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The Effect of Maternal Maltreatment on the Prefrontal Cognitive Function of Juvenile Rhesus Monkeys

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An abstract of
A thesis submitted to the Faculty of the Graduate
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Abstract

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By Kevin Fomalont

Early life stress can have a major impact on the biological and behavioral development. Using a nonhuman primate model of early life stress (infant maltreatment in rhesus monkeys), offspring were cross-fostered to either mothers that spontaneously maltreat their infants or mothers that exhibit species-appropriate behaviors. Previous research has shown that early life stress has deleterious effects on executive function, response inhibition and cognitive flexibility. Therefore, the offspring were studied during the prepubertal period (20-24 months of age) on four different cognitive tasks with a main focus on prefrontal cortex-related functions: object retrieval detour, delayed non-match to sample trial unique/session unique, and object discrimination. These tasks revealed no significant differences between control and maltreated monkeys in working memory, impulsivity, cognitive flexibility, or perseveration. These results failed to demonstrate maltreatment-induced long-term deficits in prefrontal cognitive function at least during the prepubertal juvenile period.

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1. Introduction

1.1 Early Life Stress

In humans, early life stress has been defined as "the exposure to a single or multiple events during childhood that exceeds the child's coping resources and leads to prolonged phases of stress" (Pechtel & Pizzagalli, 2011). Early life stress in humans can take many forms including interpersonal loss such as parental divorce, death, or other prolonged separations. Parental maladjustment may also cause early life stress and includes parental mental illness, substance abuse, childhood maltreatment, criminality, or family violence. Parental maltreatment, such as physical or sexual abuse (Nemeroff, 2004), verbal/emotional maltreatment (Tomoda et. al, 2011), or neglect is a devastating form of early life stress for children (Green et. al, 2010). While there are many different types of childhood adversity, one very important component involves alterations in parental care. Parents are often the primary caregivers and they provide the fundamental source of physical care and social interaction for their offspring. Childhood maltreatment is not only a devastating experience for the individual, but also a significant social and health problem with high prevalence rates. Thus, in 2010, 3.3 million children were reported as victims of abuse or neglect in the United States (US Department of Health and Human Services, 2011). Socioeconomic disadvantage is the other well-studied causative factor of early life stress, and socioeconomic disadvantage is also correlated with parental maltreatment of children (Crouch et. al, 2000). Chronic stressful events during childhood can cause 'wear and tear' of physiological systems (allostatic load) (McEwen, 2007), but also of behavioral and cognitive systems through which chronic early life stress can alter normal development (Howell & Sanchez, 2011).

Early life stress can have a powerful effect on human cognitive development. For example, physical abuse during early childhood is associated with deficits in language, attention, and

memory (Chugani et. al, 2001; De Bellis et. al, 2009; Bremner et. al, 2003). While it may be possible to generally conceptualize the effects of early life stress, it may be more informative to isolate the effects of different types of early life stress in human research: different types of early life stress may cause different developmental outcomes. One study compared the differential effects of community stress and individual stress. Fishbein and colleagues (2009) found that community stressors, such as neighborhood violence, were not correlated to deficits in neurocognitive function as measured by the Tower of London task that assesses planning behavior. Individual stressors, such as physical abuse, however, were correlated to deficits in neurocognitive function, including impulsivity and cognitive flexibility. Exposure to sexual abuse, just one form of early life maltreatment, results in deficits in inhibitory control (Navalta et. al, 2006) and an increased likelihood of developing drug dependence (Harrison, Fulkerson & Beebe, 1997). The wide variety of deleterious behavioral outcomes described in these studies suggests that early life stress affects brain circuits that are involved in the formulation of complex behaviors; and more generally, that different early adverse experiences may lead to different developmental outcomes.

Early life stress disproportionately affects fronto-striatal and fronto-temporal circuits and their associated functions (Roth & Sweatt, 2011; Holmes & Wellman, 2009). A recent publication from Holmes and Wellman (2009) summarizes the relationships among chronic stress, the prefrontal cortex (PFC), and executive function:

> "A growing literature from studies in laboratory animals demonstrates that the PFC not only plays a major role in orchestrating the behavioral and systemic response to stress, but that neurons in the rodent PFC are highly sensitive to stress and undergo significant remodeling following stress exposure. These findings support the notion that stress-induced alterations in PFC function

represent a principle neural insult underlying deficits in executive function observed in stressed rodents, and the executive component of many neuropsychiatric diseases."

Studies have revealed specific associations between early life stress and executive dysfunction in adulthood (Spann et. al, 2012; Navalta et. al, 2006; Marsh et. al, 2008). Prasad and colleagues (2005) studied children who had recently been hospitalized due to physical maltreatment. The participants suffered reduced general cognitive ability and adaptability to social life. In all of the studies cited here, the participants did not suffer any chronic physical damage as a result of the maltreatment. Work from Pears and Fisher (2005) similarly indicated overall cognitive deficits in maltreated children, as well as a specific deficit in executive function. While most research does not distinguish between maltreatment by parents or by others, one recent study found a more significant effect between familial maltreatment and a deficit in executive function compared to non-familial maltreatment and a deficit in executive function (DePrince, Weinzierl & Combs, 2009). In a slightly different population of post-institutionalized children who had been exposed to a combination of maltreatment and neglect, researchers found deficits in working memory (Bos et. al, 2009; Pollak et. al, 2010), cognitive flexibility (Colvert et. al, 2008), and inhibitory control (Pollak et. al, 2010). These studies demonstrate the causative influence that early life stress has on executive functions.

In animals, early life stress has been modeled using many different methods, including those that use social stressors versus those that use physical stressors. Restraint of movement in rats is a common physical stressor that induces increased corticosterone release (Scheuer, 2010). Unpredictable shock with low-voltage electricity can also be used to produce chronic stress. These physical stressors successfully activate the hypothalamic-pituitary-adrenal (HPA) neuroendocrine

axis and result in increased corticosterone release, similarly to the stress-induced release of cortisol seen in humans. But applicability of those stressors to the most common early adverse experiences in humans is weakened by a lack of face validity. For this reason, stress researchers have moved toward the use of social stress in animal models.

Many human stressful stimuli are of a social nature, and therefore it is best to use animal models that involve exposure to an ethologically relevant social stressor. In early life, the social interaction between neonate and mother is extremely important. The newborn offspring of most mammalian species, including rats (Cromwell, 2011) and monkeys (McCormack et. al, 2006), have little social interaction with anything other than their mother. Thus, maternal separation shortly after birth produces stress in both rats (O'Mahony et. al, 2011) and rhesus monkeys (Feng et. al, 2011). When maternal care is appropriate, the monkey mother also serves as a buffer of the infant's behavioral and physiological responses to stressors, mitigating its effects. In contrast, when maternal care is not optimal, such as in the case of monkey mothers that maltreat their offspring, these mothers fail to buffer the infant's reactivity to stressors resulting in an hyper-activation of the hypothalamic-pituitary-adrenal (HPA) axis and in an increase in the offspring's stress susceptibility (Sanchez, Ladd & Plotsky, 2001; McCormack et al., 2009).

What are the mechanisms by which stress can affect cognitive functions? Chronic stress modeled by chronic restraint (McEwen, 2000) or heightened blood corticosterone (Moghaddam et. al, 1994) in rodents can cause cognitive impairment through different mechanisms, including stress-induced excessive release of glutamate leading to excitotoxic damage to the neurons. Chronic stress has been reported to cause cognitive impairment in a prefrontal-mediated task through the suppression of glutamate receptor expression. This impairment is caused by chronic stress-induced elevations in glucocorticoids (Yuen et. al, 2012), steroid hormones that can cross

the blood brain barrier and access the brain and bind to glucocorticoid receptors expressed in the prefrontal cortex and leading to downregulation of glucocorticoid receptor expression (Sanchez, 2006). Reduced hippocampal dopamine (Dronjak & Gavrilovic, 2006) and decreased presynaptic 5-HT function in the frontal cortex and hippocampus (Lapiz et. al, 2003) may also result from the stress-induced elevation of glucocorticoids. Research on the effects of chronic stress is not as well characterized as the effect of acute stress, but research on both types of stress indicates prefrontal cortex-related impairments. For example, an acute psychosocial stressor modeled by the Trier Social Stress Test reduces prefrontal cortex-mediated cognitive flexibility in humans (Plessow et. al, 2011). Because corticosteroids such as cortisol can cross the blood-brain barrier, they can modulate working memory ability in the prefrontal cortex (Henckens et. al, 2011). One potential mechanism of action is via acute glucose metabolic changes, which have been reported in the superior frontal gyrus of the prefrontal cortex as associated with increased salivary cortisol after exposure to the Trier Social Stress Test (Kern et. al, 2008). Activation of more medial portions of the prefrontal cortex was associated with lower salivary cortisol. The findings of Kern and colleagues (2008) demonstrate the relationship among stress, cortisol, metabolic changes in the prefrontal cortex and its underlying functions. Chronic stress, including social stress, can affect prefrontal cortex-mediated cognition via physiological changes. The monkey model of maltreatment in this study is a stressful experience for the infants, and our group is investigating the physiological changes it produces.

In addition to the HPA axis, there are other systems that become activated in response to stress and contribute to the already complex stress-induced behavioral changes, including the immune system. After exposure to an acute stressor such as restraint stress, blood leukocytes migrate to the skin (Dhabhar & McEwen, 1996). It has been suggested that this migration is an

evolutionary adaptation to augment immune activation in response to possible injury (Dhabhar & McEwen, 1996). This relocation is evidence of the activation of both the innate and adaptive immune systems (Dhabhar, 2002). Acute stress causes biphasic changes in the numbers of blood helper T-cells, cytotoxic T-Cells, natural killer cells, B-cells, and monocytes (Dhabhar, 2002); within an initial rise and a later drop that depends on the time course of the stressors. This rise in the number of blood leukocytes is coincident with the increased gene expression of cytokines in the blood: interleukin-1α (IL-1α), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and interferon-γ (IFN-γ) (Dhabhar, 2009). These are pro-inflammatory cytokines that have the ability to activate leukocytes and other types of immune cells. Acute stress causes proliferation and relocation of leukocytes that release pro-inflammatory cytokines that can cause physiological changes beyond the circulatory system (Dhabhar, 2009), including even the brain.

While the blood-brain barrier has been known to block the entrance of cytokines to the brain, there are at least three open routes of entry: cytokines may access the brain through the circumventricular organs, by active transport through the endothelial cells, or they may initiate a cascade at the endothelial cells that results in the production of cytokines in the brain (Raison, Capuron & Miller, 2006). Chronic early life stress is associated with the activation of the innate immune system and concomitant release of pro-inflammatory cytokines such as IL-6 in response to an acute stressor in adulthood (Carpenter et. al, 2010; Miller et. al, 2009).

Once in the brain, cytokines can mediate some of the effects of stress, by stimulating local inflammation, modulating the trafficking of both glucocorticoid receptors and serotonergic receptors and transporters (Pineda et. al, 2010) and even affecting 5HT synthesis by raphe neurons (Lowry et. al, 2007). Brambilla and colleagues (2007) found that a pro-inflammatory cytokine, IL-1, can also enhance GABAergic inhibitory tone in the raphe nucleus causing inhibition

of serotonergic neurons. Pro-inflammatory cytokine IFN-α reduces expression 5HT-$_{1B}$ receptor mRNA in the prefrontal cortex, demonstrating that cytokines can have direct effects on the serotonin system outside the raphe nucleus (Hayley, Sharf & Anisman, 2012). Our group has previously reported that maternal rejection in infant rhesus monkeys is associated with decreased 5-HIAA in the cerebrospinal fluid and with the activation of pro-inflammatory pathways in monocytes (Sanchez et. al, 2007), illustrating that inflammation is somehow linked with alterations in the brain serotonergic system in the monkey model of early life stress – the focus of these studies. It is also important to consider the effects of inflammation on the serotonin transporter, because the transporter affects the serotonin receptor's access to synaptic serotonin: "cytokines including IL-1 and tumor necrosis factor-α (TNF-α) increase the expression and activity of the serotonin transporter (SERT)" (Zhu et. al, 2005). Thus, there is solid evidence that pro-inflammatory cytokines can enter the brain and affect serotonin metabolism and transport directly or through interaction with other elements, including GABAergic neurons (Brambilla et. al, 2007) or glucocorticoid receptors (Pineda et. al, 2010).

The presence of glucocorticoids in the brain may also increase microglial release of pro-inflammatory cytokines in response to a stressor (Frank et. al, 2012). Human brain imaging during the appraisal of a stressor revealed a positive correlation between orbitofrontal cortex activation and natural killer cell proliferation, providing evidence for interaction between brain activity and the peripheral immune system (Ohira et. al, 2008). Near simultaneous activation of natural killer cells suggests the involvement of the autonomic nervous system, including the connection of the brain to the periphery via the vagus nerve (Ohira et. al, 2008). Immune activation has a direct effect on the orbitofrontal cortex, suggesting that there could be a link between inflammation and

alterations in executive function, although the Ohira group's experiment does not suggest the direction of the causation.

While there is not yet enough evidence to support the hypothesis that pro-inflammatory cytokines mediate the deficits in executive function caused by early life stress, it is known that the prefrontal cortex is particularly vulnerable to early life stress and to inflammation (Hayley, Sharf & Anisman, 2012; de Pablos et. al, 2006). Because of the strong evidence (Spann et. al, 2012; Navalta et. al, 2006; Marsh et. al, 2008) supporting a link between early life stress and impaired executive function, the anatomy, functions, and development of the prefrontal deserve more detailed discussion.

1.2 The Prefrontal Cortex

1.2.1 Prefrontal Cortex Anatomy

The subdivisions of the prefrontal cortex have been most commonly described using the cytoarchitectonic map created by Brodmann in 1909 (Rajkowska & Goldman-Rakic, 1995) based on one individual's brain. While other cytoarchitectonic maps have been created since Brodmann (Sarkissov et. al, 1955; Sanides, 1962) they are not as frequently used. Brodmann areas will be used in this thesis to distinguish the dorsolateral prefrontal cortex and the orbitofrontal cortex.

The dorsolateral region of the prefrontal cortex (DLPFC) in humans consists of Brodmann areas 9 and 46 (Rajkowska & Goldman-Rakic, 1995), and the corresponding areas 9 and 46 in monkeys have some architectonic similarities (Petrides & Pandya, 1999). The DLPFC is involved in working memory (Baddeley & Salame, 1986), the visuospatial control of actions (Hoshi, 2006), and response inhibition (Blasi et. al, 2006). The orbitofrontal regions of the prefrontal cortex (OFC) consists of Brodmann areas 10, 11, 13, and 14 (Barbas 2007; Price 2007) and is located ventral to the dorsolateral PFC. The OFC may play some role in working memory (Barbey, Koenigs

& Grafman, 2011), and is involved in response inhibition during reversal learning (Schoenebaum et. al, 2009). Working memory and response inhibition fall under the umbrella of "executive function" that will be tested in our group's monkey model of early life stress.

Cytoarchitectonic mapping can also illuminate similarities in prefrontal cortex structures across species. For example, the orbitofrontal and dorsolateral cortices of primates are considered to be homologous to the rodent prelimbic and infralimbic cortices (Balleine & O'Doherty, 2010). But there is disagreement on whether the anterior cingulate exists in rodents (Preuss, 1995). There is less controversy over prefrontal homology between humans and monkeys, as it is generally agreed that each subdivision of the prefrontal cortex that exists in humans also exists in non-human primates (Kolb, 1990; Uylings & van Eden, 1990; Petrides & Pandya, 1999). Generally, layers III, IV, and V have been successfully used to distinguish between subregions of the prefrontal cortex (Petrides & Pandya, 1999) in primates. A study of the dorsolateral prefrontal cortex of the macaque monkey demonstrated that only a portion of area 46 in the Walker (1940) map is homologous to area 46 in the Broadmann human map, because only a portion of monkey area 46 has the well-developed layer IV of the human area 46 (Petrides & Pandya, 1999). Layer IV of Broadmann area 46 is better developed than in Broadmann area 10, part of the orbitofrontal cortex (Barbas & Pandya, 1989). This difference in layer IV helps distinguish the boundary between the dorsolateral and orbitofrontal regions. Regions from the monkey map do not necessarily perfectly correspond to the regions in the human map, and homologous regions are not well represented by the numbered regions in either the Broadmann or Walker maps. Nonetheless, cytoarchitectonic differences in the prefrontal cortices of monkeys and humans are relatively minor, and lesion studies suggest that the prefrontal cortex of humans and of rhesus macaques have similar functions (Kolb, 1990; Uylings & van Eden, 1990; Petrides & Pandya, 1999)

The connectivity of a region can also reveal structural homology between species. The dorsolateral prefrontal cortex has connections with the mediodorsal thalamus (Ray & Price, 1993). It was previously thought that there was no specific subregion of the mediodorsal thalamus that had projections to the dorsolateral prefrontal cortex (Ray & Price, 1993), but recent studies have shown that the dorsal portion of the mediodorsal thalamus is preferentially connected to the dorsolateral prefrontal cortex (Ray & Price, 1993). These connections are similar in macaques and in humans, a finding that supports the validity of the rhesus macaque as a model of human brain function (Klein et. al, 2010).

The dorsolateral region also has connections with other regions in the prefrontal cortex. There are dorsolateral prefrontal connections with the orbitofrontal cortex (Moghaddam & Homayoun, 2008). It is thought that the connections within the prefrontal cortex provide additional processing power and control over executive functions, and over subcortical regions. The orbitofrontal cortex itself has strong connections to limbic regions, including the basolateral amygdala, hippocampus, and entorhinal cortex, suggesting involvement in emotional regulation (Bachevalier & Loveland, 2006). The different connectivities of the dorsolateral and of the orbitofrontal regions suggest different roles in prefrontal cortex-mediated cognitive function.

Finally, research has demonstrated that there are functional similarities in the dorsolateral prefrontal cortex of macaques and humans in cognitive monitoring (Petrides, 1996; Petrides, 2005). High-level planning and multi-tasking capacities have also been found to involve the orbitofrontal cortex of both macaques and humans (Petrides, 2005).

1.2.2 Prefrontal Cortex and Executive Function

Executive function is comprised of several interrelated cognitive processes (Ardila, 2008). Because executive function is a psychological construct, disagreement on its definition remains.

For the purpose of neuropsychological testing, it can be divided into eight subdomains: (1) Response Inhibition, (2) Shift, (3) Emotional Control, (4) Working Memory, (5) Initiate, (6) Planning/Organizing, (7) Organization of Materials, and (8) Monitor (Gioia et. al, 2010). This study will focus on working memory and response inhibition due to our group's interest in the effect of early life stress on the functioning and development of the dorsolateral and orbitofrontal cortices.

Baddeley (1986) famously described working memory as the mind's "scratch-pad." It is the type of memory that holds information for a few seconds while it is being manipulated or receiving attention. Working memory is different from relational memory, in which a long-term memory is formed as an association between two pieces of information. Working memory is for the temporary manipulation of information, while associative memory is for storage and later retrieval (O'Reilly, Braver & Cohen, 1996). Lesions of the dorsolateral prefrontal cortex in rhesus macaques produce deficits in working memory as measured by a delayed-response task (Goldman-Rakic, 1996). When lesioned monkeys perform the task without a delay and do need to utilize working memory function, there is no performance deficit (Mishkin & Pribram, 1954). The delay differentiates this task from one that would rely on striatal-mediated habitual memory. Macaques with dorsolateral prefrontal lesions performed the no-delay task successfully, because working memory function was not needed for such a task. The Mishkin and Pribram experiment demonstrated that the dorsolateral prefrontal cortex played a role in working memory.

One experiment further clarified the nature of dorsolateral working memory in an oculomotor, delayed-response task (Funahashi, Bruce & Goldman-Rakic, 1993). Monkeys were trained to remember to saccade in a certain direction after the presentation of a cue in order to receive a reward. When lesions were made in one hemisphere of the dorsolateral region, monkeys were unable to remember that the cue signaled them to saccade in the retinotopic field

contralateral to the lesioned hemisphere for reward, because of deficient working memory function. If the lesions were bilateral, the deficits occurred in all parts of the retinotopic field. With only a short delay of 1.5 seconds between the disappearance of the saccade cue and the disappearance of the fixation point for reward, the lesioned monkeys had only a small deficit in performance compared to controls. The saccade cue remained on screen 0.5 seconds, but the monkey could not receive a reward unless it made a saccade only after the fixation point disappeared. With a delay of 5 seconds between the saccade cue and the disappearance of the fixation point, the lesioned monkeys had severely impaired performance. Funahashi, Bruce, and Goldman-Rakic (1993) summarized the importance of this finding: "the behavioral deficits observed here…are caused by the disruption or elimination of a transient spatial memory trace that holds the memory of a given spatial coordinate 'on-line' to direct the response at the end of the delay." Lesion experiments and assessment with delayed-response cognitive tasks have solidified the dorsolateral prefrontal cortex as the essential region for working memory.

While the dorsolateral prefrontal cortex has garnered a lot of attention, the orbitofrontal cortex also plays a role in working memory. A study of humans with traumatic brain injury found that damage to the medial orbitofrontal cortex, but not to the lateral orbitofrontal cortex, was associated with deficits in working memory tasks (Barbey, Koenigs & Grafman, 2011). These working memory tasks were a subset of the Wechsler Adult Intelligence Scale (WAIS II), including a digital span forward test. However, a different group performed a PET scan on intact humans and found increased cerebral blood flow in the lateral orbitofrontal cortex, but not in the medial orbitofrontal cortex (Inoue et. al, 2004). The scarcity of studies in humans has left ambiguous the importance of the contribution of the orbitofrontal cortex to working memory (Barbey, Koenigs & Grafman, 2011).

Another important component of prefrontal cortex functions is the inhibitory control or suppression of prepotent behaviors. Impulsivity is the result of the failure of the prefrontal cortex to suppress the prepotent behaviors (Kim & Lee, 2011). It has been proposed that "state alteration of this circuit can contribute to adaptive coping such that response inhibition, behavioral flexibility and problem solving are affected during increasing levels of emotional stress or challenge" (Li & Sinha, 2008). That is, temporary changes in prefrontal tone can mitigate the deleterious effects on executive function caused by stress. While lesion studies have implicated the orbitofrontal cortex (Gallagher, McMahan & Schoenebaum, 1999; Roberts & Wallis, 2000), other research has identified the involvement of the dorsolateral region (Sala et. al, 2011; Stenbeis, Bernhardt & Singer, 2012), and perhaps even the entire prefrontal cortex (Roberts & Wallis, 2000) in these functions. Both the orbitofrontal cortex (Walker et. al, 2006; Man et. al, 2009) and the dorsolateral prefrontal cortex (Diamond, 1990; Jentsch et. al, 2000) are involved in the maintenance of inhibitory control over the striatum (Roitberg et. al, 2002). However there is some evidence to show that the OFC is preferentially involved in inhibitory control over the DLPFC (Wallis et. al, 2001). The orbitofrontal cortex mediates a different kind of response inhibition than the dorsolateral cortex – the inhibition of an unwanted response during a reversal. During a reversal, the contingencies of a task change and require the opposite response. The altered response through the suppression of the stereotyped response is controlled by the orbitofrontal cortex in a reversal contingency (Iversen & Mishkin, 1970). The failure of this suppression of an inappropriate response is known as perseveration (Iversen & Mishkin, 1970). Monkeys with dorsolateral prefrontal lesions performed suboptimally on the object retrieval task, in which the monkeys are required to retrieve a food reward from a transparent box with only one side open. After lesioning of the dorsolateral prefrontal cortex, infant monkeys were unable to

retrieve the food reward from the open side, without mistakenly reaching and hitting the closed side. While both dorsolateral and orbitofrontal cortices are involved in inhibitory control (Man et. al, 2009; Diamond, 1990), the orbitofrontal cortex suppresses inappropriate response specifically after a reversal of contingencies (Iversen & Mishkin, 1970).

1.2.3 Prefrontal Cortex Development

1.2.3.1 Prefrontal Cortex Anatomical Development

In order to investigate how early life stress affects the executive functions, it is necessary to understand the normative development of the prefrontal cortex. In the rhesus macaques, the first synapses in the burgeoning prefrontal cortex are observed on embryonic day 60, 3 months before birth (Bourgeois, Goldman-Rakic & Rakic, 1994). Synaptogenesis proceeds slowly for the next month, and then accelerates until 2 months after birth. From 2 months until 3 years of age (at puberty), there is a plateau in the formation of new synapses, but the number of synaptic contacts (and axons) declines until puberty (approx. 3 years of age) due to pruning, and continues to decline until 20 years of age or later, paralleled by increased myelination (Bourgeois, Goldman-Rakic & Rakic, 1994). Compared to other cortices, the prefrontal cortex is the last to develop (Huttenlocher & Dabhlokar, 1997). The long period of postnatal development of the prefrontal cortex is an important detail that suggests its vulnerability to early experience and stress; stress in the maternal maltreatment model (mostly from birth through the 3rd month of life) (Maestripieri & Carroll, 1998; McCormack et. al, 2006) occurs at a time of rapid synaptogenesis in the prefrontal cortex. Early life is a time of rapid development for the prefrontal cortex.

The development of the prefrontal cortex in humans follows a similar trajectory, with a peak in synaptic connections at 3.5 years. The time course of synaptogenesis is more compressed in macaques than in humans. In macaques, synaptogenesis is at its peak from 2 months before

birth to 2 months after birth (Bourgeois, Goldman-Rakic & Rakic, 1994), but in humans rapid synaptogenesis begins at 8 months and continues through the second year (Huttenlocher & Dabholkar, 1997). In humans, pruning of these synaptic connections begins in dorsal and parietal sections around puberty, and gradually begins moving rostrally (Paus, 2005). The dorsolateral prefrontal cortex is the last region to experience synaptic pruning in late adolescence (Marsh et. al, 2008). Myelination of neurons is thought to preserve the fidelity of the connections created through maturation in preparation for the experience of the adult environment (Paus, 2005). Myelination of the prefrontal cortex is especially notable because it continues well into adulthood (Paus, 2005).

1.2.3.2 Prefrontal Cortex Functional Development

Working memory performance of the dorsolateral region is expressed by 2-4 months of age (Goldman-Rakic, 1987; Diamond & Goldman-Rakic, 1986). Rhesus macaques can perform working memory tasks, such as the delayed-response task, that involve the dorsolateral prefrontal cortex beginning at 4 months of age. However, a lesion of the DLPFC will produce no effect until 18 months of age (Goldman-Rakic, 1987). The development of the DLPFC means that working memory may not become a mature function until 18 months, that point at which lesion working memory deficits can be observed. Humans, like rhesus macaques, are able to perform working memory tasks at a young age and gradually improve through out childhood (Davidson et. al, 2006), reflecting the trajectory of functional onset to functional maturity.

To determine the progression of working memory ability, Diamond (1990b) tested human infants and infant macaques on a delayed-response task. In the task, the experimenter would hide a desirable object (or food reward for the monkeys) in one of several wells that would be covered after placement of the object. The infant's vision of the wells would then be blocked for the

duration of the "delay." This delay provides the possibility for the infant to forget where the object had been placed. The task requires working memory ability because the infant has to keep in mind the location of the object for a short period of time without being able to see the covered wells. At the earliest age of testing for humans of 7.5 months, a delay of 2.1 seconds or more was enough to thwart the infant from correctly retrieving the object. There was gradual improvement in performance. By 12 months of age, a delay of 11.6 seconds or less could be tolerated with success. Infant monkeys showed a similar progress in performance in this delayed-response task. The monkeys were first able to physically perform the task at 3 months of age, and succeeded in retrieving a food reward with a 6-second delay or shorter. By 4 months of age, the monkeys could tolerate a 12-second delay – similar to the performance of a 12-month-old human (Diamond, 1990b). The delayed-response task demonstrated similarities in the development of working memory, but also demonstrated that humans succeed in the task at a later chronological age compared to monkeys.

Between 6 and 12 months of age, human infants make great progress in a task of response inhibition (Diamond, 1990). Using a task that is similar to the Object Retrieval Detour task, Diamond (1990) tested the ability of human infants to retrieve a toy from a transparent box with one opening. Between 6.5 months and 8 months, the infants were unable to retrieve the toy if the closed side of the box was facing them. Infants of that age were unable to inhibit the response to reach directly for the toy, instead of trying to reach a different side of the box. It was only until 9 months of age that the infants were unable to alter their reaches to access the open side of the transparent box when the closed side was directly facing them. Finally, by 11 months, the infants succeeded in retrieving the toy from an open side not facing them directly, without needing to look through the open side. Infant monkeys performing the same task, in contrast, were able to

move and look through sides of the transparent box from the earliest age tested – 1.5 months. However, the behavior of the 1.5-month-old monkeys resembled 7.5-month-old humans in that the monkeys were unable to actually retrieve a food reward if the closed side was facing them directly. By 2 months of age, the monkeys succeeded in retrieving rewards from open sides not facing them directly. Finally, by 3-4 months of age, the monkeys performed the task well, as had 11-month-old humans. As with the delayed-response task, this response inhibition task revealed that both species show gradual progress as they age but monkeys are more successful at a younger chronological age (Diamond, 1990). Knowledge of the developmental trajectory of working memory skills is crucial for this study. With knowledge of working memory development in macaques it is possible to interpret data from this study that investigates differences in executive function at 18 months, an age characterized by rapid changes.

Davidson and colleagues (2006) gave human children a battery of cognitive tests including those designed to assess working memory and response inhibition. The working memory ability to remember a number of rules for a cognitive task showed improvement up to the highest age in the study, 13 years. The youngest participants, 4 years of age, were able to inhibit their prepotent response during a trial that required a suddenly different response above the chance level. The ability to inhibit the prepotent response also increased up to the age of 13. The increased difficulty of the response inhibition task was measured by reaction time. Even with an increased requirement in the number of objects needing to be kept in memory, the increased inhibitory demand produced a larger change in reaction time. That is, increasing the inhibitory demand caused a greater increase in difficulty than increasing the number of objects held in working memory. Working memory tasks are less difficult than those that require prepotent inhibition (Davidson et. al, 2006). The Davidson research demonstrates that improvements in working

memory and response inhibition continue at least through early adolescence, tracking with the late myelination (Paus, 2005) of the prefrontal cortex.

1.3. The Rhesus Monkey Model and Maternal Maltreatment

The rhesus monkey (*Macaca mulatta*) is used particularly in research that investigates primate brain function and development. The rhesus macaque is more closely related to humans than the rodents used most commonly in biological research. Their similarity to humans in behavior and in biology makes them an optimal model for research in early life stress (Barr et. al, 2003). In the wild, rhesus macaques live in troops of dozens of individuals with a strict dominance hierarchy in which status is passed through the maternal line (Altmann, 1962; Bastian et. al, 2003). An "alpha" family of related individuals controls access to food and other resources (Altmann, 1962). When male monkeys reach maturity, they leave their birth troop to search for another troop on their own. In contrast, female monkeys remain in the same troop for a lifetime. Among species of monkeys, the rhesus macaque has the strictest dominance hierarchy and the highest rates of aggression (Bernstein & Gordon, 1974; Bernstein et. al, 1974).

Both rhesus macaques and humans are semiprecocial species (Becker et. al, 2002). Both species can themoregulate, urinate, and defecate at birth (Becker et. al, 2002). Infants of both species are vulnerable and dependent on maternal care. Rhesus macaques exhibit strong mother-infant bonds. From 3-6 months of age, rhesus macaques become more independent, but the mother strictly limits their interactions with other members of the troop. Social play develops at a young age in both species, as they slowly gain independence from their mothers (Hinde & Spencer-Booth, 1967). Two to five percent of mother rhesus macaques spontaneously abuse their offspring in the wild, at least based on prevalence rates reported in the captive populations

(Maestripieri & Carroll, 1998; Maestripieri, 2005; McCormack et. al, 2006), which is highly co-morbid with high rejection of the infant early in life and stressful for the infants (Sanchez, 2006).

As in humans, maternal maltreatment has biological and cognitive consequences in infant rhesus macaques. The maternal maltreatment triggers behavioral signs of distress (e.g., screams, tantrums), as well as HPA axis activation in infant macaques (Sanchez, 2006), suggesting this is a stressful experience for the infants. It also has long-term behavioral, neuroendocrine and neurobiological consequences (Sanchez, 2006), including blunted ACTH responses to a CRH injection, which suggests downregulation of CRH receptors in the pituitary as a consequence of chronic stress exposure (CRH overactivity) (Sanchez et. al, 2010).

There is also evidence in this rhesus model of maltreatment of long-term activation of pro-inflammatory pathways in the periphery, associated with alterations in brain serotonin systems (Sanchez et. al, 2007). The activation of p38 MAPK, a kinase in the pro-inflammatory cytokine pathway, during the juvenile period is positively correlated with the maternal rejection experienced by those infant macaques (Sanchez et. al, 2007). Early life stress may potentiate the immune system toward an inflammatory state through an elevated baseline secretion of pro-inflammatory cytokines including IL-1 and IL-6 (Leonard, 2005).

Although there is not enough evidence so far in this maltreatment model, research using other nonhuman primate models of early life stress supports the link between stress and prefrontal cortex-mediated changes in behavior (Pryce et. al, 2004). In an early deprivation (ED) model using marmosets, infants were separated from their parents every day for the first 4 weeks of life for between 30 and 120 minutes. Like the maltreated rhesus macaques, the ED marmosets had a dysregulated HPA axis. The ED marmosets had lower basal urinary cortisol levels compared to controls, suggesting hypersensitivity in glucocorticoid feedback. The marmosets were given the

same Object Retrieval Detour task (ORD) used in this study, beginning at 18 weeks of age. The ED marmosets made more impulsive reaches than the controls, suggesting disturbed response inhibition normally mediated by the dorsolateral prefrontal cortex. Additionally, the marmosets were given a visual discrimination task in which the reward contingencies were reversed after a period of time. While there was no difference in performance between control and ED marmosets on simple discrimination, ED marmosets performed more poorly than controls after the reversal. This result suggests a lack of inhibitory control normally mediated by the orbitofrontal cortex. Research from our own group demonstrated reduced prefrontal cortex white matter volume in rhesus juveniles raised in a nursery without contact with their mothers (Sanchez et al., 1998). In the same study, nursery-reared monkeys required more trials to complete an object reversal task in which reward contingencies were switched. In conclusion, there is evidence that early life stress, including maternal maltreatment and separation, can cause dysfunction in prefrontal cortex-mediated cognition.

1.4 Goals

This study investigates the effects of a form of early life stress, infant maltreatment, on cognitive function associated with the prefrontal cortex in juvenile rhesus monkeys. Previous and ongoing parallel longitudinal studies have verified that maltreatment causes behavioral, physiological and neurobiological alterations in maltreated macaques, both short- and long-term. The Object Retrieval Detour and Delayed Non-Match to Sample Session Unique Tasks were used to investigate how early life stress affected impulsivity, cognitive flexibility, perseveration, and working memory, via hypothesized alterations of the orbitofrontal cortex and dorsolateral prefrontal cortex functions.

Since our group has evidence that early life stress affects prefrontal cortex development in infant rhesus monkey exposed infant maltreatment (Howell et. al, 2011), it is hypothesized that the maltreated infants in this study will perform more poorly on the cognitive tasks than controls. The maltreated infants will make more impulsive reaches and perseverative reaches in the Object Retrieval Detour task and make more errors and require more trials to reach criterion in the Delayed Non-Match to Sample tasks compared to controls. On the other hand, it is hypothesized that there will be no difference in the number of errors or trials to criterion between the control and maltreated groups in the object discrimination task.

The increased impulsive reaches and perseverative reaches would suggest dysfunctional response inhibition mediated by the dorsolateral and orbitofrontal cortices, respectively. A larger number of errors and trials to criterion in the Delayed Non-Match to Sample Session Unique task would suggest impaired working memory mediated by the dorsolateral prefrontal cortex. Finally, the lack of a difference in performance on the object discrimination task would suggest that there is no difference in perceptual or motor functions, or motivation, between the maltreated and control groups.

2. Methods

2.1 Maternal Maltreatment

The rhesus monkeys (*Macaca mulatta)* in this study were housed at the Yerkes National Primate Research Center Field Station (Lawrenceville, GA) in three different social groups housed in outdoor/indoor compounds. There were 80-150 animals in each compound including 20-50 adult females and 2-5 unrelated adult males. The remaining animals were the infant and juvenile offspring of the adult females. Animals were occasionally and temporarily removed from group housing to perform health checks or for behavioral and physiological studies. This study focused

on a small subset of animals from a larger study that followed animals from birth until two years of age for longitudinal studies of brain, behavioral, and physiological consequences of infant maltreatment.

A total of 13 rhesus monkeys entered the study at birth and were divided into a control group of 5 animals (2 males, 3 females), and a maltreatment group of 8 animals (4 males, 4 females). The infant maltreatment inclusion and exclusion criteria followed previously published protocols (Maestripieri, 1998; Maestripieri 2005; McCormack et. al, 2006). Before the study began, mothers were identified based on prior records of maltreatment of their offspring or inability to provide typical maternal care. Observations were made from towers located above the compounds to get measures of maternal behavior since birth. If a macaque mother exhibited any of 5 abusive behaviors three times during the first 3 months after birth, the mother was assigned to the study as a "maltreating" mother. These abusive behaviors included (1) Crushing: the mother uses her hands to push the infant into the ground, (2) Dragging: the mother drags the infant along the ground, (3) Throwing: the mother tosses the infant into the air, (4) Stepping on: the mother puts her feet on the infant and presses, and (5) Rough grooming: the mother cleans the infant's hair with too much force causing distress in the infant. A second criterion for inclusion in the maltreatment group was a high rate of maternal rejection in the first 3 months of life. Maternal rejection involved the mother's prevention of the infant in contacting the mother's body, or the forced removal of the infant from her body. Mothers that physically abuse offspring also frequently reject offspring early in life (McCormack et. al, 2006; Maestripieri, 2005; Sanchez, 2006).

When two infants were born to mothers identified as potential control or maltreating, an attempt was made to cross-foster the infants within 48 hours. If the cross-foster was not

performed within 48 hours of birth, the probability of adoption success is diminished significantly (Maestripieri, 2005). The cross-foster at birth served to isolate the effects of early experiences (e.g. maternal maltreatment) on the cognitive and behavioral development of the offspring. Without the cross-foster paradigm, any changes observed in the offspring could be attributed to genetic inheritance. Cross-fostering was performed in all four combinations between maltreating mothers and control mothers. That is, an infant cross-fostered to a maltreating mother was a "maltreatment" infant, and an infant cross-fostered to a control mother was a "control" infant. For the purpose of this study, the infant's group classification was determined by the behavior of the foster mother, as described in Howell et. al, (2011).

2.2 Cognitive Testing

Beginning around 18 months of age, the juvenile offspring were studied in four different cognitive tasks selected to assess impulsivity and working memory: object retrieval detour (ORD), delayed non-match to sample trial unique (DNMS-TU), delayed non-match to sample session unique (DNMS-SU), and object discrimination. The ORD task assessed the function of the orbitofrontal prefrontal cortex that mediates inhibition of a response (Jentsch et. al, 2000). An older study found that lesions of the prefrontal cortex, including dorsolateral and orbitofrontal regions resulted in impaired inhibition of a thwarted reach by a transparent barrier (Moll & Kuypers, 1977). The failure to inhibit a behavioral response may be "due to a failure of inhibitory modulation of conditioned behavior by working memory or executive processes of the frontal cortex" (Jentsch et. al, 2000). The prefrontal cortex exerts inhibitory control over the striatum via the frontostriatal circuit as a component of its executive function (Passarotti & Pavuluri, 2011). When the prefrontal cortex does not exert inhibitory control, the behavioral outcome may be perseveration. In perserveration, a response is repeated despite an observable change in

circumstances (Passarotti & Pavuluri, 2011). In this experiment the ORD task was used to differentiate the ability of the subjects to exert inhibitory control over their responses.

The DNMS-TU task was used as a training to prepare the subjects for the DNMS-SU, and DNMS-TU is affected by lesions of the ventrolateral prefrontal cortex (Kowalska et. al, 1991). The DNMS-SU task assesses the function of the dorsolateral prefrontal cortex (Malkova et. al, 2000) that mediates working memory. Working memory, as a component of executive function, allows the holding of a piece of information in mind temporarily for the purpose of manipulation (Jeneson & Squire, 2012). This type of learning is different from hippocampal associative memory in which a piece of information is stored for the long-term (Jeneson & Squire, 2012). The DNMS-SU task was used to differentiate the ability of the subjects to manipulate information temporarily.

The object discrimination task served as a control task, because it relies on the function of the striatum, and not the prefrontal cortex (Fernandez-Ruiz et. al, 2001). The striatum encodes habitual learning unrelated to any executive function (Bachevalier, 1990). The purpose of the object discrimination task in these studies was to rule out that any impairment detected on the prefrontal tasks are related to a more generalized cognitive impairment due to visual, perceptual, motor or motivational problems.

Equipment:

Prior to each task, the monkey was removed from group housing and transported to a testing room where it was placed in a modified cage with bars that allow the monkey to reach through and manipulate objects as intended. Testing occurred in a sound-attenuated room with a noise generator to mask external noises that could distract the animals' performance. The cage was rolled into the Wisconsin General Testing Apparatus (WGTA), which provides the support for a tray and a set of 2 sliding doors that can be raised and lowered to begin and end a trial,

respectively. The WGTA is commonly used for cognitive testing in rhesus monkeys and provides a controlled environment for a monkey to interact with objects (Davenport, Chamove & Harlow, 1970; Machado & Bachevalier, 2007; Rudebeck & Murray, 2011). Stimuli used will be described separately for each task below and food rewards included small candies and pieces of fruit tailored to the preference of the animals. The order of task presentation followed the sequence in which they are described below.

Object Retrieval/Detour (ORD) task:

In the ORD task (Jentsch et. al, 2000), a transparent box with one open side was screwed into the tray so that it cannot be moved. Before beginning the ORD task, the monkeys undergo shaping training. Food rewards were placed on and around the transparent box and the box opening faced the monkey to provide easy access to the food rewards. The door of the WGTA was raised and the monkey is given 3 minutes to retrieve all of the food rewards. After all the rewards had been retrieved, or after 3 minutes, the door is lowered. This type of habituation trial was repeated 5 consecutive times daily for as many days as it took for the monkey to quickly and confidently remove all the candy rewards. The number of habituation trials was recorded to examine potential differences between control and maltreated animals in the time it took to get them to retrieve the rewards proficiently due to differences in fear/anxiety or motivation, for example.

After the shaping phase had been completed, the monkey was allowed to start the ORD task. The ORD task involved 15-21 trials daily for 7 days. The monkey was allowed 3 minutes and an unlimited number of reaches to retrieve a food reward that had been placed inside the box. On Day 1 trials, a reward was placed on the edge of the open side of the box that faces the money (these are “easy” trials). On Days 2-4 the location of the box, the orientation of the box, and the

location of the candy reward were altered between trials. The orientation of the box could change by 90° or 180°. The box remained at the same distance from the monkey but can be moved to the left or right. The open side of the box could be pointed to face left, right, or toward the monkey. The food reward could be placed right at the opening of the box, 1/4 of the way inside, halfway inside, or 3/4 of the way inside. On days 5-7, the food reward was placed inside the box, and the box was pointed to face left or right. Several trials in a row maintained the orientation and location of the food reward constant. On three different occasions each day, the streak of repetitive trials was broken by a change in orientation of the box by 180°. If the monkey lost interest in the task, the daily session was stopped and the animal was allowed to finish the day's trials another day, or was given shaping training until it retrieved the candy rewards efficiently again.

The trials were divided according to the difficulty to retrieve the reward. Trials in which the open face of the box was directed toward the monkey and trials in which the reward was protruding from the opening of the box, rendering it directly visible, were defined as "Easy" trials. "Difficult" trials were defined as trials in which the opening of the box was facing towards the left or right and followed a trial where the opening of the box was directed in the opposite direction (e.g., left-to-right switch of the opening of the box). Some trials that satisfied neither criterion were scored as "Moderate" (i.e. when the open side has moved 90° or not at all, but is not directly facing the monkey). The trial difficulty becomes important when analyzing the reaches made to retrieve rewards.

Delayed Nonmatching-to-sample-Trial Unique (DNMS-TU) and DNMS-Session Unique (DNMS-SU):

After completing the ORD task, animals were first trained on the DNMS-trial-unique task so that they acquired the non-matching rule, i.e. to avoid the familiar object and select the new one

on any given trial. The testing tray for this task contains three recessed food wells (5cm in diameter and 20cm away from the monkey) spaced 10cm apart that could hold small food rewards.

The objects were 360 common household items that vary in shape, color and texture and were not easily destroyed. Objects were placed over the wells to disguise the food reward located within the wells.

During shaping training rewards were placed inside the wells until the subject retrieved them consistently. Then an object was introduced, placed near a well baited with a candy reward. If the monkey successfully retrieved the reward, in future trials the object was gradually moved to cover a larger percentage of the well. In the most difficult phase of the training the object covered the entire well so that the candy reward was not visible to the monkey. The monkey learned to displace the object and retrieve the food reward. The DNMS-TU task began when the monkey consistently displaced objects quickly and efficiently.

In the DNMS-TU task, two different objects were presented per trial, for 30 trials per day. Each trial consisted of two phases, a familiarization phase and a choice phase. During the familiarization phase, a novel object was placed over the middle well covering a food reward. The door was raised and the monkey was allowed to retrieve the reward. There was a 10-s delay after which the choice phase was presented. In this phase, the object previously seen by the monkey was placed over an empty well – either the left or the right well and a novel object was placed on the opposite well and cover a candy reward. In order to retrieve a reward, the subject must displace the novel object. The location of the object was guided by a predetermined pseudorandom order. If the monkey displaced the familiar object, the door was immediately lowered and no food reward was retrieved. After a 30-s intertrial interval, the next trial was

presented in exactly the same way but using two new objects. The monkey was given 30 trials of DNMS-TU each day. The criterion was reached for the DNMS-TU task when the monkey correctly displaced the novel object in 90 out of 100 consecutive trials. After having acquired the non-matching rule, i.e. avoiding responding to an object that had been seen few seconds earlier in favor of a new one. The monkey was transferred to the DNMS session unique.

The DNMS-SU (Heuer & Bachevalier, 2011) was administered in a similar way to the DNMS-TU, but only 2 objects, different from those used in the DNMS-TU, were used for the 30 daily trials. Because the objects were re-used from trial to trial, the animal had to avoid responding to an object it had seen most recently (that is, during the familiarization) and had to select the object it had seen earlier (i.e. in previous trials). So the task changes from a measure of recognition memory to a measure of recency working memory.

As for the DNMS-TU, during the familiarization phase, one of the objects was placed over the center well over the food reward. After the monkey retrieved the reward, there was a 5-s delay during which the view of the testing tray was obstructed by a screen. For the choice test, the sample object now unbaited was presented together with the other baited object with both objects positioned over the lateral wells of the test tray, with the position of the objects (left versus right) pseudorandomly varied to preclude the use of a spatial strategy. Training continued in this way for 30 trials presented at 30-sec intervals and both objects served as the sample or the choice in a random order. Thus, starting with the second trial and for all remaining daily trials, both objects had been seen and baited such that successful performance required the animal to remember the object seen during the sample phase of a given trial (i.e. the object he had seen the most recently). The following day a new pair of objects was selected for the 30 daily trials and so on for all subsequent testing days. Learning criterion was set at 27 correct choices (90%) or better on one

day followed the next day by 24 correct choices (80%) or better. Training was discontinued after a maximum of 1000 trials.

Object Discrimination task:

In the object discrimination task (Fernandez-Ruiz et. al, 2001), two entirely different objects were used. In the original trial, the two objects were placed over the right and left well, and both wells had food rewards. Whichever object the monkey chose first was designated as the rewarded object for the rest of the trials that day. On the remaining trials, the baited object and unbaited object were placed over either the left or right well following a pseudorandom order. 30 trials daily were given daily at 30-s intertribal intervals. Criterion was reached when the monkey correctly selects the rewarded object 27 out of 30 trials for two days in a row.

2.3 Coding Procedures

All ORD task sessions were recorded by video camera. During testing, the experimenter recorded the duration of each trial and whether the monkey successfully retrieved the treat. The video was analyzed by a coder blind to experimental group and trained by a collaborating laboratory that specializes in cognitive testing of rhesus macaques at the Yerkes National Primate Research Center. The coder recorded all the reaches made by the monkey in the attempt to retrieve the food reward from the transparent box. A “Reach” was coded when the animal’s arm moves out towards the transparent box and animal reaches directly and successfully towards the treat. A “Barrier” reach was recorded when the animal attempted to retrieve the reward using a close wall of the transparent box. If after a “Barrier” reach, the animal continued (perseverated) in pushing the closed wall of the box in consecutive trials, these reaches were defined as Global Perseverative Reaches. In Days 5-7, in which the opening of the box was presented in the same side for few trials (i.e. Left, Left, Left) and then switched to the opposite side (Right), a “Reversal

perseverative" was scored when the animal failed to switch its reach from the left to the right side. Any other reach that involved a movement through the bars of the cage, but did not hit a closed side of the transparent box, was a "miscellaneous" reach.

In the DNMS-TU, DNMS-SU, and in the object discrimination tasks, the experimenter recorded correct or incorrect responses per trial. When the monkey displaced the object covering a reward, the trial was labeled as "correct." Conversely, if the monkey displaced the object covering the empty well, that trial was marked as "incorrect." Video footage was not collected during the DNMS tasks or the object discrimination task. Number of errors committed and number of trials completed prior to criterion performance were used to measure learning performance.

2.4 Statistics

To compare cognitive performance between the groups of maltreated and control juvenile macaques, Student's t-tests were used, except for variables that were not normally distributed, where a non-parametric Mann-Whitney test was used to compare both groups of animals. The number of habituation or shaping days before the ORD and DNMS-TU tasks was also compared between the two groups. For the ORD task the number of perseverative, barrier, reversal, and total reaches (both overall and per trial difficulty -easy, moderate, difficult-) were compared between the maltreated and control groups. For the DNMS-SU, DNMS-TU, and object discrimination tasks, comparisons were made between the number of trials to criterion and error to criterion between the control and maltreatment groups. Significance level was set at $p<0.05$. Finally, a Spearman Correlation was conducted to compare the rates of abuse per hour and rejection to the number of perseverative reaches in the ORD task.

3. Results

3.1 Object Retrieval Detour

As described in the methods, the monkeys were given habituation training before beginning the ORD task. The numbers of days of habituation training were tallied for each monkey to analyze differences between the control and the maltreatment groups. Because the number of the habituation training days was not a normally distributed variable, a Mann-Whitney U Test was carried out to determine the significance of the difference. There was no statistically significant difference in the mean number of habituation days between the control group (6.2±1.8 days; 1.6 - mean±standard error of the mean (SEM) and the maltreatment group (3.4±0.4 days; ($U=28.5$, $p=0.22$) (Figure 1).

The total number of reaches made by each monkey during the seven days of ORD testing was also calculated. There was no difference in mean reaches made during ORD between the control group and the maltreatment group across all days and trial types [$t(12) = 0.7$, $p=0.95$] (Figure 2).

Barrier reaches are those reaches that come into contact with a closed side of the transparent ORD box. There was no difference in mean barrier reaches between the control group and the maltreatment group [$t(12) = 0.48$, $p=0.64$] (Figure 3). Global perseverative reaches are those that contact the same closed side as the previous reach had. In a reversal perseverative reach the monkey reaches to the closed side after a 180° change in orientation of the transparent box. The total number of perseverative reaches is the total of the global perseverative reaches and the reversal perseverative reaches. There was no difference in mean global perseverative reaches, [$t(12) = 0.25$, $p=0.81$] (Figure 4), in mean reversal perseverative reaches[$t(12) = 1.4$, $p=0.18$]

(Figure 5), or in overall perseverative reaches between the control and maltreatment groups [t(12) = 0.48, p=0.64] (Figure 6).

When the trials are divided into easy, moderate, and difficult, comparisons can be made between the performance of the control group and the maltreatment group. Reversal perseverative reaches only occur during difficult trials, and are shown separately in Figure 5. There was no significant difference in the mean number of total reaches [t(12) = 0.28, p=0.78] (Figure 7) or barrier reaches [t(12) = 0.72, p=0.40] (Figure 8) during easy trials in the control and maltreatment groups. There were too few global perseverative reaches during easy trials to permit analysis. Only four instances of global perseverative reaches were recorded in total for both groups combined. There was no significant difference in the mean number of total reaches [t(12) = 0.39, p=0.70] (Figure 9), barrier reaches [t(12) = 0.20, p=0.85] (Figure 10), or global perseverative reaches [t(12) = 0.37, p=0.72] (Figure 11) during moderate trials in the control and maltreatment groups. Finally, there was no difference in the mean number of total reaches [t(12) = 0.02, p=0.99] (Figure 12), barrier reaches [t(12) = 0.09, p=0.93] (Figure 13), or global perseverative reaches [t(12) = 0.70, p=0.50] (Figure 14) during difficult trials in the control and maltreatment groups. Finally, there was no significant correlation between the rates of abuse per hour and the number of perseverative reaches made during the ORD task (p=0.147) (Figure 15).

3.2 Delayed Non-Match to Sample (DNMS)

Just like for the ORD task, the group differences in the days of shaping training before starting the DNMS-TU task were examined. There was no difference between the control (4.0±0.70 days) and maltreatment (3.0±0.38 days) groups in the number of needed shaping days [t(12) = 1.4, p=0.20] (Figure 16).

There was no difference in the mean number of errors to criterion [t(12) = 0.44, p=0.67] (Figure 17), or in the mean number of trials to criterion [t(12) = 0.81, p=0.44] (Figure 18) between the control and maltreatment groups in the DNMS-Trial Unique version.

There was no difference in the mean number of errors to criterion [t(12) = 0.66, p=0.53] (Figure 19), or in the mean number of trials to criterion [t(12) = 0.49, p=0.64] (Figure 20) between two groups in the DNMS-Session Unique version either.

3.3 Object Discrimination

There was no difference in performance between groups in the object discrimination task (which was administered to rule out that any differences in the cognitive tasks above were due to overall cognitive issues related with visual processing, motivation, etc). There was no difference in the mean number of errors to criterion [t(12) = 0.45, p=0.66] (Figure 21), or in the mean number of trials to criterion [t(12) = 1.9, p=0.08] (Figure 22) between the control and maltreatment groups.

4. Discussion

The results from these studies demonstrated no significant impairment in inhibitory control of behavior or working memory of maltreated juvenile rhesus monkeys, in comparison to controls, at least in the cognitive tasks used. Although there is evidence from human studies that early life stress has a deleterious effect on working memory (Bos et. al, 2009; Pollak et. al, 2010) and inhibitory control (Pollak et. al, 2010), as well as from cognitive studies of nonhuman primate models of early life stress (Sanchez, 2006; McCrory & Viding, 2010; Pryce et. al, 2004), and from maternal separation experiments in rats (Frankola et. al, 2010; Mehta & Schmauss, 2011), the studies presented here showed no evidence of such effects.

However, there are some differences between these studies and this study of maternal maltreatment of infant monkeys. Bos and colleagues (2009) and Pollak and colleagues (2010) studied children who were institutionalized in group foster care and measures of executive function were not taken until 8 years of age. The institutionalized children did not have parents; only caretakers and perhaps their circumstances are most similar to that of "peer-reared" monkeys. Peer-rearing tends to produce a more severe behavior phenotype than infant maltreatment (Feng et. al, 2011). The Bos study tested executive function slightly later in development than the maltreated monkeys of this study were tested, leaving open the possibility that any deficiencies in executive function might appear later in maltreated monkeys.

In the study from Pryce and colleagues (2004), marmosets were separated from their mothers every day for the first 4 weeks of life for the duration of 30-90 minutes. This deprivation of maternal care is different from the maternal maltreatment experienced by the infant monkeys in this study and may have produced a different cognitive outcome. The deprivation started and ended much sooner than the maternal maltreatment, which generally begins to fade only after the third month of life (Sanchez, 2006). The stress produced by the deprivation occurred at an earlier age in the Pryce study and was relegated during the time of rapid synapse formation. Our group of infant monkeys was exposed to maternal maltreatment during the time of rapid synapse development into the period when period of slowed synaptic proliferation (Bourgeois, Goldman-Rakic & Rakic, 1994). Since the deprivation from the Pryce study was concentrated during rapid synaptic development, the deprivation might have made a more severe impact than the maltreatment that occurred during stagnation in synaptic proliferation. Synaptic pruning proceeds rapidly during the second half of the first year (Rakic et. al, 1983), while maternal maltreatment is waning. Because rapid synaptic pruning is not occurring simultaneously with the

period of most frequent maternal maltreatment, it likely does not account for any differences in executing functioning later in life.

In a study by Mehta and Schmauss (2011), different strains of rodents were exposed to infant maternal separation as a form of early life stress. The stress-resilient strain (C57Bl/6) and the stress-susceptible strain (Balb/c) were separated from their mothers for 3 hours daily from post-natal day (PND) 2 to PND 15. The working memory task training began on PND 16. The task used to evaluate working memory involved retrieval of a reward from the arm of a T-maze after a delay. The Balb/c rats performed the working memory task less successfully than the C57Bl/6 rats, suggesting perhaps that genetic susceptibility plays a major role in the effect of early life stress on working memory ability. Our groups of maltreated monkeys were not genotyped and no individual genotypic differences in stress susceptibility were determined.

Frankola and colleagues (2009) also exposed rats to an early-life maternal separation paradigm and then evaluated working memory using a variation of the water maze task. In this study, the rats were also separated from their mothers daily from PND 2-15, but only for a shorter 15 minutes. The study demonstrated that males showed impairments in working memory, while females did not. Sex differences in working memory were not analyzed in our groups, because there were too few individuals for statistical comparison. Another rodent study demonstrated that males were preferentially vulnerable to early life stress and exhibited altered prefrontal cortex development (van Hasselt et. al, 2012).

There are several further possible explanations for these findings, including the small sample size and the immaturity of the neurobiological systems and cognitive functions studied during the juvenile period (Hoftman & Lewis, 2011; Mandel & Ward, 2011). Thus, it is possible that differences in the cognitive functions tested emerge at later ages or with bigger samples sizes.

Nonetheless, studies from rats, monkeys, and humans have demonstrated that minor differences in the timing and type of early life stress can have drastic consequences for executive dysfunction later in life.

4.1 Object-Retrieval Detour

There was no significant difference in the number of habituation days needed to begin the ORD task in the control or maltreatment groups. For these juvenile rhesus macaques, this was their first exposure to the Wisconsin General Testing Apparatus (WGTA). Having been raised in a large social group of monkeys, and rarely exposed to a different environment, they were naturally frightened by their introduction to the WGTA. In general, it took an average of a couple days of exposure to the WGTA for subjects to make their first reach to retrieve a food reward. The habituation stage ended when the monkey retrieved all the food rewards without hesitation. As such, the analysis of number of habituation days that took each subject to retrieve food rewards was an attempt to examine whether the increased emotional reactivity reported in this animal model of maltreatment (e.g. McCormack et al, 2006; McCormack et al., 2009) potentially interfered with measures of cognitive performance. However, the lack of group differences in the habituation length suggests that there was no different degree of emotional reactivity to the testing procedures between controls and maltreated animals that could have differentially interfered with cognitive testing.

There was no difference in the number of global perseverative reaches or reversal perseverative reaches between the control and maltreatment groups. In a global perseverative reach, the monkey reached toward the same, closed side of the transparent box as it had in the previous reach. This perseverative reach reflected impulsivity, or lack of inhibitory control of behavior or lack of cognitive flexibility because the monkey failed to change the prepotent

response in the context of a new situation (Hauser, 1999; Aron, 2007). In a reversal perseverative reach the monkey reached to the side that had been open for reward retrieval during the previous trial. The reversal perseverative reach is another example of the reliance on a previous type of movement to yield reward. Weakened prefrontal function is associated with perseveration (Jentsch et. al, 2000). The lack of group differences suggests that infant maltreatment did not affect impulsivity or cognitive flexibility, at least during the juvenile (pre-pubertal) period studied.

There was no significant difference in the mean number of total reaches and barrier reaches between the control and maltreatment groups. If one of the groups needed more reaches to retrieve food rewards, then that group was less successful in performing during the ORD task. But a larger number of reaches does not necessarily signify greater impulsivity. There was also no significant difference in the number of reaches at any level of difficulty between the two groups. Early life stress may be a subtle insult when compared to treatment with MPTP (Taylor et. al, 1990) or phencyclidine (Jentsch et. al, 2000), substances that were introduced as the independent variable in other experiments using the ORD task.

The lack of effects of maternal maltreatment on the cognitive functions measured by the ORD is puzzling, given the strong consequences reported for social and emotional behavior, and other physiological, immune and neurobiological functions (McCormack et al., 2006; Maestripieri et al., 2006; Sanchez et al., 2007; Sanchez, 2006). It is possible that the effects of maternal maltreatment on prefrontal cortex function are too subtle to be detected by the ORD task, at least at this age. A different study tested control adult macaques for executive function using the ORD task, and demonstrated that they made on average 46 barrier reaches over the 7-day testing period. The control and maltreatment groups from our study made 63 and 71 barrier reaches on average, respectively (Figure 3). Since the monkeys of our maltreatment study seemed to make

more barrier reaches, it is likely that they would improve on the ORD task as they aged. Perhaps if the monkeys from our group's study were tested for executive function at a later age, the differences between the maltreatment and control groups would be observable.

Finally, there was no correlation between the abuse rates per hour and the number of perseverative reaches made during the ORD task (Figure 15). Our group has not yet found evidence that individual differences in early life maltreatment can better predict deficiencies in cognitive function in later life than group differences.

4.2 Delayed Non-Match to Sample

There was no difference in the number of shaping days between the control and maltreatment groups. Just like the habituation days for the ORD task, the lack of difference suggests no effects on basic learning/memory processes (e.g. treat permanency once this is covered by an object), and that any maltreatment-related underlying differences in emotional reactivity, fear or anxiety were not apparent in the WGTA context.

Previous work has suggested that the DNMS-TU is affected by lesions of the ventrolateral prefrontal cortex (Kowalska et. al, 1991). Since no significant difference was found in DNMS-TU, damage to the ventrolateral cortex could not be expected.

In the Delayed Non-Match to Sample Session-Unique (DNMS-SU) task, the same objects were used in all the trials of a single daily session. The monkey again must shift away from the previously rewarded object to retrieve a food reward. This task is more difficult, because the monkey must learn only to remember what happened in the first stage of the current trial, while forgetting all the interfering trials performed earlier in the session. In the DNMS-SU task there was no significant difference in the number of errors to criterion or number of trials to criterion. In experiments on rhesus macaques, bilateral lesions of the DLPFC did not impair working memory

up to the age of 16 months. It is only at 19 months of age that a DLPFC lesion begins to affect working memory performance (Alexander & Goldman, 1978; Hoftman & Lewis, 2011). In this study, monkeys began the DNMS tasks around 18 months of age, and completed them around 24 months of age. It is possible that these monkeys would begin to show severe deficits in working memory if testing were performed later in development. One study used the DNMS-SU task on adult macaques that given hippocampal lesions and to macaques that were left intact (Heuer & Bachevalier, 2011). The two control macaques in the study reached criterion after only 30 trials. Every monkey except 2, of the 12 lesioned monkeys, reached criterion in less than 250 trials. In contrast, the control and maltreatment groups of our group's study reached criterion in 328 and 280 trials, respectively (Figure 17). This suggests that the monkeys exposed to maternal maltreatment in this our group's study had not reached their full potential performance. If we had allowed the maltreated monkeys to age, the differences in performance on the DNMS-SU task between the control and maltreated groups might have become apparent.

Since there were no differences between the control and maltreatment groups in either of the DNMS tasks or the ORD task, it is necessary to consider the possibility that maternal maltreatment does not have an effect on the cognitive functions studied.

4.3 Object Discrimination

There was no difference in the number of errors to criterion or trials to criterion between the control and maltreatment groups in the object discrimination task. The object discrimination task served as control task to the ORD and DNMS tasks. A lesion to the orbitofrontal cortex does not affect performance on the object discrimination task (Kowalska, Bachevalier, & Mishkin, 1991). A lesion to the ventromedial prefrontal cortex, but not the dorsolateral prefrontal cortex, affects performance on the object discrimination task (Bachevalier & Mishkin, 1986). In the object

discrimination task, the monkey learns to make an association between one object and a food reward regardless of spatial location. The other object in the task is never rewarded. This habitual learning involves neither the DLPFC, nor the OFC. The striatum mediates this habitual learning (Bachevalier, 1990). Since there was no difference in performance on the object discrimination task between the two groups, any differences in performance on other tasks would not likely be due to dysfunction of the striatum. Nor could visual or motivational problems explain any differences on other tasks.

4.4 Implications

Since there were no differences between the control and maltreatment groups found on any of the tasks, the results suggest that the early adverse experience did not affect the cognitive functions examined, at least during the juvenile age. However, it is possible that group differences emerge at later ages (when the controls reach mature performance in the tasks), and/or with bigger sample sizes. It is widely known that childhood maltreatment in humans has a deleterious effect on cognitive function of the offspring (Chugani et. al, 2001; De Bellis et. al, 2009; Bremner et. al, 2003) and on their mental health in adulthood (McCrory, De Brito & Viding, 2012). The cognitive measures in studies by the Chugani group and the De Bellis groups were taken in middle childhood; participants in each study had an average age of 8 years and 9 years, respectively. The stressors occurred any time before the study. The participants in the study from the Bremner group (2003) were all female adults, and the sexual abuse occurred before age 13. Again, this shows that much of the supporting human literature performed the cognitive testing at a later developmental stage than in our group's study of infant maltreatment.

With regard to human anatomy, self-reported stress over the lifespan was correlated with decreased prefrontal cortex volume and poorer executive function (Hanson et. al, 2012). Although

individual characteristics can increase the vulnerability (or resilience) to early life stress resulting in different biological and cognitive outcomes (Champagne, 2010; Claessens et. al, 2011) so that, for example, children with inhibited temperament combined with early life stress are more likely to develop anxiety or depression than children with a non-inhibited temperament (Lewis & Olsson, 2011), and children with higher cortisol responses to bullying had higher intensity of depressive symptoms later in life (Rudolph, Troop-Gordon & Granger, 2010), in the current studies we controlled for important variables that could contribute to differential vulnerability to early life stress, such as 5HTT polymorphisms, maternal social status, biological mother caregiving, etc. Future studies from our group may have large sample sizes and the capability to make comparisons between those factors.

Myelination of the prefrontal cortex continues into adulthood (Tsujimoto, 2008). Since other studies have demonstrated the mature macaques perform better on the ORD and DNMS-SU tasks, it is possible that this improved performance has something to do with the late myelination of the prefrontal cortex. Although it may just as likely the DNMS-SU and ORD tasks were unable to detect subtle differences between the control and maltreatment groups. Late adolescence and early adulthood is a time when humans are particularly vulnerable to neuropsychiatric disorders (Freedman & Brown, 2011). Schizophrenia, for example, is most likely to appear in late adolescence and involves symptoms of executive dysfunction (Freedman & Brown, 2011). In fact, early life stress is associated with the development of schizophrenia later in life (Lim, Chong & Keefe, 2009). Perhaps deficits in working memory and response inhibition in response to early life stress are too subtle for detection, or maybe the deficits are only apparent in late adolescence or early adulthood.

4.5 Future Directions and Conclusions

Other behaviors including social play, aggression, or solitary behavior seem to be more sensitive to maltreatment than impulsivity or executive function, at least based on the small sample sizes used for the subset of animals included in the cognitive tests. In the future computer screen tasks could be used on the maltreated infants at a relatively immature 18 months of age. If no humans are needed in the testing room for computer screen test, the juvenile macaques may complete these tasks more willingly. This efficiency would increase our sample size and prevent juveniles from failing to complete the tasks. It could also be useful to test the maltreated macaques only once they have reached maturity at 3 years of age.

Future studies could also include a battery of physiological measures to clarify the mechanisms by which early life stress results in executive dysfunction. The measurement of inflammatory cytokines or proliferation of peripheral blood mononuclear cells would provide an immune profile of the infants exposed to early life stress. This combined with the already planned measurements of blood cortisol, and serotonin metabolite concentration in cerebrospinal fluid will create a comprehensive understanding of effects of early life stress on neuroendocrine, immune and neurobiological development of primates. While the cognitive testing revealed no significant differences between the control and maltreatment groups, there is an opportunity for future endeavors to involve cognitive testing once the animals reach maturity and its relationship with different aspects of the behavior and physiology of early life stress.

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Figures

Figure 1. There is no significant difference in the mean number of ORD habituation days in the control and maltreatment groups. Graphs represent Mean±standard error of the mean (SEM); number inside graphs represent Mean.

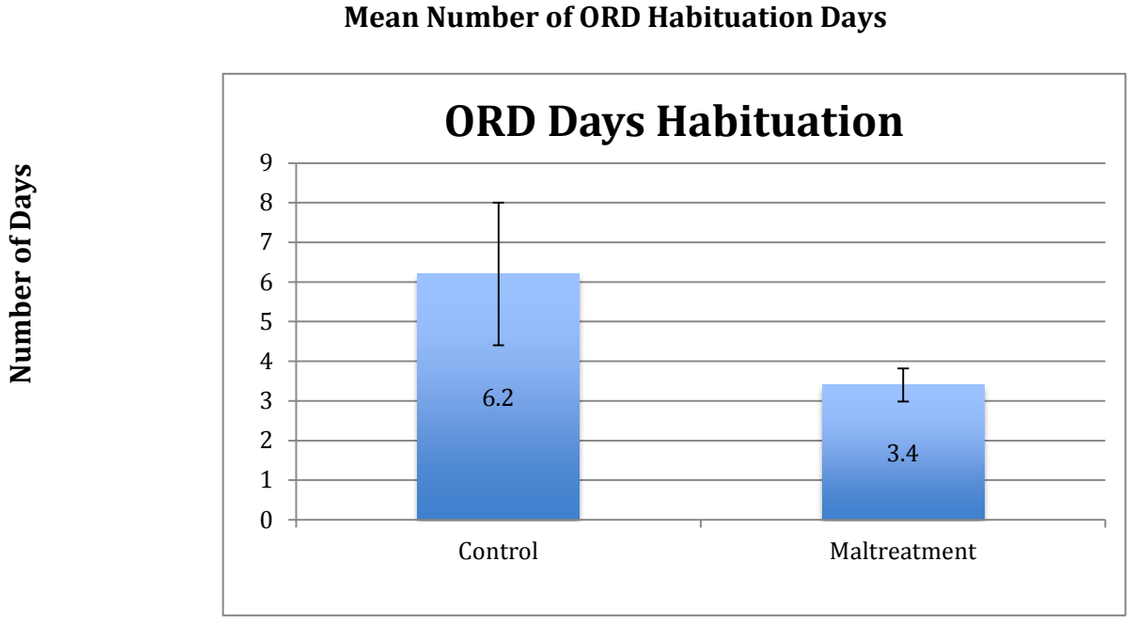

Figure 2. There is no significant difference in the mean number of reaches made during the ORD Task between the control group and the maltreatment group.

Mean Total Reaches during ORD Task in Control and Maltreatment Groups

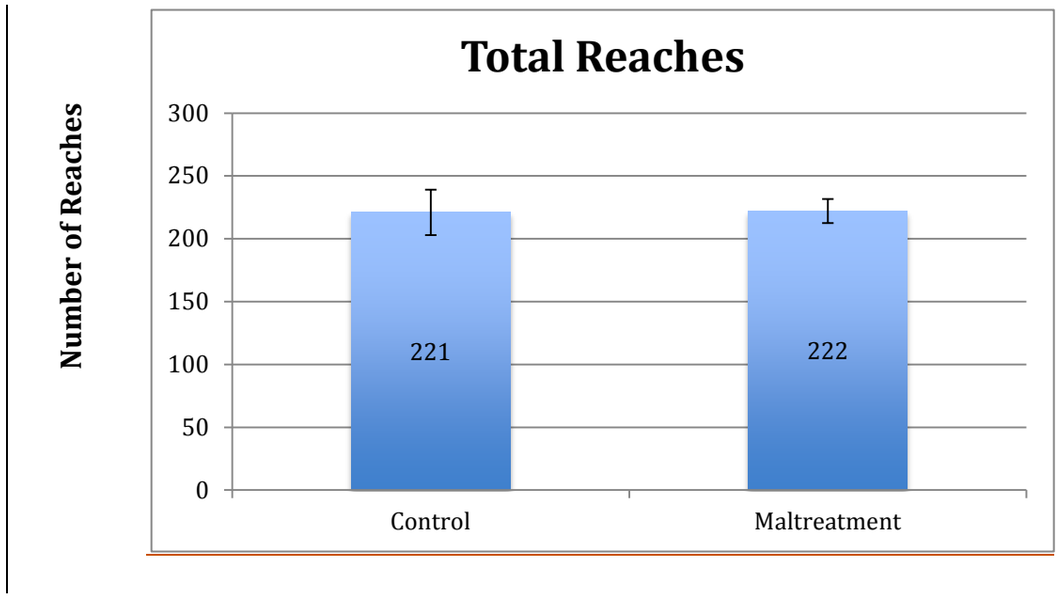

Figure 3. There is no significant difference in the mean number of barrier reaches made during the ORD Task between the control group and the maltreatment group.

Mean Barrier Reaches during ORD Task in Control and Maltreatment Groups

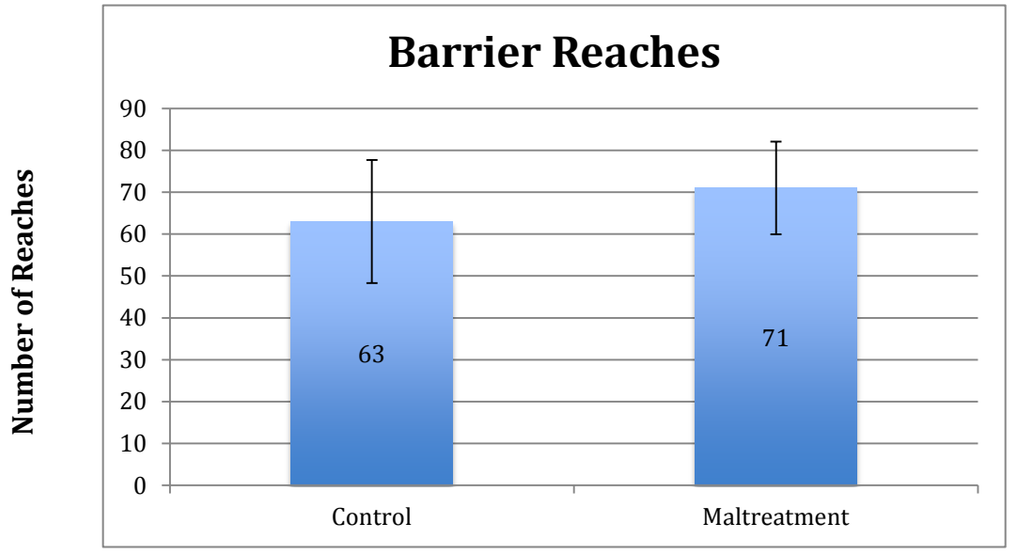

Figure 4. There is no significant difference in the mean number of global perseverative reaches made during the ORD Task between the control group and the maltreatment group.

Mean Global Perseverative Reaches during ORD Task in Control and Maltreatment Groups

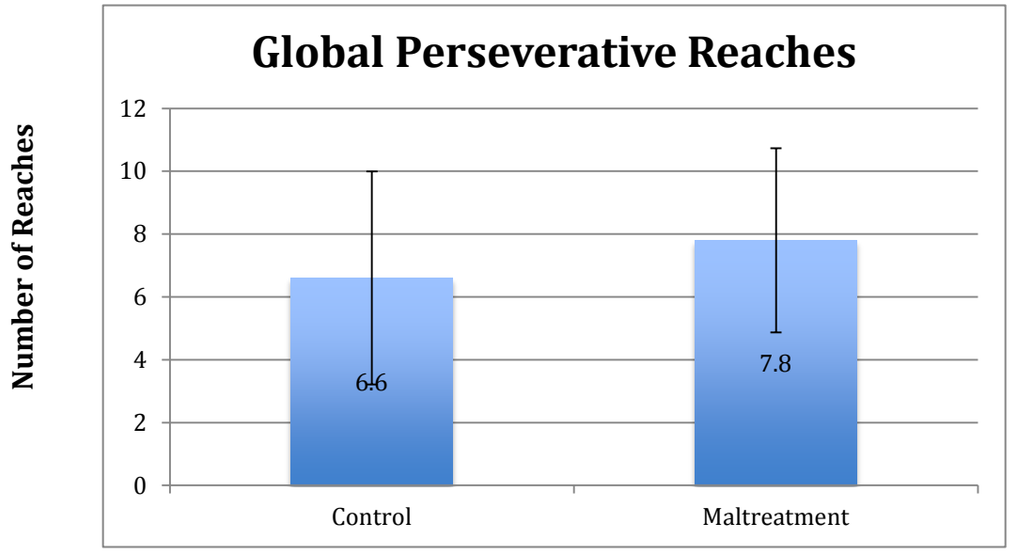

Figure 5. There is no significant difference in the mean number of reversal perseverative reaches made during the ORD Task between the control group and the maltreatment group.

Mean Reversal Perseverative Reaches during ORD Task in Control and Maltreatment Groups

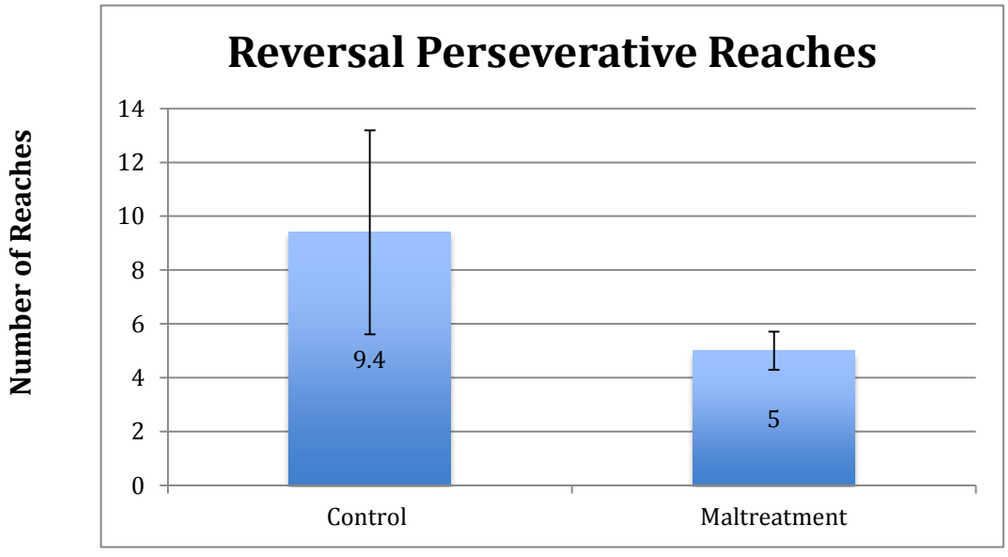

Figure 6. There is no significant difference in the mean total number of perseverative reaches made during the ORD Task between the control group and the maltreatment group.

Mean Total Perseverative Reaches during ORD Task in Control and Maltreatment Groups

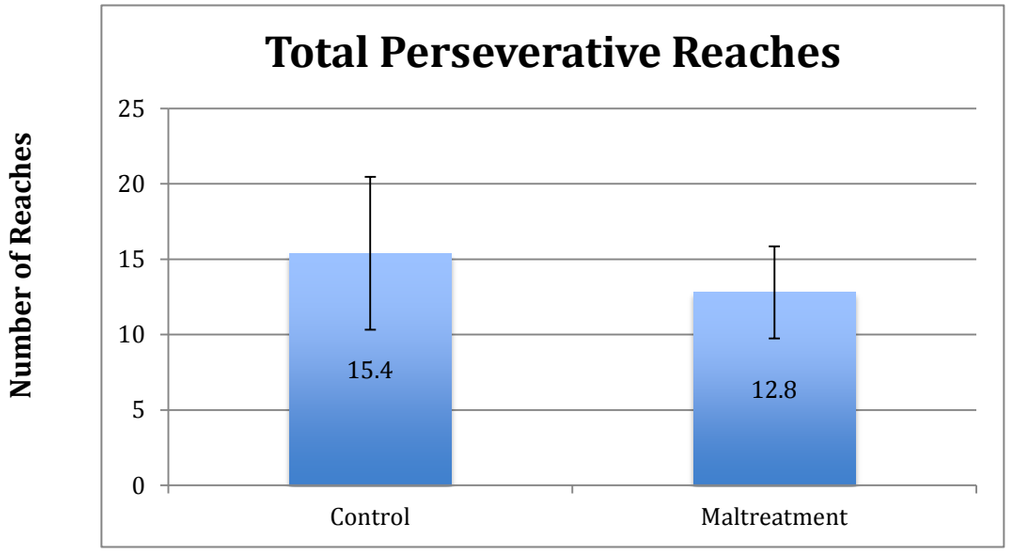

Figure 7. There is no significant difference in the mean number of total reaches during easy trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Total Reaches during Easy Trials of the ORD Task between the Control and Maltreatment Groups

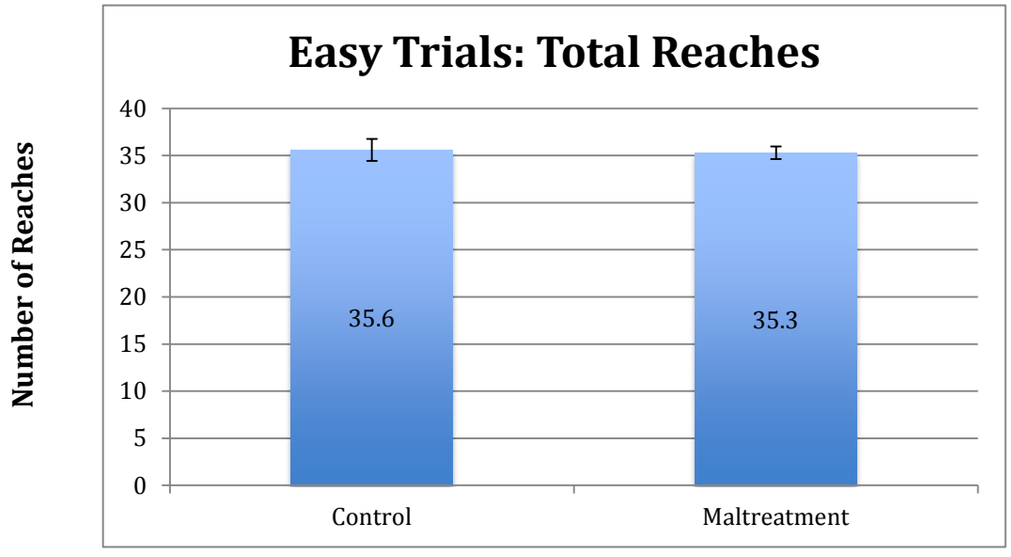

Figure 8. There is no significant difference in the mean number of barrier reaches during easy trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Barrier Reaches during Easy Trials of the ORD Task between the Control and Maltreatment Groups

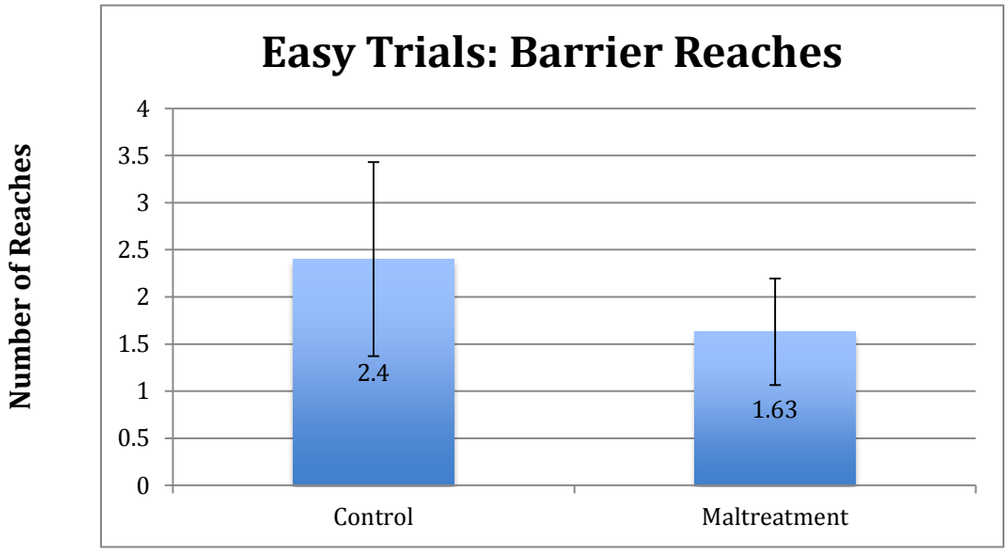

Figure 9. There is no significant difference in the mean number of total reaches during moderate trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Total Reaches during Moderate Trials of the ORD Task between the Control and Maltreatment Groups

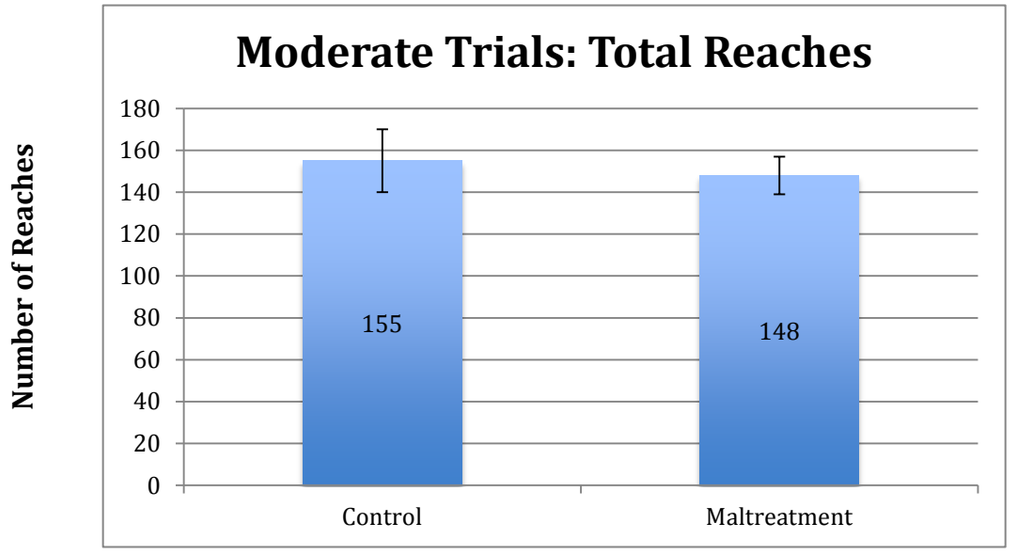

Figure 10. There is no significant difference in the mean number of barrier reaches during moderate trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Barrier Reaches during Moderate Trials of the ORD Task between the Control and Maltreatment Groups

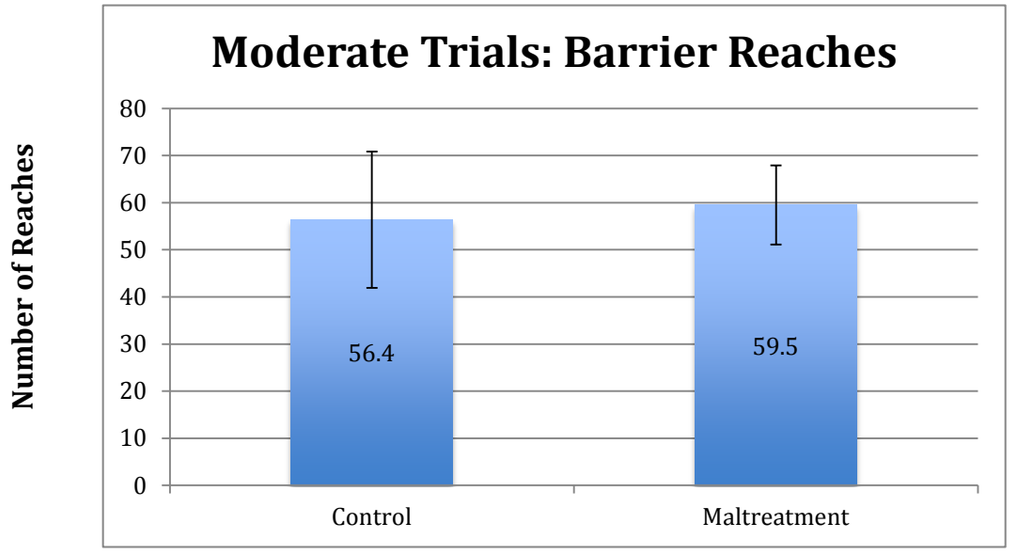

Figure 11. There is no significant difference in the mean number of global perseverative reaches during moderate trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Global Perseverative Reaches during Moderate Trials of the ORD Task between the Control and Maltreatment Groups

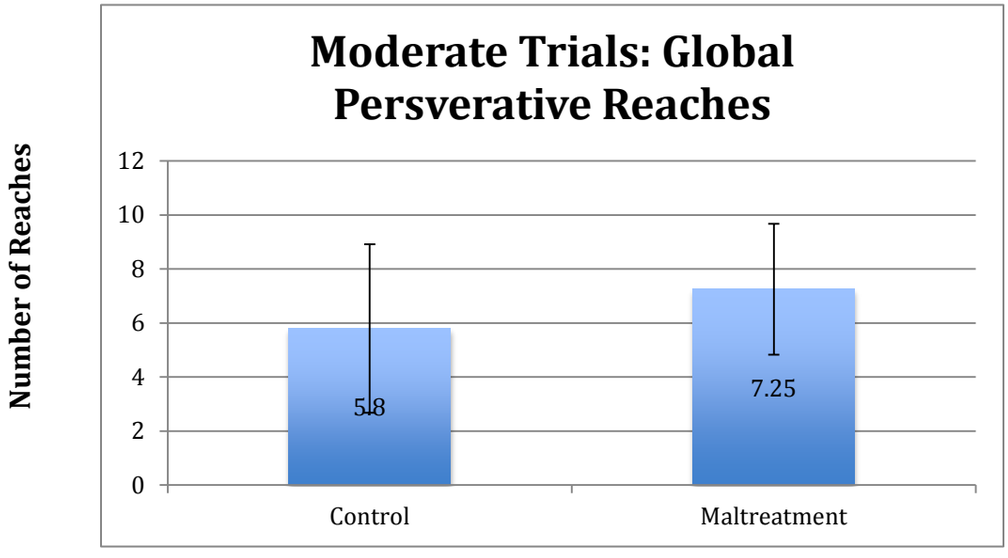

Figure 12. There is no significant difference in the mean number of total reaches during difficult trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Total Reaches during Difficult Trials of the ORD Task between the Control and Maltreatment Groups

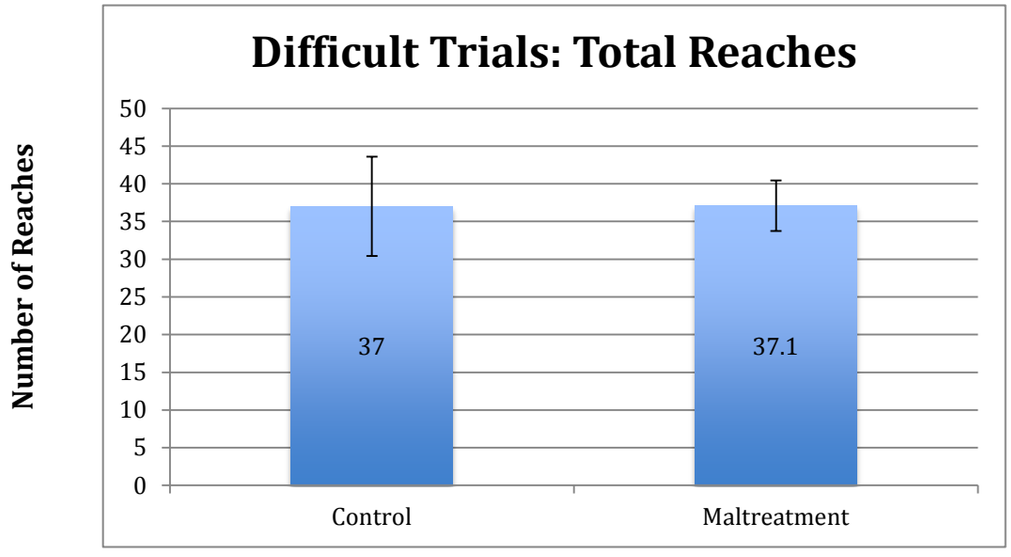

Figure 13. There is no significant difference in the mean number of barrier reaches during difficult trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Barrier Reaches during Difficult Trials of the ORD Task between the Control and Maltreatment Groups

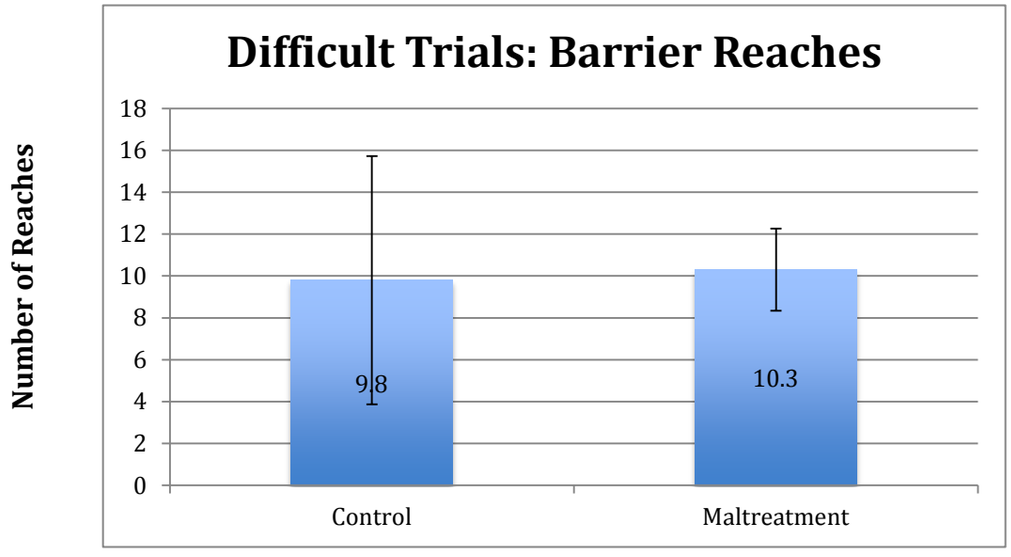

Figure 14. There is no significant difference in the mean number of global perseverative reaches during difficult trials of the Object Retrieval Detour Task between the control and maltreatment groups.

Mean Number of Global Perseverative Reaches during Difficult Trials of the ORD Task between the Control and Maltreatment Groups

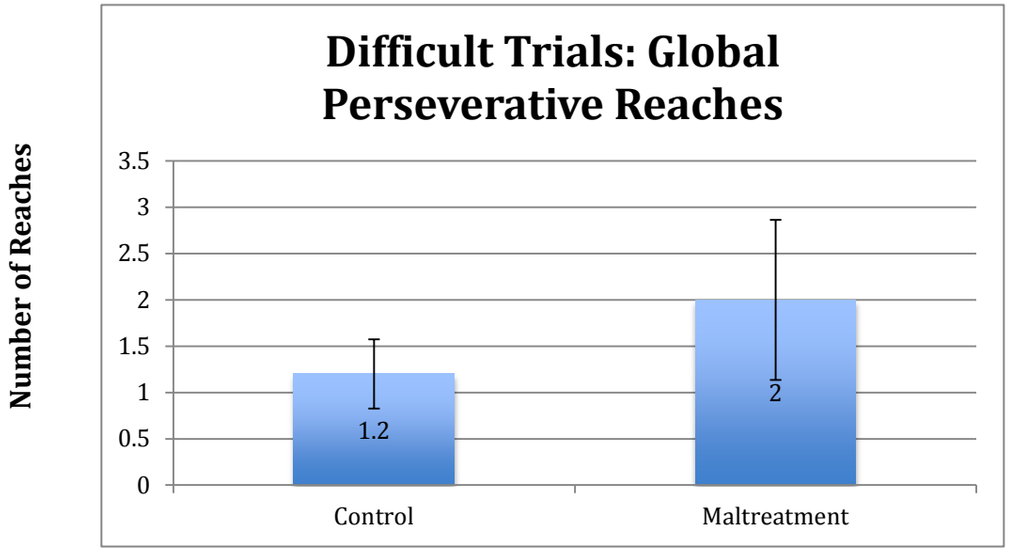

Figure 15. There is no significant correlation between the abuse rates per hour and the number of perseverative reaches made during the ORD task, although abuse contributes to a high percent of variance.

Pearson Correlation between Abuse Rates per Hour and Number of Perseverative Reaches in the ORD Task

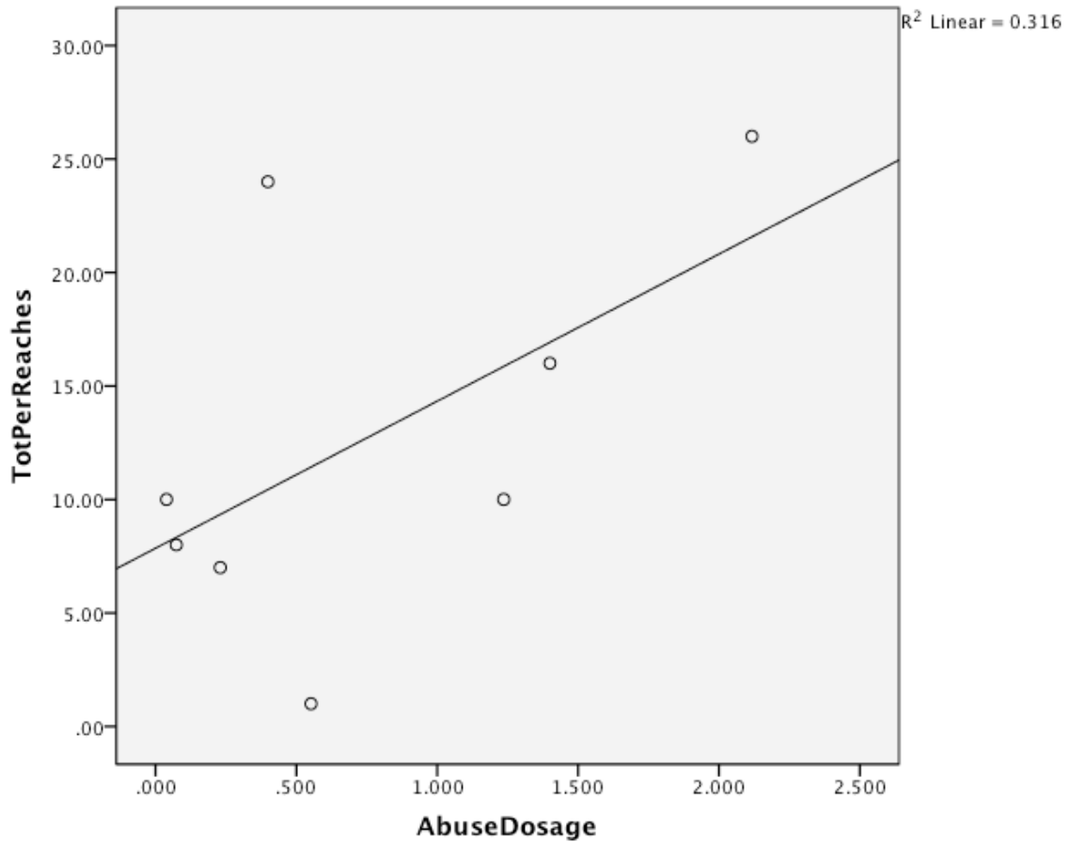

Figure 16. There is no significant difference in the mean number of shaping days of the control and maltreatment groups before the Delayed Non-Match to Sample Trial Unique Task.

Mean Number of Delayed Non-Match to Sample Shaping Days in Control and Maltreatment Groups

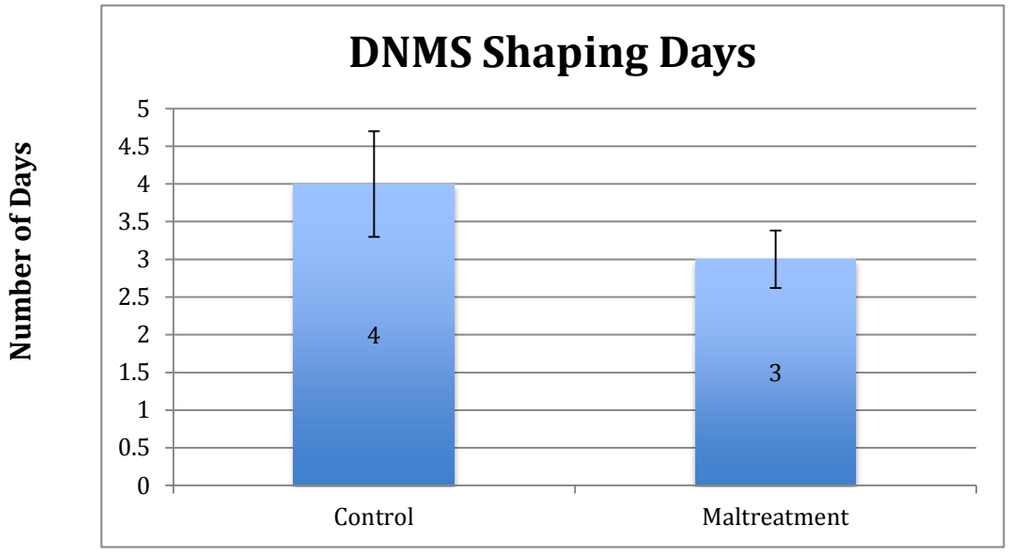

Figure 17. There is no significant difference in the mean number of errors made by the control and maltreatment groups before reaching criterion in the Delayed Non-Match to Sample Trial Unique Task.

Mean Number of Errors to Criterion in the Control and Maltreatment Groups during the Delayed Non-Match to Sample Trial Unique Task

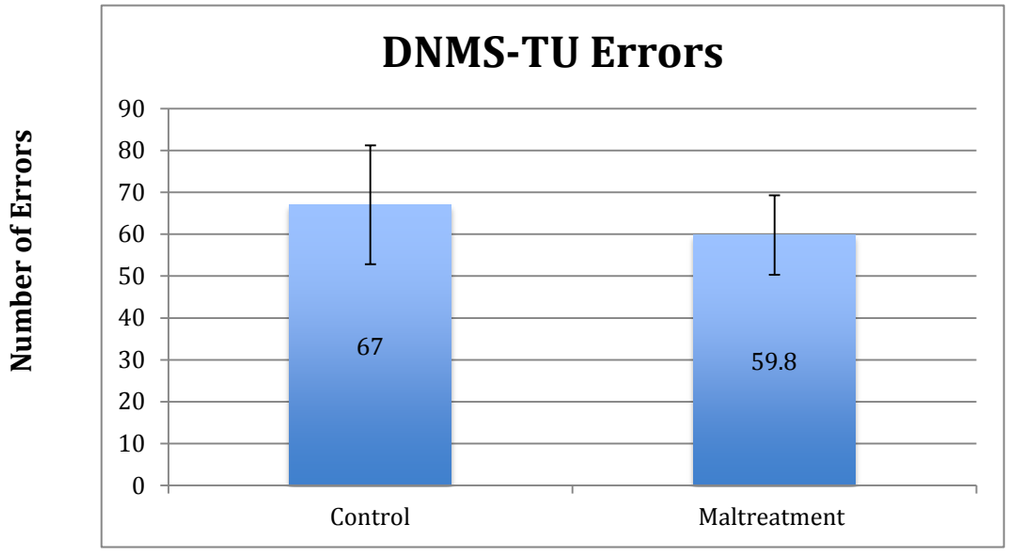

Figure 18. There is no significant difference in the mean number of trials to criterion in the control and maltreatment groups in the Delayed Non-Match to Sample Trial Unique Task.

Mean Number of Trials to Criterion in the Control and Maltreatment Groups in the Delayed Non-Match to Sample Trial Unique Task

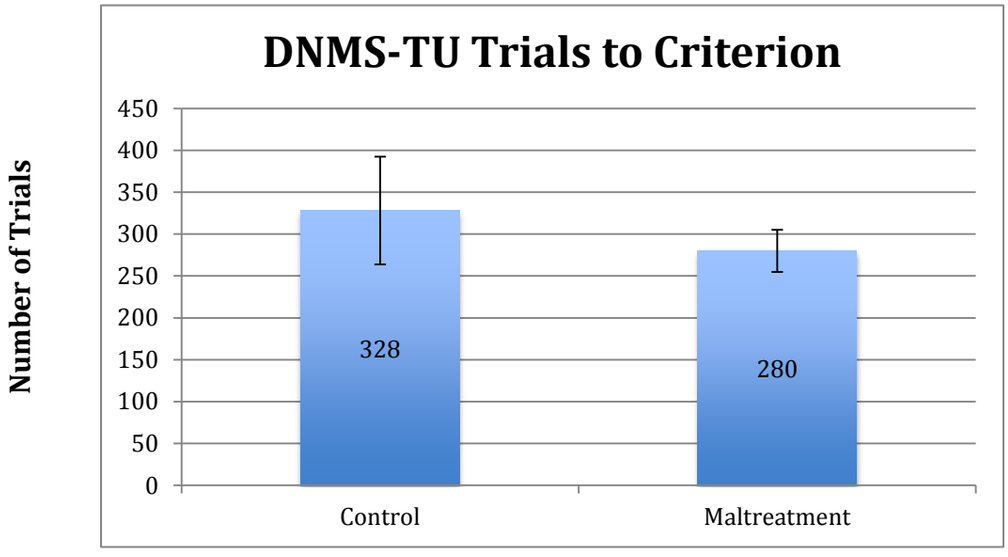

Figure 19. There is no significant difference in the mean number of errors to criterion in the Delayed Non-Match to Sample Session Unique Task.

Mean Number of Error Trials in the Control and Maltreatment Groups during the Delayed Non-Match to Sample Session Unique Task

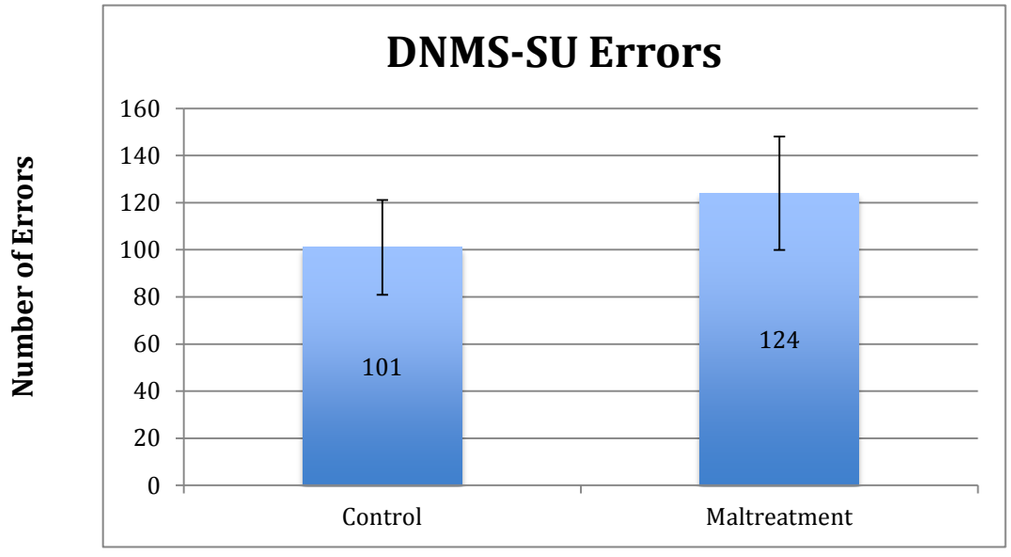

Figure 20. There is no significant difference in the mean number of trials to criterion in the Delayed Non-Match to Sample Session Unique Task.

Mean Number of Trials to Criterion in the Control and Maltreatment Groups in the Delayed Non-Match to Sample Session Unique Task

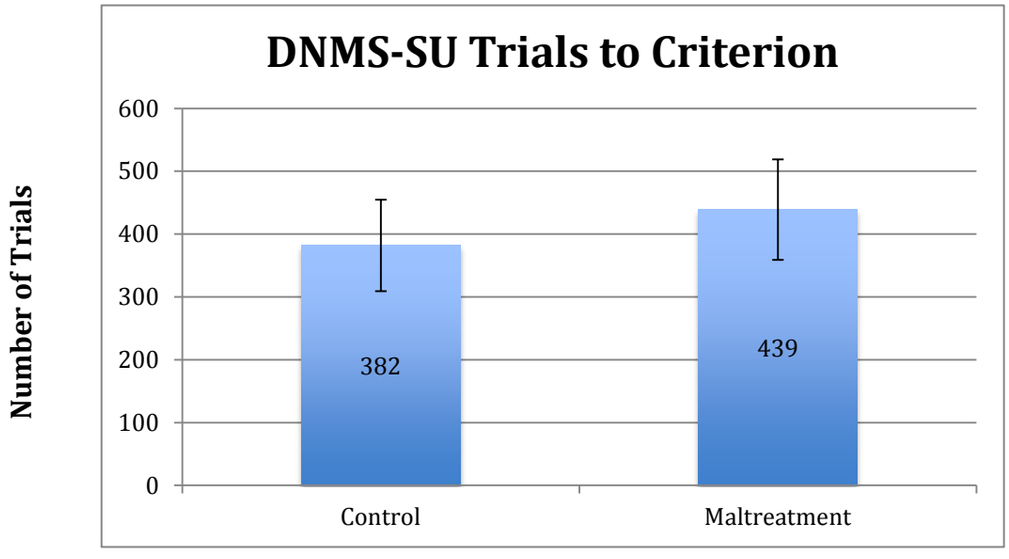

Figure 21. There is no significant difference in the mean number of errors made by the control and maltreatment groups before reaching criterion in the Object Discrimination Task.

Mean Number of Errors to criterion in the Control and Maltreatment Groups during the Object Discrimination Task

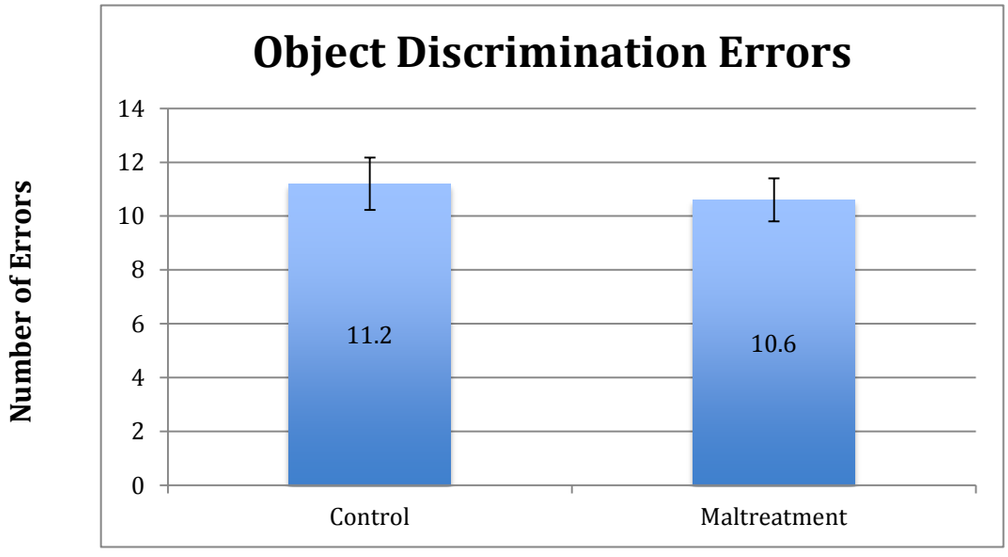

Figure 22. There is no significant difference in the mean number of trials to criterion in the Object Discrimination Task.

Mean Number of Trials to Criterion in the Control and Maltreatment Groups in the Object Discrimination Task