). Therefore, gamma oscillations modulate spike-timing dependent plasticity, which is important for LTP to occur and, by extension, strengthens memory and facilitates learning.

There is also evidence supporting that gamma oscillations are directly involved in LTP (Bikbaev & Manahan-Vaughan, 2009). More specifically, following tetanisation-driven activation to induce LTP in the HC, there were changes in gamma oscillations as well as oscillations in the theta frequency (see 'Theta Oscillations' below). For example, when theta and gamma power both increase following tetanisation, it is more likely that arriving stimuli (e.g. action potentials) will not only spike at the theta peak, but within 10-30 msec, these stimuli will reach their post-synaptic target. This time window of 10-30 msec is within the gamma frequency (Dan & Poo, 2004). The activation of glutamate receptors (mGluRs) is one mechanism involved in increased gamma power following the induction of LTP, since inhibiting mGlur5 is shown to suppresses gamma oscillations and impairs LTP (Bikbaev et al., 2008). A hypothesis that could come out of these studies is that, if deficits in recognition memory are observed in MD animals and if gamma is also altered, then it is possible that LTP is not facilitated in this group due to changes in gamma in MDs, possibly underlying impairments in memory.

Basal and Evoked Gamma Power Altered in SZ

Basal and evoked gamma power are shown to be altered in patients with SZ (Williams & Boksa, 2010). For example, patients have reduced cortical theta and gamma power during encoding and retrieval during a delayed match to sample working memory task (Haenschel et al., 2009). Furthermore, during an auditory task that contains a train of clicks, evoked gamma power is significantly reduced in patients compared to controls (Kwon et al., 1999; Wilson et al., 2008). Reduced gamma power has also been observed in SZ patients during sensory gating, speech, and arithmetic tasks (Uhlhaas et al., 2006; Uhlhaas & Singer, 2010). Not only do studies show altered gamma power in patients with SZ, alterations in a number of neuropsychiatric disorders, including addiction (Liu et al., 2005) and bipolar disorder (Oda et al., 2012) are also observed. Therefore, it is possible that alterations in the gamma frequency plays a critical role in the etiology of cognitive impairments observed in these populations.

Although many studies support that gamma power is reduced in this population, there is controversy as to how gamma is altered. Recently, studies have started to assess resting-state gamma power in patients, and the results are opposite of that observed for evoked gamma power. More specifically, these inconsistencies stem from the fact that some studies assess evoked gamma power and observe decreases in gamma in patients, and other studies assess resting-state gamma power and see increases in gamma (Spencer, 2012; Mitra, Nizamie, Goyal, & Tikka, 2015; Tikka, Nizamie, Das, Katshu, & Goyal, 2013). Although there are many inconsistencies in the human literature, the current set of experiments will improve and clarify the role of resting-state and evoked- theta and gamma oscillations using the MD model of early-life trauma.

Theta Oscillations

Generation of Theta

Similar to gamma oscillations, theta is observed in the HC, entorhinal cortex, PFC, striatum, amygdala, and visual cortex (DeCoteau et al., 2007; Roux & Uhlhaas, 2014). Various neural networks generate theta oscillations on a systems or local level. On

a systems level, the medial septum acts as a pacemaker that controls the theta rhythm (Vertes & Kocsis, 1997) that helps synchronize hippocampal and entorhinal networks (Stewart & Fox, 1990). More specifically, in this septo-hippocampal network, activity of Parvalbumin GABAergic interneurons in the medial septum precedes hippocampal activity, suggesting that the activity of these interneurons is important for the generation of theta oscillations in the HC (Hangya et al., 2009; Steward, 1976; Tóth, Freund, & Miles, 1997). On a local level in the HC, theta oscillations are thought to be maintained by hippocampal-entorhinal system networks and are shown to be the most prominent field potential in this network (Alonso & García-Austt, 1987). More specifically, stellate excitatory neurons from layer II of the entorhinal cortex send excitatory inputs to the dentate gyrus and CA3 region of the HC (Steward, 1976). Input to the CA1 region originates in layer III of the entorhinal cortex (Amaral & Witter, 1989; Kenji Mizuseki, Sirota, Pastalkova, & Buzsáki, 2009). It is also shown that theta oscillations in the HC occurs through an interaction between excitatory principle cells and slow stellate inhibitory interneurons that act on slow GABAa receptors (Buzsáki, 2002; Rotstein et al., 2005). In conclusion, theta oscillations are observed throughout the cortex and can be generated on a systems or local level.

Theta and LTP/Theta Phase Precession

Theta oscillations are also thought to be critical for learning and memory by modulating LTP (Nyhus & Curran, 2010). More specifically, theta depolarizes a cell (e.g by stimulating CA3 Schaffer collaterals) which induces calcium influx due to the opening of NMDA channels (Huerta & Lisman, 1995). Some studies show a direct role on theta oscillations on LTP or learning and memory. For example, in the dentate gyrus and CA1 region of the HC, stimulating theta frequency induces LTP (Grover et al., 2009). Furthermore, theta activity is correlated with the rate of acquisition on a classical conditioning paradigm, such that increased theta increases the rate of acquisition on the task (Berry & Seager, 2001; Chen et al., 2014). Also, blocking serotonin receptors (Stäubli & Xu, 1995) or depleting serotonin (López-Vázquez et al., 2014) enhances theta oscillations and increases successful performance on a radial maze task. HC theta also

positively correlates with successful performance on a Morris water maze task (Olvera-Cortés, Cervantes, & González-Burgos, 2002), during decision making (Belchior, Lopes-Dos-Santos, Tort, & Ribeiro, 2014), during episodic memory (Lega, Burke, Jacobs, & Kahana, 2014) and during working memory tasks (Hsieh & Ranganath, 2014).

Type 1 theta (6-12 Hz) is strongly present during locomotion and orienting (i.e. voluntary movements) (Belchior et al., 2014; Kahana, 2006; Sainsbury, Heynen, & Montoya, 1986), whereas type 2 theta (4-9 Hz) is present during immobility (Kenji Mizuseki & Buzsaki, 2014; Sainsbury et al., 1986). More specifically, firing of $VGluT2^{+}$ neurons in the medial septum are observed before the start of locomotion (Fuhrmann et al., 2015). Then, hippocampal theta oscillations (Whishaw & Vanderwolf, 1973) and CA1 pyramidal neurons (Card, 2007) couple during locomotion and are both important for processing spatial stimuli (Buzsáki, 2002; Card, 2007). Interestingly, on the Morris Maze, which requires spatial memory for successful performance, slow theta (5.5-8 Hz) emerges during the earlier stages of learning whereas high theta (7.5-10 Hz) emerges during the later stages of learning (Hernández-Pérez, Gutiérrez-Guzmán, & Olvera-Cortés, 2016). These authors speculate that the slower oscillations may be relevant during encoding, whereas the higher oscillations may be important during retrieval. In another study, there was a positive correlation between the velocity of locomotion and theta power, such that as velocity increases, so does theta (McFarland, Teitelbaum, & Hedges, 1975). Interestingly, when the medial septum was inactivated with Procaine hydrochloride, a local anesthetic, animals no longer engaged in locomotor activity and theta oscillations also decreased in the HC (Oddie, Stefanek, Kirk, & Bland, 1996), suggesting that theta oscillations are important for the initiation and/or maintenance of locomotion.

Learning and memory, especially during spatial navigating, could also be explained by theta phase precession. In theta phase precession, spikes from a place cell (a pyramidal neuron in the HC that fires if the animal enters the place field) will initially fire at late phases of the theta cycle. As the animal enters the cell's place field, spikes will start to fire at earlier phases of the theta cycle (O'Keefe & Recce, 1993; Skaggs et al., 1996). Theta phase precession is found in the HC, subiculum, entorhinal cortex, and ventral striatum (Kim, Ganguli, & Frank, 2012; Kenji Mizuseki et al., 2012, 2009; van

der Meer & Redish, 2011). Collectively, these studies show the importance of theta oscillations to facilitate processes such as LTP and theta-phase precession in the service of learning and memory.

Altered Basal and Evoked Theta Oscillations in Individuals with SZ

Similar to gamma oscillations, patients with SZ have increased resting-state theta power (Andreou et al., 2015). However, during cognitive or auditory tasks, patients show reduced theta activity during an N-back task (Pachou et al., 2008), during a Go/No-Go task (Bates, Kiehl, Laurens, & Liddle, 2009; Doege et al., 2010), and during a working memory task (Haenschel et al., 2009). Collectively, these disturbances in theta and gamma activity may represent an aspect of neural network processing that is critically altered in these populations.

Theta and Gamma Oscillations During Recognition Memory

Theta and Gamma Oscillations in Humans

Oscillations in the gamma and theta range are important during recognition memory tasks in humans (see review: Nyhus & Curran, 2010). In human EEG recordings, frontal theta power was increased on a word recognition test when an individual correctly remembered a previously seen word (hits or familiar word) compared to when the individual correctly rejected a word (novel word that was not previously seen) (Burgess & Gruzelier, 1997). Similar findings were observed with gamma in cortical regions, such that gamma power was increased for recognized words compared to novel words (Gruber, Tsivilis, Montaldi, & Müller, 2004). Also in humans, theta increases during verbal working memory tasks during EEG recordings (Gevins, Smith, McEvoy, & Yu, 1997; Jensen & Tesche, 2002; Raghavachari et al., 2001). Furthermore, theta power is increased during successful memory encoding and during recognition of previously encoded items (Klimesch et al., 2006; Klimesch, Doppelmayr, Russegger, & Pachinger, 1996; Sederberg, Kahana, Howard, Donner, & Madsen, 2003; Weiss &

Rappelsberger, 2000). Given the importance of theta and gamma oscillations during encoding and recall of items, reduced recognition memory in patients with SZ could be due to altered oscillations in these frequencies.

Theta and Gamma Oscillations in Rodents

During cognitive states, studies in animals have examined the role of theta, beta (13-30 Hz), gamma, high frequency-oscillations (110-160 Hz), and sharp-wave associated ripples (150-250 Hz) (Buzsáki, 2002; Colgin et al., 2009; Ego-Stengel & Wilson, 2010; Tort, Scheffer-Teixeira, Souza, Draguhn, & Brankačk, 2013). One study found prominent bursts of beta2 (23-30 Hz), theta, and gamma power in the CA1 and CA3 regions of the HC when an animal explored novel objects (França et al., 2014). Also, the power was highest at the beginning of the sessions when objects were most novel. Interestingly, a decrease in beta2 power correlated with a decrease in locomotor activity, suggesting that beta2 could also be directly related to locomotion. Collectively, these results suggest that power in these oscillations, specifically in the theta and gamma band, are important during the NOR task.

Gamma and theta frequencies are observed during encoding and retrieval of episodic memories (Başar, Başar-Eroglu, Karakaş, & Schürmann, 1999; Herrmann, Munk, & Engel, 2004; Wolfgang Klimesch, Freunberger, & Sauseng, 2010). During encoding, when a stimulus is presented (e.g. a yellow rubber duck), there is an increase in synaptic strength between cortical and hippocampal neurons. Then, the HC takes these representations and makes them into a single memory trace that could be retrieved later. This theory is known as the 'hippocampal memory indexing theory' (Teyler & DiScenna, 1986). For retrieving, the theory by Teyler & DiScenna (1986) states that when presented with a single memory representation of the item that was encoded (e.g. duck), cortical activity could activate the whole memory trace (e.g. the duck was also yellow and made out of rubber) in the HC. More specifically, cortical gamma oscillations could provide activity as a coherent pattern to the HC. This allows for each memory representation (e.g. duck, yellow, rubber) of the unified memory trace to be retrieved due to an interaction of theta and gamma (Axmacher, Mormann, Fernández, Elger, & Fell, 2006; Berry & Seager,

2001; Buzsáki, 2002). Interestingly, it is thought that low gamma helps couple CA1 and CA3 processes, which promotes memory retrieval, whereas high gamma promotes memory encoding (Colgin et al. 2009). As mentioned previoulsy in the human literature, theta power is increased during memory encoding and retrieval. Interestingly, gamma power is increased during detection of novelty (Gruber, Tsivilis, Giabbiconi, & Müller, 2008). Although the amount of contribution of theta versus gamma during encoding or retrieving information in humans is less clear, these two frequency oscillations could be assessed individually in animals exploring a familiar versus a novel object. The current set of experiments will determine if theta and gamma are altered during object recognition in MD animals.

Theta-Gamma Comodulation

Cross-frequency comodulation or cross-frequency coupling (i.e. coordination or synchronization of two frequencies), plays a functional role during information processing and learning and memory (Axmacher et al., 2010; Canolty & Knight, 2010). Correlated power fluctuations between different frequencies may provide a mechanism for coding episodic sequences by coordinating neuronal activity at different temporal and spatial scales, which may be important for integrating information within and across brain regions (Buzsaki & Chrobak, 1995; Pascal Fries, 2005). Comodulation could occur between local neural assemblies at higher frequencies (e.g. gamma) or between long-range brain assemblies at lower frequencies (e.g. theta) (Pascal Fries, 2005). As such, when these oscillations become synchronized, this could allow for local ensembles and large-range populations of neurons to interact (Womelsdorf et al., 2007), which may be a mechanism that integrates complex processes (i.e. encoding and retrieval) during higher-levels of cognitive function. One study showed that TGC was disrupted in mice that had ablated synaptic inhibition (mediated by fast $GABA_A$ receptors) in Parvalbumin-positive neurons (Wulff et al., 2009). These data support that the coupling between the two frequencies depend on synaptic inhibition onto neurons that express Parvalbumin.

Theta and gamma also work together (e.g. exhibit comodulation) during memory encoding and retrieval. In the HC, gamma oscillations are superimposed onto theta

oscillation. In other words, there are 7 cycles of gamma that occur during the same time a single theta oscillation occurs. In each of these gamma cycles, different cell ensembles can become activated that may represent different parts of a memory representation (Lisman, 2005). These cells that fire on specific gamma cycles will form a sequential temporal code. Spikes that occur at earlier phases represent the animal's current location, whereas spikes that occur at later phases depict the rat's upcoming location (Lisman & Redish, 2009). When this occurs, comodulation between theta and gamma occurs and comodulation will change over time with learning (Jensen & Colgin, 2007; Lisman, 1999; Lisman, 2005). Through projections between the HC and cortex, theta and gamma patterns cause memory representations to be retrieved (Nyhus & Curran, 2010). It is also suggested that spike-timing dependent plasticity, a phenomenon driven by gamma as mentioned previoulsy, is important for theta phase precession (Florian, Razvan and Murescan, 2006).

In the HC, the amplitude of gamma rhythm is modulated by the phase of the theta oscillation (Sirota et al., 2008). However, low (30-50 Hz) and high (50-100 Hz) gamma occurs during different theta cycles. Low gamma is largest at the falling slope of the theta wave (Belluscio, Mizuseki, Schmidt, Kempter, & Buzsaki, 2012) and is associated when HC CA1 and CA3 regions synchronize (Carr, Karlsson, & Frank, 2012; Colgin et al., 2009). One specific study assessed theta and gamma comodulation during NOR (Trimper et al., 2014b). This NOR paradigm consisted of a circular track where rats had to rotate clockwise and encounter new and repeated objects. Each rat underwent up to 24 training trials and two tests sessions. Each trial consisted of three novel objects at three different locations (1st lap) and a second lap with one object replaced by an identical copy of the same object. During test sessions, one object was replaced by a duplicate object but in a different location, and another object was replaced by a novel object in the same location. LFP electrodes were placed in the CA1 and CA3 region of the HC. As rats explored the novel objects, CA1-CA3 synchrony in the gamma range increased, especially when rats subsequently showed good memory on the previous trial. Furthermore, comodulation of gamma was highest at the falling slope and trough of the theta wave. Lastly, the peaks of gamma oscillations in the CA1 region lined up with the troughs of the gamma oscillation

in the CA3 region during novel object exploration. In conclusion, theta and gamma comodulation have been shown to be robust during successful novel object exploration.

As mentioned above, low gamma helps couple CA1 and CA3 processes, which promotes memory retrieval, whereas high gamma promotes memory encoding (Colgin et al., 2009). In one study that assessed TGC, TGC predicted memory retrieval performance better than either theta or gamma power separately. This study also observed that the magnitude of the theta power and gamma power correlation predicted memory performance from trial to trial (Shirvalkar, Rapp, & Shapiro, 2010), which was examined by assessing power fluctuations between gamma and theta bands. In conclusion, based on these studies, the interaction between the two frequencies are critical for successful memory encoding and retrieval.

Collectively, these studies suggest the importance of theta and gamma interactions on successful memory performance. However, to date, there have been a very few number of studies assessing TGC in patients with SZ. One study assessed cross-frequency comodulation between theta-phase and gamma-amplitude (Kirihara, Rissling, Swerdlow, Braff, & Light, 2012), since the interaction between these frequencies is thought to play a role in information processing (Canolty & Knight, 2010) and has been observed during visual perception and working memory tasks (Axmacher et al., 2010; Demiralp et al., 2007). During an auditory state-state response task, patients with SZ had higher theta amplitude but decreased gamma intertrial phase coherence (i.e. at a given latency, gamma phase was not consistent across trials), suggesting that patients had altered neural oscillations compared to healthy individuals. However, in both groups, theta phase modulated gamma amplitude during the auditory task as well as during a verbal memory task, which supports that TGC was intact in both groups. Collectively, these findings suggest that although patients had similar TGC and similar dynamics of cross-frequency interactions, patients still had altered theta and gamma oscillations. Furthermore, it is possible that altered TGC could be observed during tasks that utilize higher cognitive functions. Another study assessed TGC in patients with SZ when they were having auditory verbal hallucinations versus when they were in a hallucination free state (Koutsoukos, Angelopoulos, Maillis, Papadimitriou, & Stefanis, 2013). Patients had increased TGC during states of auditory verbal hallucinations in the frontotemporal lobe

compared to during hallucination free states. TGC was not recorded from healthy controls. These data suggest that TGC is one of the mechanisms that may be producing verbal auditory hallucinations in these patients. However, no study to date has assessed TGC using the MD model, and how it influences performance on NOR. Therefore, this was the first experiment to conduct TGC analyses to assess how theta modulates gamma when exploring the novel and familiar object in a rodent model of SZ.

Preliminary Studies

To evaluate if MD impairs recognition memory, preliminary studies were conducted. Animals were maternally deprived for 24 hours (*n = 13*) or were left undisturbed (sham) (*n = 10*) on PND 9. On PND 74, animals were tested on NOR to assess recognition memory. First, they were exposed to two identical objects (trial 1). After a one-hour ITI, rats were placed back in the chamber with two identical objects different than the objects experienced previously (trial 2). After a 45-minute ITI, rats were exposed to one object from each previous trial (trial 3). NOR testing took place after a 45-minute ITI when rats were exposed to the object from trial 3 and a novel object (trial 4). Rats had four minutes to explore objects in all four trials.

Total time interacted with both objects was examined. A NOR preference score (time spent with novel object)/ (time spent with novel + familiar object) was obtained from each animal and compared between groups and to 50% chance performance. There were no differences in total time interacted with both objects between groups ($t(21) = 1.081$, $p = 0.2921$) (Figure 1A). When examining total time interacted with each object (Figure 1B), there was a main effect of object ($F(1, 19) = 7.21$, $p = 0.0146$), but no main effect of group ($F(1, 19) = 0.5035$, $p = 0.4866$), or a group by object interaction ($F(1,19) = 0.29$, $p = 0.597$), showing that in general, time exploring one object was higher than the other object. Bonferroni planned comparisons revealed that sham animals spent more time with the novel compared to the familiar object ($t(9)=3.399$, $p=0.009$), but there were no differences in exploration time between objects in MD animals ($t(12)=1.465$, $p=0.1685$). Furthermore, there were no group differences when examining NOR performance score ($t(21) = 0.800$, $p = 0.432$) (Figure 1C). However, only shams

performed better than chance ($t(9) = 3.121$, $p = 0.012$), suggesting that MD animals did not perform the task successfully. Although the strongest indication of an effect selective in MDs would have been a significant interaction, in these analyses, a Bonferroni planned comparison (alpha = 0.025) was used because of the a priori hypothesis that control animals will spend significantly more time with the novel object compared to the familiar because of their natural tendency to explore novelty (Cohen & Stackman, 2015; A. Ennaceur & Meliani, 1992).

These data suggest that neurodevelopmental perturbation on PND 9 was associated with alterations in cognition that lasted into adulthood, given that MDs, but not shams, had impaired recognition memory. Based on these preliminary data, this model provides a useful tool to explore the neural basis of impaired recognition memory following early life trauma that may result in mental psychiatric disorders, including SZ.

Study Rationale

This dissertation addresses a possible factor that may contribute to the impairments observed in recognition memory in the MD group as previously seen in our lab (Janetsian et al., *in progress*). Understanding the fundamental mechanisms by which the impairment in recognition memory may be occurring will provide new information on possible etiological factors that may be associated with this neurodevelopmental disorder. For example, it is unclear whether patients have impaired recognition memory due to deficits in encoding or retrieving information. Therefore, brain function in the theta and gamma frequencies was assessed to observe whether there was a deficit in brain activity during the encoding or retrieval of objects in deprived compared to control animals.

This was the first study to use electrophysiological techniques in awake-behaving animals to assess the properties and correlates by which MD alters electrophysiological properties in these rats during cognitive function. Theta and gamma frequency oscillations were assessed, given their role in coordinating cellular processes that facilitate neural communication, which influence learning and memory (Fell & Axmacher, 2011). Towards this goal, the current project recorded LFPs from the dorsal HC, a region involved in encoding, storage, and retrieval of memories (Squire, Stark, &

Clark, 2004), in rodents that underwent MD and in control rats. Collectively, the goal of these experiments was to understand a potential mechanism that is altered during cognitive function in a pre-clinical rodent model of SZ, which may be helpful in identifying novel treatment approaches in the future. It was hypothesized that MD animals would not spend significantly more time with the novel compared to the familiar object. Furthermore, power in the theta and gamma frequencies would be lower compared to sham animals. It was also hypothesized that TGC would be higher during novel object compared to familiar object exploration in sham animals. Lastly, TGC would be higher in shams compared to MDs.

MATERIALS AND METHODS

Animals

Sprague-Dawley male (*n = 8*) and proven female (*n = 16*) rats were used as breeders and were shipped at eight weeks of age from Harlan Laboratories (Indianapolis, IN). They were individually housed under a 12:12 hour reverse light-dark cycle (lights on at 08:00pm) with *ad libitum* access to food and water. After two days of acclimation to the housing facility, one male rat and one female rat were co-housed for copulation at the start of the dark cycle for approximately two weeks. Each male was paired with a total of two females, and each litter was eventually placed in a different experimental group from the other. PND 0 was the day pups were born. On PND 1, litters were culled to 10 pups (five females and five males when possible) and then were left undisturbed until PND 9. All procedures were approved by the Purdue School of Science Animal Care and Use Committee and conformed to the Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research (Research, 2003).

Maternal Observation

Maternal care was assessed following MD. See Figure 2 for the timeline for maternal observation. On PND 2, PND 6, PND 10, and PND 11, the frequency of maternal behavior was assessed for each litter (sham *n = 8;* MD *n = 8*). Each litter was observed in the home cage in the colony room and was left undisturbed during the observation period. Observations occurred for one hour in the light cycle (9:00 pm – 10:00 pm) and for one hour in the dark cycle (10:00 am – 11:00 am). There were 21 observations per hour. Therefore, there were a total of 42 observations per day and 168 observations in total over the four days/per litter. Every three minutes, the observer observed the cage and determined what kind of behavior the dam was engaged in at that moment. The behaviors included the following: whole body licking and grooming while nursing, whole body licking and grooming without nursing, anogenital licking and

grooming while nursing, anogenital licking and grooming without nursing, arched-back nursing (obvious arch in her back when nursing), flat back nursing (dam engages in nursing postures with no obvious arch in her back), passive nursing (dam is laying down on her side while nursing), and if there was no contact with pups. Maternal care characterization was chosen based on the methods described by Champagne, Francis, Mar, & Meaney (2003) and Parent, Del Corpo, Cameron, & Meaney (2012). The score for each behavior was expressed as a percentage. For example, if considering all occurrences on each day to assess maternal care pre and post MD, then the formula was as follows: (number of occurrences/42) x 100. For licking and grooming behavior, nursing behavior, or the amount of contact for each day, the percentage was calculated as follows: (number of occurrences for each behavior/42) x 100. To analyze the three separate behaviors during the two different light cycles (light versus dark) collapsed on days, the formula was as follows: (number of occurrences for each behavior/84) x 100. For licking and grooming behavior, any dam with one standard deviation above the mean was considered a dam engaging in 'high' maternal care, and the mean - 1 SD was considered a dam engaging in 'low' maternal care. Groups were collapsed to determine high and low lickers and groomers.

Maternal Deprivation

See Figure 2 for the timeline of MD/sham procedure. On PND 9, litters were either maternally deprived for 24 hours ($n = 8$) or were left undisturbed (sham) ($n = 8$). For MD, the mother of the litter was removed at 10:00 am, weighed, and placed in a different cage with food and water in a different room with an identical light cycle. Then, each pup from the litter was weighed and placed back into the same cage without its mother and with no access to food or water. During this period, a heating pad was placed underneath the cage and was maintained between 30-33°C to prevent pups from developing hypothermia. Twenty-four hours later, on PND 10 at 10:00 am, pups were weighed, the mother of the litter was returned to the colony room and weighed, then returned to the original cage with her pups. For the sham group, the mother of the litter was removed at 10:00 am on PND 10, weighed, and then temporarily placed in a

different cage and room. Then pups of her litter were then weighed and placed back in their home cage. Immediately after, the mother was returned to her home cage with her pups. All rats were left undisturbed with access to food and water until they are weaned on PND 21, except for weekly cage cages on Tuesday mornings.

Weaning, Handling, and Weighing

On PND 21, all males from the same litter were group housed to two or three per cage. All females were euthanized using CO_2. Male rats were handled five days a week (two minutes per day) starting on PND 25 until PND 60. On PND 60, two rats per litter were randomly chosen for experimentation and were individually housed. The males that were not used for experimentation were euthanized using CO_2 (see 'Euthanasia' below for details). Animals were weighed daily from PND 10, PND 25 - 84.

Probe Design and Construction

To build the electrophysiological probe for implantation during surgery, a Mill-Max connector (Mill-Max Manufacturing Corporation, Oyster Bay, NY) (9 x 4) was constructed using liquid super glue. Then, four copper wires were soldered to a Pin Receptacle Connector (0.38mm ~ 0.51mm) (Mill-Max Manufacturing Corporation). Each wire was then fed through the 5^{th} hole on each row. Twenty-eight pieces of 34-gauge microfil tubing (World Precision Instruments, Sarasota, FL) were aligned and super-glued (2x14) to build a matrix. Then, 28 three-inch pieces of 25 μm stainless steel wire (California Fine Wire; Grover Beach, CA) were cut and each stainless-steel wire was first fed through a microfil tubing, then wired through the Mill-Max connector, which was then secured by a gold pin. After all stainless-steel wires were fed through and pinned, the probe was secured with epoxy. On the day of surgery, the impedance was checked for each wire and was maintained at 100-300 kilo ohms. Then the probe was placed under the UV ray for sanitation purposes until it was implanted in the brain.

Surgery

On PND 60, two randomly selected animals from each litter (sham *n = 9;* MD *n = 11*) were anesthetized with isoflurane (3% induction, 2% maintenance) and placed into a Kopf stereotaxic frame for surgery. After an animal was anesthetized, eyes were coated with eye ointment to protect from drying out and an injection of Ketoprofen (5 mg/kg, subcutaneous (SC) in a volume of 0.1 ml / 100g) was administered, followed by a subdural injection of 2.5 mg/kg Bupivacaine over the incision site. The respiratory rate of the animal was monitored throughout surgery. When the animal no longer responded to a toe and tail pinch, the scalp was shaved and sterilized using Betadine. Then, an anterior to posterior 1.5 cm midline incision was made on the scalp and the fascia was removed. After the fascia was removed, six holes were drilled and miniature skull screws were implanted throughout the scalp. Two of the screws were implanted over the cerebellum and acted as ground screws. Using the stereotaxic frame, coordinates for the HC were located (AP -3.6, ML -2.6, DV -2.2, relative to bregma) and the probe was implanted into the brain. Probes were then secured with dental acrylic. All surgical tools were pre-sterilized using autoclave and were sanitized with 70% ethanol followed by a glass bead sterilizer. All animals had at least one week to recover from surgery before beginning any experimentation.

Novel Object Recognition

See Figure 3 for detailed timeline and trials for NOR. On PND 74 and 75 (HAB1 and HAB2), each animal was exposed to an open field chamber (86.36 × 93.98 × 31.24 cm) for 10 minutes on each day. This habituation phase was to familiarize the rats with the arena before testing with no objects present. On PND 76 (NOR1), 80 (NOR2), and 84 (NOR3), rats underwent NOR to assess recognition memory (Figure 3A). NOR was tested in the dark phase of the light/dark cycle under the same lighting conditions as in the colony room. More specifically, animals were tested under dim red light. Darker lighting condition was chosen since animals tend to explore darker areas compared to lighter areas (HascoëT & Bourin, 1998).

Experimental procedures were conducted identical to previous experiments conducted in our lab (Janetsian, Linsenbardt, & Lapish, 2015). However, a baseline trial was added in the current set of experiments. Also, three days of NOR testing was conducted (instead of one day) to increase the interaction time with each object, which was required to increase power for electrophysiological analyses. Furthermore, if only one day of testing was used and if for some reason (e.g. not enough habituation), an animal did not interact with objects on that one day, then that animal would not be used for analyses and would be excluded from experimentation. To avoid exclusion of animals, three days of testing were used to assure that animals performed the task (i.e. interacted for at least 20 seconds) on at least one day of testing. This increased power for the electrophysiological analyses, which could have otherwise been compromised if only one day of testing was conducted.

Each day of testing contained five trials (Figure 3B). Before each trial, the tether was plugged into the Mill-Max connector on the rat's head and the rat was placed into a circular chamber (54.61-cm diameter × 41.91-cm height) for three minutes. The circular chamber was placed in the center of the open field chamber. This allowed for the animal to acclimate to the environment and chamber immediately after being connected to a tether, since this process can be stressful for an animal. After three minutes, the animal was picked up, the circular chamber was removed, and the animal was placed directly in the center of the open field chamber.

In trial 1 (baseline), each animal was able to freely explore for four minutes with no objects present. A one-hour ITI followed. Animals were exposed to two identical objects in trial 2. After a one-hour ITI, rats were placed back into the chamber with two identical objects different than the objects experienced previously (trial 3). After a 45-minute ITI, rats were placed in the chamber again and were exposed to one object from each previous trial (trial 4). NOR testing took place after a 45-minute ITI when rats were exposed to the object from trial three and a novel object (trial five). Rats had four minutes to explore objects in all four trials. A one-hour ITI between trials 2-3 followed by a 45-minute ITI between the last two trials is identical to previous experiments conducted in our lab (Janetsian et al., 2015) and the preliminary data discussed herein (Figure 1 and 4). Using this procedure, sham or control animals spend significantly more time with the

novel object compared to the familiar object. Furthermore, other studies used ITIs around one hour and observed intact recognition memory in control animals (Marco, Valero, De La Serna, et al., 2013). Therefore, this dissertation used identical procedures and ITIs to try to replicate previous findings.

The open field chamber contained a magnet approximately 16.5 cm from the wall in two opposite corners of the chamber. The 10 objects used in these set of experiments included rubber ducks (8.89 x 7.62 x 6.35 cm), Rubik's cubes (5.8 x 5.8 cm), glass cups (7.62 x 4.57 cm), plastic cups (8.89 x 3.81), glass jars (9.525 x 7.62), plastic containers (10.16 x 7.62 x 3.81 cm), salt shakers (9.652 x 3.81 x 3.81), circular tape dispensers (7.62 x 4.445), toy race cars (5.08 x 10.16 x 7.62), and toy fire trucks (8.9 x 3.81 x 5.08 cm). Each object contained magnetic tape beneath them. Rats were left undisturbed (except for being weighed) between each testing day. The order in which the objects were used was randomized and the novel object was placed in one of two locations for each animal. Also, animals had a different set of objects on each NOR day and therefore, each animal never experienced the same object on two different days. Lastly, the open-field chamber, circular chamber, and objects were thoroughly cleaned with Clidox between each trial.

Interaction was recorded by ANY-maze using a video camera that was mounted above the chamber. Then, total interaction time in seconds was scored by an experimenter that was blind to the animal treatment. Interaction was considered when the nose of the animal was within 2 cm of the object or when the animal was sniffing or climbing on top of the object, that was considered interaction. Only animals that had an interaction time of 20 seconds or higher were included in all analyses. Figure 3C is an example of an animal interacting with an object.

Preliminary data was collected to assess if rats show recognition memory on all three days of NOR testing using this design. Sprague Dawley rats ($n = 10$) were habituated for two consecutive days for 10 minutes a day. Then, they underwent NOR testing as described above. Rats spent more time with one object compared to the other, which was revealed by a main effect of object ($F(1,18) = 21.38$, $p = 0.0002$) (Figure 4A). Bonferroni post-hoc comparisons showed that rats spent more time with the novel object compared to the familiar on all three days ($p < 0.05$). Interestingly, the degree of novelty detection became stronger as the days progressed. The degree of significance might be

explained by the animals' having more exposure to the chamber by Day 3 compared to Day 1. When looking at preference score, rats performed better than chance on all three days of testing ($p < 0.01$) (Figure 4B). Furthermore, rats spent significantly more time with the novel object on Day 3 compared to Day 2 ($p = 0.0335$), further supporting that novelty detection strengthened over days. Collectively, these preliminary data show that control animals detected novelty on all three days, which supported the use of this design in these experiments.

Locomotor Activity and Thigmotaxis

Locomotor activity and thigmotaxis were acquired during all five days in the open field chamber via a video camera mounted above the open-field chamber and recorded using ANY-maze and using Neuralynx Cheetah recording system (Neuralynx; Bozeman, MT), which was synchronized with electrophysiological recordings. The measures of locomotor activity consisted of: total distance, mean speed, and time immobile. These data included regions in the entire chamber. Thigmotaxis was measured as an index of anxiety (Simon, Dupuis, & Costentin, 1994; Treit & Fundytus, 1988) to examine if MD animals were more anxious during the NOR test compared to sham animals. The parameters that were used to measure thigmotaxis consisted of: distance, mean speed, entries, time immobile, and total fecal matter.

Electrophysiological Recordings

Brain recording were obtained while animals freely moved around during HAB1-HAB2 and all trials of NOR1-NOR3 task. A Neuralynx Cheetah recording system was used and the signal was amplified 2000x to boost signal. Behavioral epochs consisted of when animals explored the novel or familiar objects.

Electrophysiological Data Preparation

All electrophysiological analyses were conducted using MATLAB. For data preparation and analyses, the following steps were taken:

Object Exploration

First, LFPs were sampled at 32,556 Hz then down sampled to 1017.250879498156 Hz prior to analyses. Second, each bout of interaction (with the novel or familiar object in trial 5) was extracted from each animal on each recording day using X and Y coordinates of where the novel or familiar object was placed in the chamber. Bouts that were less than 1000 msec were not used for analyses given that the pattern of lower frequencies are harder to detect with such small amounts of interaction time. After bouts that were less than 1000 msec were removed, data that was 1000 msec before the start of the interaction and 1000 msec after termination of the bout was also extracted for each bout. Taking 1000 msec before and after the interaction was advantageous because it was difficult to locate the exact time point the interaction was initiated. Therefore, it could also include times where the animal approached and left the object.

Third, after LFP data were extracted from each bout of interaction, the data underwent a spectral decomposition to compute power spectral density using a Multitaper method. Unlike the Fourier Transform, the Multitaper method is used because it provides time-frequency resolution (Mitra & Pesaran, 1999). Instead of taking the average of the signal as the Fourier Transform does, the Multitaper method acquires individual statistical estimates from each window (van Vugt, Sederberg, & Kahana, 2007), which is one reason why it provides better frequency resolution because the number of data points used in this method is larger than the Fourier Transform. In the current set of experiments, Multitaper extracted the amplitude (which provided information on power) and frequency from the raw LFP signal. In this case, any given variable consisted of 2543 frequencies (508.6 Hz x 5 time bins per second = 2543 frequencies in total).

Fourth, LFP data were separated based on group, performance, and object. For example, a MATLAB variable was created using power and frequency for each bout of interaction for sham animals that performed successfully (>60% with novel object), during exploration with the familiar object. There were a total of eight variables created (sham successful novel, sham successful familiar, MD successful novel, MD successful familiar, sham chance novel, sham chance familiar, MD chance novel, MD chance familiar). In this way, analyses comparing any of the above variables (e.g. sham successful novel versus MD successful novel) could be conducted.

Fifth, noisy wires were removed from each group. Signals with high variances were detected by using trimmed means using the 80% confidence interval for each bout of interaction (Stigler, 1973). The reason a trimmed mean was used is because it detects less extreme outliers that may otherwise not be detected with traditional outlier analyses. First, the trimmed mean removed any values that were at the tail ends (10% of largest and 10% of smallest values). Then, it took the mean of the remaining 80% of the data and calculated outliers based on the mean. If signals fell outside of the 80% confidence interval, then that bout was removed from the analyses. To find the 80% confidence interval, the following steps were taken. As an example, the 'success sham novel' variable consisted of a 2543 (rows) x 94 (columns) matrix, where 2543 corresponded to the frequency from the Multitaper analyses and 94 corresponded to the number of bouts of interaction with the novel object. The dependent variable (DV) was the power from the Multitaper analyses. The sum of each column was taken (i.e. the sum of the power for each bout that consisted of 2543 data points). The summed output consisted of a 1 x 94 vector. Then, the upper and lower limit of the 94 data points were calculated, using the following formula (upper limit = mean (1 x 94 vector) + 1.28*standard deviation (1 x 94 vector) or (lower limit = mean (1 x 94 vector) – 1.28* standard deviation (1 x 94 vector)). Then, a new variable was created that only combined the data points from the original 'success sham novel' matrix that were within the 80% confidence interval. For this specific example, this new variable consisted of a 2543 x 89 matrix. Five of the bouts were in the upper or lower limit, were considered outliers, and were therefore removed from the matrix.

Baseline Activity

The same procedures were used to extract and prepare baseline activity. Trial 1 from the NOR testing day was used to analyze baseline activity. Since animals had already experienced the chamber multiple times (HAB1 and HAB2), only the last minute of baseline activity was used for the baseline analyses. This was done to avoid brain activity that was related to novelty of being in the chamber on that day. Then, PSD via Multitaper was used to extract the power and frequency during this period. LFP data were then separated based on group and performance and noisy wires were removed using the 80% confidence interval as described above.

Ratio: Object Exploration/Baseline Activity

To analyze changes in power during object exploration (trial 5) from baseline (trial 1), a ratio was created (object exploration power/baseline power) for each bout of exploration using the following steps: 1) if noisy wires were removed during object exploration, then it was also removed from baseline and vice versa. 2) bouts of exploration were normalized to baseline (i.e. the same baseline power was used for each denominator).

Extracting Theta, Low Gamma, and High Gamma

Given the interest in assessing changes in power from baseline between groups in the theta, low gamma, and high gamma ranges, ratios were generated and extracted from those specific frequencies. To do this, a variable for theta was generated where a single ratio in the theta range was extracted (frequencies 30-60 from Multitaper, i.e. 6-10 Hz), low gamma range (frequencies 150-250 from Multitaper, i.e. 30-50 Hz), and high gamma range (frequencies 325-500 from Multitaper, i.e. 65-100 Hz), for each bout of interaction. For each bout, the mean ratio of those frequencies was generated and used for analyses. Frequencies 55-65 Hz were excluded since these values were contaminated by 60-Hz line noise.

Euthanasia

At the end of each experiment, animals were euthanized and perfused (for placement verification). First animals were anesthetized by urethane via intraperitoneal injection at a dose of 1.5 g/kg dissolved in sterile water in a volume of 0.1 ml/kg (Lavin et al., 2007; Yu et al., 2008; Hara et el., 2002). When the animal was unresponsive, a 2-inch incision was made along the abdomen to reveal the diaphragm. A 19-guage needle was then placed into the left ventricle and into the aorta and clamped down. After clamping, the right atrium was cut to allow for blood to drain out and transcardial perfusion of isotonic 0.9% saline began. After the blood was flushed from the body, tissue was fixed via 4% paraformaldehyde solution. After the perfusion, the animal was decapitated and the brain was harvested and sectioned at 30 µm for probe placement verification. Figure 5 includes a timeline of all experimental procedures.

Analyses

Maternal Observation

To determine if there were group differences in amount of licking and grooming, nursing, or contact, on all days of observation, three separate mixed-ANOVAs were conducted with group (MD versus sham) as the between subjects factor and day (PND 2, PND 6, PND 10, and PND 11) as the within subjects factor. To assess if there were group differences in licking and grooming, nursing, or amount of contact in the dark versus light cycle, three separate ANOVAs were conducted with group (MD versus sham) as the between subjects factor and cycle (light versus dark) as the within subjects factor. These analyses were collapsed on PND. Bonferroni post-hoc comparisons were conducted if there were significant interactions in the ANOVAs.

Body Weight

To determine if MD animals had decreased body weight compared to sham animals, a mixed-ANOVA was conducted with group (MD versus sham) as the between

subjects factor and day (PND 25-PND 80) as the within subjects factor and weight as the DV. A second mixed-ANOVA was conducted with family (1-16) as the between subjects factor and day (PND 25-PND 80) as the within subjects factor. Follow up Bonferroni post-hoc comparisons were conducted in the case of a significant interaction.

Novel Object Recognition

The DV to assess NOR was the amount of time (seconds) that an animal spent interacting with each object, in total or separately. Exploration time consisted of the moment when the animal's nose first came into contact (within 2 cm) with an object and terminated when the exploration of the object ended (França et al., 2014; Manns, Zilli, Ong, Hasselmo, & Eichenbaum, 2007; Trimper et al., 2014b). Total exploration time with both objects was assessed during trial 2, trial 3, trial 4, and trial 5 (recall test) using unpaired *t-tests* to compare differences between groups. These analyses were conducted on each day of NOR testing as well as the three days combined. A mixed-ANOVA was used to assess differences in exploration time with each object between groups, followed by Bonferroni planned comparisons (See Preliminary Studies for explanation).

A NOR preference score (time spent with novel object)/(time spent with novel and familiar object) was obtained from each animal and used to perform between-subject comparisons using unpaired *t*-tests. Performance scores for each group were also compared to chance (50%) using a one-sample *t*-test (Bonferroni corrected to alpha = 0.025). Analyses were conducted on each day of testing as well as on all three days of testing, combined.

Total number of bouts and number of bouts with the novel or familiar object between groups were also examined. An unpaired *t-test* was conducted between groups for total number of bouts for all data sets used in the electrophysiological analyses. A mixed-ANOVA was conducted to assess number of bouts for the novel or familiar object between groups. Furthermore, two separate mixed-ANOVAs were conducted to assess number of bouts between novel and familiar object between groups for data sets in animals that preferred the novel object above 60% of the time, and between 40-60%.

Bonferroni post-hoc comparisons were used if there were significant interactions in any analyses.

A Pearson's correlation was conducted using NOR performance score as one variable and total time interacted as a second variable to assess if interaction time was associated with how well an animal detected novelty.

Locomotor Activity and Thigmotaxis

To determine if there were group differences in locomotor activity (i.e. total distance, mean speed, and time immobile), six separate mixed-ANOVAs were conducted with group (MD versus sham) as the between subjects factor and habituation day (HAB1-HAB2) or NOR test day (NOR1-NOR3) as the within subjects factor to assess locomotor activity over days. Identical analyses were conducted to assess total time, distance, mean speed, number of entries, and time immobile in thigmotaxis. These analyses were conducted over the 7 minutes of recording (3-minute baseline, 4 minute in chamber). Bonferroni post-hoc comparisons were conducted if there were significant interactions in the ANOVAs. Lastly, number of fecal matter was used as another measure of anxiety and a mixed-ANOVA was conducted with group (MD versus sham) as the between subjects factor and day (HAB1-HAB2, NOR1-NOR3) as the within subjects factor.

Electrophysiology

To assess changes in theta, low gamma, and high gamma power from baseline, three separate three-way ANOVAs were conducted. In the first ANOVA, the ratio of theta power (i.e. object exploration/baseline for 6-10 Hz) was the DV, and the between subjects independent variables (IV) were group (MD versus sham), object (novel versus familiar), and performance (success versus chance). In the second three-way ANOVA, the IVs were the same but the DV was the ratio of low gamma power (i.e. object exploration/baseline for 30-50 Hz). To assess high gamma power, a third three-way ANOVA was conducted which consisted of the same IVs but the DV was object exploration/baseline for 65-100 Hz. If a significant interaction was detected in the

ANOVAs, follow up analyses were conducted (e.g. two-way ANOVAs or Bonferroni post-hoc comparisons) to assess which variable was driving the interaction or main effects (group, object, performance). For specific follow-up tests used and rationale for each ANOVA, see 'Electrophysiology' under 'Results'.

To assess theta to low gamma comodulation (TLGC) or theta to high gamma comodulation (THGC), two four-way ANOVAs were conducted. In the first ANOVA, ratio of low gamma power was the DV, and the between-subjects IVs were group (MD versus sham), object (novel versus recent), and performance (success versus chance). Ratio of theta power (continuous) was the predictor variable. The second four-way ANOVA had the same IVs except high gamma power was the DV. Follow up three and/or two-way ANOVAs were conducted in case there was a significant interaction between variables.

Regression analyses were also used as another measure of TLGC/THGC. The first linear regression contained ratio of theta as the predictor variable and the outcome variable was ratio of low gamma power for the following groups: sham novel success, sham familiar success, MD novel success, MD familiar success, sham novel chance, sham familiar chance, MD novel chance, MD familiar chance. The slopes of the lines were compared to assess if TLGC was different in any variable. If elevations were different, this suggested that power was significantly higher or lower in one variable compared to others. Another linear regression was conducted that had the same variables but the outcome variable was ratio of high gamma power. If the slopes between the lines were different (THGC), follow up regressions were conducted to better assess what variable was driving those changes.

To assess differences in slopes in each group, two two-way ANOVAS were conducted with object and performance as the IVs and slope as the DVs. Bonferroni post-hoc comparisons were conducted if there were significant interactions.

RESULTS

Animals included in analyses

Only animals with a successful hit to the dorsal HC were included in all analyses (Figure 6). A total of 39 surgeries were conducted (sham *n = 21;* MD *n = 18*). The goal was to have 16 animals in each group. Seven rats died during or soon after surgery. Seven animals had head caps that came off during experimentation. However, data from these animals were included on days where they had enough interaction time during NOR. Twenty-five animals successfully got through all experimentation. The total number of successful surgeries with animals having at least one day of NOR testing was as follows: sham *n = 12;* MD *n = 15*. Out of the 27 animals, four animals did not have at least 20 seconds of interaction time during any of the NOR testing days, and therefore they were not included in any analyses. Out of the 23 total animals with at least one day of NOR testing data, 11 MDs and 9 shams had correct placements in the CA1 region of the HC.

Only animals that had an interaction time of 20 seconds or higher were included in all analyses. There was a total of 78 behavioral NOR videos. After removing animals that did not have hits and after removing videos with bad video tracking, there were 62 NOR data sets. There were 12 trials performed by sham animals and 6 trials performed by MD animals that had less that 20 seconds of interaction, and were therefore removed from analyses. The total number of NOR data sets was 44 (sham data sets *n = 18;* MD data sets *n = 26*). All analyses (including weight, NOR, locomotor, and thigmotaxis) only used animals from the 44 data sets.

Maternal Observation

When assessing the percentage of licking and grooming between groups over the four days of maternal observation (Figure 7A), there was a group by day interaction ($F(3,39) = 7.829$, $p = 0.0003$) and a main effect of PND ($F(3,39) = 5.151$, $p = 0.0043$), which was driven by higher licking and grooming on PND 10 in the MD group compared

to the shams ($t(52) = 4.068$, $p = 0.001$). There were no differences in licking and grooming behavior over days in the sham group, although differences were observed over days in the MD group, which were driven by increased licking and grooming on PND 10 compared to PND 2 ($t(39) = 3.424$, $p = 0.01$), PND 6 ($t(39) = 2.782$, $p = 0.05$), and PND 11 ($t(39) = 5.349$, $p = 0.0001$) (Figure 7A). These data show that removing the mother on PND 9 and returning her on PND 10 increased the percentage of licking and grooming her pups.

Although there was no significant interaction in the percentage of nursing between the groups over days ($F(3,39) = 2.418$, $p = 0.080$), there was a trend (Figure 7B). Bonferroni post-hoc comparisons revealed a significant difference in the percentage of nursing between the two groups only on PND 10 ($t(52) = 2.769$, $p = 0.05$). Similar to licking and grooming, the percentage of nursing increased on PND 10 when mothers were returned to their litters.

There were differences in the amount of contact between groups which was apparent by the interaction ($F(3,39) = 3.030$, $p = 0.0407$) (Figure 7C). These differences were driven by PND 10, where MD animals had a lower percentage of no contact (i.e. higher contact) compared to sham animals ($t(52) = 3.273$, $p = 0.01$). Bonferroni post-hoc comparisons further revealed that although there were no differences over days in the sham animals, there was a significant decrease in percentage of no contact in MD animals on PND 10 compared to PND 6 ($t(39) = 2.896$, $p = 0.05$). These data show that mothers that were removed from their pups had more contact when they were reunited on PND 10.

There were no differences in the percentage of licking and grooming behavior during the active or non-active cycle between or within groups (Figure 7D) revealed by a non-significant interaction ($F(1, 26) = 1.186$, $p = 0.2860$), main effect of group ($F(1,26) = 0.600$, $p = 0.4456$), or a main effect of cycle ($F(1,26) = 0.0052$, $p = 0.9430$). Interestingly, the percentage of nursing was higher during the light cycle compared to the dark cycle, which was revealed by a main effect of cycle ($F(1,13) = 51.00$, $p = 0.0001$; Figure 7E). Interestingly, mothers from both groups had a higher percentage of no contact (i.e. less contact) with their pups during the dark cycle compared to the light cycle, which was revealed by a main effect of cycle ($F(1,26) = 30.02$, $p < 0.0001$; Figure

7F). Overall, mothers from the sham groups had a higher percentage of no contact (i.e. less contact) with their pups during both cycles compared to mothers from the MD group, which was revealed by and a main effect of group ($F(1,26) = 4.840$, $p = 0.0369$). This could possibly be driven by the increase in contact on PND 10 following reunion of MD pups to their mother. Collectively, these data show that nursing occurs more during the light cycle compared to the dark. Furthermore, there was more contact in the MD group compared the sham, but this could be driven by higher levels of maternal care when mothers were reunited with pups.

When combining percentages over the four days, there was a total of one MD mother and two sham mothers (z-score: -1.308) that were considered low lickers/groomers (data not shown). There was one sham mother that was considered a high licker/groomer (z-score: 2.241) (data not shown). Since there was a difference in manipulation between the two groups (MD or sham on PND 9), high or low lickers/groomers only on the first two days (combined), were examined. Groups were collapsed. There was only one sham mother that was considered a high licker/groomer (z-score: 2.679) and one sham mother that was considered a low licker/groomer (z-score: -1.217) (Figure 8).

In conclusion, these data show that licking/grooming, nursing, and contact was altered immediately following MD, suggesting that maternal care can transiently increase after separation from pup.

Weight Differences Between Groups

Although there were no significant group differences in weight over time between MD and sham animals (Figure 9A), there was a strong trend toward a main effect of group ($F(1,18) = 4.353$, $p = 0.0515$), such that MDs weighed slightly less than shams. There was, however a main effect of day ($F(56,1008) = 2072$, $p < 0.001$), but no group by day interaction ($F(56,1008) = 0.5439$, $p = 0.997$), showing that weights increased over days. When assessing weight between families (Figure 9B), there was a family by day interaction ($F(840,280) = 3.28$, $p < 0.0001$), a main effect of family ($F(15,5) = 9.369$, $p = 0.0109$), and a main effect of day ($F(5,280) = 5423$, $p < 0.0001$), indicating the effect of

family on weight is influenced by day. Family accounted for 3.03% of the variance and group accounted for 0.63% of the variance. In conclusion, there were no significant differences in weight between sham and MD animals from PND 25-82, however, in general, some families weighed more than others.

Locomotor Activity

For locomotor activity, there were two sham animals and one MD animal not included in these analyses because these animals did not fully get through all days of testing. There were no differences between groups in any of the measures of locomotor activity (Figure 10 + 11). Specially, no group by day interaction was detected in distance during the habituation ($F(1,16) = 0.00066$, $p = 0.978$) (Figure 10A) or NOR days ($F(2,32) = 2.162$, $p = 0.1316$) (Figure 10B). There was no interaction when looking at mean speed during habituation ($F(1,16) = 0.06957$, $p = 0.7953$) (Figure 10C) or NOR days ($F(2,30) = 2.188$, $p = 0.1298$) (Figure 10D). Lastly, there were no interactions detected during time immobile on habituation ($F(1,16) = 1.294$, $p = 0.2720$) (Figure 11A) or NOR days ($F(2,30) = 0.278$, $p = 0.7592$) (Figure 11B). Collectively, these data suggest that MD animals did not have altered locomotor activity compared to shams.

Thigmotaxis

There were no group differences when assessing total time spent in the thigmotaxis region during habituation, however there was a trend for an interaction ($F(1,16) = 4.472$, $p = 0.0505$) (Figure 12A), which could be driven by the slightly less time spent on the second day of habituation compared to the first in sham, but not in MD, animals. On NOR days (Figure 12B), there were no differences in total time spent in the thigmotaxis region revealed by a non-significant group by day interaction ($F(2, 30) = 0.8355$, $p = 0.4435$). There was, however, a trend for a main effect of day ($F(2, 30) = 3.089$, $p = 0.0603$). No group by day interaction was detected in distance in the thigmotaxis region during habituation ($F(1,16) = 0.6219$, $p = 0.4419$) (Figure 12C), indicating that both groups travelled the same amount in the thigmotaxis region.

Interestingly there was a group by day interaction on NOR days ($F(2,30) = 3.396$, $p = 0.468$) (Figure 12D). Bonferroni post-hoc comparisons reveal no differences between groups on any of the days ($p > 0.05$). However, shams had more distance in meters in the thigmotaxis region on NOR1 compared to NOR3 ($t(30) = 3.306$, $p < 0.01$), indicating that they may have been more anxious on NOR1 compared to NOR3. There were also no differences in mean speed or time immobile between groups during habituation or NOR days (data not shown). Collectively, there were no differences in thigmotaxis between groups on any measure. However, sham rats may have been more anxious on NOR1 compared to NOR3.

There were no group differences in number of fecal matter between groups on any of the days ($F(4,56) = 0.1931$, $p = 0.9410$) (Figure 13). As expected, there was a main effect of day ($F(4,56) = 2.948$, $p = 0.0279$), where animals had higher numbers of fecal matter on the first few days in the chamber (habituation) compared to the last few days in the chamber (during testing). This indicates that animals from both groups may have been more anxious on the first few days of being placed in the chamber compared to the later days when they were already familiar with it, although there were no differences in thigmotaxis between groups. Collectively, locomotor, thigmotaxis, and fecal matter data show that compared to shams, MD animals did not have altered locomotor activity or thigmotaxis.

Novel Object Recognition

On the NOR test, there were no differences between sham and MD animals in total time interacted with both objects, collectively, when collapsed on NOR days on Trial 2 ($t(42) = 1.221$, $p = 0.228$) (Figure 14A), Trial 3 ($t(42) = 1.845$, $p = 0.0720$) (Figure 14B), Trial 4 ($t(41) = 1.091$, $p = 0.2816$) (Figure 14C) or Trial 5 ($t(42) = 0.9188$, $p = 0.3634$) (Figure 14D). These data indicate that one group did not spend more time with the objects compared to the other group.

There were also no differences between groups in total time interacted with both objects, collectively, when looking at NOR1-3 separately (Figure 15). More specifically, there was no main effect of test day ($F(2, 38) = 1.803$, $p = 0.1785$), group ($F(1, 38) =$

1.695, p = 0.2007), or a test day by group interaction (F(2, 38) = 0.1968, p = 0.8222) on Trial 2 (Figure 15A). There was no main effect of test day (F(2, 38) = 1.884, p = 0.1658), group (F(1, 38) = 2.299, p = 0.1387), or a test day by group interaction (F(2, 38) = 0.224, p = 0.8004) on trial 3 (Figure 15B). Interestingly, on trial 4, there was a main effect of test day (F(2, 37) = 7.439, p = 0.0019) (Figure 15C), but no main effect of group (F(1, 37) = 0.7884, p = 0.3803) or a test day by group interaction (F(2, 37) = 0.6002, p = 0.5540). Bonferroni post-hoc comparisons test shows rats interacted more on NOR3 compared to NOR1 (p= 0.0016) (Figure 15C). Similarly, there was a main effect of test day on trial 5 (F(2, 38) = 4.052, p = 0.0254) (Figure 15D), but no main effect of group (F(1, 38) = 0.3203, p = 0.5748), or a test day by group interaction (F(2, 38) = 0.9567, p = 0.3932). Bonferroni post-hoc comparisons reveal a significant increase in total time interacted on NOR3 versus NOR1 (p = 0.0325) (Figure 15D). In conclusion, there were no differences in total time interacted in general between groups or test days on trials 2 or 3. However, sham animals interacted more on NOR3 compared to NOR1 on trials 4 and 5.

The next set of analyses evaluated differences in total time spent with each object, separately, during the novel object test (trial 5) (Figure 16). There was no main effect of group (F(1, 42) = 0.8442, p = 0.3634) or object (F(1, 42) = 1.442, p = 0.2365), or a group by object interaction (F(1,42) = 0.4995, p = 0.4836) (Figure 16A), indicating that there were no group differences between time spent with the novel or familiar object. When assessing time spent with each object, separately, over the three testing days in shams, there was a main effect of test day (F(2, 30) = 5.225, p = 0.0113), but no main effect of object (F(1, 30) = 0.0018, p = 0.9660) or test day by object interaction (F(2, 30) = 0.6415) = 0.5336) (Figure 16B). Bonferroni's post-hoc comparisons show that total interaction time was higher on NOR3 versus NOR1 (t(16) = 2.952, $p < 0.05$). In MDs, there was no main effect of test day (F(2, 46) = 0.7722, p = 0.4679), object (F(1,46) = 2.03, p = 0.1609), or a test day by object interaction (F(2, 46) = 2.03, p = 0.1609) (Figure 16C). In conclusion, these data show that neither shams nor MDs spent significantly more time with the novel object compared to the familiar, suggesting that both groups did not perform successfully.

When assessing preference score for the novel object when collapsed on test day, there was no difference between groups ($t(42) = 0.4694) = 0.6412$) (Figure 17A). Furthermore, shams ($t(17) = 1.215$, $p = 0.2409$) nor MDS ($t(25) = 2.284$, $p = 0.0312$) performed better than chance (Bonferroni planned comparison corrected to 0.025). When assessing preference score over days, separately (Figure 17B), there were no differences in preference of the novel object between groups on NOR1 ($t(15) = 1.096$, $p = 0.2902$), NOR2 ($t(11) = 0.02446$, $p = 0.9809$), or NOR3 ($t(12) = 0.3746$, $p = 0.7145$). Furthermore, neither group performed better than chance (Bonferroni planned comparison corrected to 0.0083). More specifically, sham animals did not perform better than chance on NOR1 ($t(7) = 1.267$, $p = 0.2456$), NOR 2 ($t(3) = 0.2797$, $p = 0.7979$), or on NOR3 ($t(5) = 1$, $p = 0.3632$). Furthermore, MD animals did not perform better than chance on NOR1 ($t(8) = 2.909$, $p = 0.0196$), NOR2 ($t(8) = 0.3756$, $p = 0.7170$) or on NOR3 ($t(7) = 3.347$, $p = 0.0123$.) These data indicate that, contrary to our hypotheses and preliminary data, that both groups did not spend significantly more time with the novel object compared to the familiar.

There were no differences in total number of bouts between sham or MD animals when collapsed over days (Figure 18A) ($t(42) = 0.9033$, $p = 0.3715$). Furthermore, there were no differences in number of bouts with the novel or familiar object (main effect of object ($F(1, 42) = 0.1805$, $p = 0.6731$)) between groups (main effect of group ($F(1, 42) = 0.8159$, $p = 0.3715$)) (Figure 18B). Also, there was no object by group interaction ($F(1, 42) = 0.2554$, $p = 0.6159$). These data show that one group did not have more bouts of interaction with both objects collectively or separately compared to the other group, indicating that groups did not interact with objects using a different behavioral pattern.

Figure 19 assesses a correlation between NOR performance score and total time interacted with both objects in animals that spent 20 seconds or more interacting. There was no correlation between the two variables in sham ($r = -0.3866$, $n = 18$, $p = 0.1130$) or MD ($r = -0.2681$, $n = 27$, $p = 0.1763$) animals. These data indicate that NOR performance score and time interacted with both objects were not related.

Given that there were no differences in novelty detection between groups, data sets were divided into 3 categories (Figure 20). The first category were data sets where animals had >60% preference for the novel object (successful novelty detection). The

second category were animals that had a 40-60% preference for the novel object (not successful/possibly chance). The last category were data sets where animals performed poorly (<40%). Data from <40% performance criteria were not analyzed given that there were only a few data sets per group and not enough power for analyses. Animals that did not have enough interaction time were also listed in the table, but were not used for any of the NOR analyses.

In animals that preferred the novel object over 60% of the time, there was a trend toward a main effect of object ($F(1,17) = 3.741$, $p = 0.0699$), indicating that both groups had slightly more bouts with the novel object compared to the familiar object (Figure 21A). There was, however, no main effect of group ($F(1, 17) = 2.728$, $p = 0.1169$) or object by group interaction ($F(1, 17) = 0.3695$, $p = 0.5513$). In animals that preferred the novel object between 40-60% of the time (Figure 21B), there were no differences in number of bouts with each object, revealed by a non-significant main effect object ($F(1,18) = 0.8922$, $p = 0.3574$), main effect of group ($F(1, 18) = 1.145$, $p = 0.2988$), or object by group interaction ($F(1, 18) = 1.621$, $p = 0.2192$). These data show that number of bouts was not different between groups for the successful trials or trials where they performed by chance, indicating that there were no group differences in the way in which they performed the task.

Electrophysiology

As mentioned previously, following removal of outliers, a ratio was created to assess theta, low gamma, or high gamma power. Figure 22 is a graph of a variable (e.g. success MD novel), after outliers were removed, showing the log 10 power at each frequency, with each line denoting a different bout of interaction with the novel object. Figure 23A is a visualization of the mean log10 power spectrum of sham versus MD animals that successfully performed NOR while interacting with the novel object. Figure 23B is the corresponding power spectrum data during baseline. However, the question of interest is how brain activity is different from baseline in each group. Therefore, to obtain a ratio, power from the test trial was divided by power from the baseline trial for each frequency.

Theta Power

A three-way ANOVA (Figure 24) with group (MD or sham), object (novel or familiar), and performance (success or chance) revealed a main effect of group ($F(1, 1325) = 35.17$, $p < 0.0001$), which was driven by a higher ratio of theta power in sham versus MD animals. A main effect of object was also significant ($F(1, 1325) = 13.48$, $p = 0.0003$), which was driven by the higher ratio of theta power during familiar object compared to novel object exploration. Lastly, there was a main effect of performance ($F(1, 1325) = 22.59$, $p < 0.0001$), driven by the higher ratio of theta power during successful trials compared to chance trials. These effects were quantified by interactions between group and object ($F(1, 1325) = 4.3$, $p = 0.0384$), group and performance ($F(1, 1325) = 30.49$, $p < 0.0001$), and object and performance ($F(1, 1325) = 6.58$, $p = 0.0104$). Furthermore, the interaction between group, object, and performance was significant ($F(1, 1325) = 8.66$, $p = 0.0033$). The main effects and interactions are likely driven by the successful sham group that interacted with the familiar object, which indicates that these animals had the largest change in theta power compared to all other groups and comparisons. To assess this, two separate two-way ANOVAs were conducted at each level of performance.

The first two-way ANOVA consisted of group (MD versus sham) and object (novel versus familiar) as the between-subjects factors during successful trials only (Figure 24, right). There was a main effect of group ($F(1, 521) = 61.08$, $p < 0.0001$), a main effect of object ($F(1, 521) = 18.11$, $p < 0.0001$), and a group by object interaction ($F(1, 521) = 11.71$, $p = 0.0007$). The main effect of group is driven by higher ratio of theta power in the sham group, and the main effect of object is driven by higher ratio of theta power during interaction with the familiar object. The interaction shows that sham animals have a significantly different change in ratio of theta power when exploring one object over another, but there is no change in ratio of theta power in MD animals between objects. Bonferroni post-hoc comparisons revealed that sham animals had a significantly higher ratio of theta power while interacting with the familiar object compared to the novel object ($p < 0.0001$), indicating that theta power significantly increased compared to baseline when they were interacting with the familiar versus the novel object. Furthermore, sham animals that were interacting with the familiar object had a

significantly higher ratio of theta power compared to MD animals that were interacting the familiar ($p < 0.0001$) or novel ($p < 0.0001$) object. Lastly, sham animals that were interacting with the novel object had significantly higher ratio of theta power compared to MD animals that were interacting with the novel ($p = 0.003$) or familiar ($p = 0.04$) object. There were no changes in ratio of theta power when comparing MD animals that interacted with the novel versus familiar object ($p > 0.05$). In conclusion, these data show that during successful trials, sham animals have the highest increase in ratio of theta power when they interact with the familiar object. Furthermore, ratio of theta power was also higher in sham animals that interacted with the familiar object. There were no changes in theta power compared to baseline when MD animals interacted with the novel or familiar object.

The second two-way ANOVA assessed ratio of theta power between groups (MD versus sham) and objects (novel versus familiar) during chance trials only (Figure 24, left). There was no main effect of group ($F(1, 804) = 0.12$, $p = 0.732$), or main effect of object ($F(1, 804) = 0.86$, $p = 0.3532$). Furthermore, there was no group by object interaction ($F(1, 804) = 0.53$, $p = 0.4658$). These data show that there was no change in theta power compared to baseline in either group or during interaction with either object. In conclusion, the changes in theta power were specific only during the successful trials and only in sham animals.

Low Gamma Power

When assessing changes in low gamma power between groups, a three-way ANOVA (Figure 25) revealed a main effect of performance only ($F(1, 1325) = 39.65$, $p < 0.0001$). Based on the figure, it seems that the change in gamma power was larger in successful trials compared to chance trials (see analysis in the next paragraph). There was no significant main effect of group ($F(1, 1325) = 0.01$, $p = 0.9353$). However, there was a trend for a main effect of object ($F(1, 1325) = 3.1$, $p = 0.0783$), such that ratio of low gamma power was slightly higher during interaction with the familiar object compared to interaction with the novel object. Interestingly, there was a group by object interaction ($F(1, 1325) = 5.51$, $p = 0.019$), a group by performance interaction ($F(1, 1325) = 39.49$, p

< 0.0001), and an object by performance interaction (F(1, 1325) = 7.22, p = 0.0073). The interaction between group, object, and performance was not significant (F(, 1325) = 0.6, p = 0.4397). The significant interactions and main effects may be driven by the changes in ratio of low gamma power in sham animals between performance criteria (possibly higher during successful trials compared to chance trials) and objects (higher during familiar object compared to novel object in successful trials only), but not in MD animals. Therefore, follow up two-way ANOVAs were conducted comparing groups and performance (collapsed on object) and performance and object (collapsed on group).

The first ANOVA assessed if there were differences in ratio of low gamma power between groups during either successful or chance performance (Figure 26). A group by performance two-way ANOVA (collapsed on object) revealed a main effect of performance only (F(1, 1329) = 35.63, p < 0.0001), but no main effect of group (F(1, 1329) = 0.17, p = 0.6806). A significant group by performance interaction was also observed (F(1, 1329) = 35.07, p < 0.0001), indicating that ratio of low gamma power was different on performance based on group. Bonferroni post-hoc comparisons revealed that sham animals during successful trials had higher ratio of low gamma power compared chance trials (p < 0.0001) and compared to MD animals during successful (p = 0.005) or chance trials (p = 0.003). Furthermore, sham animals during chance trials had lower ratio of low gamma power compared to MD chance (p < 0.0001) or MD success trials (p < 0.0001). Interestingly, there was no difference in ratio of low gamma power in MD animals when comparing success versus chance trials (p > 0.05). In conclusion, sham animals had changes in ratio of low gamma power based on performance, but there were no changes in ratio of low gamma power in MD animals between performance types.

A performance by object two-way ANOVA (collapsed on group) revealed a main effect of performance (F(1, 1329) = 22.3, p < 0.0001), indicating that ratio of low gamma power was significantly different in chance versus successful trials (Figure 27). However, there was no main effect of object (F(1, 1329) = 1.08, p = 0.2988) or performance by object interaction (F(1, 1329) = 3.28, p = 0.0704). Bonferroni post-hoc comparisons show that there was higher ratio of low gamma power in success trials during novel object exploration compared to chance trials during familiar object exploration (p = 0.03). Furthermore, familiar success trials had higher ratio of low gamma power compared to

familiar chance trials ($p < 0.0001$), or novel chance trials ($p = 0.007$). In conclusion, ratio of low gamma power was higher during successful versus chance performance in sham animals, but there were no changes in low gamma power in MD animals.

High Gamma Power

A three-way ANOVA (Figure 28) with group (MD or sham), object (novel or familiar), and performance (success or chance) revealed a main effect of performance only ($F(1, 1325) = 58.76$, $p < 0.0001$), indicating that power was higher during either chance or successful performance. Although there was a trend toward a main effect of object ($F(1, 1325) = 2.87$, $p = 0.0902$), there was no main effect of group ($F(1, 1325) = 0.11$, $p = 0.7426$). Interestingly, there was only a group by performance interaction ($F(1, 1325) = 101.06$, $p < 0.0001$), but no significant interaction for group by object ($F(1, 1325) = 2.6$, $p = 0.1068$), or for object by performance ($F(1, 1325) = 2.46$, $p = 0.1169$), indicating that group varies at the different levels of performance. Lastly, there was no three-way interaction between group, object, or performance ($F(1, 1325) = 2.27$, $p = 0.1318$).

Given that there was only a significant group by performance interaction, a two-way ANOVA was conducted with group (MD versus sham) and performance (success or chance) as the between subjects factors (Figure 29). There was a main effect of performance ($F(1, 1329) = 55$, $p < 0.0001$) and a performance by group interaction ($F(1, 1329) = 97.11$), $p < 0.0001$), but no main effect of group ($F(1, 1329) = 0.49$, $p = 0.482$), indicating that ratio of high gamma power was higher for one performance compared to another, and this varied based on group. Bonferroni post-hoc comparisons revealed that sham animals that performed successfully had significantly higher ratio of high gamma power compared sham animals that performed by chance ($p < 0.0001$), and compared to MD animals that performed successfully ($p < 0.0001$) or by chance ($p < 0.0001$). Furthermore, sham animals that performed by chance had lower ratio of high gamma power compared to MD animals that performed successfully ($p < 0.0001$) or by chance ($p < 0.0001$). Interestingly, there was no significant difference in ratio of high gamma power when comparing MD animals that performed successfully or by chance ($p = 0.156$).

In conclusion (see Figure 30), theta, low gamma, and high gamma power were lower in MDs compared to shams on successful trials and higher compared to shams on chance trials. Furthermore, power in all three frequencies were higher in sham animals that performed successfully compared to when they performed by chance. There were no differences in power between objects or performances in the MD group. These data suggest that a 24-hour MD period was enough to induce alterations in hippocampal function during recognition memory in adulthood.

Theta-Gamma Comodulation

Low Gamma

To assess TLGC, A four-way ANOVA (Figure 31) with group (MD or sham), object (novel or familiar), performance (success or chance) and theta (continuous variable) revealed a main effect of theta ($F(1, 1316) = 256.81$, $p < 0.0001$), indicating that low gamma varied as a function of theta. There was also a main effect of performance ($F(1, 1316) = 12.38$, $p = 0.0004$), but no main effect of group ($F(1, 1316) = 0.88$, $p = 0.3492$) or object ($1, 1316) = 2.27$, $p = 0.1323$). Interestingly, there was a group by performance interaction ($F(1, 1316) = 7.15$, $p = 0.0076$), indicating that the effect of group on low gamma is influenced by performance type. There was no theta by group interaction ($F(1, 1316) = 0.05$, $p = 0.8179$), theta by object interaction ($F(1, 1316) = 1.88$, $p = 0.1704$), theta by performance interaction ($F(1, 1316) = 1.64$, $p = 0.2003$), or a group by object interaction ($F(1, 1316) = 0.1394$, $p = 0.1394$). Three-way interactions revealed a group by object by performance interaction ($F(1, 1316) = 6.49$, $p = 0.0109$), indicating that group and object differed across performance. There was no theta by group by object interaction ($F(1, 1316) = 0.15$, $p = 0.7096$), theta by group by performance interaction ($F(1, 1316) = 0.09$, $p = 0.7687$), or a theta by object by performance interaction ($F(1, 1316) = 0.05$, $p = 8286$). Lastly, there was a significant four-way interaction ($F(1, 1316) = 9.63$, $p = 0.002$), indicating that three variables varied across a fourth variable. Given that there was no theta by group, theta by object, or theta by performance interaction, this

indicates that theta did not influence gamma differently in any of these measures (i.e. TLGC did not differ between performance, groups, or objects).

As mentioned previously, regression analyses were also used as another measure of TGC. A simple linear regression was calculated to predict low gamma power based on theta power and was stratified by different variables of interest. A significant regression equation was found for the following variables: sham novel success ($F(1, 73)= 37.96$, $p < 0.0001$); sham familiar success ($F(1, 45) = 8.298$, $p = 0.0061$); MD novel success ($F(1, 229) = 21.87$, $p < 0.0001$); MD familiar success ($F(1, 170) = 38.01$, $p < 0.0001$); sham novel chance ($F(1, 180)= 48.55$, $p < 0.0001$); sham familiar chance ($F(1, 172) = 63.38$, $p < 0.0001$); MD novel chance ($F(1, 200) = 44.56$, $p < 0.0001$); MD familiar chance ($F(1, 247) = 46.32$, $p < 0.0001$). These data indicate that there was a significant relationship between low gamma power and theta power.

To assess if one group had significantly different TLGC, the slopes between variables were compared (data not shown). The differences between the slopes for the eight regression lines were not significantly different ($F(7, 1316) = 1.756$, $p = 0.0925$), indicating that TLGC was not different when interacting with a specific object or performance between groups. A separate linear regression was conducted for each group (sham or MD) using the following variables: success novel, success familiar, chance novel, chance familiar. There were no significant differences in slopes in the sham group ($F(3, 470) = 2.064$), $p = 0.1041$), further supporting that TLGC was not different in sham animals that interacted with the novel or familiar object on successful or chance trials.

Two-separate two-way ANOVAs were conducted (one for sham and one for MD) with performance and object as the IVs and slope as the DV. However, the interactions were corrected to 0.025 to take into account the extra variable (group) that would have been in the three-way ANOVA. In sham animals, there was no main effect of object ($F(1, 474) = 1.206$, $p = 0.2728$), no main effect of performance ($F(1, 474) = 0.9872$, $p = 0.3209$), or no object by performance interaction ($F(1, 474) = 4.381$, $p = 0.0269$) (Figure 32A), indicating that TLGC was not stronger depending on performance or object.

Similar to shams, there were no differences in slopes between the four variables in MDs ($F(3, 846) = 1.881$, $p = 0.1312$), indicating that TLGC was not significantly

different in MD animals that interacted with the novel object versus the familiar on successful or chance trials.

A two-way ANOVA was conducted with performance and object as the IVs and slope as the DV (Figure 32B). There was no main effect of object ($F(1, 850) = 0.5454$, $p = 0.4604$), main effect of performance ($F(1, 850) = 0.5296$, $p = 0.4670$), or an object by performance interaction ($F(1, 850) = 4.534$, $p = 0.0335$). These data also show that in MD animals, TLGC was not higher for during successful or chance performance or for the novel or familiar object. In conclusion, TLGC was not higher based on performance criteria or when interacting with the novel or familiar object in either group.

High Gamma

A four-way ANOVA (Figure 33) with group (MD or sham), object (novel or familiar), performance (success or chance) and theta (continuous variable) revealed a main effect of theta ($F(1, 1316) = 113.07$, $p < 0.0001$), indicating that ratio of high gamma varied as a function of theta. There was also a main effect of object ($F(1, 1316) = 17.84$, $p < 0.0001$), and a main effect of performance ($F(1, 1316) = 0.0062$), but no main effect of group ($F(1, 1316) = 0.74$, $p = 0.3899$). There was a two-way interaction between theta and object ($F(1, 1316) = 19.3$, $p < 0.0001$), indicating that the effect of theta on high gamma is influenced by object. A significant group by object interaction ($F(1, 1316) = 4.71$, $p = 0.0302$) and a group by performance interaction ($F(1, 1316) = 21.9$, $p < 0.0001$) revealed that effect of group on ratio of high gamma is influenced by object and performance, respectively. Lastly, a significant object by performance interaction ($F(1, 1316) = 7.6$, $p = 0.0059$) indicates that the effect of object on ratio of high gamma depends on performance criteria. There was no interaction between theta and performance ($F(1, 1316) = 1.07$, $p = 0.301$). Three-way ANOVAs reveal a significant theta by object by performance interaction ($F(1, 1316) = 4.65$, $p = 0.0313$), and a group by object by performance interaction ($F(1, 1316) = 5.69$, $p = 0.0172$), indicating that two of the variables differed across a third variable. There was no theta by group by object interaction ($F(1, 1316) = 1.63$, $p = 0.2014$) or a theta by group by performance interaction

($F(1, 1316) = 0.01$, $p = 0.9428$). Lastly, there was no four-way interaction between theta, group, object, and performance ($F(1, 1316) = 2.84$, $p = 0.0922$).

A follow up three-way ANOVA was conducted with object and performance as the IVS (collapsed on performance), theta power as the predictor variable, and ratio of high gamma power as the DV. There was a main effect of theta ($F(1, 1324) = 138.93$, $p < 0.0001$), indicating that there was a relationship between theta and ratio of high gamma. There was also a main effect of object ($F(1, 1324) = 10.33$, $p = 0.0013$). No main effect of performance was observed ($F(1, 1324) = 0.26$, $p = 0.6128$). Interestingly, there was a theta by object interaction ($F(1, 1324) = 13.24$, $p = 0.0003$) and a theta by performance interaction ($F(1, 1324) = 4.61$, $p = 0.032$), Indicating that theta influenced high gamma differently based on object as well as performance. The object by performance interaction was not significant ($F(1, 1324) = 1.77$, $p = 0.1837$). Lastly, there was no theta by object by performance interaction ($F(1, 1324) = 2.33$, $p = 0.1268$). In conclusion, THGC seemed to be influenced by object and performance. Linear regressions were conducted to further explore THGC.

A simple linear regression was also calculated to predict ratio of high gamma power based on the different variables of interest. A significant regression equation was found for the following variables: sham novel success ($F(1, 73)= 51.98$, $p < 0.0001$); sham familiar success ($F(1, 45) = 0.2634$, $p = 0.6103$); MD novel success ($F(1, 229) = 23.54$, $p < 0.0001$); MD familiar success ($F(1, 170) = 8.568$, $p = 0.0039$); sham novel chance ($F(1, 180)= 35.36$, $p < 0.0001$); sham familiar chance ($F(1, 172) = 12.66$, $p = 0.0005$); MD novel chance ($F(1, 200) = 15.24$, $p < 0.0001$); MD familiar chance ($F(1, 247) = 9.82$, $p = 0.0019$). In all cases except for sham familiar success, there was a significant relationship between ratio of high gamma power and theta power.

When conducting a regression, the differences between the slopes for the eight regression lines were significantly different ($F(7, 1316) = 3.36$, $p = 0.0015$). Therefore, a separate linear regression was conducted for each group (sham or MD) using the following variables: success novel, success familiar, chance novel, chance familiar to assess which group was driving the significant difference in slope. When assessing these four variables in the sham group, there were significant differences between the slopes ($F(3, 470) = 5.93$, $p = 0.0006$). This was driven by the higher slope in the success novel

variable (Y = 0.2893*X + 0.9524), compared to the success familiar (Y = 0.02887*X + 1.565), chance novel (Y = 0.1578*X + 0.8315), and chance familiar (Y = 0.1077*X + 0.8979). These data show that THGC was highest in sham animals when they were exploring the novel object during successful trials.

Slopes of THGC were also compared in the sham group and corrected to 0.025 (Figure 34A). There was no main effect of performance ($F(1, 474) = 0.4312$, $p = 0.5117$). A main effect of object ($F(1, 474) = 14.99$, $p = 0.0001$) and an object by performance interaction ($F(1, 474) = 6.876$, $p = 0.0090$) were observed, however. Bonferroni post-hoc comparisons revealed that THGC was significantly higher in successful trials compared to chance trials when exploring the novel object ($p = 0.0216$). Furthermore, THGC was significantly higher in successful trials when exploring the novel versus the familiar object ($p = 0.0004$).

Interestingly, there were no differences in slopes between the four variables in the MD group ($F(3, 846) = 1.948$, $p = 0.1204$). The slopes were as follows: success novel variable (Y = 0.2081*X + 0.9914), success familiar (Y = 0.11*X + 1.12), chance novel (Y = 0.165*X + 1.114), and chance familiar (Y = 0.09255*X + 1.203). These data indicate that there were no significant differences between THGC in MD animals between trials or performances.

A two-way ANOVA was conducted with performance and object as the IVs and slope as the DV (Figure 34B). There was no main effect of performance ($F(1, 850) = 0.614$, $p = 0.4335$). There was, however, a main effect of object ($F(1, 850) = 4.871$, $p = 0.0276$), which could possibly be driven by higher THGC during novel object interaction. Furthermore, an object by performance interaction was not observed ($F(1, 850) = 0.1102$, $p = 0.7400$). Bonferroni post-hoc comparisons revealed that there was no significant difference in THGC between groups ($p > 0.05$), indicating that THGC was not different in MD animals whether they performed successfully or by chance, and it was also not different between objects.

In conclusion (see Figure 35), TLGC was not different between groups, performances, or objects, but THGC was higher in sham animals when they performed with the novel object during successful trials compared to chance trials, and THGC was higher when they interacted with the novel versus familiar object in successful trials.

There were no differences in TLGC or THGC between objects or performances in the MD group. These data suggest that THGC is one brain mechanism that is altered following 24-hours of MD that lasts until adulthood.

DISCUSSION

The goal of these experiments was to assess whether early-life trauma persistently alters cognitive and brain function. Towards this goal, local field potential (LFP) recordings in the theta and gamma range were obtained from the dorsal HC during a recognition memory task in an animal model that resembles certain neurocognitive features of SZ. These findings revealed that although both sham and MD rats did not spend significantly more time with the novel object, MD rats had no change in theta or low/high gamma power or TGC when interacting with the novel or familiar object during successful or chance trials. However, higher theta and gamma power and TGC was observed in sham animals depending on the object they were exploring or whether it was a successful or unsuccessful trial. These data suggest that there was a dissociation between brain activity and NOR in MDs, but not in shams, further suggesting that there may be a compensatory mechanism in MD animals that allowed them to perform well during successful trials. These data might also indicate altered functioning of the HC following MD, providing support that early life trauma can induce cognitive and physiological alterations that are long-lasting that resemble those seen in SZ.

The MD model has strengths and weaknesses, as does any animal model used to study the etiology or underlying mechanisms associated with neuropsychiatric disorders. A weakness of this model is that it is impossible to induce every symptom of SZ in one animal model, which makes it difficult to fully model the disorder. For example, according to the MATRICS, individuals with SZ have cognitive deficits in attention, working memory, processing speed, verbal and visual memory, problem solving, and social cognition (Nuechterlein et al., 2004). Although some of these measures would be impossible to evaluate in a rodent (e.g. verbal memory), studies have shown that the MD model can impair recognition memory on the NOR test (measure of working memory or attention), spatial memory on the spontaneous alternation task or information processing during prepulse inhibition (see review: Marco et al., 2015). Therefore, it is difficult to know if MD is the most effective to model all the neurocognitive features observed in individuals with SZ. Another weakness is that the causes or etiology of SZ are not known

definitively, and therefore MD may not be the best to model this disorder. Another growing body of evidence is that the risk of developing SZ increases if there are at least two traumatic or adverse events during the lifetime (one during early brain development and one during adolescence or adulthood) (i.e. two-hit hypothesis) (Maynard, Sikich, Lieberman, & LaMantia, 2001). The MD model is only used as the first 'hit' (i.e. adverse event during neurodevelopment) and therefore combining an adverse event later in life can be more translational to the neuropsychiatric disorder being studied. A strength of this model is that the 24-hour insult (i.e. traumatic event) is conducted during a period where brain circuits are being established, and any perturbation during this time can lead to a subset of symptoms that are also present in individuals with SZ. Another strength is that this model has face validity because currently, one of the leading hypotheses for the development of SZ is that it a neurodevelopmental disorder that disrupts brain development, which is observed in this MD model (see review: Marco et al., 2015). This allows for the field to further study the specific changes that occur in the brain immediately following deprivation or the long-lasting effects of the stressful event to better understand the course of development of this mental disorder. Furthermore, the MD procedure is easy and safe to conduct compared to other models of SZ, such as those that require injecting viruses prenatally or ones that require lesions neonatally (neonatal ventral hippocampal lesion). In conclusion, although this model has weaknesses, it also has many strengths and was used specifically to model and study the neurodevelopmental component of neuropsychiatric disorders.

Novel Object Recognition Behavior Following MD

In the current experiments, MD and sham animals did not differ in the amount of time they interacted with both objects when testing days were collapsed (Figure 14). These findings were similar to the preliminary study that showed no group differences in interaction time with both objects (Figure 1A). The same pattern of interaction times was also detected in each group. For example, in the preliminary study, sham animals interacted for ~50 seconds, whereas MDs interacted ~60 seconds (Figure 1A). In these studies, interaction times were similar for sham (~47 seconds) and MD (~50 seconds)

animals on trial 5 on the NOR testing days (Figure 14D). Although there were no overall differences in total time interacted between groups, there were differences in total interaction time when looking at each day separately. More specifically, sham animals spent significantly less time interacting with both objects on NOR1 versus NOR3 (Figure 15D), but there were no MD differences. Lower interaction time on NOR1 is consistent with the results observed in locomotor activity in the thigmotaxis region, which was higher on NOR1 versus NOR3 (Figure 12D). These data suggest that sham animals may have been anxious on NOR1, which resulted in less exploration with objects in general. Although there were differences in total interaction on one day of testing, these data conclude that there were no overall between-group differences in anxiety-like behavior or locomotor activity (i.e. hyperactivity could result in decreased investigation) which could each disrupt exploratory behavior (Asin, Wirtshafter, & Kent, 1979; Baker & Kim, 2002; Crawley, 1985).

When assessing novel versus familiar object exploration, there were no between-group or within-group differences when collapsing on days (Figure 16A) or when looking at days separately (Figure 16B + C). Although findings were consistent for MD animals between the preliminary data and the current experiments (i.e. no significant difference in novel object versus familiar exploration), the findings for the sham group was unexpected (i.e. shams had impaired recognition memory in current experiments but not in preliminary study) (Figure 1B). Control animals spending more time with the novel object compared to the familiar has been shown consistently (A. Ennaceur, 2010; A Ennaceur & Delacour, 1988; Janetsian et al., 2015). Therefore, it was surprising to see not only a lack of preference for novel object in the MD group, but also in sham animals. Episodic memory was also measured by observing a preference score. The preference score is a way to control for differences in exploration time between groups before assessing how long animals spend with one object or the other. Neither group preferred the novel object significantly greater than chance (Figure 17). Furthermore, MD and sham groups did not significantly differ from each other when comparing preference scores. In conclusion, these data show there were no differences on the NOR task between groups.

Given that these results were unexpected, other behaviors during NOR were observed to assess if there were different behavioral characteristics during successful or chance performance between groups. There were no group differences in total number of bouts with each object (Figure 18), time to approach first object (data not shown), and first object approached (novel or familiar; data not shown). Another measure that was assessed was total time interacted with objects versus NOR performance score. This was conducted to explore if interaction times predicted preference score, more specifically, if longer interaction times lowered preference for the novel object. It is possible that the more animals interacted with objects, the worse their performance score was because it has been shown that the novel object becomes less novel over time (Dix & Aggleton, 1999). Time interacting with each object did not correlate with NOR performance score (Figure 19) throughout the recording session. In conclusion, these data indicate that sham and MD rats did not have perform the task differently (i.e. behave differently) during the NOR test.

One explanation for unsuccessful performance is that it is possible rats had postoperative cognitive dysfunction (POCD). There is evidence suggesting that young adult Sprague-Dawley rats (3 months old) that undergo anesthesia via Isoflurane (5% induction, 1.2% maintenance) have impaired working memory on the Morris Water Maze (Callaway, Jones, & Royse, 2012; Zhang et al., 2010) and on the NOR task (Lopez-Astacio et al., 2012). Specifically, in the NOR study, rats underwent Isoflurane anesthesia 14 days prior to NOR training. These animals had impairments on the NOR test, even two-weeks after recovery. Reasons why impairment in cognitive function can occur is because Isoflurane can cause cell death in the HC (Jevtovic-Todorovic et al., 2003). There is also evidence suggesting that Isoflurane inhibits synaptic plasticity in this region (Simon, Hapfelmeier, Kochs, Zieglgänsberger, & Rammes, 2001). One way this could occur is through over activation of NMDA receptors, which could lead to apoptosis (cell death), and as an extension, could cause memory deficits. This was postulated based on a study that showed that administering memantine (NMDA partial antagonist), reversed the isoflurane-induced elevations in apoptosis (Zhang et al., 2008). Therefore, although not tested, it is possible that in the current set of experiments, NOR performance is affected due to anesthesia during the surgeries via impaired recognition due to cell death, synaptic

plasticity, etc. To test whether Isoflurane impacts recognition memory, control animals and animals that undergo Isoflurane anesthesia can perform the NOR task. If there are no group differences on the task, that would suggest that Isoflurane did not affect performance.

The lack of significant difference between interaction time with the novel versus familiar object in the sham group was surprising. The discrepancy in results between this study and the preliminary data could be due to the different experimental procedures used in each study. Although animals habituated to the chamber for two-days prior to experimentation, this may not have been enough time for the animals to get used to the environment, specifically when implanted with a probe and connected to a tether. More specifically, animals were connected to a commutator and tether (cable connected to commutator) during NOR testing. Although a commutator is supposed to address the following problems, the cable can twist while the animal is exploring objects and it could be uncomfortable for the animal, there may be some force or pressure on the head cap if for some reason the cable twists or pulls, and there could be visual distractions away from the objects if the animal is able to see the tether. If a wireless system was used, the problems listed above could have been prevented (Pinnell, Almajidy, Kirch, Cassel, & Hofmann, 2016). However, it is impossible to test the effects of the tether in this experiment and how it influenced performance on NOR.

There are a few studies that have assessed novelty detection using the same MD model, and it is apparent that results differ based on the age of testing, the NOR behavioral procedure, and the type of analysis used. This is evident in the current set of experiments, where sham animals are impaired in the two different ways (interaction time with each object (Figure 16A) or preference score (Figure 17)). However, MD animals had an impairment only when looking at interaction time with each object (Figure 16A), but not when looking at the preference score (Figure 17A), given that they performed slightly better than 50%. This suggests that results can differ based on the analysis approach.

One study assessed recognition memory on PND 40 in male Wistar rats and found no impairment in episodic memory between control and MD animals (Marco, Valero, De La Serna, et al., 2013). These animals were habituated to the testing chamber for five

minutes a day on three consecutive days. On testing day, animals were able to explore identical objects for three minutes, and after a one-hour ITI, animals were exposed to one novel and one familiar object and were able to explore for another three minutes. During the training period, control animals spent ~32 seconds interacting with both objects, whereas MD animals spent ~35 seconds interacting. Although this study observed no impairment on the NOR task in MD animals, there are some caveats to this study. For example, only the first minute of the testing session was analyzed. It is possible that if the entire three minutes of testing was assessed, a stronger recognition memory in one group compared to the other would be observed. It is important to note that this study used a different strain of rat than the current set of studies, which could result in behavioral differences (Andrews, Jansen, Linders, Princen, & Broekkamp, 1995). Lastly, another major difference was the age of testing between experiments. Considering that recognition memory develops as the brain matures (Reger et al., 2009), it is not surprising that no differences were observed between juvenile control animals and MD animals.

Another study assessed recognition memory in male Sprague-Dawley rats on PND 65 (Zamberletti et al., 2012). In this study, animals were exposed to two identical objects for three minutes, then after a three-minute retention period, animals were placed back into the chamber with one familiar and one novel object and could explore for a total of five minutes. There were no significant differences in novel object exploration between control and MD animals, suggesting that neither group was impaired on this task. A few differences between this study and the current set of experiments are that animals were not habituated to the chamber prior to the testing day. However, this did not seem to influence performance, given that animals were able to interact with the novel object more than the familiar. Another major distinction between the studies is that this study used a three-minute ITI rather than a one-hour ITI, which could be tapping more into working memory rather than short term memory (Carlini, 2011). Tests that utilize retention periods of less than five minutes measure working memory, whereas retention periods of two-hours measure short-term memory, and a period of 24-hours measures long-term memory (Carlini, 2011). Therefore, it is possible that MD does not induce impairments in working memory in adulthood, but it does influence short-term or long-term memory.

Three studies assessed novelty detection following a longer, four-hour retention period in adult Wistar rats. In the first study, rats were habituated to the testing chamber for five minutes a day for four consecutive days (Llorente-Berzal et al., 2012). For the training period, rats were exposed to two identical objects on PND 60, were placed in the chamber for a maximum of four minutes and removed until they interacted with the object for a minimum for 30 seconds. After the retention period, they were placed back into the chamber with one novel and one familiar object and could explore for a total of three minutes. Interestingly, using these procedures, MD males were impaired on this task compared to control animals. Another study used similar procedures but testing was conducted on PND 82 (Llorente et al., 2011b). This study also shows that male MDs had decreased discrimination index compared to controls, suggesting that they had an impairment on NOR. It is important to note that these studies did not test whether there were differences in total interaction time during the testing trial between groups. If interaction time was less in one group compared to the other, this could indicate that group may have been more anxious. However, no measures of anxiety were assessed during testing. In conclusion, these studies indicate that when using longer retention periods (4 hours), MD animals are impaired on this task compared to control animals.

The last study that used a long retention period assessed NOR performance on PND 70 (Mela et al., 2015). In this study, animals were habituated to the chamber for five minutes a day on three consecutive days. Then on testing day, rats were first exposed to two identical objects for three minutes, and after a four-hour ITI, they were exposed to one novel and one familiar object for three minutes. There were no differences in discrimination index between control and MD animals. It is important to note that studies only looked at the first minute of the test session, and results could have differed if they looked at the entire test session. For example, control animals could have spent significantly more time with the novel object compared to the familiar in the second minute of testing, which could have resulted in significant differences in novelty detection between the two groups. It is also important to note that these animals were injected with leptin multiple times during early-postnatal life and this manipulation could have somehow protected MD animals from producing deficits in adulthood on the NOR test.

In conclusion, these studies demonstrate that shorter retention periods do not impair recognition memory in MD rats; However, a longer retention period of four-hours was enough to impair recognition memory. This could indicate that MD animals could have difficulty detecting a familiar object if they must keep the information in memory for periods longer than one hour. However, encoding is not necessarily affected because reducing the retention period does not influence encoding. It is important to note that none of these studies had animals that underwent surgery or had probes implanted that were connected to a tether during testing. Also, none of these studies compared discrimination index (novel-familiar/novel + familiar) x 100) to chance performance. It is therefore possible that control animals or even MD animals were not performing better than chance. If they were not performing better than chance, that suggests that animals were impaired on the NOR test.

It is important to note major differences in experimental procedures between the current set of experiments and the aforementioned NOR studies. In this dissertation, animals were placed under a heating pad to prevent animals from developing hypothermia (Zimmerberg & Shartrand, 1992). None of the studies described above (Llorente et al., 2011b; Marco, Valero, De La Serna, et al., 2013; Mela et al., 2015; Zamberletti et al., 2012) reported the use of a heating pad. Interestingly, one study demonstrated that rats that were separated from their mothers but remained in a warm environment at nest temperature had higher body and brain weight compared to animals that were placed in room temperature (Zimmerberg & Shartrand, 1992). Furthermore, the pups that were placed in a nested environment were less sensitive to an amphetamine injection (measured by locomotor activity) compared to animals that were placed in room temperature, indicating that these animals may have had a down regulation of the DAergic system (e.g. due to fewer receptors or reduced DA release). Although there are differences in development when animals are placed in a warm environment compared to room temperature during separation, it is difficult to tell if the results in the current set of experiments would have been different if animals were not placed under a heating pad.

Another difference is that animals in the current study were handled five days a week for two-minutes a day from PND 25-73. None of the studies reported handling animals during experimentation (Llorente et al., 2011b; Marco, Valero, De La Serna, et

al., 2013; Zamberletti et al., 2012). One study, however, mentioned handling animals during injections from PND 9-13 (Mela et al., 2015). There is evidence supporting that rats that were handled 30 seconds daily from 3 weeks of age (~PND 21) to 9 weeks of age (~PND 63) explored more in an open field chamber compared to rats that were not handled (Cowley & Widdowson, 1965). Another study observed that handling pups from PND 9-21 reversed the effects observed on the glucocorticoid system following perinatal stress (dam was restrained to a cylinder for 45-minute sessions on three consecutive days), suggesting that handling may play a protective role following early-life stress (Vallée et al., 1999).. These data are interesting, because it is possible that the handling procedure used in the current set of experiments somehow protected animals or made animals more resilient to the stress experienced early in life. However, since animals did not spend significantly more time with the novel versus familiar object, it is difficult to know if handling had a protective effect on exploratory behavior or on behaviors that were not measured.

As mentioned in the introduction, the HC and perirhinal cortex are structures critical for successful memory encoding, consolidation, and retrieval (Broadbent et al., 2010; Buckmaster et al., 2004; Clark et al., 2000; Hannesson et al., 2004; Winters & Bussey, 2005). More specifically, the HC is crucial when spatial or contextual information is present in the NOR task (Goulart et al., 2010), whereas the perirhinal cortex's involvement revolves around scent, vision, and somatosensory stimuli (Clark et al., 2000). Therefore, any impairment on this task could implicate that at least one of these brain regions is not properly functioning. Given that MD and sham animals had impaired recognition memory, it was therefore hypothesized that successful encoding, consolidation, or retrieval is not occurring, which could be a result of an impairment on one or a combination of these structures.

It is possible that rats were not performing NOR successfully because NOR is not a reliable task to measure recognition memory, and not because sham or MD rats have altered brain function as discussed above. For example, one study found that there was no relationship between time spent with the familiar object during the familiarization trial and preference for novelty during the testing trial, which suggests that spending more time with a familiar object (i.e. more encoding) in the previous trial does not necessarily

predict that rats will prefer the novel object more than the familiar during the testing trial (Gaskin et al., 2010). These data further indicate that although rats encoded the object in the familiar trial, they still may not spend significantly more time with the novel object, suggesting that this task is not necessarily a measure of memory performance. There is also evidence supporting that rats could either be neophobic (not liking novel or unfamiliar objects or places) or neophilic (having a strong preference for novelty) (Delini-Stula & Hunn, 1988; A. Ennaceur, Michalikova, & Chazot, 2006), which would either increase or decrease time spent with the novel object. If animals are indeed neophobic, they may spend more time with the familiar object and that may be falsely interpreted as an 'impairment' in either encoding or retrieval. Therefore, although the NOR results were interesting, this task has many limitations as discussed above.

Theta Power During Novel Object Recognition

For many years, studies have focused on assessing the effects of different oscillations using electroencephalography (EEG) in patients with SZ on a variety of cognitive and auditory tasks, and have seen impairments on a variety of measures. More specifically, individuals with SZ have increased resting-state theta and gamma power compared to healthy controls (Andreou et al., 2015). However, during increased cognitive load, the opposite is true, such that theta and gamma power is reduced compared to healthy individuals (Bates et al., 2009; Doege et al., 2010; Haenschel et al., 2009; Pachou et al., 2008). For example, on a delayed match to sample working memory task, SZ patients have lower theta and gamma power during both encoding and retrieval (Haenschel et al., 2009). Reduced gamma in patients has also been observed during sensory gating, speech, and tasks that involve math (Kwon et al., 1999; Uhlhaas et al., 2006; Uhlhaas & Singer, 2010; Wilson et al., 2008). These data indicate that theta and gamma power is not working similarly between healthy controls and patients with SZ, such that power in these frequencies may be generally high basally but when they are needed during cognitive task performance, oscillatory power is not utilized or working efficiently, which may be associated with the impairment seen in cognitive function in this population. Disturbances in theta and gamma activity may represent an aspect of

neural processing that is critically altered in these populations. Therefore, the current set of experiments aimed to assess if early-life trauma altered brain activity in these frequencies and whether alterations were associated with impaired cognition.

The current set of experiments aimed to assesses whether brain activity, specifically theta, low gamma, and high gamma power and comodulation in the dorsal HC, was altered during the NOR task. The dorsal HC was chosen, as mentioned previously, because of its involvement with theta and gamma oscillation generation and/or maintenance (Buzsáki & Wang, 2012; Csicsvari et al., 2003), which are important in driving spike-timing dependent plasticity and theta-phase precession (Grover et al., 2009; Mizuseki et al., 2012). Since sham animals also performed poorly as a group, data sets were divided based on performance criteria. Dividing the data allowed to explore whether brain activity was different on successful versus chance trials, and whether there were differences in brain activity between groups for the two performance criteria and during exploration with the novel or familiar object. The sections below will discuss in detail the current findings and possible implications

Theta oscillations are prominently found in the HC (Buzsáki, 2002) and are observed when rats engage in voluntary behaviors. These behaviors include locomotor activity (Fuhrmann et al., 2015), which changes with running speed in the CA1 region of the HC (Vanderwolf, 1969), walking, rearing, jumping (Vanderwolf, 1969), and sniffing (Kay, 2005). Interestingly, smaller jerky movements during immobility or during grooming or feeding behavior are associated with decreased amplitude of the theta wave (Vanderwolf, 1969), further supporting that theta is related to behaviors that are intended. Changes in theta are also linked to complex behaviors, including approach and avoidance, extinction, reversal learning, information processing, encoding, retrieving, and working memory (see review: Buzsáki, 2009). Therefore, experiments have aimed to understand the neural mechanisms that underlie processes that are related to these behaviors. In the current set of experiments, theta power was assessed and measured during the NOR task.

Sham and MD groups had overall impairments on the NOR task, suggesting that they either had an impairment in encoding, consolidation, or retrieval of objects. The initial goals of these experiments were to first replicate findings that MD, but not sham,

animals were impaired on NOR. The next, more broad goal, was to understand the neural mechanisms that were related to these impairments by assessing brain oscillations in frequencies (theta and gamma) that are critical for successful performance on memory tasks. Given that MD and sham animals were both impaired on this task, the neural mechanisms that were associated with successful performance (i.e. novelty detection/memory retrieval of familiar object) and chance performance (i.e. did not necessarily prefer the novel object (40-60% preference)) were elucidated. This also allowed for the assessment of whether there were differences in brain activity between groups, which could possibly not be detected by only observing behavior. It was still possible that that the 24-hour MD period induced long-lasting alterations in brain activity. Therefore, the first set of analyses centered around assessing theta power during trial 5 (testing) of the NOR task.

As mentioned previously, power during object exploration was first extracted. Then, power during each bout of interaction was normalized to power during baseline for each animal, generating a ratio (exploration power/baseline power). Each frequency of interest was then extracted to assess group, performance, and object differences in power. When assessing ratio of theta power, there was no difference between sham and MD animals during chance performance (Figure 24, left). Also, ratio of theta power was not higher for either object. The ratio for both groups lingered around 1.4-1.5 for both objects, showing slightly higher ratio of theta power compared to baseline. These data are interesting because they indicate that ratio of theta power is not different when animals interact with either the novel or familiar object during testing trials where they do not prefer one object over the other, and this could be related to the inability of animals to detect novelty (encoding) or recognize a familiar object (consolidate or retrieve).

When assessing ratio of theta power during successful performance (Figure 24, right), sham animals had higher power compared to MD animals overall. MD animals had a ratio of around 1.4 for both objects. However, in shams, ratio of theta power for the familiar object was significantly higher (~ 2.4) than when interacting with the novel object (~1.7). There have been a few studies to date that have assessed the role of theta power or amplitude on encoding and retrieving objects during NOR and the current set of studies are not necessarily consistent with those findings. One group assessed theta power

between novel and familiar object exploration in the CA1 region of the HC (Naber, Witter, & Lopes Da Silva, 1999). Female BALB/CJ mice were implanted with electrodes and habituated to the NOR chamber four times for 15 minutes each. Then, they were placed in the chamber and had a five-minute sampling trial, where they could explore two identical objects. Following a 10-minute retention period, animals were exposed to one novel and one familiar object for five minutes. Theta power was not higher when exploring either object. This suggests that theta power in the HC may not necessarily be involved with successful performance on this task (i.e. successful encoding or retrieving). Although the study observed increased theta power during familiar exploration, it is important to note that the current set of experiments used different analyses methods. For example, this group created a theta ratio for the sample trial (right object theta power/left object theta power), and for the choice trials (novel object theta power/familiar object theta power). Not only were there no differences in power ratio between objects, there were also no differences in power ratio between the sample and choice trials. Differences in normalization of data, as well as strain of rodent, sex, and NOR paradigm could have led to these inconsistent results.

Another study assessed theta power in a recognition memory task (Trimper, Stefanescu, & Manns, 2014a), although this NOR task was vastly different than the typical paradigm. In this study, six male long evens rats were placed in a circular track where they had to run two laps per trial, for a total of 24 trials. At the end of each track, there was a piece of chocolate for the rat to obtain. Rats were exposed to objects at three different locations on the track in lap 1, then in lap 2, one object was replaced by an identical copy, but the two other objects were removed. During testing, objects were either placed in different locations, or they were replaced by a novel object in the same location. Amplitude (i.e. power = amplitude^2) of theta oscillations were higher when animals explored the novel objects. Furthermore, when animals showed good memory (i.e. at least 75% reduction of exploration on second encounter) compared to poor memory (i.e. less than 75% reduction in object exploration on second counter), the dynamics of the theta wave were different compared to when animals showed poor memory for an object. More specifically, during good memory, at the falling slope of the wave, there was more asymmetry and the slope was more elongated. In conclusion, one

study showed no differences in theta power when exploring the novel or familiar object, whereas another study showed higher theta power during interaction with the novel object. The inconsistency between this study and the current set of experiments could also be due to the different paradigms used (traditional NOR versus NOR in a circular track), different strains, or different methods of analyses. It could also suggest that this task produces variable results and is not a reliable task to measure recognition memory.

In the data presented here, it is possible that sham animals underwent a network shift when they explored the novel (encoding) versus the familiar object (retrieving). The increase in ratio of theta for the familiar object could indicate that the neural network for recognizing familiarity (i.e. retrieval) was dominant over the network involved in detecting novelty (i.e. encoding). Interestingly, it has been proposed that when object encoding occurs, the entorhinal cortex sends strong synaptic input to CA1 and CA3 of the HC near the trough of the theta rhythm. However, during retrieval, the CA3 sends strong synaptic inputs to the CA1 near the peak of theta (Hasselmo, 2005; Hasselmo et al., 2002). Although differences in synaptic input from the entorhinal cortex or CA1/CA3 regions were not assessed in the experiments here, it is possible that the network involved in retrieval was predominant.

Since ratio of theta power was lower in MD animals during successful performance compared to shams, this may suggest that theta power may not have been driving successful encoding and/or retrieval of the objects in MDs and that there was a dissociation between brain theta activity and NOR performance. Synaptic input from varying structures onto specific phases of theta determine whether there is stronger encoding or retrieving of objects. Therefore, it is possible that the dynamics of encoding (i.e. inputs from entorhinal cortex to CA1 and CA3 at theta trough) and retrieving (input from CA3 to CA1 near theta peak) is occurring similarly in sham and MD animals, which by extension, is promoting successful performance on this task.

In conclusion, there were no differences in ratio of theta power during chance performance in either group. However, sham animals had higher ratio of theta power during good performance compared to MDs. Furthermore, ratio of theta power was higher for the familiar object compared to the novel. These data suggest that theta power alone may not be driving successful performance on the NOR task, given that there were

no differences in theta power in MD animals during successful performance. These data also suggest that depriving animals for 24-hours induced long-lasting changes in brain activity that lasted up to adulthood.

Gamma Power During Novel Object Recognition

Gamma oscillations are associated with complex cognitive processes (Colgin & Moser, 2010), including working memory (van Vugt, Schulze-Bonhage, Litt, Brandt, & Kahana, 2010), encoding (Sederberg et al., 2007) and retrieval (Montgomery & Buzsáki, 2007), to name a few. These processes may be driven by gamma's role in synaptic plasticity via LTP (Bragin et al., 1995) or in integrating neural activity into coherent ensembles of neurons, also known as dynamic grouping (Fries, Roelfsema, Engel, König, & Singer, 1997). In other words, gamma binds neurons together that encode specific aspects of a stimulus, including shape, color, or even movement orientation. Neurons that encode the same aspect of an object will fire synchronously, whereas neurons that do not encode the same information will not fire in synchrony. Gamma's significance in binding neurons together is therefore important to encode memories that may have to be recalled in the future. In the current set of experiments, gamma oscillations were assessed during NOR in sham and MD animals during encoding and retrieving objects on successful and chance trials.

In chance trials, sham animals had lower low gamma power compared to MD animals, with no differences in power between objects for either group (Figure 25, left). Low gamma power was ~1 for shams, suggesting that there were no significant changes in gamma power from baseline trials. It is possible that sham animals did not perform well on these trials because they did not prefer the initial object during the familiarization phase and therefore did not spend time with it. This could explain why animals did not retrieve the object (in trial 5) that was supposed to be encoded during trial 3. However, given that objects were randomized, it is unlikely that object preference was the factor. In the MD group, ratio of low gamma power was ~1.2 for the novel and ~1.15 for the familiar object, which indicates that low gamma power was slightly higher compared to

baseline when MD animals interacted with objects during trials where they did not perform successfully.

The pattern of results was very similar for high gamma power. During chance trials, ratio of high gamma power was higher in MD animals compared to shams, with no differences in power between objects (Figure 28, left). However, it seems that the magnitude of the ratio was higher for high gamma power compared to low gamma power in the MD animals. In sham animals, the ratio of high gamma power was around 1.1 for both objects, with shows that there was a slight change from baseline, such that there was higher high gamma during object exploration compared to baseline. In MD animals, there was increased high gamma power (~1.3) for both objects compared to baseline. In general, these data show that low and high gamma power are marginally higher than baseline in shams, and considerably higher in MDs, supporting that low and high gamma can increase during periods of exploration.

A few studies to date have assessed gamma power on various NOR tasks. In the first study, ten male Long Evans rats were habituated to the NOR chamber for ten minutes a day for three consecutive days (Zheng, Wood Bieri, Hwaun, & Lee Colgin, 2016). After habituation, animals could explore two identical objects on day 1 (familiarization phase). On day 2, identical objects from the familiarization phase were placed in the chamber on sessions 1 and 3. On session 2, however, one familiar object was replaced with a novel object. These animals were not able to successfully perform NOR, such that they did not interact significantly more with the novel object on session 2 compared to the familiar object during the same session. This is interesting, given that the sham animals in the current set of experiments were also not able to perform the NOR task successfully. When assessing power, gamma in the CA1 region of the HC was assessed as a change from session 2 on day 2 when animals were interacting with the novel object compared to day 1 when animals were interacted with the familiar object. In this case, neither low nor high gamma power was increased during novel object exploration in session 2 (Zheng et al., 2016). These data are similar to what was observed in the current set of studies, such that there was no change in low gamma or high gamma power when sham animals were interacting with the novel or familiar object during chance trials (Figure 25 and Figure 28, left). It is important to note that although both

studies did not find differences in low or high gamma power in control animals that did not perform successfully, there were significant differences between the studies including strain of rats, NOR paradigms, and ways to calculate low and high gamma power. Nonetheless, there were no differences in gamma power when rats were interacting with the novel or familiar object during chance trials, suggesting that significant increases in gamma from baseline may be important for encoding or retrieving objects, as seen in successful trials.

During successful trials (Figure 25, right), sham animals had a higher ratio of low gamma power in general compared to MD animals. The pattern of low gamma power was similar to that of theta power in MDs, such that there were no differences in power between chance and successful trials. This could also be observed when collapsed on objects (Figure 26). More specifically, when looking at performance between groups, it is apparent that shams have higher power during successful trials (~1.3) compared to chance trials (~1). In MD animals, these numbers linger around 1.15 for both chance and successful trials. Collectively, these data show that power did not differ in MD animals during successful or chance trials.

A study by França et al. (2014) used an atypical NOR paradigm to assess low-gamma power in five C57BL/6 mice that underwent pre-exploration, object exploration (trial 1), and post-exploration trials. During the exploration period, animals could explore four different objects for ten minutes. Twenty-four hours later, they were placed back into the chamber with two familiar objects and two novel objects (trial 2). Animals spent more time with the two novel objects compared to the two familiar objects, which was assessed by examining exploration time in seconds as well as a novelty index (time spent with two objects that were the same in sessions 1 and 2/time exploring other objects in sessions 1 and 2). In trial 1, gamma power was higher during the beginning of exploration compared to later in the session, suggesting that gamma could increase when animals explore objects. It is unclear if gamma power was higher during session 2, but in Figure 10A, right (see França et al., 2014), it appears that animals had slightly lower gamma power in the 30-40 Hz range when rats interacted with the novel object compared to when they interacted with the familiar object. These data are interesting, because it suggests that, although possibly not significant, low gamma power may be higher during

familiar object exploration compared to novel object exploration, which is what was observed in the current set of experiments during successful trials.

The ratio of high gamma power was also higher in sham animals compared to MD animals during successful performance (Figure 28, right). Ratio of high gamma power was ~1.3 for MD animals for both objects, indicating that high gamma power increased when animals were interacting with either object compared to baseline. In sham animals, ratio of high gamma power was ~1.6 during familiar object exploration, whereas it was ~ 1.4 for during novel object exploration. No significant change in ratio of high gamma power in MDs between performance criteria was observed when collapsed on object (Figure 29), where they lingered around 1.3-1.35 for both performance criteria. However, sham animals had significantly higher high gamma power compared to baseline during successful performance compared to chance performance. It is important to note that although MD animals had no differences in power between trials or objects, these animals still had increased gamma power compared to baseline. It has been shown that when animals explore novel objects in locations where there were objects previously, then low gamma can increase (Trimper et al., 2014b). Therefore, although there were higher levels of gamma in MD animals, this could indicate that they remembered that there were objects in those specific locations.

Trimper, Stefanescu, & Manns (2014a) also evaluated the role of gamma in a recognition memory. Details regarding this study performed on a circular track are explained above (see 'Theta-Gamma Comodulation'). There were no differences in CA1 power between periods of novel object exploration versus periods of baseline. These results were inconsistent with what was observed in the current set of experiments, such that during successful trials, shams had slightly higher low and high gamma power compared to baseline when exploring the novel object (Figure 25 and Figure 28). Furthermore, they observed no differences in CA1 power in the gamma range between good memory performance (able to spend time with novel object), compared to poor performance (spent little time with the novel object), which suggests that they either had poor encoding of the previous object or poor retrieval. In the same study, it would be interesting to assess gamma power when animals were interacting with the familiar object. In conclusion, this study found no differences in gamma power compared to

baseline during novelty detection, which was inconsistent with the current findings, which could be due to the different experimental procedures used.

By looking at the results of low and high gamma power, it appears that these frequencies may be critical for retrieving and encoding objects in sham animals, because these ratios were higher for both objects during the successful trials compared to the chance trials, suggesting that increased gamma can promote encoding of the novel object and/or retrieval of the familiar object. These data may also suggest that theta (Figure 24), may not necessarily be critical for encoding the object, given that the ratio of theta power was different between novel object exploration during the successful trial versus novel object exploration during chance trials.

One hypothesis that was initially considered when looking at a lack of gamma power between objects and performances in MD animals was that there may have been weakened LTP via spike-timing dependent plasticity driven by gamma. It could be possible that spike-timing dependent plasticity was impaired during trials of encoding (trial 2 and 3, trial 5 with novel object). If this was indeed occurring, then it would be hypothesized that MD animals would not be able to strengthen memory for the object during encoding trials and they would not be able to perform successfully because they would not be able to retrieve (in trial 5) the encoded object (in trial 3/4). However, this was not the case given that MD animals were clearly able to encode and retrieve objects (13/32 total data sets in MD animals).

Although these mechanisms have not been assessed in the current set of experiments, it is possible that the ING and/or PING networks are altered following MD. For example, the ING mechanism postulates that gamma oscillations will increase based on the timing and pattern of synaptic inputs (Brunel & Hakim, 1999; Tiesinga et al., 2004), such that greater spiking activity increases gamma activity (Montgomery, Sirota, & Buzsáki, 2008). Although firing activity has not been assessed using the MD model, one study had assessed firing activity using maternal separation (remove the mother from her pups 3-6 hr/day from PND 2-14) (Stevenson et al., 2008). This study observed decreased spiking activity in the PFC following early life trauma. It is possible that the MD model also alters spiking activity, resulting in decreased gamma oscillations.

Although these studies have not been conducted, changes in firing patterns may be altering gamma activity in the MD group compared to shams.

In conclusion (see Figure 30 for main findings of power analyses), it is possible that in sham animals, theta may be critical for retrieving objects but not encoding, because power during novel object exploration is not significantly different between chance and success, but it is for the familiar object. However, for encoding and retrieval, low and high gamma power could be important given the significant increases in power during exploration with both objects in the successful compared to the chance trials. It is unclear why there are no differences in power in the theta, low gamma, or high gamma range in MD animals between successful versus chance trials and when interacting with novel or familiar objects. The lack of changes in theta and gamma power suggests that power in these frequencies is not the core mechanism that is involved in successfully encoding and retrieving memories. An example of another mechanism that is critical for successful encoding of objects includes NMDA receptor neurotransmission which is shown to be necessary for LTP (Bliss & Collingridge, 1993), and perhaps this mechanism is enough for successful performance. It is also a possibility that theta and low/high gamma power may indeed be critical for successful encoding and/or retrieval, but there is another mechanism compensating (see section below) for altered theta and gamma power in MD rats that is leading to successful encoding and retrieval of objects. Collectively, these data show that early life trauma induced long-lasting alterations in theta, low gamma, and high gamma power compared to control animals. However, alterations in power were not sufficient to impair performance on this task in MD animals.

Theta-Gamma Comodulation During Novel Object Recognition

Alterations in TGC have been hypothesized to be a mechanism that is altered in individuals with SZ that may be driving impairments in cognitive function (Lisman & Buzsáki, 2008). One study observed impaired TGC on an N-back task, which measures working memory, compared to healthy controls (Barr et al., 2017). Another recent study observed decreased TGC in anterior cingulate cortex and medial frontal gyrus in patients during a Stroop-task, which measures executive function. These two studies support that

TGC may be a mechanism that is disrupted in SZ. However, another study observed that, during an auditory steady state stimulation task, TGC was not different compared to controls (Kirihara et al., 2012). In conclusion, these data support that altered comodulation may be necessary for higher-order cognitive functions (e.g. working memory and executive function), rather than for auditory tasks that may not require cognitive load.

The current set of experiments also assessed comodulation of theta and gamma frequencies to understand how coupling between these frequencies might influence encoding and retrieval (Nyhus & Curran, 2010). Comodulation may work by coordinating local neuronal assemblies or even by coordinating long-range neuronal assemblies between brain regions (Fries, 2005). More specifically, neural communication between ensembles of neurons depends on the coherence between those two ensembles. According to the communication-through-coherence hypothesis (Fries, 2005), neuronal groups can oscillate because their time windows for input and output are open simultaneously. For this to occur, output (i.e. spikes) from the sending neuronal ensemble takes place when the receiving group is excitable. A group of neurons increases its firing in order to successfully send a message to the receiving group. For the most effective communication, the sending neurons need to bundle spikes into bursts and these bursts also need to be synchronized with one another (Salinas & Sejnowski, 2001). When there is no synchronization between the two ensembles of neurons, inputs from the sending neuron can arrive at phases of the cycle that are not excitable, and this could dampen communication (Fries, 2015). Gamma is important during this process because these neuronal ensembles synchronize in the gamma-frequency band (Fries, 2001). During a gamma cycle, excitatory neurons can interact with inhibitory neurons within 3 msec. Inhibition dominates the rest of the gamma cycle. During the period of inhibition, synaptic input is reduced. Interestingly, theta resets the gamma cycle. There is also evidence supporting that there are seven gamma cycles in one theta cycle, and it is shown that separate ensembles of neurons code a specific type of memory on each theta cycle, and therefore the phase of theta is important for this process (Lisman & Buzsáki, 2008). This mechanism promotes successful learning because it prevents different memories to be coded by the same ensemble of neurons, thereby preventing overlap of schemas and

potential confusion. In conclusion, groups of neurons can communicate by synchronizing in the gamma band. Furthermore, theta and gamma interact to code specific memories.

It has also been proposed that theta-phase gamma-amplitude coupling is important for coding items in order (i.e. theta/gamma discrete phase code) (Lisman, 2005), such that each item is coded at an earlier phase of theta (theta-phase precession). More specifically, an ensemble of neurons will fire simultaneously in each gamma cycle, and due to inhibition during the gamma cycle, the next set of neurons fire on the next gamma cycle, given that neurons cannot fire until the inhibition decays. Theta is involved in structuring different ensembles of neurons in order (i.e. different ensembles that code different aspects of a memory), such that neurons with strong input are activated earlier in the theta phase. This theory suggests that two to seven items per theta cycle can be processed. On the other hand, the communication-through-coherence hypothesis suggests that one item is coded per theta cycle. Interestingly, these two mechanisms (communication-through-coherence and theta and gamma discrete phase code) can co-exist in the brain (McLelland & VanRullen, 2016) and one can be dominant depending on whether the animal is engaged in selective processing or exploratory processing, respectively.

There is also evidence supporting that coupling between theta and gamma power, rather than theta phase-gamma amplitude interactions, could be important for successful memory performance (Shirvalkar et al., 2010). Therefore, in the current set of experiments, TLGC/THGP was assessed during NOR in sham and MD animals during object recognition to assess whether TGC was higher during successful performance and whether this was observed in both groups.

When assessing TLGC during the NOR test, there were no differences during chance trials in shams between novel and familiar object exploration (Figure 32A). There were also no differences in MD animals in TLGC during chance or successful trials (Figure 32B). These data suggest that high TLGC was not important for encoding or retrieving objects, because if this was the case, the coupling (as indicated by the slope) would be higher during successful trials.

One study assessed TLGC during NOR in animals that explored objects on a circular track (see ‘Theta-Gamma Comodulation’ for details regarding this study)

(Trimper et al., 2014b). The phase of theta was extracted from the CA1 region of the HC, and modulation of gamma amplitude by theta phase was assessed. CA1-CA3 low gamma coherence was modulated by the phase of theta. Although there were no differences between good and poor memory performance, coherence between CA1-CA3 was lower at the rising slope and peak of theta, but higher during the falling slope and trough of theta. This study is interesting, given that theta-low gamma interactions were not different between poor and good memory performance. These findings are consistent with the current study, where sham animals did not have higher TLGC for the novel or familiar objects in successful trials compared to chance trials. However, given that there were many differences in study design and analyses between the two studies, it is difficult to directly compare the results. Some of the differences included the NOR paradigm used (circular track versus traditional chamber), analyses (phase of theta versus power of theta), the strain used (Long Evans versus Sprague Dawley rats) and brain regions (CA3 and CA1 versus CA1).

Another study assessed TLGC and power in six adult male Long Evans rats performing a working memory task (Shirvalkar et al., 2010). Rats were implanted with recording electrodes in the dorsal HC, a stimulating electrode in the fimbria-fornix (a region that can generate oscillations), and an infusion cannula in the medial septum, since lesions in this region are shown to reduce HC theta (Winson, 1978). Rats were trained on a 6-arm radial water maze where they had to locate a platform at the end of an arm to escape from the water. Each testing day consisted of 10 trials, where they had to encode the location of the platform on trial 1 and return to it on the next nine trials by retrieving that memory. Theta power and TLGC, but not gamma power, was significantly decreased in the dorsal HC when animals received muscimol (GABAa receptor agonist) before the trial, suggesting that inactivating the medial septum influenced hippocampal theta power and coupling, and these alterations were associated with impaired encoding and/or retrieval. TGC was higher during successful trials (<1 error) where they had to remember where the platform was (retrieving). The impairments in theta power were also reversed (by giving 7.7 Hz pulses in the fimbria-fornix). What they concluded was that successful performance on this task was correlated with theta-low gamma power (i.e. TLGC), but during poor performance (≥ 2 errors), these two frequencies were not correlated.

Furthermore, TLGC was higher when animals had to retrieve memories compared to when animals had to encode memories. Lastly, theta power or gamma power alone did not predict memory performance, but the coupling of the frequencies did. These data contradict the current set of experiments where TLGC was not different between novel or familiar objects on successful or chance performance, and this was true for both groups.

The results for THGC are intriguing. In sham animals, there were no differences in THGC between the novel and familiar object during chance trials. However, in successful trials, THGC was significantly higher when animals interacted with the novel object compared to the familiar object (Figure 34A). THGC was also significantly higher when exploring the novel object in successful trials compared to chance trials, supporting that, in sham animals, THGC influences encoding. In MD animals (Figure 34B), there were no significant differences in slope in either the chance or successful trials, suggesting that THGC did not necessarily influence encoding or retrieval of objects in MD animals. These data also provide evidence that there was a dissociation between THGC and NOR in MD animals.

Although no study to date has assessed theta or gamma power, or TGC using the MD model, one study has looked at power and comodulation during NOR using early maternal separation (Reincke, Hanganu-Opatz, Eichenbaum, Kopell, & Teicher, 2017). In this study, Wistar rats were separated from their mothers for three hours a day from PND 3-16. From PND 17-20, control and 'early life separated' rats underwent a NOR task. Rats could explore two identical objects for seven minutes (familiarization phase). After a 5 minute ITI, one novel and one familiar object was placed in the chamber and rats could explore for another 7 minutes. Brain activity was recorded from the CA1 region on PND 21-22 while animals were under urethane anesthesia. Theta and gamma (30-100 Hz) frequencies were filtered and theta phase and gamma amplitude were extracted. Early life separation did not alter performance on the NOR task compared to control animals, which was similar to the current set of experiments that showed no overall impairment in recognition memory in MD animals. They observed no differences in theta or gamma power in the HC between early life separation or control animals. They did, however, observe lower theta power in early life separated animals in the prelimbic region of the PFC, which is shown to interact with the HC during development

(Brockmann, Pöschel, Cichon, & Hanganu-Opatz, 2011). Theta in the prelimbic region and gamma in the HC did not couple, which supported that, in these animals, communication between the prelimbic region and HC was slightly altered. It is possible that communication between these regions are decreased because of the lower theta power in the prelimbic region that may be driving these slight decreases in TGC.

It is not surprising that there were differences between TLGC and THGC in sham animals that successfully performed the task. This is interesting, given the recent literature on the differences between low and high gamma. Studies support that gamma oscillations are important for facilitating information transfer within hippocampal structures and surrounding areas by synchronizing ensembles of neurons that code information about specific stimuli (Colgin & Moser, 2010; Fell & Axmacher, 2011; Gordon, 2011). However, the two frequencies of gamma (low or high) differentially synchronizes and communicate with specific structures more efficiently than others (Colgin & Moser, 2010). For example, low gamma in the CA1 region couples with low gamma in CA3 (i.e. more CA3 cells phase lock to low compared to high gamma in the CA1), whereas high gamma in CA1 couples with high gamma in the medial entorhinal cortex.

In the same study, low and high gamma occur at different phases of the theta cycle in the CA. It is suggested that gamma oscillations differentially play a role in the CA3-CA1 and entorhinal cortex-CA1 pathways when retrieving old memories or encoding new memories (Hasselmo et al., 2002). For example, it is hypothesized that low gamma may be involved with retrieval rather than encoding in the CA3-CA1 circuitry. Contrary to low gamma, the projection from CA1 to medial entorhinal cortex is hypothesized to provide information about where the animal is in space (Vegard H Brun et al., 2002; Vegard Heimly Brun et al., 2008), suggesting that high gamma plays a critical role in encoding, especially about the animal's position in the environment. Interestingly, it is postulated that the switch from encoding to retrieving an object could be due to a switch from a high gamma cycle to a low gamma, and it is predicted that one frequency of gamma will follow the other frequency of gamma (i.e. high gamma cycle followed by a low gamma cycle) (Atallah & Scanziani, 2009). The two frequencies usually never co-occur on a given theta cycle in a familiar environment where there is no

encoding that needs to be conducted (Colgin et al., 2009). These findings are important because they suggest that these frequencies play a different role during encoding or retrieving objects, such that high gamma is important for encoding whereas low gamma is important for retrieval. In the current set of experiments, low and high gamma power were higher compared to baseline during retrieval rather than encoding in sham animals that performed successfully. Interestingly, THGC was higher during encoding an object (Figure 34A), suggesting that perhaps interactions between theta and high gamma were necessary for encoding in shams, rather than power alone. However, TLGC was not higher during retrieval rather than encoding. It is unclear if these findings would remain constant if data were not normalized to baseline and future analyses could assess these questions.

It is difficult to know why no changes in theta power, gamma power, or TGC were observed following MD between performance criteria or objects, but these animals were still able to perform successfully. This is especially difficult to reconcile with an abundance of data supporting that TGC could predict successful performance (Colgin, 2015; Shirvalkar et al., 2010) (Lisman & Jensen, 2013). It is a possibility that other behaviors were taking place during NOR that were not directly measured. For example, hippocampal theta and/or gamma oscillations are present during odor-based learning, sensorimotor processing during sniffing (Kay et al., 2009), and during spatial memory (Ma et al., 2009). All of these behaviors could be occurring while animals are interacting with objects which could potentially influence oscillatory activity. Therefore, it is possible that it is not just novelty detection or recognizing familiarly that is being measured, but a combination of many behaviors that is driving these oscillations.

Another behavior not captured during NOR that may be related to increases in brain activity in the shams but not in MDs during successful trials is feature binding, or integrating and combining components of objects for later retrieval. During spatial navigation, the dorsal visual stream ("where") may be involved, whereas the ventral stream ("what") is important for integrating features such as color, shape, and material of the object (Goodale & Milner, 1992). There is also evidence supporting that the ventral stream leads into the perirhinal and lateral entorhinal cortex, whereas the dorsal stream leads to the parrahippocampal and medial entorhinal cortex (Eichenbaum, Yonelinas, &

Ranganath, 2007). These two pathways then converge into the HC. The dorsal HC encodes information about the locations of objects, whereas the ventral HC is involved with distinguishing between different contexts (Komorowski et al., 2013). Information (i.e. encoded representations) from these two brain regions are then communicated to the PFC. The PFC can then retrieve representations of these items via interacting with the perirhinal and entorhinal cortex. A recent study also supports a direct projection from the PFC to the CA3 region of the HC during retrieval (Rajasethupathy et al., 2015). In the current set of experiments, it is possible that in sham animals, information about the novel object is being integrated with a pre-existing schema of the familiar object (and they did indeed successfully encode the previously seen objects). However, this is not occurring in MDs. Although not tested, this process may be driving the differences in brain oscillations between groups.

As mentioned in the Introduction, the brain undergoes significant maturation during the first few postnatal weeks. Therefore, perturbation of normal brain development during this time could potentially alter brain activity. One study conducted an elegant set of experiments that assessed the emergence of theta-gamma oscillations in the rat HC and PFC (Brockmann et al., 2011). More specifically, LFP from the HC and medial PFC were recorded in rats that were anesthetized with urethane. They observed that between PND 0-2, the PFC developed spindle bursts (12-14 Hz). On PND 5, gamma oscillations emerge and become superimposed on the spindle bursts. Around the second postnatal week (PND 10-11), the PFC exhibited continuous theta and gamma band activity, where theta bands emerged and were superimposed on gamma oscillations. These data suggest that the networks involved in generating oscillations and rhythms underwent organization and maturation. During this time, HC gamma oscillations were phase-locked to neurons firing in the PFC, suggesting that gamma oscillations synchronize neurons to fire in the PFC. In the HC, theta oscillations were already present on PND 1. However, gamma oscillations do not develop until the end of the first postnatal week and, at this time, they are superimposed on theta oscillations (Lahtinen et al., 2002). Given that the CA1 region has dense projections to the medial PFC (Hoover & Vertes, 2007), the time when connectivity between these regions begin to emerge was assessed. What they observed was initially, hippocampal theta oscillations drove

prelimbic oscillations and firing of PFC neurons, but with maturation, the prelimbic region and HC mutually influenced each other. There is supporting evidence suggesting that HC theta-PFC neuron-gamma interactions are necessary for information transfer, consolidation, organization, and storage (Hyman, Zilli, Paley, & Hasselmo, 2010; Sirota et al., 2008; Wierzynski, Lubenov, Gu, & Siapas, 2009). Collectively, these data suggest that the HC-prefrontal network does not emerge until the first couple of postnatal weeks, and there is ongoing maturation of these regions that eventually lead to the PFC and HC mutually influencing each other. In conclusion, it is possible that although MD on PND 9 altered theta and gamma power in the HC, mechanisms between PFC-HC network communication were not altered and were enough to drive successful performance in this group. To test this, coupling of PFC-HC networks could be assessed in MD animals during performance on the NOR task and compared to sham animals.

It is also a possibility that there was a compensatory mechanism in MDs during successful trials that was not driven by theta activity, gamma activity, and/or TGC. For example, MD rats that underwent deprivation on PND 9-10 had changes in acetylcholine levels (Marković, Radonjić, Aksić, Filipović, & Petronijević, 2014). More specifically, when brains were collected on PND 60, MD rats had increased acetylcholine activity in the CA1 region of the HC. Furthermore, cholinergic fiber density was increased in the same study. Interestingly, acetylcholinesterase inhibitors (i.e. a chemical that inhibits the breakdown of the neurotransmitter acetylcholine) (Colović, Krstić, Lazarević-Pašti, Bondžić, & Vasić, 2013) improve memory performance on tasks including the Morris water maze (Bejar, Wang, & Weinstock, 1999), object recognition (Lieben et al., 2005), and a delayed-match to position tasks (Yamada et al., 2005), indicating that acetylcholine plays a role in learning and memory. More specifically, in one study (Sambeth, Riedel, Smits, & Blokland, 2007), rats were impaired on recognition memory after being injected with scopolamine, a competitive antagonist at muscarinic receptors, thirty-minutes before the start of NOR. During this task, rats were placed in an arena for three minutes and could explore two identical objects. One-hour later, rats were placed back into the chamber and could explore one novel and one familiar object. In this study, donepezil, a cholinesterase inhibitor that increases synaptic acetylcholine, reversed the impairments

observed on NOR following scopolamine, which supports the importance of acetylcholine during NOR.

There is evidence supporting that although theta oscillations and acetylcholine release are highly correlated, acetylcholine does not contribute to the initiation/generation of theta (Zhang, Lin, & Nicolelis, 2010). Rather, they may interact to promote successful learning and memory. Alternatively, another study observed that gamma and TGC in the PFC is driven by acetylcholine release during a cued appetitive response task (Howe et al., 2017) in rats. However, this study did not assess the effects of acetylcholine on hippocampal oscillations. Lastly, using slice electrophysiology in hippocampal slices, an increase in gamma power was observed following low carbachol administration, which is an analogue of acetylcholine (Betterton, Broad, Tsaneva-Atanasova, & Mellor, 2017). However, a decrease in gamma power was observed following high carbachol administration, indicating bidirectional modulation of gamma in a dose-dependent manner. In conclusion, although there is evidence supporting or refuting that acetylcholine drives these oscillations (based on the brain region or recording methodology), data presented in this dissertation may indicate that although brain activity in the theta and gamma range were lower in MDs compared to controls on successful trials, there may be higher levels of acetylcholine activity that may act as a compensatory mechanism which drove successful memory performance in this group. However, future studies need to be conducted to directly assess if acetylcholine levels are increased in the MD model and if they are correlated or modulate theta, gamma, or TGC.

In conclusion, theta and gamma power or TGC were not different between objects and performances in MD animals, although they were in shams. These data provide support that there was a dissociation between brain activity and NOR performance in the MD animals. These data also indicate that there may be compensatory mechanisms in MD animals that allowed them to perform successfully.

Maternal Observation

In the current study, measures of maternal care were observed to assess whether there were differences in maternal behavior following MD and to detect whether high or

low licking/grooming behaviors affected NOR performance. These sets of studies confirmed that maternal care was altered following MD.

Interestingly, mothers of MD pups licked and groomed more on PND 10 compared to all other days and compared to sham mothers on PND 10 (Figure 7A). This is not surprising, given that on PND 10, maternal care was assessed for one hour immediately after the mother was brought back to her litter following 24-hours of being removed. During this time, pups had no access to food or the care of their mother. Interestingly, licking and grooming dropped on PND 11 and was significantly less compared to PND 10. It is possible that the mother was exhausted since she had to compensate for licking and grooming on PND 10, where she was not able to care for her pups on PND 9. Results are similar when assessing nursing behaviors (Figure 7B). Mothers nursed more on PND 10 upon returning to their pups compared to mothers that were not taken away from their litter on PND 9-10. It is not surprising that mothers that were removed from their pups nursed more, given that their pups had no access to milk for 24 hours. Another measure that was assessed was the percentage of contact mothers had with their pups. As expected, on PND 10, mothers that were removed from their pups on PND 9 for 24 hours had more contact with their pups compared to mothers in the sham group (Figure 7C). As expected, mothers in the MD group has more contact on PND 10 compared to PND 6. In conclusion, MD mothers licked/groomed, nursed, and had more contact with their pups upon returning to the litter on PND 10. These differences could possibly be driven by compensatory licking, grooming, and nursing on PND 10.

These findings are similar to a study assessing maternal care in animals that were subject to 180 minutes of maternal separation from 10:00 am-1:00 pm from PND 3-15 (Biggio et al., 2014). In this study, nursing and licking/grooming behaviors were assessed every day of maternal separation at 8:00 am (dark phase), 9:15 am (light phase), 1:30 pm (light phase + mother gets returned), and at 4:30 pm (dark phase). Mothers that were separated from their pups had a higher frequency of nursing and licking/grooming behaviors when collapsed on days and times, when compared to control mothers. Furthermore, when mothers were returned to their pups after 180 minutes of separation at 1:30 pm, there was more nursing and licking/grooming compared to shams and compared

to 8:00 am, 9:15 am, and 4:30 pm. Another study assessed nursing following maternal separation. Mothers were removed from their pups on PND 1-13 for four hours a day (10:00 am-2:00 pm). Mothers that were separated from their pups engaged in higher nursing behaviors compared to controls when they were reunited with their pups every day (Macrí, Mason, & Würbel, 2004). Collectively, these data suggest that reuniting pups with their mothers increases the frequency of which mothers' lick and groom or nurse, suggesting that disruption of maternal care induced a compensatory response upon reunion.

Next, differences in the percentage of licking/grooming, nursing, or contact during the dark or light cycle was assessed. Dams licked/groomed the same amount in the active versus the inactive phase (Figure 7D), but nursed more during the inactive period (Figure 7E). Interestingly, mothers in the sham group did have less contact with their pups compared to MDs, which could be due to the increases in licking/grooming behavior and nursing behavior upon reunion of pups to their mothers (Figure 7F). Contrary to the current findings, one study showed that licking/grooming is higher during the light cycle (Biggio et al., 2014). Only nursing was higher in the light phase in the current experiments. A reason for the inconsistent findings could be the significant increase in licking and grooming in MD animals on PND 10 (in the dark cycle), when mothers were reunited with their pups (Figure 7A). Interestingly, one study that assessed licking/grooming behavior on PND 1-10 observed that behavior was highest at 6:00 am compared to 10:00 am, 1:00 pm, 5:00 pm, and 9:00 pm (Champagne et al., 2003). It is important to note that the dark cycle for this study was from 8:00 pm- 8:00 am. Therefore, the licking/grooming behaviors was highest in the dark cycle, which is similar to the current findings. In conclusion, some studies show that licking and grooming can be higher during the light cycle (Biggio et al., 2014) or higher during the dark cycle as observed in the current study (Champagne et al., 2003), and these inconsistencies could possibly be due strain, time of light/dark cycle (i.e. more activity in building at certain times could stress out mother), or experimental procedures (e.g. MD altered maternal care on PND 10).

Variations in maternal care can alter neonatal development, which can be manifested as changes during adolescence and in adulthood (Champagne et al., 2003).

For example, low licking reduced LTP in the dorsal HC (Nguyen, Bagot, Diorio, Wong, & Meaney, 2015). Furthermore, offspring of low lickers/groomers had increased NMDAR synaptic function which suggests that this group had chronic alterations in NMDAR function. This may underlie impairments in LTP in these animals (Bagot et al., 2012). Low licked/groomed animals also had less dendritic spine complexity (Bagot et al., 2009). They also had shorter dendritic branch length and lower spine density in the CA1 region of the HC compared to pups that had high licking/grooming mothers (Champagne et al., 2008). Animals that had high levels of licking/grooming showed increased HC glucocorticoid receptor expression (Hellstrom, Dhir, Diorio, & Meaney, 2012). High licking/grooming was also associated with higher synaptic density in the HC compared to low licking/grooming (Bredy, Grant, Champagne, & Meaney, 2003). Collectively, these studies show that low licking/grooming can induce changes in the brain including LTP, NMDA receptor function, and dendritic spine complexity and length. Therefore, in the current set of experiments, cognitive or electrophysiological impairments seen in the MD group could have been due to alterations in maternal care (e.g. no licking/grooming between PND 9-10), that may have altered any of these mechanisms.

In the current set of studies, there was only one sham litter that was one standard deviation above and one below the mean (Figure 8). Studies that separated litters based on high or low licking/grooming and then assessed an array of behaviors including cognition used over 100 litters (Champagne et al., 2003). Therefore, in the current experiment, it is difficult to assess the effects of high or low licking/grooming on behavior because there was only a total of 16 litters in the experiments. Out of the 16 litters, only two litters were considered high or low lickers/groomers. Although there was not enough power to conduct analyses on cognitive function in litters that were in the low or high licking/grooming, the effects of low or high licking/grooming on recognition memory in the offspring of the two litters was assessed. In the litter with low licking/grooming, one offspring preferred the novel object 40-60% on two days of NOR testing and on one day, he did not have enough interaction time. The offspring of the high licking/grooming mother underwent one day of testing and did not have enough

interaction on that day. Collectively, there were not enough litters to determine whether mothers engaged in significantly higher or lower maternal care.

To conclude, upon returning to their pups on PND 10, mothers from the MD group licked and groomed more, nursed more, and had more contact with their pups, suggesting that being away from pups for 24-hours altered maternal care. These increases in maternal care normalized on PND 11 (i.e. similar levels compared to PND 6), possibly due to compensation. Altered maternal care or malnutrition on PND 9-10 may be a critical factor that plays a role in the development of impairments observed in the current set of experiments.

Body Weight Changes Following MD

In the current study, body weight of MD and sham animals increased from PND 25-80 as expected. Interestingly, there were no statistical differences in weight between MD and sham animals (Figure 9A). A trend toward a main effect of group ($p = 0.0515$) is most likely driven by the decreases in weight during these early time periods. When assessing the contribution of weight differences in each family, it appears that one sham family had lower body weight compared to the other families that underwent sham manipulation (Figure 9B). It is likely that removing animals from this group would drive the trend in differences between weight toward significant levels.

Although not significantly different, the trend toward the slight decreases in body weight in MD animals compared to sham was expected. There are several studies that have observed similar findings. For example, in the early postnatal period up until adulthood, MD animals weighed less than shams when assessed on PND 16-22 (Llorente et al., 2011a), PND 10-34 (Marco, Valero, de la Serna, et al., 2013), PND 0-40 (Llorente et al., 2007), PND 30-50 (Peñasco, Mela, López-Moreno, Viveros, & Marco, 2015), and PND 26-60 (Llorente-Berzal et al., 2011). All of these studies used male Wistar rats. One study using BALB/c mice also observed decreased body weight in MD animals compared to shams from PND 10-56 (Akillioglu, Yilmaz, Boga, Binokay, & Kocaturk-Sel, 2015). Collectively, these studies show that MD animals weight less compared to control animals before reaching adulthood.

Group differences in weight during adulthood are less clear in the literature. Contradicting studies show that MD Wistar male rats weighed less compared to shams from three weeks-14 weeks (Choy, de Visser, Nichols, & van den Buuse, 2008), from PND 9-69 (Rentesi et al., 2010) and from PND 22-101 (Mela et al., 2012). Similar to the current study, others have shown initial decreases in weight in MD animals but a normalization in weight compared to shams during adulthood. One group assessed body weight in rats from Hungary (strain unknown) on PND 21 and PND 75 (Barna et al., 2003). In this study, decreased weight was only observed on PND 21 but not in adulthood. Furthermore, one study observed lower weight in MDs only until puberty, and weights were normalized when tested on PND 75 (Viveros et al., 2010). Lastly, another study found that male MD Wistars weighed less compared to shams on PND 27-49, but not from PND 55-73 (Llorente-Berzal et al., 2012). It is unclear why some studies show decreased body weight in MDs compared to shams during adulthood, but others do not. These differences could be due to the experimental procedures that animals undergo. For example, one study administered Olanzapine or Saline injections during adolescence (Llorente-Berzal et al., 2012). Results in weight could be very different compared to animals that did not undergo the stress of receiving injections.

Although there are contradictory findings in the literature regarding weight after MD, the current study is different because it is the first that performed in vivo neural recordings also assessed weight differences between sham and MD animals. It is possible that animals had a different response to anesthesia and surgery compared to the other studies. Therefore, depending on the study design and experimental procedures, animals could have different weights from one study to the next. In conclusion, the weights of MD and sham rats did not differ in the current experiments, indicating that differences in weight between groups could not be responsible for impairments observed in brain function.

Locomotor Activity and Thigmotaxis

The purpose of measuring locomotor activity and thigmotaxis in the current set of experiments was to assess if there were behavioral differences (e.g. motor behavior,

anxiety, exploratory behavior) between the groups, and if increased or decreased motor behavior may explain potential differences in recognition memory. There are many ways to measure spontaneous activity, general locomotion, or anxiety in rodents. Some of these tests include the open field test (Christmas & Maxwell, 1970; Hall, 1934), elevated plus-maze (Rodgers & Dalvi, 1997), the light-dark exploration test (Crawley & Goodwin, 1980), the social interaction test (File & Hyde, 1978), and the hole board test (File & Wardill, 1975). The open field test assesses exploration, general locomotor activity, and anxiety (e.g. via thigmotaxis) in a novel environment (Prut & Belzung, 2003). In the current set of experiments, these measures were assessed in the same open field chamber that the animal performed the NOR task to assess if behavioral differences (e.g. anxiety or motor behavior) were associated with differences in recognition memory.

Interestingly, there were no differences in distance traveled (in meters), mean speed, or time immobile in the chamber during the two days of habituation or during the three days of testing between groups (Figure 10 & 11). Therefore, these data suggest that MD and sham animals did not differ in their level of locomotor activity on any day of testing.

A few studies to date have assessed general locomotor activity during adolescence or in adulthood following MD. One study observed decreased locomotor activity on the elevated plus maze and decreased general motor activity on the hole board test (i.e. an animal that has lower levels of head-dipping in the hole board has higher anxiety) in MD animals during adolescence, but not in controls (De la Fuente et al., 2009). Those data suggest that MD rats were more anxious with less activity during adolescence compared to control animals. Two other studies also assessed changes in locomotor activity compared to control animals following MD. More specifically, male MD Wistar rats had decreased vertical activity in the hole board test and decreased locomotion on the elevated plus-maze (Llorente et al., 2007). In another study, male Wistar rats were tested for locomotor activity on PND 55 (Marco et al., 2007). MD animals exhibited increased locomotor activity five and ten minutes into the session compared to control animals. There were no differences in locomotor activity 15-30 minutes into the session. Given that this was the first-time animals were placed in this chamber, these data indicate that

MD animals, compared to controls, had higher levels of locomotor activity in a novel environment.

Two studies assessed locomotor activity in MD animals during adulthood. Male Wistar, Lewis, or Fischer rats did not have altered locomotor activity compared to control animals when tested on PND 69 in an open field chamber (Ellenbroek & Cools, 2000). Lastly, there were no differences in male or female MD rats compared to controls on locomotor activity when tested on PND 90 (Garner, Wood, Pantelis, & van den Buuse, 2007). There was also one study in male Balb/c mice that observed no differences in horizontal or vertical activity in an open field chamber, suggesting that MD mice did not have increased locomotor activity compared to shams (Akillioglu et al., 2015). However, it was unclear when testing was conducted in these animals. In conclusion, these studies show that in adulthood, MD and control animals do not differ on measures of motor behavior.

Based on the aforementioned studies, it appears that MD animals have decreased locomotor activity and higher anxiety during adolescence (De la Fuente et al., 2009; Llorente et al., 2007), increased locomotor activity before reaching adulthood (Marco et al., 2007), but no changes in locomotor activity or anxiety during adulthood (Ellenbroek & Cools, 2000; Garner et al., 2007). Interestingly, in the current set of experiments, there were also no differences in locomotor activity in adulthood in MD animals when compared to shams. Decreased locomotion during adolescence but not during adulthood could be due to age-dependent sensitivity of stress. There is evidence suggesting that adolescent mice are more sensitive to stress (Acevedo, Pautassi, Spear, & Spear, 2013). More specifically, adolescent rats that were introduced to social stress or restraint stress were more anxious and had less entries in the open arm in a plus-maze compared to adult rats (Stone & Quartermain, 1997). One reason for age-dependent effects on stress could be due to the level of testosterone in these animals. When testosterone is present, behavioral effects driven by stress are not as robust (Handa et al., 1994). Since young rats have less testosterone compared to adults (Minerly et al., 2010), it is possible that adult animals are somehow less sensitive to stressful situations (e.g. being in a novel environment) compared to young rats. The experiments in this dissertation do not assess locomotor activity in young/adolescent rats following MD, it is difficult to determine

whether these affects are age-dependent and whether differences in locomotor activity are due to changes in sensitivity levels following stress.

As mentioned previously, thigmotaxis and fecal matter were used to measure anxiety in the open field chamber. Rats are prone to exploring novel environments, but usually when rats are placed in the chamber for the first time, they will spend more time in the periphery (i.e. thigmotaxis) compared to the center of the chamber (Lamprea, Cardenas, Setem, & Morato, 2008). Fecal matter or boli were also assessed, given that increased fecal matter is shown to be a measurement of anxiety or autonomic reactivity (Lund, Rovis, Chung, & Handa, 2005; Sullivan & Gratton, 1999). The goal was to assess whether MD animals were more anxious compared to shams during NOR habituation and testing.

When assessing the time spent (in seconds) in the thigmotaxis region, there was a trend in in the sham group during habitation days such that on HAB2, they spent slightly less time in this region compared to HAB1 (Figure 12A). This suggests that they were more anxious during the first time they were placed in the chamber compared to the second time. Interestingly, MD animals spent similar amounts of time in the thigmotaxis region on both days. This may suggest that MD animals were less prone to stress during novel situations compared to control animals. If MD animals were stressed, higher levels of thigmotaxis on the first day compared to the second day would be expected.

There were no changes in time spent in the thigmotaxis region during the NOR testing days (Figure 12B). It is possible that by this time, all animals had been habituated to the chamber. Interestingly, distance travelled in the thigmotaxis region was decreased on NOR3 compared to NOR1 only in the sham group (Figure 12C), suggesting that they were possibly more anxious on the third day of testing compared to the first day. Although speculative, this could also be attributable to the possibility that sham animals were overly habituated to the chamber by NOR3 trial 5, and lacked motivation to move around. It is also possible that MD animals were not habituated to the chamber since there were no changes in distance travelled over days.

There are many studies that have assessed thigmotaxis in MD animals following deprivation from PND 9-10. In one study, there were no differences in MD male Wistar rats compared to controls on peripheral ambulation during the hole board test when tested

on PND 30-34 (Llorente et al., 2007). This shows that MD animals were not moving around the periphery of the chamber, which suggests that they were not engaging in thigmotaxis (i.e. not anxious). Another study assessed general motor activity including internal ambulation (i.e. spending time by the squares not adjacent to the walls) and total ambulation (including both peripheral and internal ambulation) during a novel object test. Tests were conducted on PND 37 while animals were being habituated to the novel object testing chamber with no objects present (Marco, Valero, de la Serna, et al., 2013). There were no differences in total or internal ambulation between MD versus control Wistar male rats. These data suggest that MD animals were not more anxious compared to controls. Lastly, in another study, male Wistar MD versus control rats were tested in the open field on PND 45 (Girardi, Zanta, & Suchecki, 2014). MD rats spent less time in the center of the open field chamber compared to controls. There were no differences in total distance travelled and there were no reports of distance travelled in the periphery. It is difficult to interpret these results given that there were no measures of time immobile in the center or peripheral area, number of entries, mean speed, etc. It is possible that although MD rats spent less time in the center, that they were not necessarily engaging in thigmotaxis. Collectively, these studies show that before reaching adulthood, there were no differences in thigmotaxis between MD and shams, suggesting that one group was not more anxious compared to the other.

Similar to young MD rats, adult rats have no to slight differences in thigmotaxis. One study assessed nine week old male Wistar rats on a swim stress test (Gruss, Braun, Frey, & Korz, 2008). Briefly, animals were placed in a circular water tank for two minutes and total length of swim path and duration of thigmotaxis was measured. There were no differences in either measure when comparing groups. Similarly in another study, there were no differences in male Wistar MD versus control rats on time spent in the periphery or time spent in the center of an open field test when measured on PND 60 (Llorente-Berzal et al., 2013). Interestingly, one study did observe increases in time spent in the peripheral area in an open field in male Wistar MD, but not in control, animals (Rentesi et al., 2010). More specifically, MD rats spent more time in the periphery and less time in the center compared to controls. However, control rats also spent significantly more time in the periphery compared to the center in the open field.

Collectively, these studies show that generally, MD animals are not more anxious than controls when tested in adulthood.

In conclusion, numerous studies support that there are no differences in thigmotaxis in MD animals when compared to shams during adolescence in a hole board or novel object test, or during adulthood in an open field or swim-stress test. These findings are similar to the current set of studies that show no differences in thigmotaxis between MD and sham animals on any of the testing days. There are a few studies that do show that MD animals exhibit thigmotaxis more than controls in an open field test. It is important to note that the studies mentioned above use different strains of animals and testing procedures and timelines, and therefore, inconsistent findings are not uncommon. Collectively, no changes in locomotor activity or thigmotaxis between MD and sham animals indicate that differences in brain function cannot be attributable to altered motor behavior or anxiety.

The current set of experiments observed alterations in underlying neural mechanisms that were induced by early life trauma. For example, theta, low gamma, and high gamma power, and well as TGC were altered compared to sham animals during a task that required encoding and retrieval of objects. These oscillations were altered in a way such that they generally did not change based on the performance type or the objects being observed. Alterations in these frequencies could potentially point to biomarkers that link specific mechanism of this disease that are altered in the human condition. For example, theta oscillations and TGC are reduced in animals that have low synaptic inhibition on interneurons that are positive for Parvalbumin (Wulff et al., 2009), which is a type of GABAergic interneuron. Given that individuals with SZ have GABAergic abnormalities, it is possible that alterations in GABA could be related to dysfunction in these oscillations. As a future direction, it would be interesting to find another cognitive task that animals are impaired on that is directly correlated with power or coupling, such that lower power correlates with lower success on the task. It would be interesting to assess if increasing theta or gamma oscillations strengthening TGC could prevent these cognitive impairments. If so, it could be possible that increasing power or comodulation in patients with SZ could reverse deficits in cognitive function. In conclusion, this MD model could be used as a tool to further understand alterations in these neural

mechanisms either before or following the progression of the illness, and how the illness may persistently alter these networks and the cognitive processes they are associated with.

Limitations

There are many caveats and limitations to consider when interpreting the results of the current data. One example is that sham animals did not successfully perform NOR as was hypothesized. This made it difficult to claim that the impairments on the NOR task in MD animals were due to the 24-hour deprivation period, because sham animals were also impaired. Another possibility is that the NOR test was not the optimal task to measure recognition memory in these rats, as described in detail above. However, another interesting question (i.e. neural processing during NOR) was answered by dividing groups into successful and chance performance.

Another limitation was that objects were not tested before experimentation to assure that the objects were equally interesting to the rats. It is possible that rats preferred some objects more than others. Although they were of equal size, objects were made from various materials including glass, rubber, and plastic. Future studies will only use objects that are equally as interesting to rats to avoid any bias toward certain objects.

Furthermore, there were many data sets that were omitted from the analyses because animals did not interact for over 20 seconds or they did not make it through experimentation because of lost head caps. Since removing data sets decreased the number of bouts per group, testing days had to be combined. These data sets include days where animals were in the box for the 3rd total time (NOR1), 4th time (NOR2), or even the 5th time (NOR3). Brain activity from a data set from NOR1 could be different than a data set from NOR3 because on the third day of testing, animals have been exposed to the box multiple times and may feel more comfortable in the chamber compared to the first day of testing. This is true in sham animals, where distance travelled in the thigmotaxis region was higher on NOR1 compared to NOR3, indicating that they may have been more anxious on the first day of testing. Anxiety may influence brain activity and

grouping the three days of testing may potentially obscure the results (i.e. is anxiety influencing brain activity on Day 1 but not on Day 3).

It was also difficult to look at recognition memory over days within one animal because in some cases, animals performed successfully on one day but not on another day, reducing power for conducting within-subjects analyses. For example, three sham and five MD animals performed inconsistently, such that on one day they performed successfully and on another day, they performed by chance. This also provides support that NOR is an unreliable task to measure recognition memory. Therefore, there was not enough power to assess how successful performance varied over days in each animal, and how habituating to the chamber could have an impact on brain activity. An interesting question would be to assess if the activity of theta and gamma power and TGC was consistent over days in an animal that performed successfully on each day, which would further support that these neural mechanisms are indeed important for encoding and/or retrieval of objects. However, it could answer another question such as is TGC stronger in an animal that performs over 60% on one day and between 40-60% on another day? This could be an interesting future direction. Differences in performance scores could be due to the amount of habituation to the chamber or that animals were not interested in object exploration.

Another limitation during electrophysiological analyses was that many bouts of interaction were less than 1000 msec which made it difficult to analyze smaller frequencies. Therefore, an approach was to include 1000 msec before and after the interaction. This could be a caveat because brain activity during the actual interaction time may be different than 1000 msec before or 1000 msec after the interaction. However, it is difficult to know exactly know when the interaction of the animal began. It could have been when the animal started to approach the object.

Future Studies

As mentioned previously, it would be informative to look at NOR over days. If one animal performed well on one day (>60%) but by chance on another day (40-60%), it would be interesting to assess if theta and gamma power and comodulation were stronger

on the day where they performed well. This would shed light on the importance of these frequencies on successfully encoding or retrieving these objects, and that these frequencies and cognition can differ from day to day.

Another future direction would be to use a task where the encoding and retrieval requirements are better separated in order to explore which frequencies are important during each cognitive domain. It is difficult to know whether the NOR task is the most appropriate task to measure power and TGC in animals. Perhaps using a more sensitive task to measure memory (e.g. radial arm maze) would be strongly correlated with memory performance (Shirvalkar et al., 2010). On a radial arm maze, perhaps MD animals that have low power and TGC will also have impaired working memory compared to sham animals that perform well and have high power and TGC. These data would indicate that altered neural activity may be more critical for tasks that involve working memory.

To better understand the involvement of theta and gamma power or TGC in object encoding and/or retrieval, it would be interesting to assess if and how brain activity changes as an animal interacts with an object by assessing bouts over time on successful trials. Studies suggest that animals spend more time with the novel object earlier in the trial, specifically in the first two-minutes (Dix & Aggleton, 1999), compared to later in the trial (Clark et al., 2000). Therefore, if these neural mechanisms are critical for encoding or retrieving an object, then it is expected that these mechanisms should change over time. For example, if TGC is higher when an animal detects novelty and/or encodes an object for the first time, then TGC should decrease as the animal interacts with that object, suggesting that interactions between theta and gamma power in the HC is a critical mechanism associated with novelty detection/encoding. Furthermore, by assessing bouts over time, it would be possible to detect changes in power or TGC between groups over time. As an example, it may be possible that it takes longer for MD animals to encode objects on successful trials compared to shams, such that in shams, TGC was highest in the first 20 seconds of interaction with the novel object, whereas in MD animals TGC was highest in the first 40 seconds. This would indicate that, although both MDs and shams were able to encode objects on successful trials, it took longer for MDs to do so.

As another future direction, it would be interesting to increase theta (via repeated pulses with inter-stimulus interval of 125 msec (8 Hz) in fimbria-fornix- fiber tract that connects HC to medial septum, (Lipponen, Woldemichael, Gurevicius, Tanila, & Soriano, 2012; Shirvalkar et al., 2010)), which could modulate LTP and strengthen encoding (Nyhus & Curran, 2010), during the training trial when animals could explore two identical objects. More specifically, in the CA1 region of the HC, if theta is stimulated during encoding in sham animals that performed by chance, then it would be possible that they are able to retrieve the objects successfully and detect familiarity in the testing trial.

In the current set of experiments, sham animals had higher TGC during successful trials while interacting with the novel compared to the familiar object. However, there was no TGC in MD animals during successful trials while they were interacting with either object. Firstly, it would be interesting to transiently disrupt the CA1 region of the HC via Muscimol, a $GABA_A$ agonist, or via Lidocaine, a fast voltage-gated NA^+ channel blocker, to see if it abolishes or reduces TGC and impairs recognition memory during the NOR task in sham animals. If animals still perform well but TGC has decreased, then this suggests that TGC may not be the best predictor of successful memory performance. If animals perform poorly and TGC is reduced or abolished, this suggests that high TGC may predict successful memory performance. This, however, would not explain why MD animals that performed successfully had low TGC while interacting with both objects. As mentioned previously, this could be due to MD animals encoding the novel object/retrieving the familiar object early in the phase compared to sham animals; however, this was not assessed.

As mentioned previously, the medial septum is involved in regulating theta between the HC and entorhinal cortex (Stewart & Fox, 1990; Vertes & Kocsis, 1997). These theta rhythms are thought to be generated by Parvalbumin GABAergic interneurons, given that they precede activity in the HC (Hangya et al., 2009; Steward, 1976; Tóth et al., 1997). Although there are no studies to date that assessed changes in Parvalbumin-containing GABAergic interneurons using the MD model, alterations in these neurons could potentially change the way in which theta rhythms are being generated in the HC. More specifically, it would be interesting to assess if lower

Parvalbumin-containing GABAergic interneurons are directly correlated with lower theta oscillations in the MD model. This would suggest that altered activity of Parvalbumin-containing GABAergic interneurons may play a key role in impaired theta activity.

Summary

The neonatal period is critical for brain development and can be influenced by early traumatic experiences (Marco et al., 2015), which could possibility lead to increased likelihood of developing a mental illness, such as SZ, later in life (Llorente et al., 2010; Meyer & Feldon, 2010). Therefore, it is important to determine how early life stress could potentially alter neural function and increase the risk for psychopathology.

The current set of experiments aimed to assess whether a 24-hour MD period on PND 9 persistently altered recognition memory in rats. Another goal of this dissertation was to assess whether brain activity, specifically oscillations in the theta, low/high gamma range, and TGC in the dorsal HC, were altered in MD animals during adulthood. Furthermore, the importance of theta and low/high gamma power and TGC in sham animals during chance trials compared to successful trials on the NOR task was assessed. This was the first study to record LFPs from awake-behaving animals to assess the mechanisms by which MD alters electrophysiological properties in these rats, and how these alterations were associated with impaired cognitive function. Furthermore, it explores how these oscillations are involved in successful or unsuccessful performance in control animals. Collectively these data were critical to understand altered brain activity following early life stress with the goal of improving the ability of a pre-clinical model to identify novel treatment vectors in the future.

Contrary to preliminary findings, both MD and sham animals were impaired on the NOR task, such that both groups did not spend significantly more time with the novel object compared to the familiar object. Unsuccessful performance on this task might indicate altered function of the HC, providing additional support that early life trauma can induce persistent, long lasting impairments in cognition, which is thought to be a risk factor in psychosis-related disorders (Reichenberg, 2005). Since sham animals also had impaired recognition memory, groups were divided into successful versus chance

performance and brain activity was assessed. During successful trials, theta power was higher when sham animals interacted with the familiar versus the novel object, supporting that theta may be associated with retrieving previously encoded objects. Low and high gamma power were higher in sham animals compared to MD animals during successful trials, but the opposite was true during chance trials. There was generally no change in power in MD animals between performances or objects when assessing theta, low gamma or high gamma power. These data support that oscillations in these frequencies are not necessarily critical for successful encoding or retrieval of recognition memory, given that MD animals were able to perform successfully while having altered brain activity. TLGC was not different between performances or objects in either group, which suggests that TLGC is not critical for successful recognition memory. However, THGC was significantly higher in sham animals when exploring the novel object on successful trials compared to the familiar object. These data suggest that THGC may be associated with encoding objects; however, given that MD animals were able to perform successfully with no changes in THGC, these data support that THGC may also not be necessarily critical for successful performance. It is therefore possible that MD animals have neural mechanisms that compensate for the alterations observed in these frequencies. It is also possible that MD animals may have alterations in different types of cognitive tasks that were not measured in this dissertation, such as those that measure working memory or long-term memory.

In conclusion, these data identify a model of early life stress with a translational potential, given that there are points of contact between human studies and MD. These data provide insight into how early life stress could lead to altered neural function in early adulthood, which may underlie the increased probability of developing psychopathology later in life, including SZ. Furthermore, these data provide a set of tools that could be used to further explore how these altered neural mechanisms may influence cognition and behavior.

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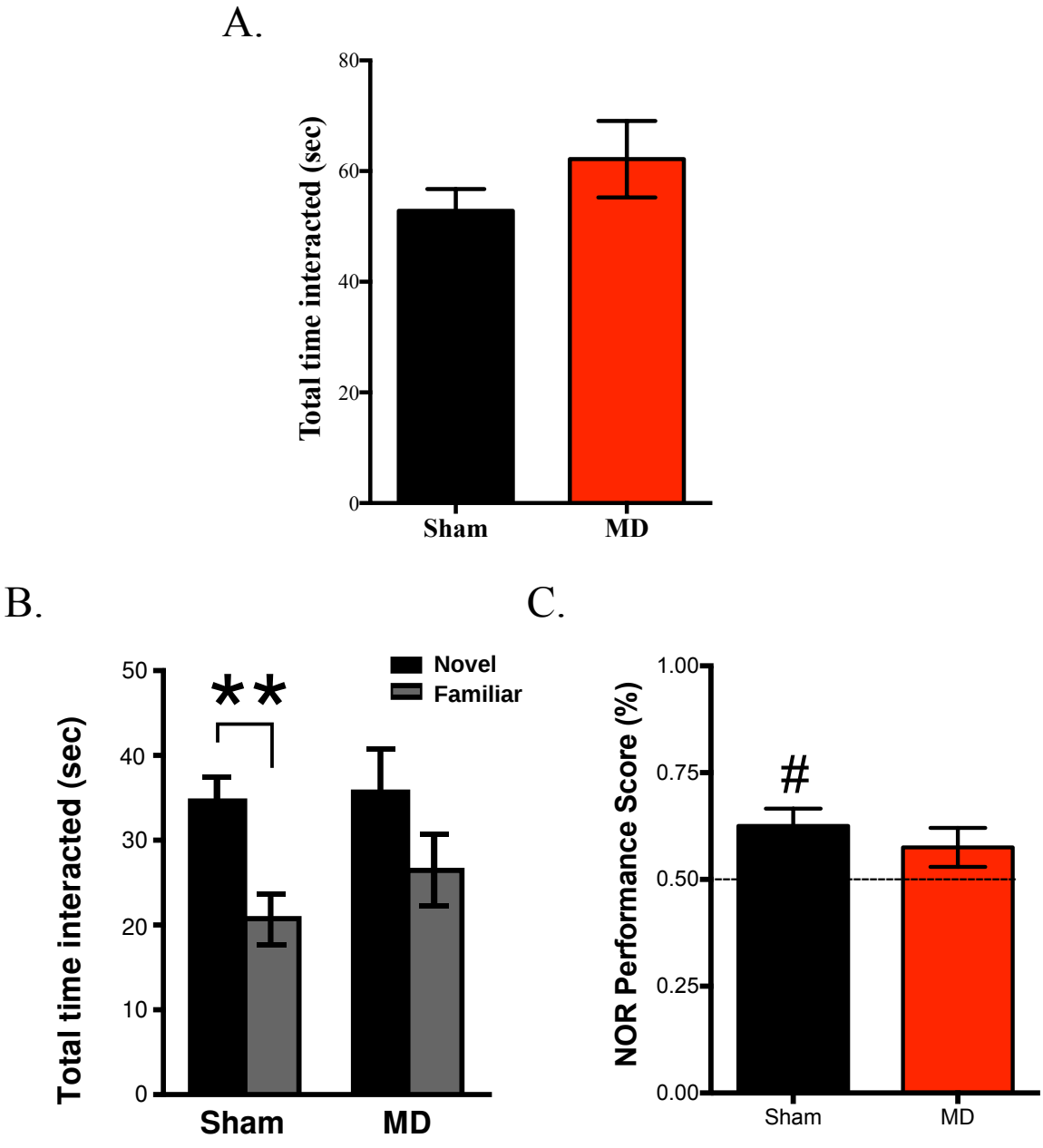
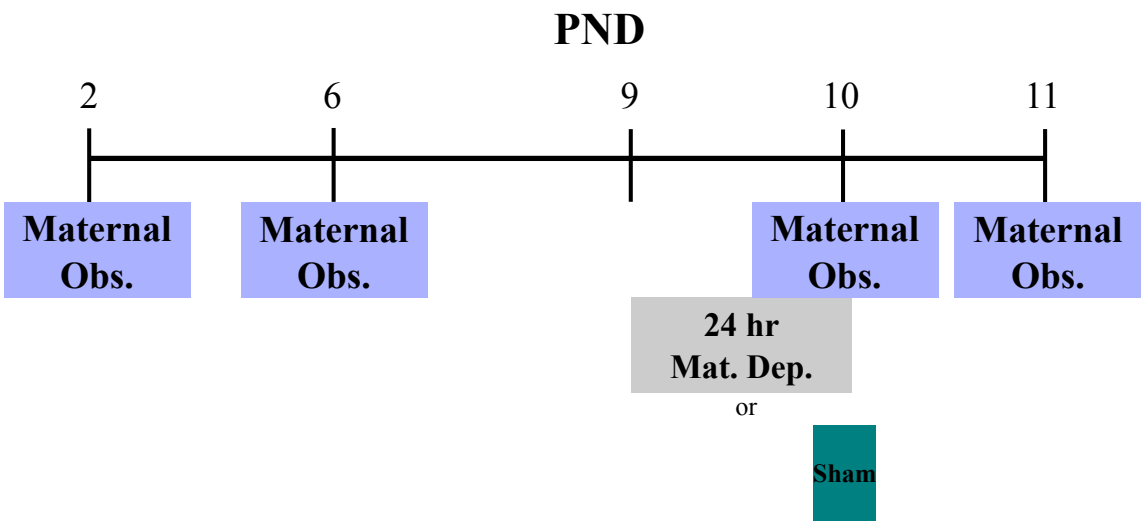
APPENDIX



Preliminary Studies: Novel Object Recognition

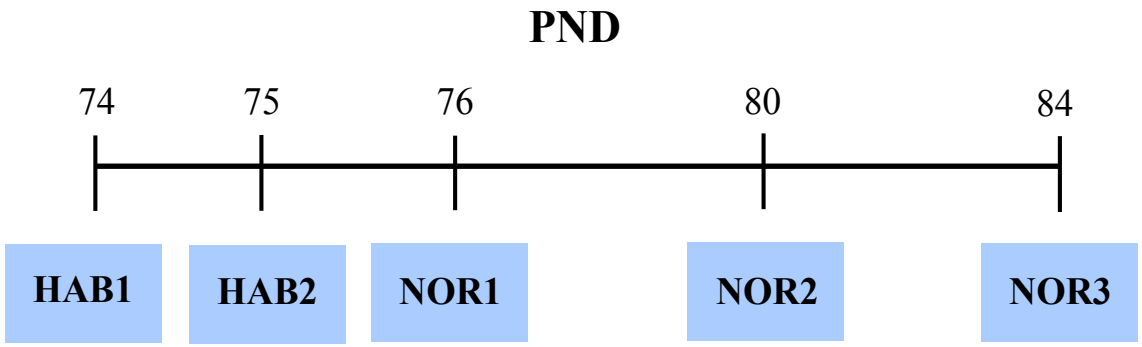
Figure 1: Novel Object Recognition in adulthood following MD or sham. (A) Total time interacted (sec) with both objects collectively. (B) Total interaction time (sec) with the novel or familiar object, separately. (C) NOR performance score between groups and compared to chance (50%) (one-sample t-test, #p<0.05). (sham *n = 10*; MD *n = 13*) (Bonferroni corrected planned comparison, **p<0.01; significantly different than familiar object).



Timeline of Maternal Observation/Deprivation

Figure 2: Detailed Timeline of Maternal Observation and Maternal Deprivation/Sham. On PND 2, 6, 10, and 11, all litters underwent maternal observation from 10:00-11:00 am and from 9:00-10:00 pm ($n = 16$). On PND 9, half of the litters underwent maternal deprivation, where the mother was removed from her litter at 10:00 am for 24 hours until 10:00 am on PND 10 ($n = 8$). The other half of the litters underwent a sham procedure at 10:00 am on PND 10 ($n = 8$), where mothers were breifly removed from her litter, all animals were weighed, and then she was immediately placed back with her litter.

A.



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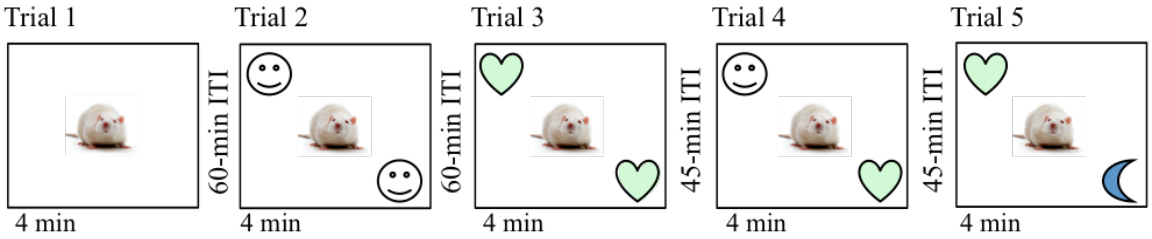
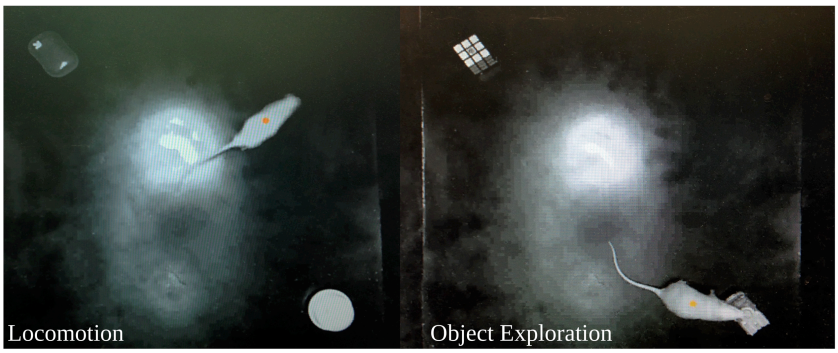
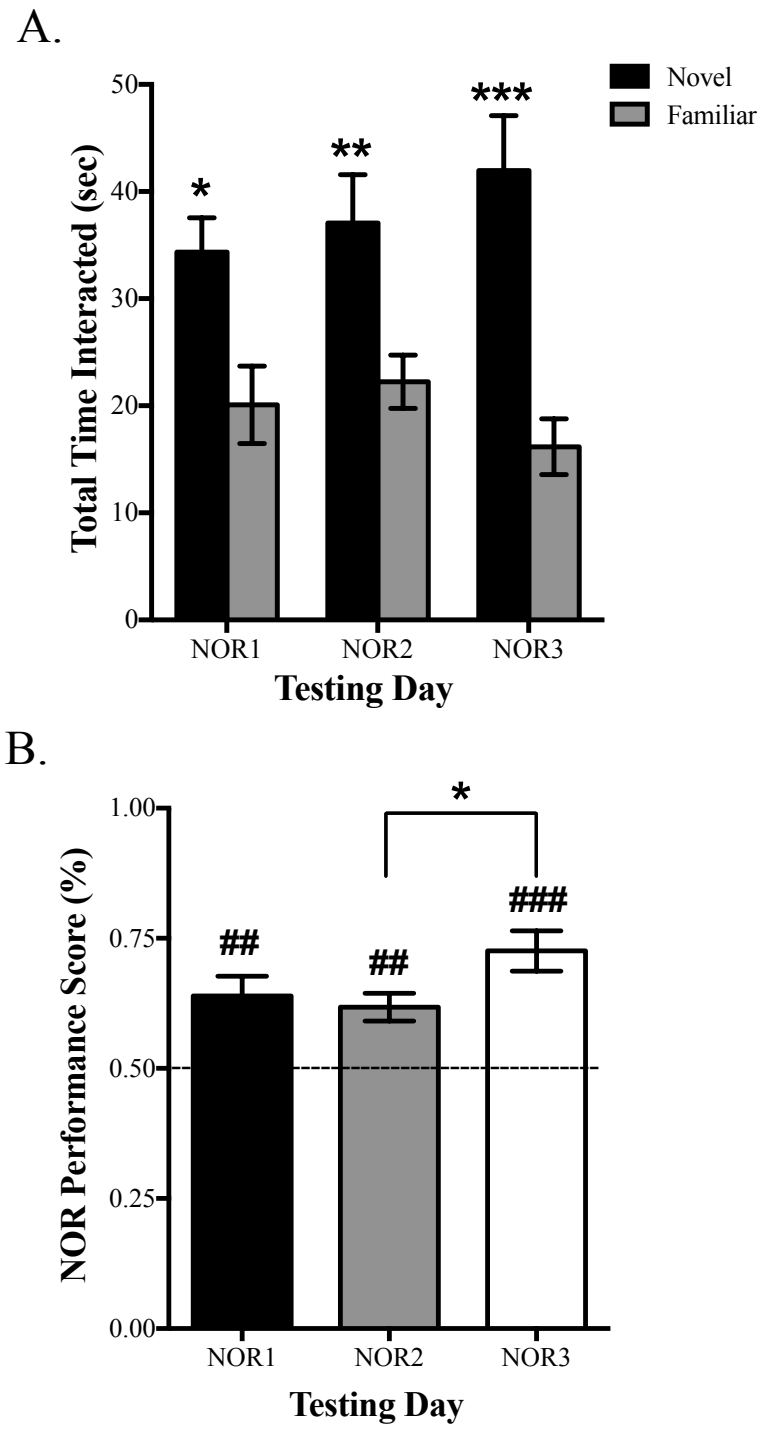


C.



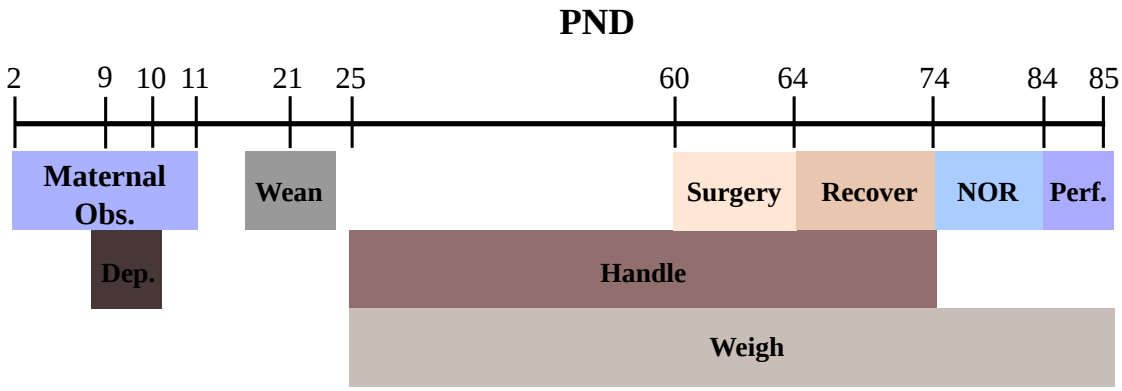
Timeline of Novel Object Recognition Testing and Interaction Example

Figure 3: Detailed Timeline and Trials During the NOR Task and an Example of Object Exploration. (A) On PND 74 and 75, animals underwent 10 minutes of habituation on each day. Animals were plugged in and electrophysiological recordings were obtained while they freely moved around. On PND 76, 80, and 84, NOR1, NOR2, and NOR3 took place, respectively. (B) There were five 4-minute trials on each day. Trial 1 consisted of the animal freely moving around the NOR chamber with no objects present. In Trials 2 and 3, after a 60-min inter-trial interval (ITI), the animal was placed back into the chamber with two separate identical objects. In Trial 4, after a 45-min ITI, the animal had access to the object from Trial 2 and 3. Recognition memory testing took place in Trial 5, where the animal had access to the object from Trial 3 along with a novel object. (C) On the left, the animal is engaged in locomotor behavior. On the right, the animal is exploring an object.



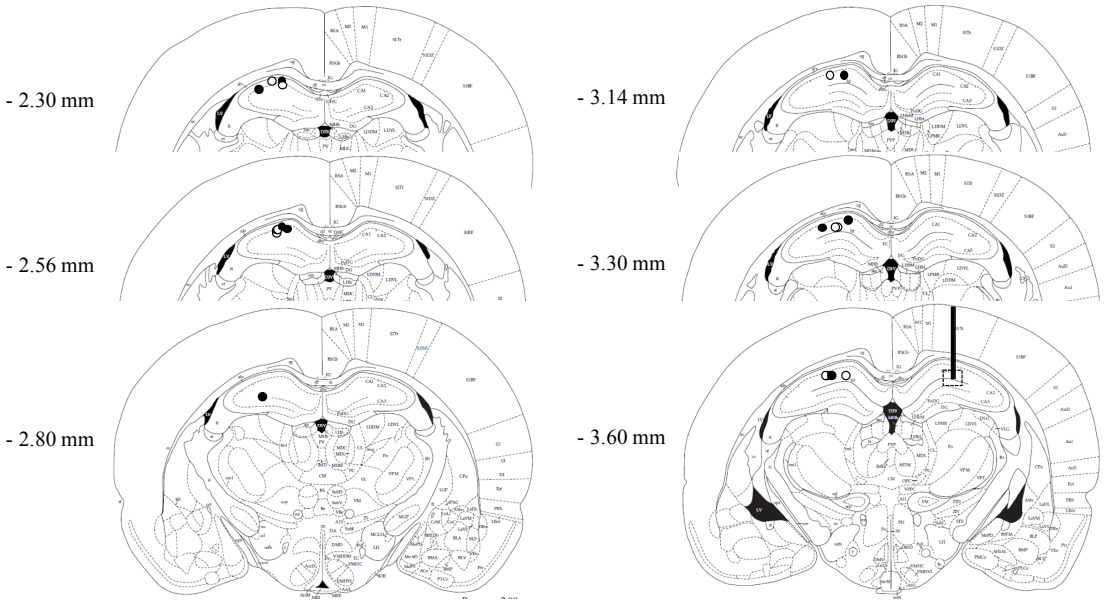
Preliminary Studies: Three Days of NOR

Figure 4: Novel Object Recognition Preliminary Studies. (A) Total time interacted (sec) on Trial 5 with each object and (B) NOR performance score on each day of testing. (Bonferroni post-hoc *p<0.05, **p<0.01, ***p<0.001; one-sample t-test, #p<0.05, significantly different than 50%); (*n = 10*). All data are depicted as mean ± SEM.



Timeline of All Experimentation

Figure 5: Timeline of the all experimental procedures. The day pups were born was considered PND 0. On PND 2-85, animals underwent manipulations and/or procedures.



Placements of LFP Probes in the Dorsal Hippocampus

Figure 6: Placements of LFP probes in the Hippocampus. Coronal sections of the dorsal hippocampus (from -2.30 mm to -3.60 mm) to depict the unilateral placement of probes (HC: AP, -3.6; ML, -2.6; DV, -2.2; relative to bregma). Open circles represent placements for sham animals (*n=9*) and closed circles represent placements for MD animals (*n=11*). Example of probe shape and thickness is depicted in the -3.60 mm section.

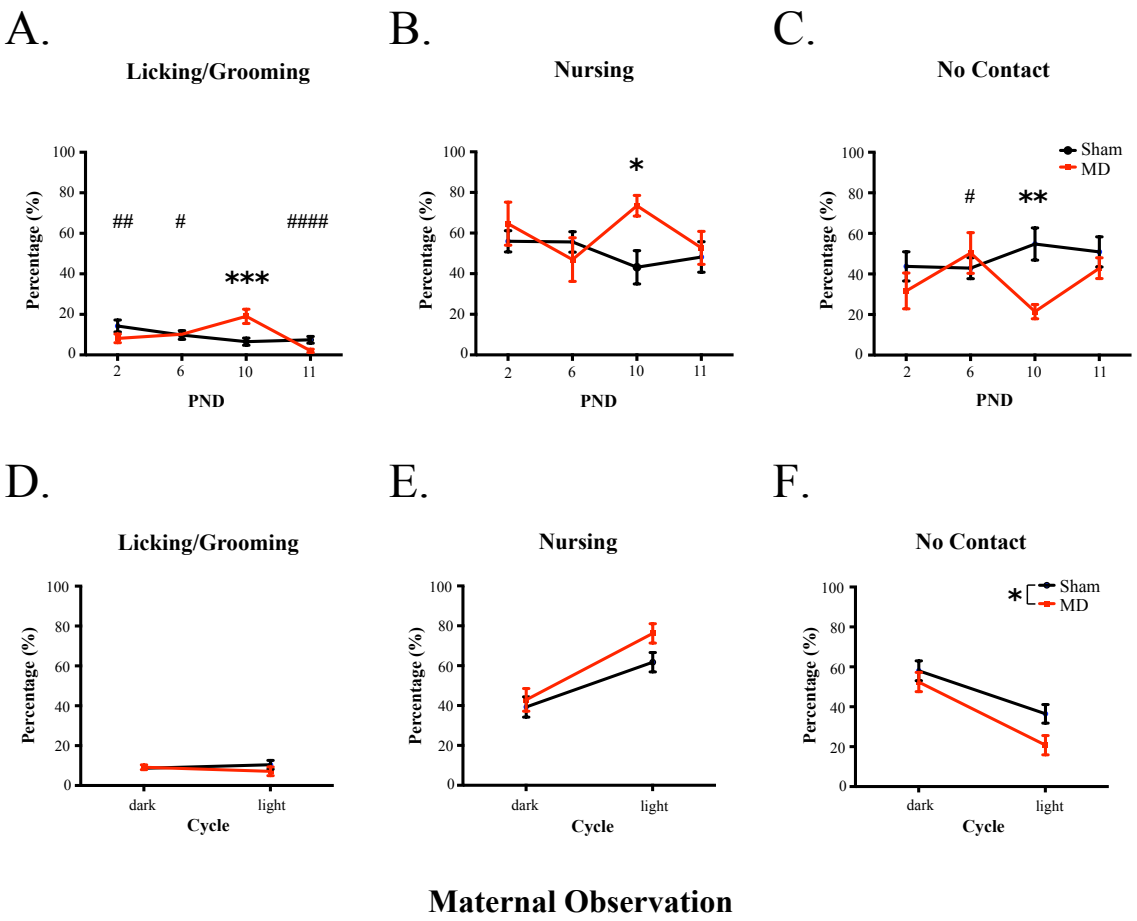
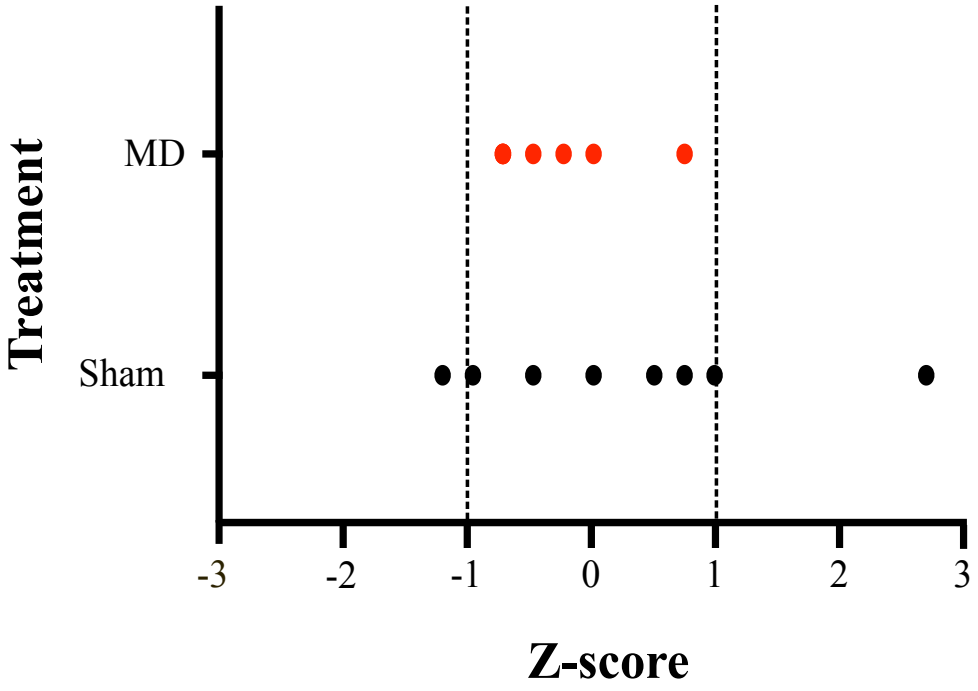


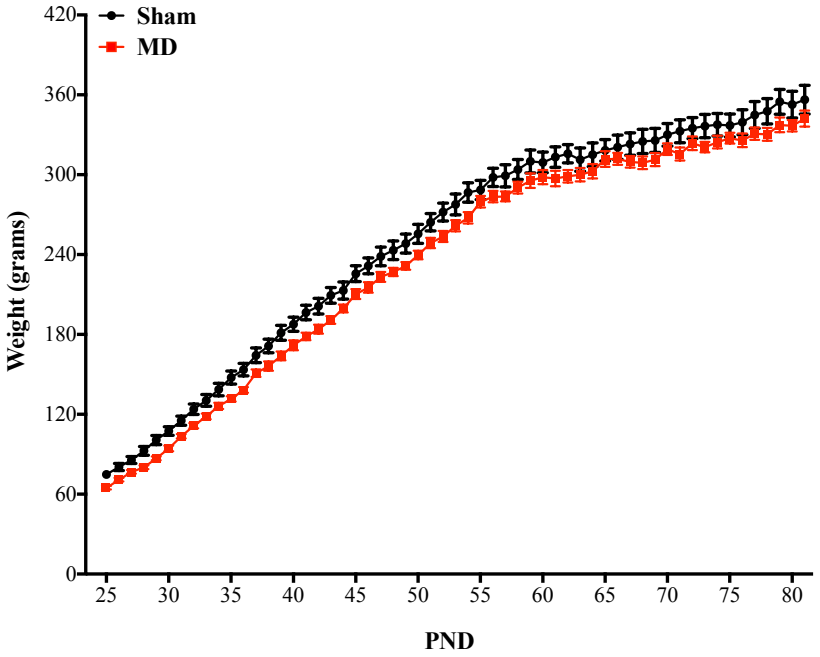
Figure 7: Maternal Care between groups over days and in the dark or light cycle. (A) Percentage of licking and grooming behavior was higher in the MD mothers compared to sham mothers (PND X treatment interaction, main effect of treatment) on PND 10 (Bonferroni post-hoc comparison, $^{***}p<0.001$). In MD mothers only, licking and grooming was higher on PND 10 compared to PND 2, PND 6, and PND 11 (Bonferroni post-hoc comparison, $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#\#}p<0.0001$). (B) Percentage of nursing behavior was higher in MD mothers on PND 10 only (Bonferroni post-hoc comparison, $^{*}p<0.05$). (C) MD mothers had more contact with their pups compared to sham mothers (PND X treatment interaction) on PND 10 (Bonferroni post-hoc comparison, $^{**}p<0.01$). MD mothers had more contact with pups on PND 10 compared to PND 6 (Bonferroni post-hoc comparison, $^{\#}p<0.05$). (D) There were no differences in the percentage of licking and grooming between groups in the dark or light cycle. (E) Although there were no group differences, mothers from both groups nursed more during the light cycle compared to the dark cycle (main effect of cycle). (F) Mothers from both groups had higher contact during the light cycle compared to the dark cycle (main effect of cycle). Furthermore, sham mothers had less contact overall compared to MD mothers (main effect of treatment, $^{*}p<0.05$) (sham mothers $n = 8$; MD mothers $n = 7$). All data are depicted as mean ± SEM.



High vs. Low Licking/Grooming

Figure 8: Quantification of high and low lickers/groomers based on maternal care on PND 2 and 6 only. After combining the percentages of licking and grooming over the two days when collapsed on treatment (sham *n = 8;* MD *n = 7*), only one sham mother was considered a high licker/groomer (z-score: 2.679) and one sham mother was considered a low licker/groomer (z-score: -1.217).

A.



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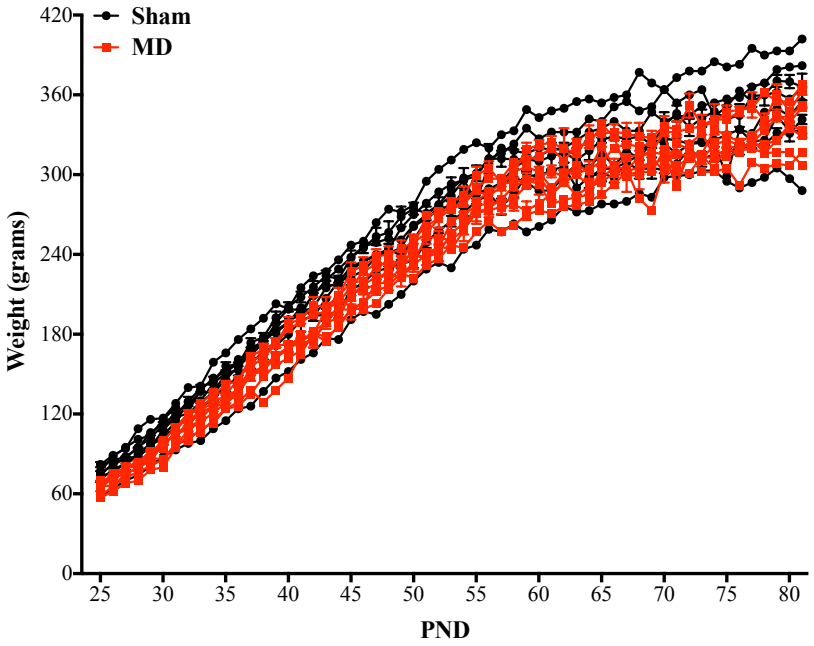
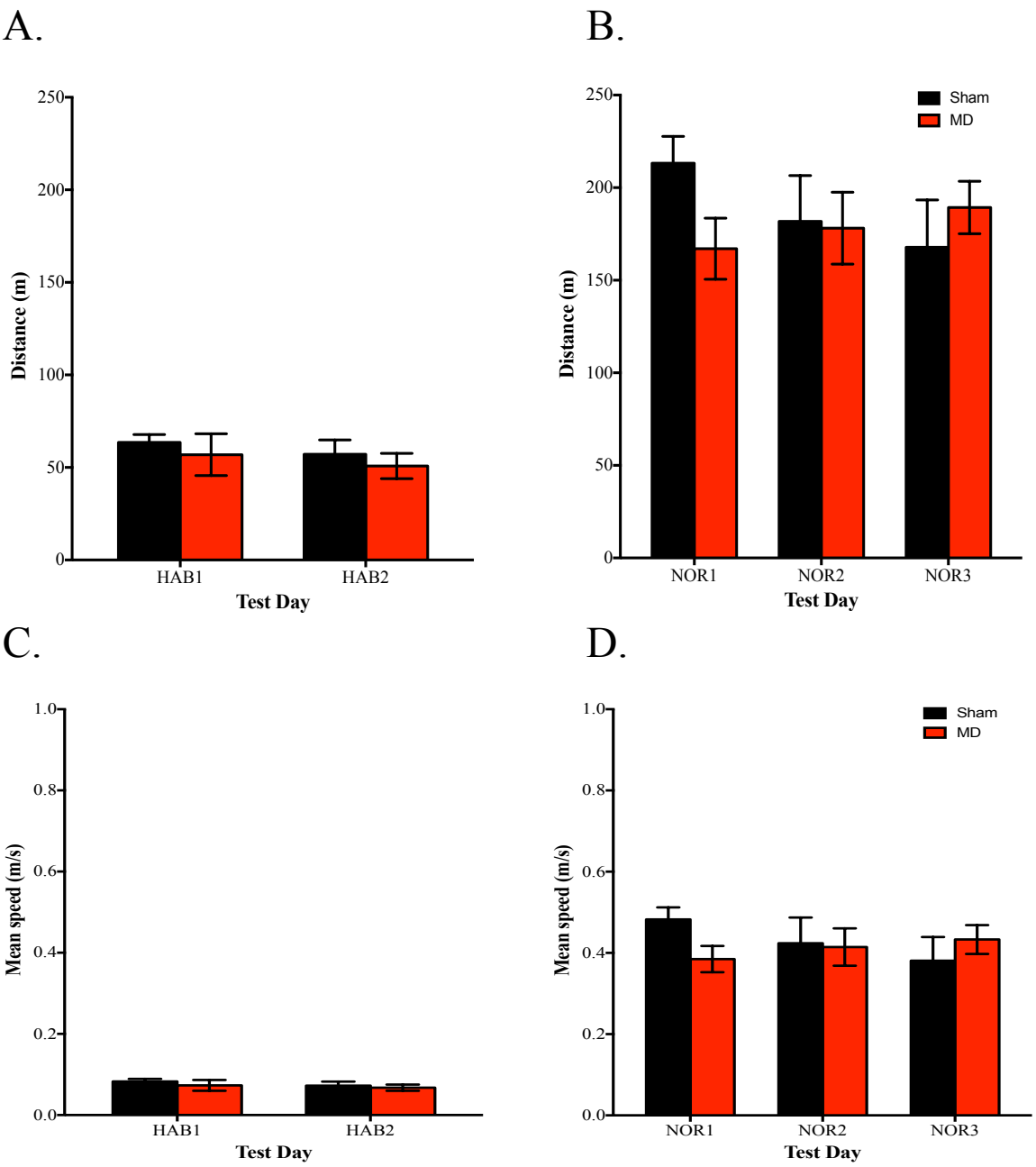


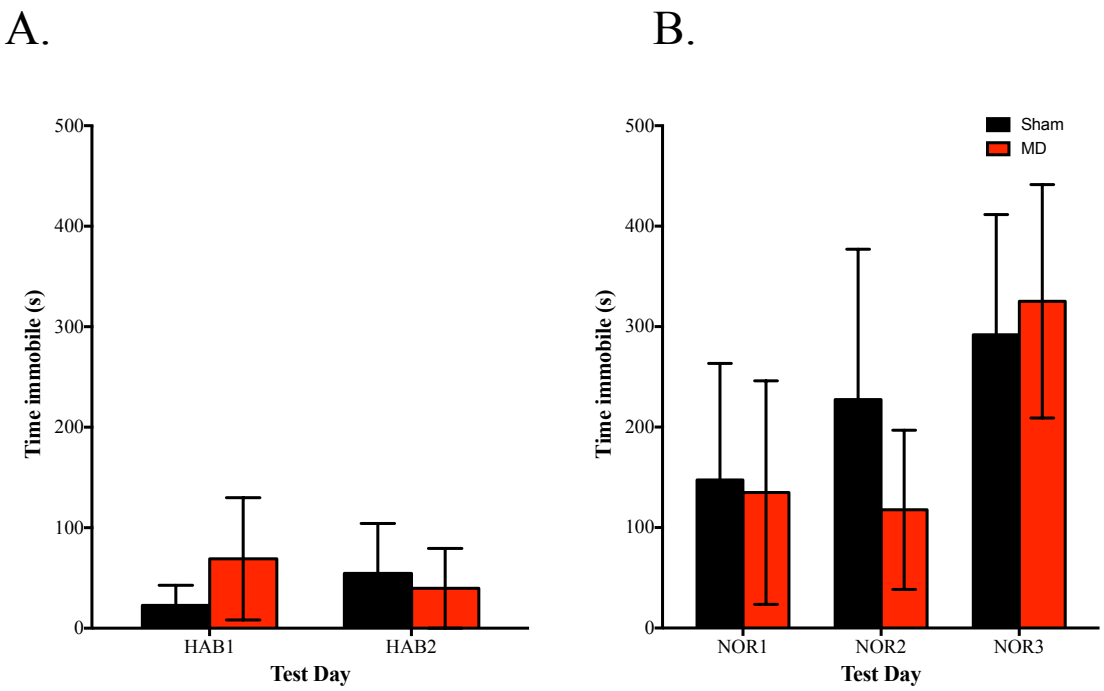
Weights

Figure 9: Weights in grams: (A) Weights of each sham (*n = 9*) and MD (*n = 11*) animal during experimentation from PND 25 to PND 80. (B) Weights of each sham (*n = 8*) and MD (*n = 8*) family during experimentation. All data are depicted as mean ± SEM.



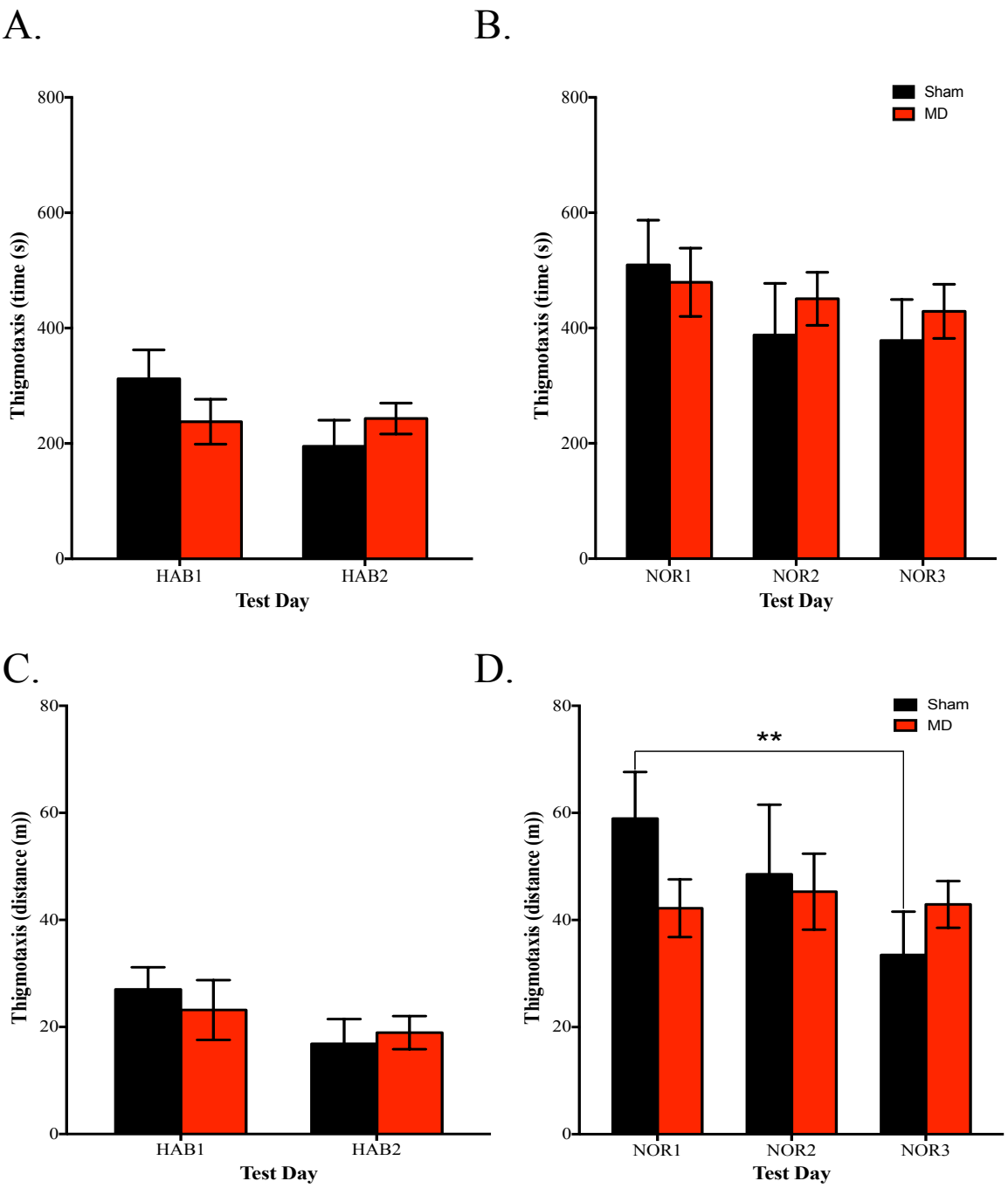
Locomotor Activity

Figure 10: Locomotor activity during both habituation days and on all three days of NOR, collapsed on all five trials: (A) Distance in meters on the habituation and (B) NOR days between groups. (C) Mean speed in m/s on habituation and (D) NOR days between groups (sham *n = 7;* MD *n = 10*). All data are depicted as mean ± SEM.



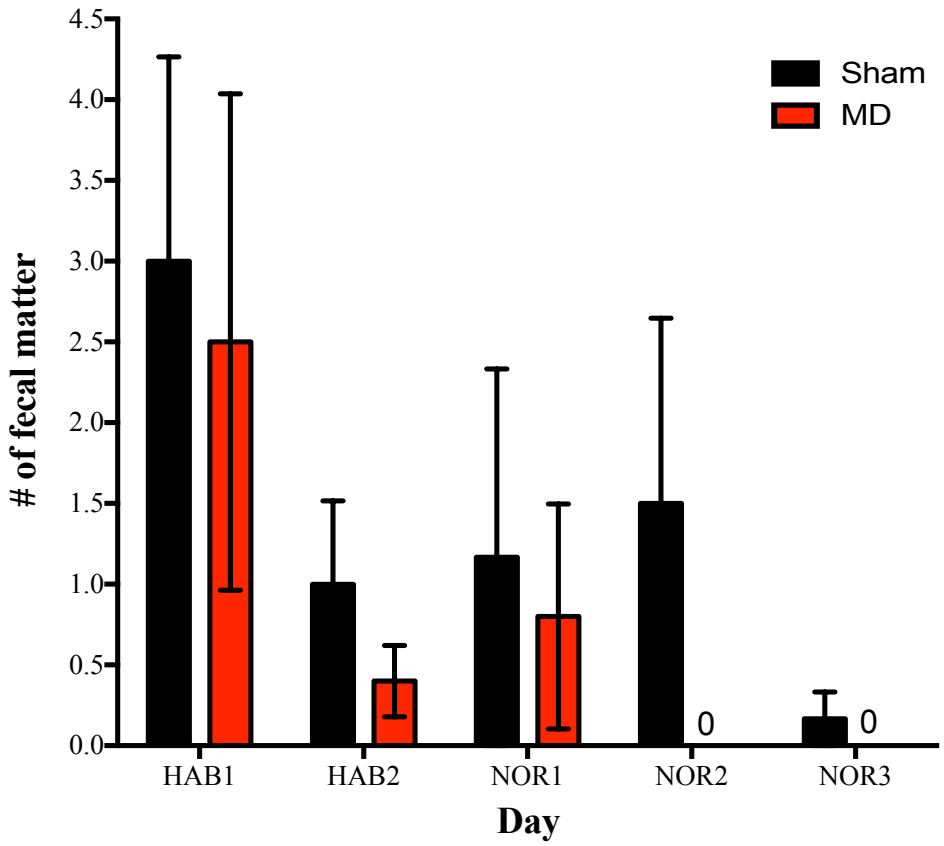
Time Immobile

Figure 11: Time immobile during both habituation days and on all three days of NOR, collapsed on all five trials: (A) Time immobile in seconds on the habituation and (B) NOR days between groups (sham *n = 7;* MD *n = 10*;). All data are depicted as mean ± SEM.



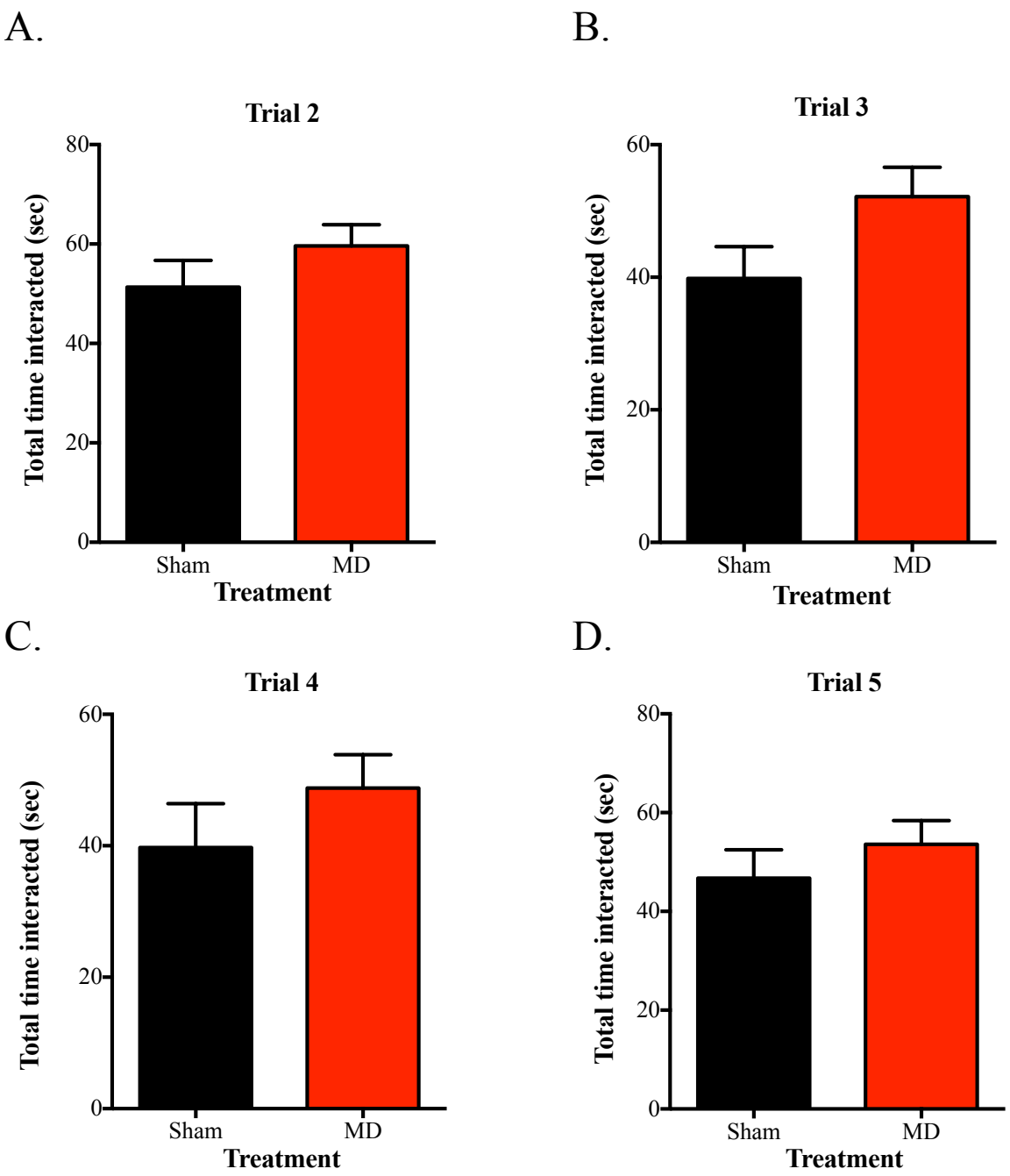
Time Spent and Distance Travelled in Thigmotaxis Region

Figure 12: Time spent and distance travelled in thigmotaxis region during both habituation days and on all three days of NOR, collapsed on all five trials: (A) Time spent in seconds in thigmotaxis region during habituation and (B) NOR days. (C) Distance travelled in meters on the habituation and D) NOR days. (sham *n = 7;* MD *n = 10*); (Bonferroni post-hoc comparison, **p < 0.01). All data are depicted as mean ± SEM.



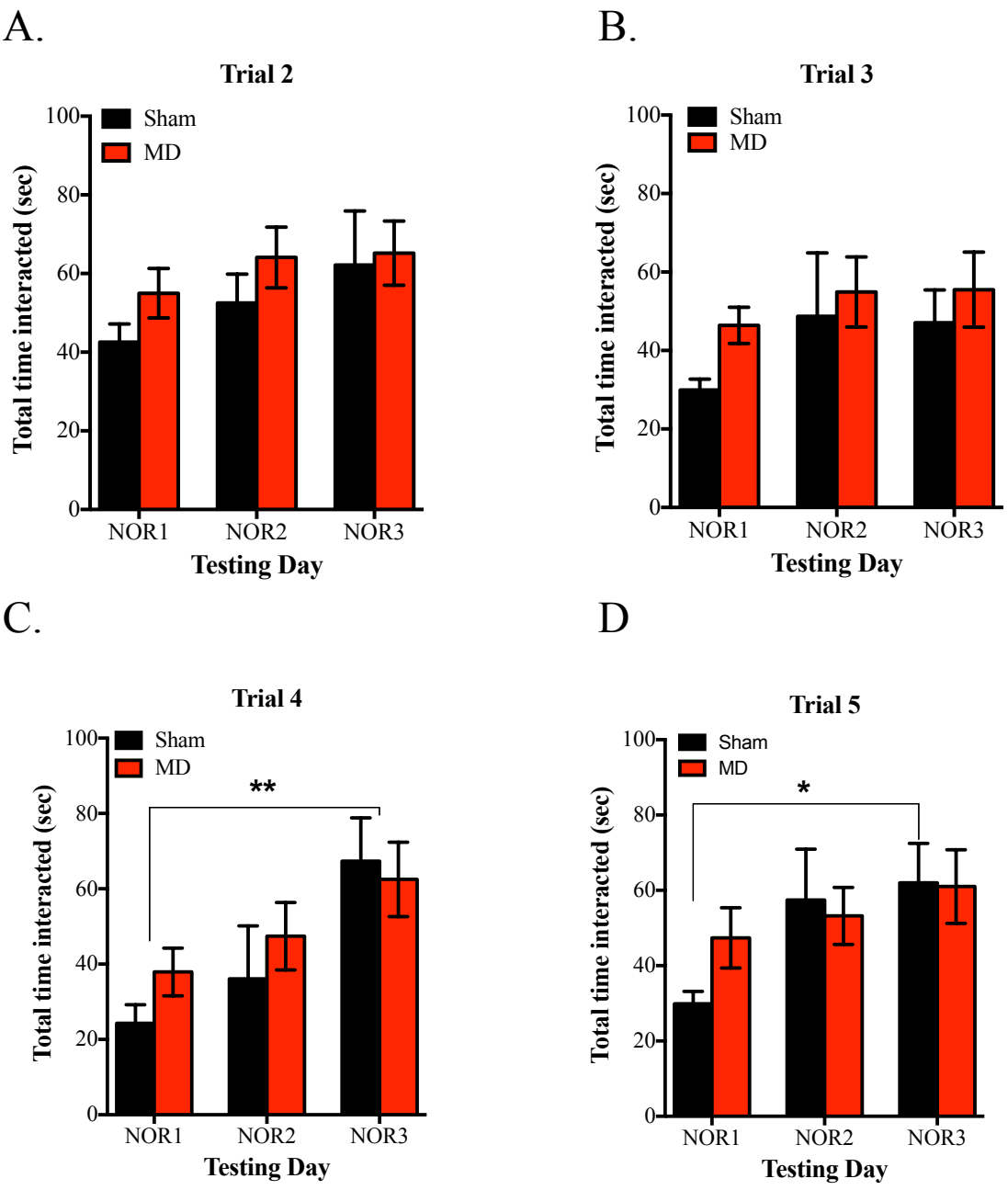
Defecations During Novel Object Recognition

Figure 13: Number of fecal matter during both habituation days and on all three days of NOR, collapsed on all five trials: Number of fecal matter between sham and MD animals during habituation and testing days, collapsed on trials (sham *n = 7;* MD *n = 10*). All data are depicted as mean ± SEM.



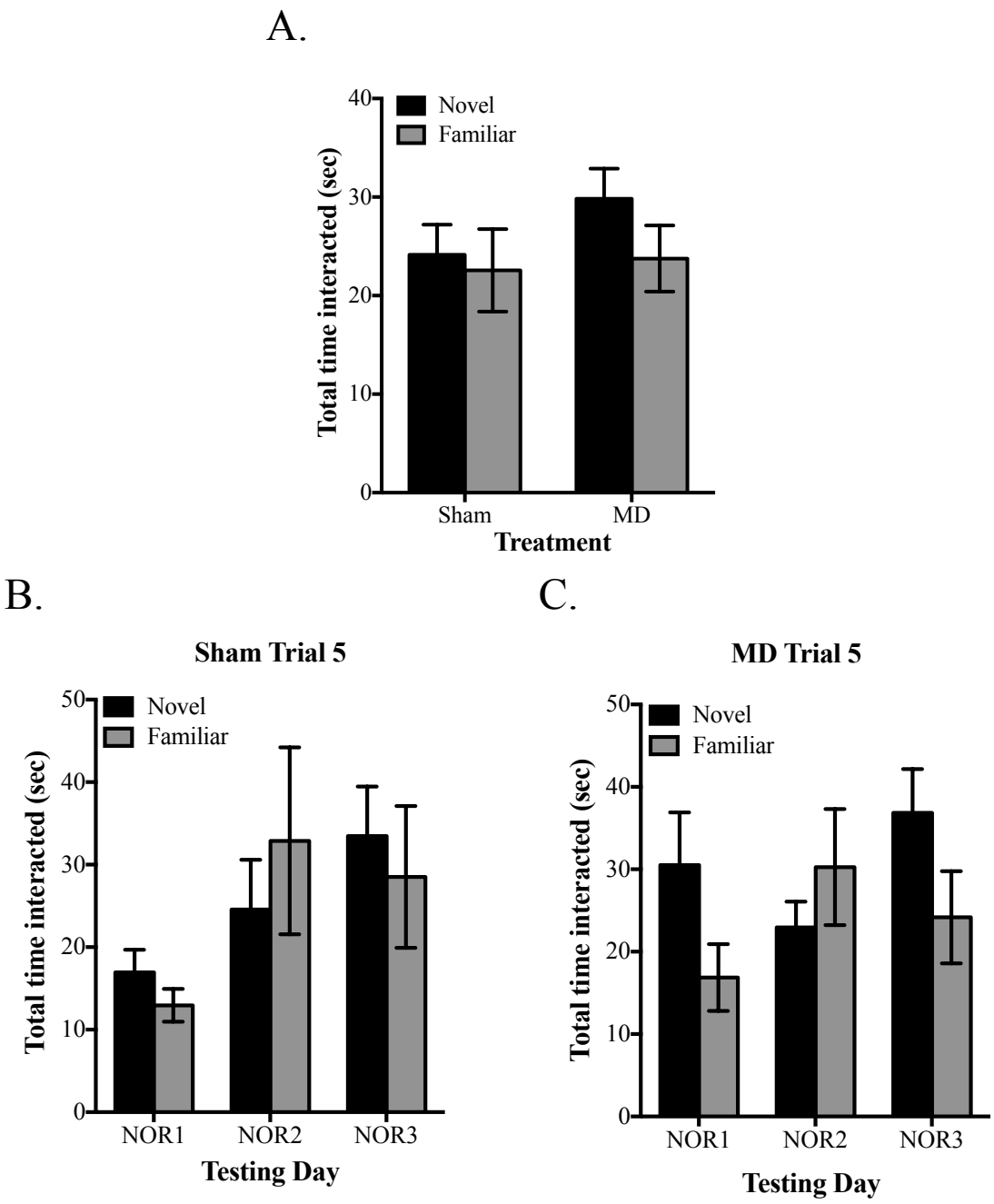
Individual Data Points for Total Interaction Time on all Trials with Both Objects

Figure 14: Total time interacted with both objects collectively between groups during trials 2-5 on all three days, collectively: Time spent interacting in seconds with both objects in (A) Trial 2 (B) Trial 3 (C) Trial 4 and (D) Trial 5. (sham *trials = 18;* MD *trials = 26*). All data are depicted as mean ± SEM.



Total Interaction Time on Each Day for Each Trial

Figure 15: Total time interacted with both objects collectively between groups during trials 2-5 on each day, separately: (A) Time spent interacting in seconds with both objects in Trial 2, (B) Trial 3, (C) Trial 4, and (D) Trial 5. (sham: Day 1, $n = 8$; Day 2, $n = 4$; Day 3, $n = 6$; MD: Day 1, $n = 9$; Day 2, $n = 9$; Day 3, $n = 8$). (Bonferroni post-hoc comparison, *$p < 0.05$, day 1 significantly different than day 3 in sham animals only; **$p < 0.01$, day 1 significantly different than day 3 in both groups). All data are depicted as mean ± SEM.



Total Interaction With Each Object During Novel Object Recognition

Figure 16: Total time interacted with the novel and familiar object between groups on all three days of testing, collectively and separately. (A) Time spent interacting in seconds with each object separately during during the NOR test (trial 5), collapsed on days (sham, *n = 18*; MD, *n = 26)*. Total time interacted with each objects in (B) shams or (C) MDs on each NOR day. (sham: Day 1, *n = 8*; Day 2, *n = 4*; Day 3, *n = 6;* MD: Day 1, *n = 9*; Day 2, *n = 9*; Day 3, *n = 8*). All data are depicted as mean ± SEM.

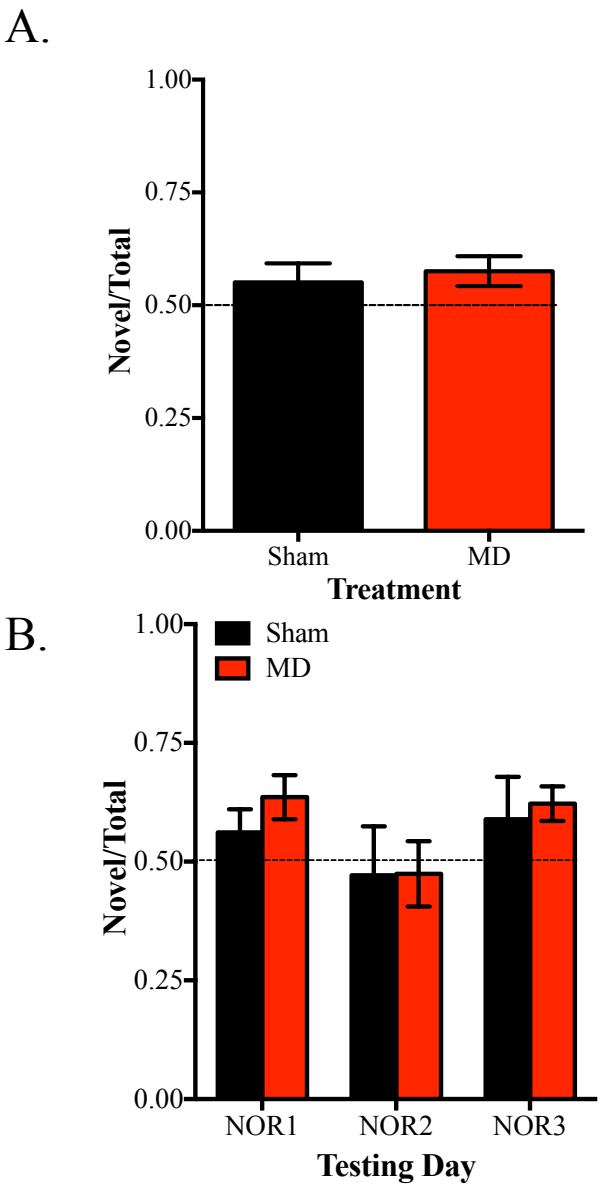


Figure 17: Preference for the novel object between groups on all three days of testing, collectively or separately. (A) Preference score for novel object during NOR testing on all days collectively. Dotted lines represent preference for novel object, if above 0.50. Each dot signifies a data point from a single trial (sham data sets *n = 18;* MD data sets *n = 26)*. (B) Preference score on each day, separately (sham: Day 1, *n = 8*; Day 2, *n = 4*; Day 3, *n = 6;* MD: Day 1, *n = 9*; Day 2, *n = 9*; Day 3, *n = 8*). All data are depicted as mean ± SEM.

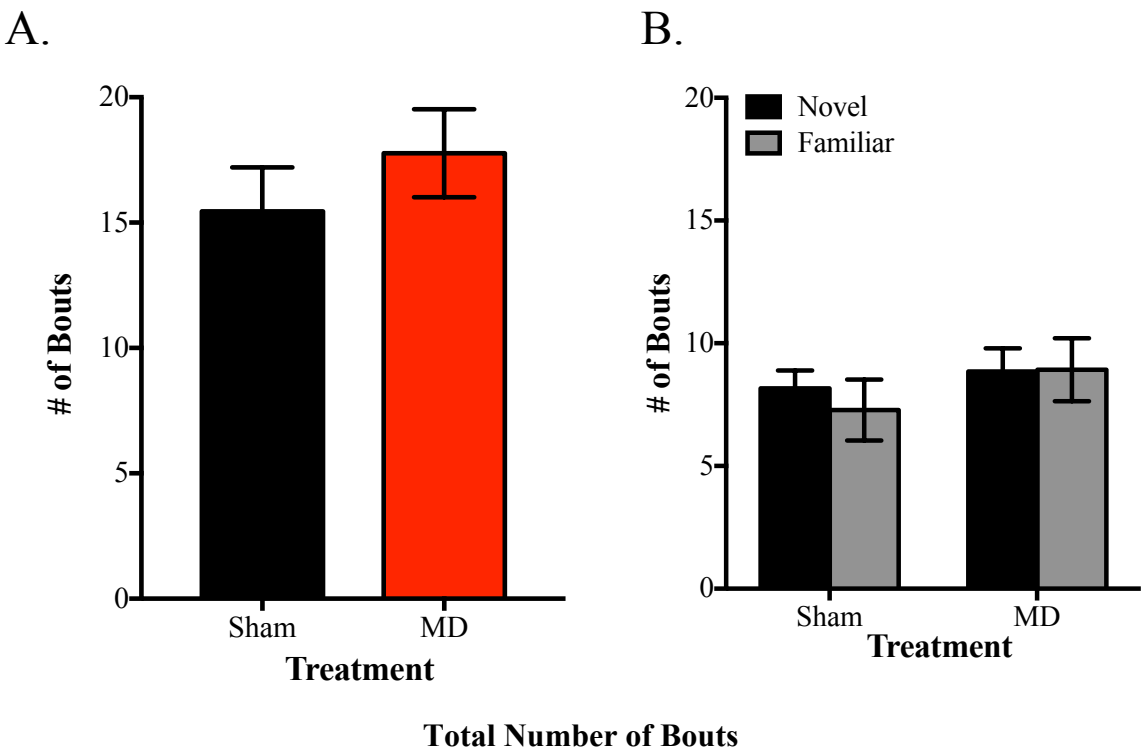
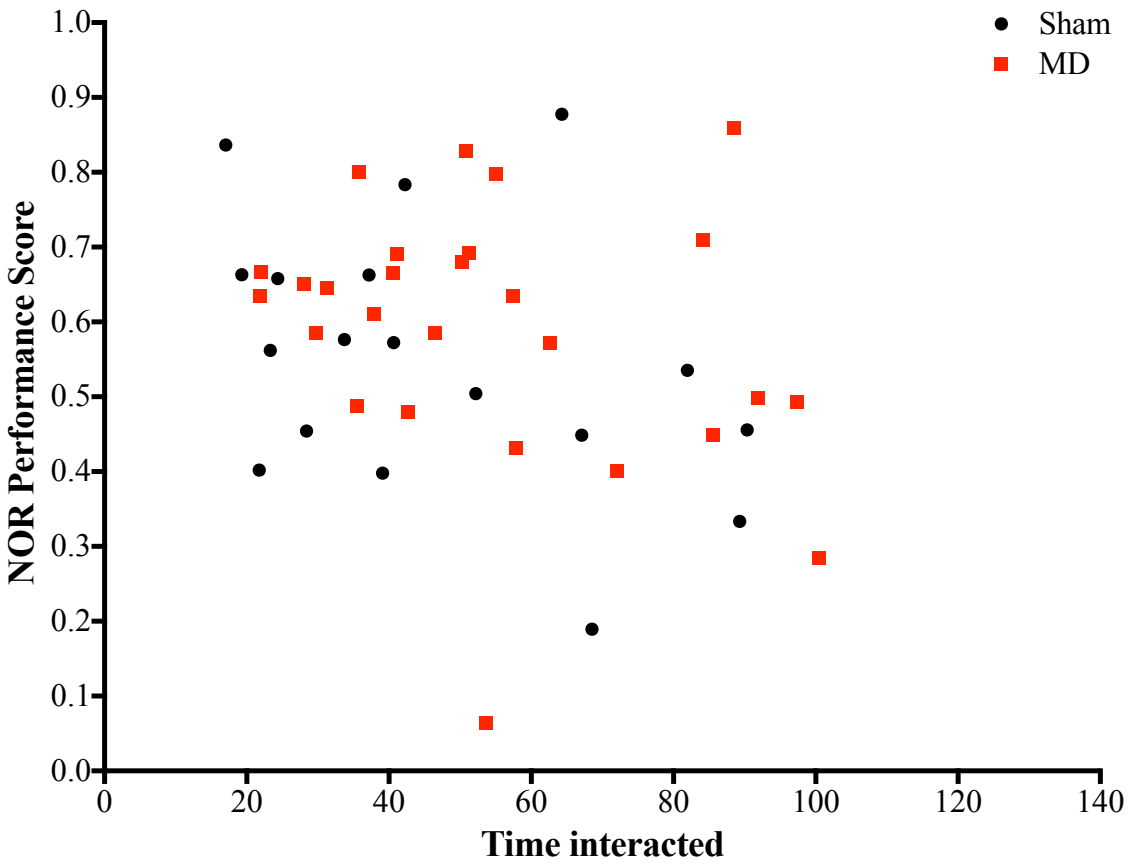


Figure 18: Total number of bouts with both objects collectively or separately on trial 5. (A) Total number of bouts between groups. (B) Number of bouts with the novel or familiar object in the MD and sham groups (sham data sets *n = 18;* MD data sets *n = 26).* All data are depicted as mean ± SEM.



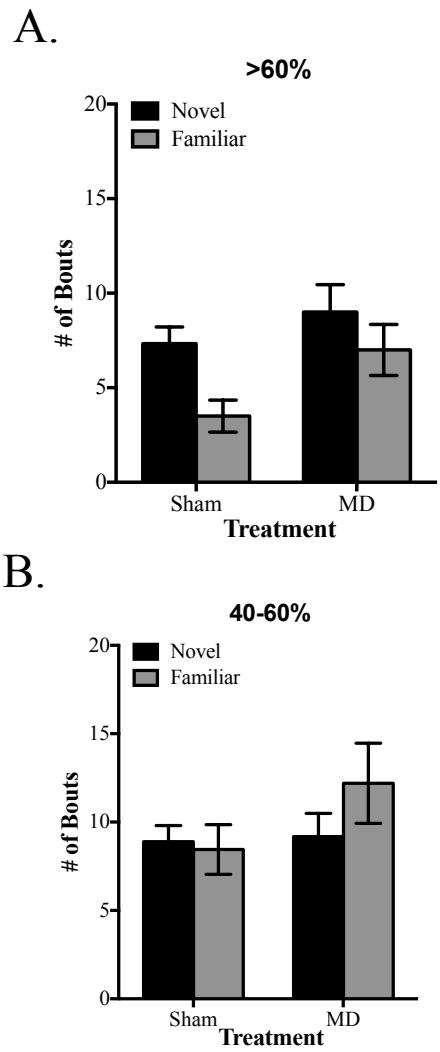
NOR performance Score and Total Time Interacted

Figure 19: Correlation between NOR performance score and time interacted with both objects, collectively on all NOR trials. This graph includes all successfully recorded NOR trials that have at least 18 seconds of interaction time with both objects. Each dot signifies a data point from a single trial in NOR testing. Data points below 0.4 are animals that did not succesfully perform novel object recognition. Animals over 0.6 successfully performed successful novel object recognition (sham $n = 18$; $R^2 = 0.1494$, $p = 0.1130$; MD $n = 28$; $R^2 = 0.07188$, $p = 0.1763$).

	>60%	40-60%	<40%	Not Enough Interaction
Sham	6	9	3	12
MD	13	11	2	6

Number of Data Sets from Each Performance Criteria

Figure 20: Number of data sets during NOR recall trials (trial 5). This table includes the number of data sets in the different performance criterias. More than 60% is considered preferrence for the novel object, 40-60% is considered no preference, and less than 40% is considered no preference for the novel object. Lastly, data sets that had less than 20 seconds of interaction were not considered for the electrophysiological analyses. These data sets don't include animals with missed placements.



Number of Bouts in Animals with Different Performance Criteria

Figure 21: Number of bouts with each object in animals that preferred the novel object >60%, 40-60%, or <40% of the time. Number of bouts for novel and familiar object exploration in animals that explored the novel object (A) >60% (success) of the time (sham *n = 6;* MD *n = 13)* and (B) between 40-60% (chance) (sham *n = 9;* MD *n = 11)*. All data are depicted as mean ± SEM.

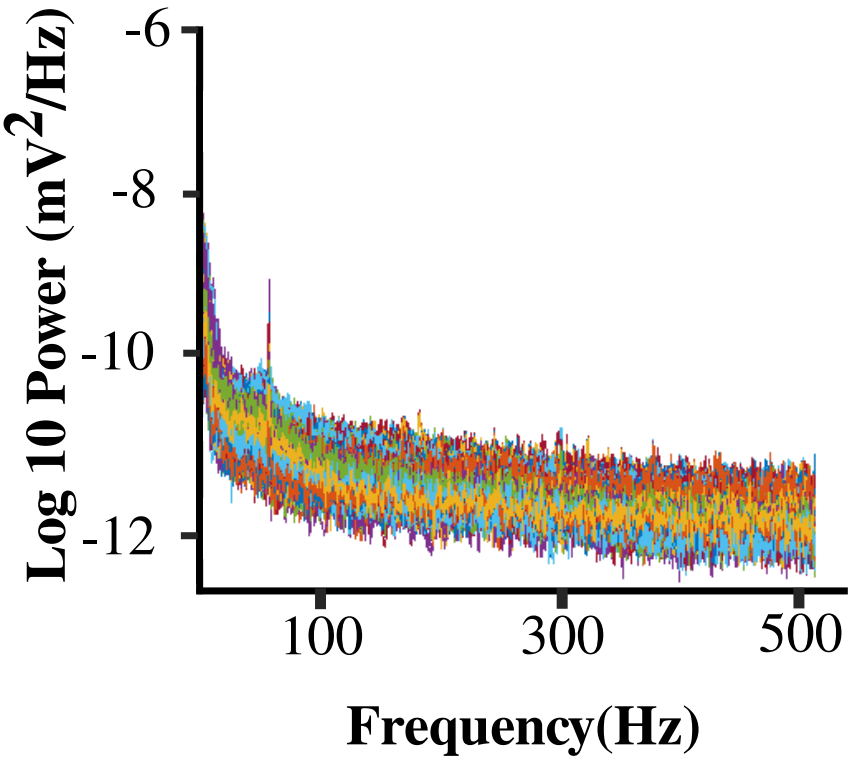
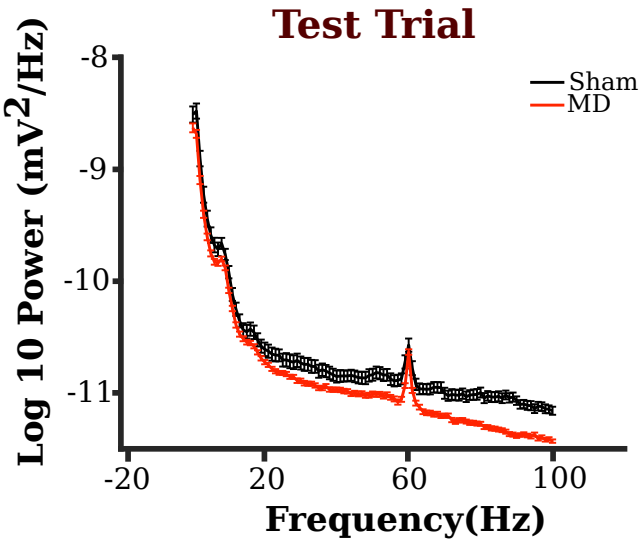


Figure 22: Power Spectrum of data for the variable 'success MD novel' after outliers were removed. Each line is an individual bout of interaction, with log 10 power on the y-axis and frequency on the x-axis. (*n = 237 bouts of interaction)*.

A.



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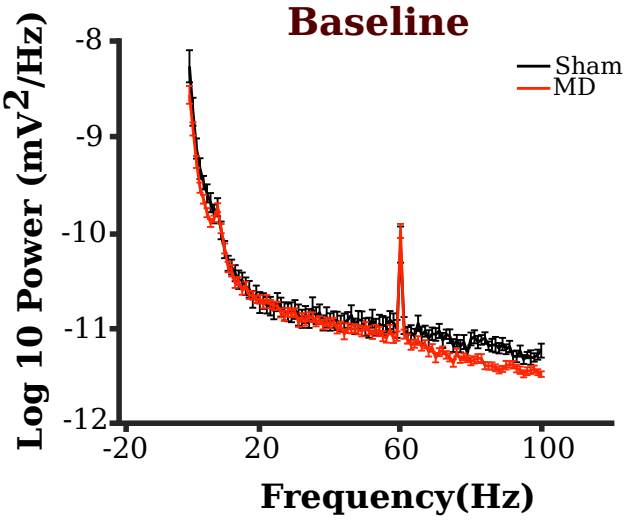
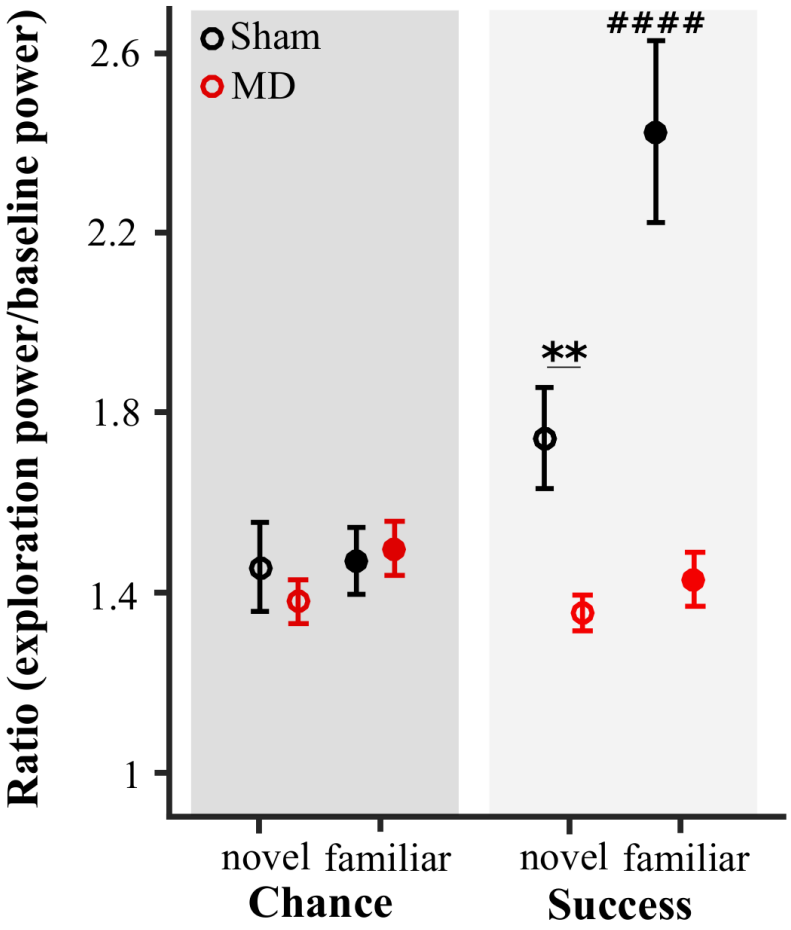


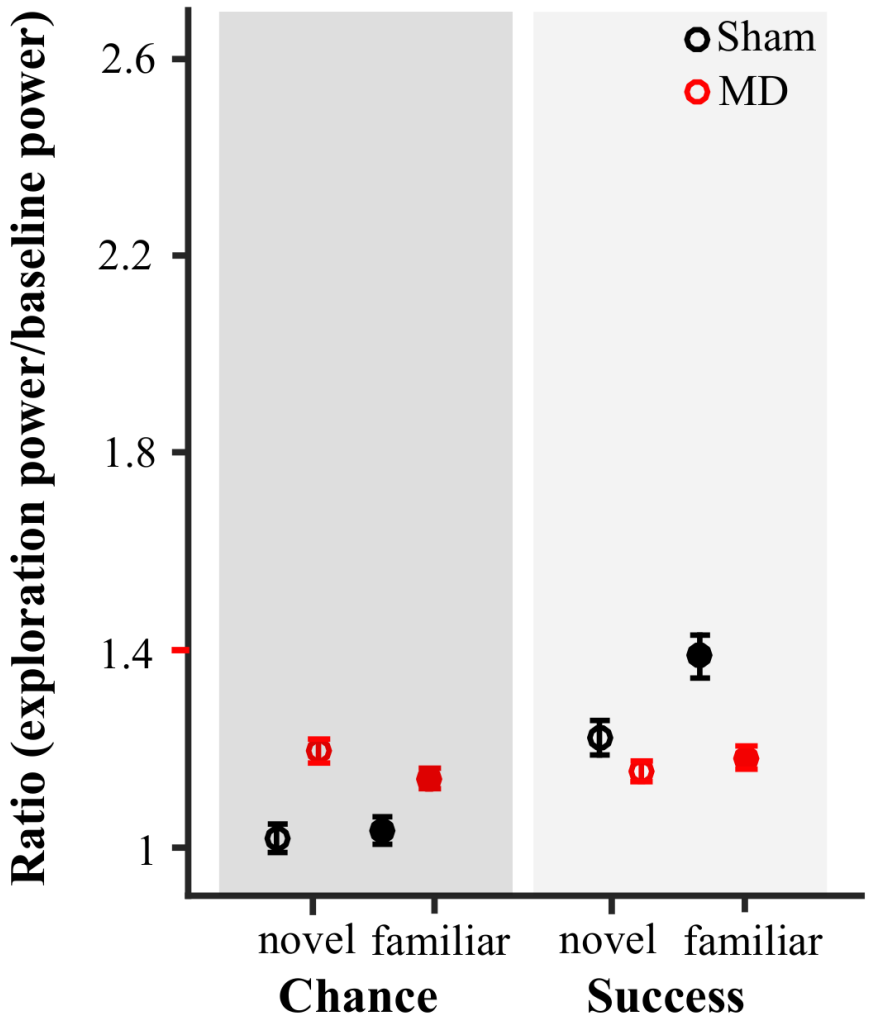
Power Spectrum Between Groups During Test Trial and Baseline

Figure 23: Power spectrum during successful performance with the novel object and its corresponding baseline power spectrum. (A) Power spectrum (log 10) of MD and sham animals during the testing trials and (B) during baseline. (sham bouts *n = 80;* MD bouts *n = 237).* All data are depicted as mean ± SEM.



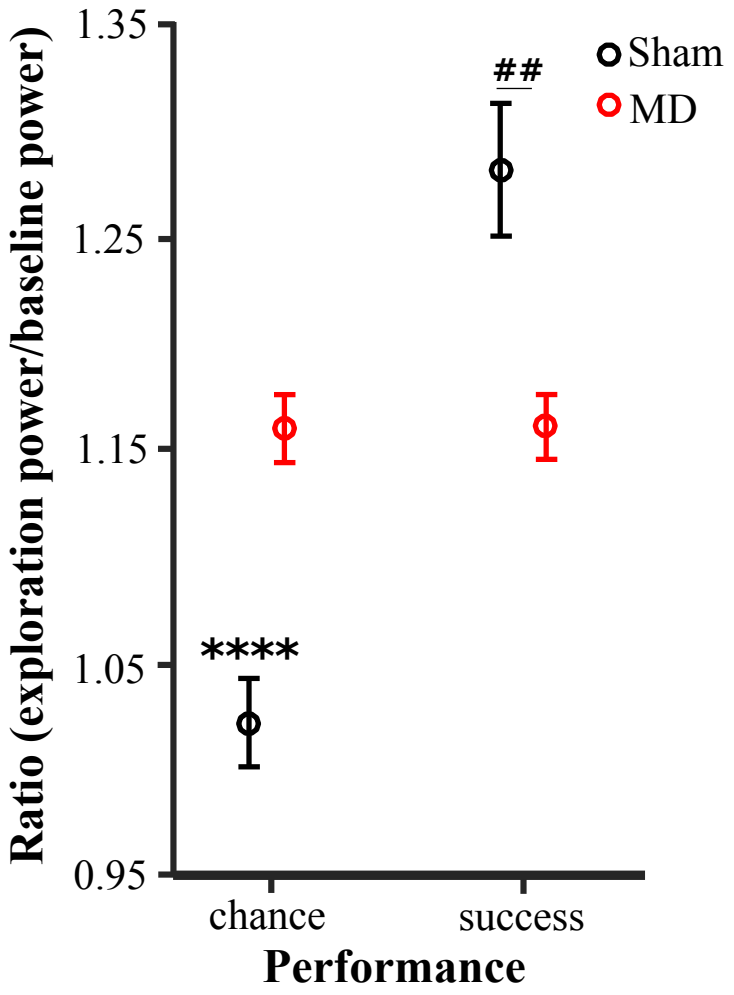
Theta Power Between Groups, Objects, and Performance

Figure 24: Changes from baseline in theta power between groups, objects, and performance. Ratios depict the change in theta power from baseline during novel (open circles) or familiar (closed circles) object exploration in success (light shaded region) or chance (dark shaded region) trials between MD (dark blue) or sham (black) animals. Chance bouts (sham novel *n = 183;* MD novel *n = 202;* sham familiar *n = 174;* MD familiar *n = 249).* Success bouts (sham novel *n = 75;* MD novel *n = 231;* sham familiar *n = 47;* MD familiar *n = 172).* (Successful trials: Bonferroni post-hoc comparison, $^{\#\#\#\#}p<0.0001$, sham animals interacting with familiar object significantly different than all other groups; $^{**}p<0.001$, significantly different than sham animals interacting with novel object). All data are depicted as mean ± SEM.



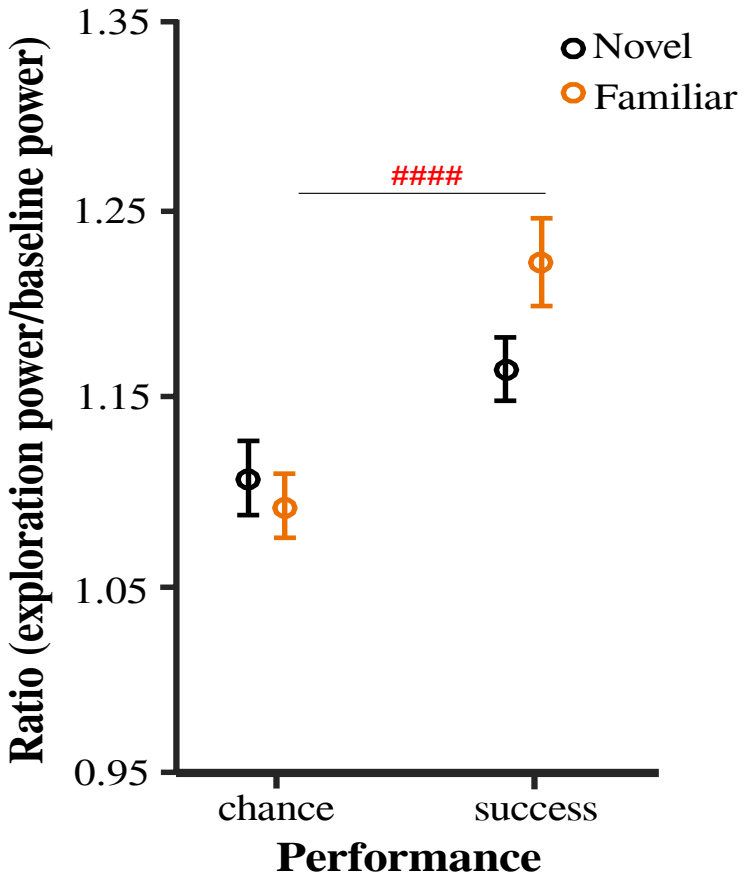
Low Gamma Power Between Groups, Objects, and Performance

Figure 25: Changes from baseline in low gamma power between groups, objects, and performance. Ratios depict the change in low gamma power from baseline during novel (open circles) or familiar (closed circles) object exploration in success (light shaded region) or chance (dark shaded region) trials between MD (dark blue) or sham (black) animals. Chance bouts (sham novel *n = 183;* MD novel *n = 202;* sham familiar *n = 174;* MD familiar *n = 249).* Success bouts (sham novel *n = 75;* MD novel *n = 231;* sham familiar *n = 47;* MD familiar *n = 172).* All data are depicted as mean ± SEM.



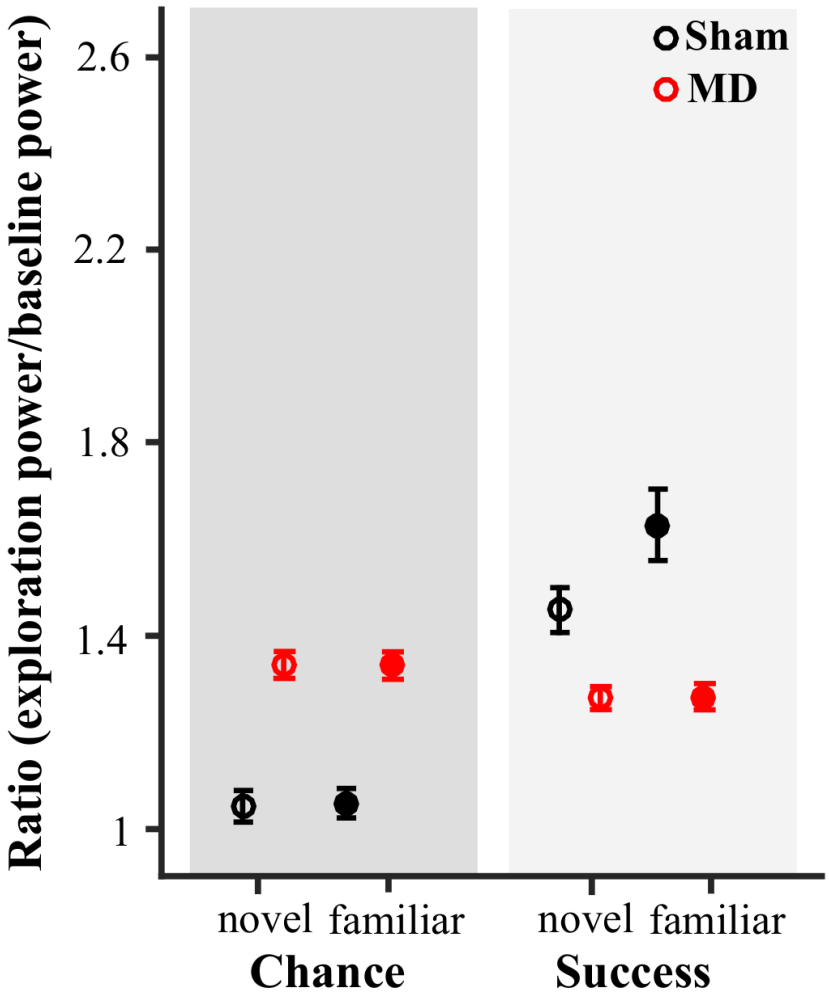
Low Gamma Power Between Groups and Performance (Collapsed on Object)

Figure 26: Changes from baseline in low gamma power between groups and performance, collapsed on object. Ratios depict the change in low gamma power from baseline during successful or unsuccessful trials between MD (dark blue) or sham (black) animals. (sham success *n = 122;* MD success *n = 403;* sham chance *n = 357;* MD chance *n = 451).* (Bonferroni post-hoc comparison, $^{\#\#}p<0.001$, significantly different than sham animals in successful trials; $^{***}p<0.005$, significantly different than all other groups). All data are depicted as mean ± SEM.



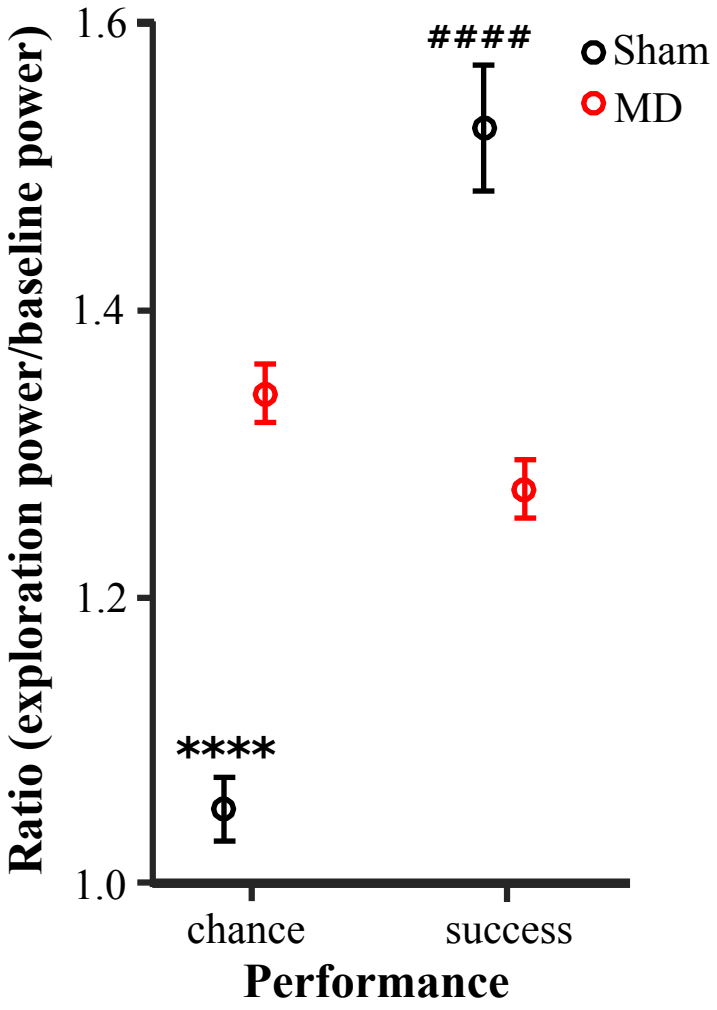
Low Gamma Power Between Objects and Performance (Collapsed on Group)

Figure 27: Changes from baseline in low gamma power performance and objects, collapsed on group. Ratios depict the change in low gamma power from baseline during successful or unsuccessful trials between novel (black) or familiar (dark blue) objects. (novel chance *n = 385;* familiar chance *n = 423;* novel success *n = 306;* familiar success *n = 219).* (Bonferroni post-hoc comparison, $^{\#\#}p<0.001$, $^{\#\#\#}p<0.001$ significantly different than familiar object exploration during successful trials). All data are depicted as mean ± SEM.



High Gamma Power Between Groups, Objects, and Performance

Figure 28: Changes from baseline in high gamma power between groups, objects, and performance. Ratios depict the change in high gamma power from baseline during novel (open circles) or familiar (closed circles) object exploration in success (light shaded region) or chance (dark shaded region) trials between MD (dark blue) or sham (black) animals. Chance bouts (sham novel *n = 183;* MD novel *n = 202;* sham familiar *n = 174;* MD familiar *n = 249).* Success bouts (sham novel *n = 75;* MD novel *n = 231;* sham familiar *n = 47;* MD familiar *n = 172).* All data are depicted as mean ± SEM.



High Gamma Power Between Group and Performance (Collapsed on Objects)

Figure 29: Changes from baseline in high gamma power between groups and performance, collapsed on object. Ratios depict the change in low gamma power from baseline during successful or unsuccessful trials between MD (dark blue) or sham (black) animals. (sham chance *n = 357;* MD chance *n = 451;* sham success *n = 122;* MD success *n = 403).* (Bonferroni post-hoc comparison, ####p<0.0001, sham animals during successful trials significantly different than all other groups; ****p<0.0001, sham animals during chance trials significantly different than all other groups). All data are depicted as mean ± SEM.

Chance vs. Success	Theta	Low Gamma	High Gamma
Sham	↑Success	↑Success	↑Success
MD	-	-	-

Summary of Findings for Theta, Low Gamma, and High Gamma Power

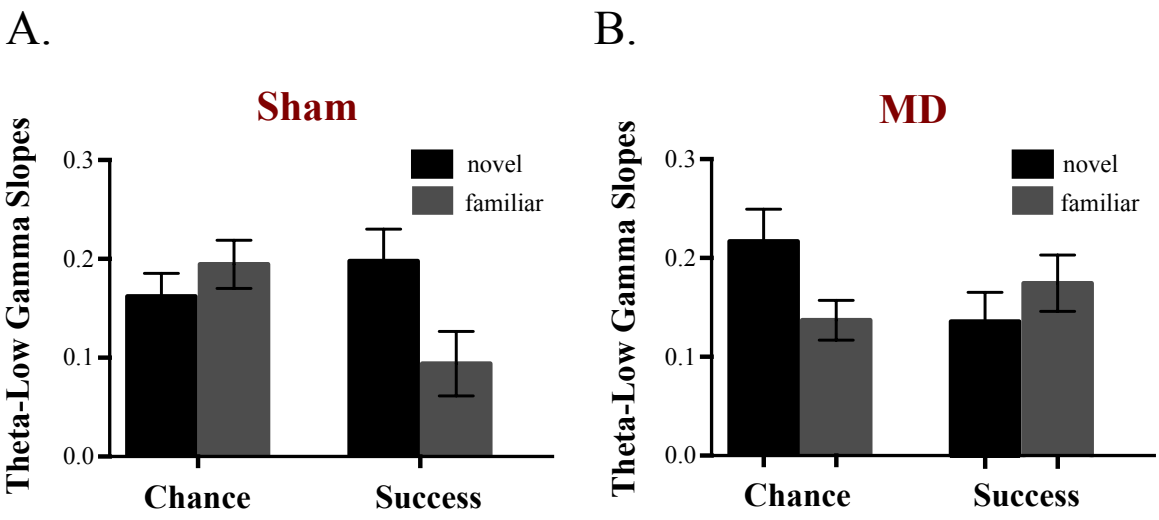
Figure 30: Summary of main findings for theta, low gamma, and high gamma power. In general, there were no changes in theta, low gamma, or high gamma power between objects or between performances in MD animals.

Analysis of Variance

Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
Theta	25.026	1	25.0259	256.81	0
Group	0.085	1	0.0855	0.88	0.3492
Object	0.221	1	0.221	2.27	0.1323
Performance	1.207	1	1.2067	12.38	0.0004
Theta*Group	0.005	1	0.0052	0.05	0.8179
Theta*Object	0.183	1	0.1833	1.88	0.1704
Theta*Performance	0.16	1	0.16	1.64	0.2003
Group*Object	0.213	1	0.2132	2.19	0.1394
Group*Performance	0.697	1	0.6969	7.15	0.0076
Object*Performance	0.253	1	0.2534	2.6	0.1071
Theta*Group*Object	0.014	1	0.0135	0.14	0.7096
Theta*Group*Performance	0.008	1	0.0084	0.09	0.7687
Theta*Object*Performance	0.005	1	0.0046	0.05	0.8286
Group*Object*Performance	0.633	1	0.6328	6.49	0.0109
Theta*Group*Object*Performance	0.938	1	0.9381	9.63	0.002
Error	128.243	1316	0.0974		
Total	167.756	1331			

Theta-Low Gamma Coupling Four-Way ANOVA Table

Figure 31: Four-way ANOVA table for theta-low gamma coupling. Theta and gamma coupling does not differ based on performance, object, or group.



Theta-Low Gamma Slopes Between Objects and Performance (Groups Separated)

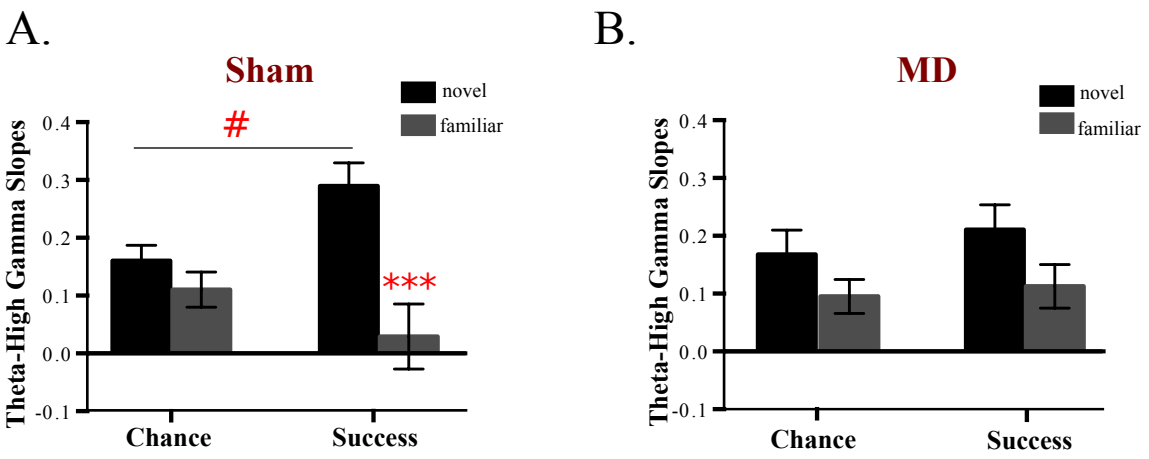
Figure 32: Theta-low gamma coupling between novel and familiar object in chance or successful trials, separated by group. Slopes from four separate regressions were extracted and performance by object comparisons were made in (A) sham and (B) MD animals. (sham novel chance *n = 182;* sham familiar chance *n = 174;* sham novel success *n = 75;* sham familiar success *n = 47); (*MD novel chance *n = 202;;* MD familiar chance *n = 249*; MD novel success *n = 231*, MD familiar success *n = 172*). All data are depicted as slope ± SEM.

Analysis of Variance

Source	Sum Sq.	d.f.	Mean Sq.	F	Prob>F
Theta	19.416	1	19.4159	112.07	0
Group	0.128	1	0.1282	0.74	0.3899
Object	3.091	1	3.0911	17.84	0
Performance	1.301	1	1.3014	7.51	0.0062
Theta*Group	0.001	1	0.0009	0.01	0.9419
Theta*Object	3.345	1	3.3446	19.3	0
Theta*Performance	0.185	1	0.1854	1.07	0.301
Group*Object	0.815	1	0.8153	4.71	0.0302
Group*Performance	3.794	1	3.7942	21.9	0
Object*Performance	1.317	1	1.3171	7.6	0.0059
Theta*Group*Object	0.283	1	0.283	1.63	0.2014
Theta*Group*Performance	0.001	1	0.0009	0.01	0.9428
Theta*Object*Performance	0.805	1	0.805	4.65	0.0313
Group*Object*Performance	0.986	1	0.9855	5.69	0.0172
Theta*Group*Object*Performance	0.492	1	0.4921	2.84	0.0922
Error	228.003	1316	0.1733		
Total	279.974	1331			

Theta-High Gamma Coupling Four-Way ANOVA Table

Figure 33: Four-way ANOVA table for theta-high gamma coupling. Theta and high gamma coupling differ based on object and performance.



Theta-High Gamma Slopes Between Objects and Performance (Groups Separated)

Figure 34: Theta-high gamma coupling between novel and familiar object in chance or successful trials, separated by group. Slopes from four separate regressions were extracted and performance by object comparisons were conducted in (A) sham and (B) MD animals. (sham novel chance *n = 182;* sham familiar chance *n = 174;* sham novel success *n = 75;* sham familiar success *n = 47); (*MD novel chance *n = 202;;* MD familiar chance *n = 249*; MD novel success *n = 231*, MD familiar success *n = 172*). (Bonferroni post-hoc comparison, $^{\#}p<0.05$, novel chance significantly different than novel success; $^{***}p<0.001$, novel significantly different that familiar in successful trial). All data are depicted as slope ± SEM.

Theta-Low Gamma

Chance vs. Success	Novel	Familiar
Sham	-	-
MD	-	-

Theta-High Gamma

Chance vs. Success	Novel	Familiar
Sham	⬆Success vs. Chance	⬇ Success vs. Novel
MD	-	-

Summary of Findings for Theta-Low Gamma and Theta-High Gamma Comodulation

Figure 35: Summary of main findings for theta-low gamma comodulation and theta-high gamma comodulation. Theta-low gamma comodulation was not different between groups performances, or objects. However, theta-high gamma comodulation was higher in sham animals when performing with the novel object during successful trials versus the familiar object and compared to chance trials. Interestingly, there were no differences in theta-high gamma comodulation in MD animals.