Social Salience Attribution in Opioid Use Disorder

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by

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List of Abbreviations and Symbols

α .....Alpha

ACC .....Anterior Cingulate Cortex

AI .....Anterior Insula

ASI ..... Aberrant Salience Inventory

AVP .....Arginine Vasopressin

ß .....Beta

BOLD ..... Blood Oxygenation Level Dependent

CBT .....Cognitive Behavioral Therapy

CM .....Contingency Management

CNS ..... Central Nervous System

δ .....Delta

dACC ..... Dorsal Anterior Cingulate Cortex

DSM-5 .....The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition

EG.....Experimental Group

FDCR ..... fMRI of Drug Cue Reactivity

fMRI .....Functional Magnetic Resonance Imaging

GABA .....Gamma-aminobutyric acid

HPA .....Hypothalamic-Pituitary-Adrenal

iRISA .....Impaired Response Inhibition and Salience Attribution

MCQ30.....Metacognition Questionnaire - 30

NAc .....Nucleus Accumbens

OD .....Opioid-dependent

OFC .....Orbitofrontal Cortex

OR ..... Opioid Receptor

OTX .....Oxytocin

OTXR.....Oxytocin receptor

OUD ..... Opioid Use Disorder

PFC ..... Prefrontal Cortex

SN .....Salience Network

SUD .....Substance Use Disorder

VMPFC .....Ventromedial Prefrontal Cortex

VTA .....Ventral Tegmental Area

Abstract

SOCIAL SALIENCE ATTRIBUTION IN OPIOID USE DISORDER

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Opioid Use Disorder (OUD) remains a significant health burden across various societal roles. Mothers experiencing OUD demonstrate a disruption in the maternal-child bond, preventing them from adequately caring for their children. In 2016, parental drug use accounted for removing 92,107 children from their homes, and the percentage of children entering foster care resulting from parent opioid use rose from 26% to 34% between 2009-2016. Little research exists on the psychological and neurobiological processes underlying the disruption of fulfilling parental responsibilities. Neurobiological hallmarks of OUD include limbic system neuroadaptations, dysregulation, and changes in the salience network. This leads to drug craving and drug-seeking behavior at the expense of attachment, social cognition, and meta-cognition, with stronger emotional affect. Negative behavioral patterns arise as salience attribution shifts away from natural rewards like social relationships, including the maternal-child bond, toward increased drug seeking and use. In this study, a questionnaire battery of social cognition, mood symptoms, anxiety,

attachment, social networks, and metacognition was employed in a group of mothers with OUD (OUD=15), who were in residential treatment for substance dependence and a group of healthy control mothers (NHC=17). Both groups completed the questionnaire battery and underwent functional magnetic resonance imaging (fMRI) while performing the Incentive Cue task (ICT), which consisted of several cue conditions, including photos of opioids and photos of their child. This thesis focused on the response measures to the questionnaire battery and the behavioral responses (response time, RT; and error rate, ER) to the ICT. The results demonstrated group differences in the questionnaire battery related to meta-cognition, social anxiety, and social network size. The experimental group (EG) results indicated a stronger negative metacognitive belief regarding danger and uncontrollability of their thoughts, an attachment style that trends away from anxious and towards avoidant-dismissive, and a significantly smaller social network size. Further, the results showed significant group differences in behavioral measures (RT, ER) in response to the opioid cues, indicating that the EG took less time and had a higher rate of error in completing the ICT. However, there was no difference in the behavioral response in RT and ER to the own child cues. These findings highlight changes in meta-cognition, social anxiety, and social network size associated with OUD. Findings also emphasize the benefit in using cues in varying valence levels with incentive tasks as a valid experimental paradigm to study salience attribution in OUD mothers.

1. Introduction

1.1 Problem Statement and Study Objective

Opioid use disorder (OUD) represents a chronic condition characterized by the prolonged and excessive consumption of opioids, affecting approximately 2.1 million individuals in the United States and 16 million globally (Dydyk et al., 2023). This widespread affliction leads to an annual death toll of 120,000 worldwide (Dydyk et al., 2023). The prevalence of OUD in women in the US increased by 400% between 1999-2010, and approximately 31 women experience fatality from opioid overdoses daily (Campbell et al., 2018). The term opioid encompasses naturally occurring substances including heroin, opium, morphine, codeine, and semisynthetic and synthetic substances including hydromorphone, fentanyl, methadone, and oxycodone. The etiology of opioid addiction involves complex neurobiological alterations resulting in a cycle of binge, intoxication, craving, upregulation in stress systems, negative affect/ reinforcement, and relapse (Koob & Volkow, 2010, 2016a). The cycle includes : 1) compulsion to seek and take opioids; 2) loss of control in limiting the drug intake; and 3) emergence of a negative emotional state including dysphoria, anxiety, and/or irritability, reflective of the negative withdrawal symptom as the patient is prevented from accessing the drug (Koob & Volkow, 2010, 2016a). Then, the cycle will repeat at the patient seeks out the drug to counteract the negative state of withdrawal (Koob & Volkow, 2010, 2016a). Consequently, individuals with OUD experience numerous harmful consequences at the level of psychosocial

functioning. This has far-reaching effects beyond the person with OUD, affecting family members and the mother-child dyad (Romanowicz et al., 2019).

CDC research indicates that childbearing women with OUD at the point of parturition have increased by 131% between 2010 and 2017, with the number rising still (Hirai et al., 2021). Further CDC data collected via self-report in 2019 indicates that 7% of women used prescription opioids during their pregnancy, and 1 in 5 of those reported abuse/misuse of the drug (PRAMS, cdc.gov). In 2016, parental drug use accounted for removing 92,107 children from their homes, and the percentage of children entering foster care resulting from parent opioid use rose from 26% to 34% between 2009-2016 (Crowley et al., 2019). Women with OUD have higher rates of psychiatric comorbidities including major depressive disorder, anxiety disorder, and bipolar disorder compared to men (Khan et al., 2022). Evidence also indicates that estrogen is a risk factor for the development of OUD. Further, estrogen fluctuations throughout the menstrual cycle affect μ-opioid receptors in the limbic system and hypothalamus (Eckersell et al., 1998). Higher serum estrogen concentration will alleviate pain perception, while dips in estrogen will increase pain perception (Eckersell et al., 1998).

Women with OUD experience decreased emotional attachment to their children, and decreased fulfillment of their parental duties, favoring drug seeking and use (Romanowicz et al., 2019). The parent-child attachment bond is disturbed, and salience attribution shifts away from the child in favor of the drug (Romanowicz et al., 2019). There is a discounting of maternal duties in favor of drug preoccupation, seeking, and use (Romanowicz et al., 2019). There is a gap in knowledge regarding the changes in social

cognition, attachment, and metacognition that occur in mothers with OUD. Understanding these changes can provide a guide towards designing practices that would rebuild behavior patterns to restore the maternal-child bond.

Study objectives. The study aimed to understand the neurobehavioral changes in social cognition and maternal attachment in mothers with OUD. A central part of the project was to pilot an fMRI task that examines the neural response underlying the shift in salience attribution from child attachment in favor of drug stimuli. The task involved a behavioral component measuring response times and error rates in responding to cues of varying valence. We present here the analysis of the fMRI task behavior; the imaging outcomes will not be presented here. We also examined the effect of OUD on measures of social cognition including parent-child attachment, and metacognitive abilities in mothers with OUD. Information gleaned from this study may be used for further research, hypothesis generation, and interventional strategies.

The direction of this study was informed by previous research conducted on the maternal-child bond, maternal reflective function, Theory of Mind research applications to addiction studies, and previous fMRI studies that aimed to observe differences in the neural response to drug cue exposure in individuals with OUD compared to controls. (Harter, 2019).

1.2 Attachment Theory and Maternal-Child Bond

Attachment theory has two sides in the scope of the maternal-child bond. First, the psycho-biological system motivating individuals to seek proximity to significant individuals, specifically the child to the mother, which manifests as children expressing

neediness through verbalizing, approaching behavior, and moving to maintain proximity to their mother (Mikulincer & Shaver, 2012). Second, in response to these behaviors, the mother will guarantee the maintenance of her proximity to the child during times of need, and create a safe haven/secure base for the child during physical/emotional distress wherein comfort can be administered (Ainsworth et al., 1978). Regulation of the child's emotional state is integral to the mother's feeling of security (Rosso et al., 2015).

The mother's proper response to child distress will be maintained by maternal sensitivity developed and guided by the maternal reflective function (RF), wherein the mother can "ascribe [her child] various mental states, i.e., intentions, motivations, and feelings" during infancy, which then informs maternal behavior throughout raising the child (Slade et al., 2005). Maternal reflective functioning is the mother's ability to keep the child and the child's mental state at the "forefront of [her] mind," which is shown to play a vital role in intergenerational transmission of attachment and strengthen the maternal-child bond (Slade et al., 2005). This state of cognition and behavioral regulation/management typically begin postpartum when the child is in infancy (Lenzi et al., 2015). Neurobiological changes favoring the maternal caregiving system will develop structurally and functionally during the transition to motherhood even prior to birth throughout pregnancy, birth, and continuing post-partum (Lenzi et al., 2015).

Based on attachment theory, individuals affected by OUD will typically turn to substance abuse as a self-medication method to cope with a lack of attachment strategies in personal relationships (Schindler, 2019). The inability to form normative social attachments can predispose patients to OUD, and conversely, OUD harms attachment

security in the patient (Schindler, 2019). Longitudinal studies indicate that insecure attachment styles will lead individuals towards patterns of substance abuse as a method of self-medication (Schindler, 2019).

Overall, individuals with OUD exhibit insecure patterns of attachment (Schindler, 2019). The fearful-avoidant attachment subtype is frequently identified in heroin addicts, and the history of insufficient attachment strategies in OUD patients experiencing motherhood will theoretically exact a negative affect on the maternal-child bond (Schindler, 2019). An ideal attachment system between infants and mothers will lend itself to the child's survival while optimizing their social, emotional, and cognitive development (Lenzi et al., 2015). Limbic system dysfunction stemming from addiction will adversely affect the maternal-child bond, as hallmarks including love, protection, security, responsive engagement, and encouragement will not be extended from the mother to her child in a normative context, which can in turn affect developmental milestones of the child (Lahousen et al., 2019).

Empirical studies indicate that mothers with OUD exhibit various negative behavioral traits, such as irritability, decreased attentiveness, ambiguity towards their children, and heightened difficulty in interpreting children's social and behavioral cues (Romanowicz et al., 2019). Furthermore, the DSM-5 diagnostic criteria identify several pertinent social consequences of OUD, encompassing the failure to fulfill familial obligations, interpersonal conflicts exacerbated by substance use, and persistent cravings, as well as unsuccessful attempts to reduce or discontinue opioid consumption (Hasin et al., 2013).

1.3 OUD Symptoms and Social Cognition Battery

Psychometric and physiological assessments are widely used measures of state testing for patients with addiction (Santos et al., 2020). These include but are not limited to assessments of vital signs, positive and negative emotional states, craving, and mood. Physiological changes that indicate opioid withdrawal include changes in pupil dilation, abnormally high pulse, sweaty/clammy skin, nausea, and increased feelings of anxiety and depression as measured by the Clinical Opiate Withdrawal Scale (COWS) (Wesson & Ling, 2003). As previously stated, 74% of OUD patients will experience an affective personality disorder in their lifetime, otherwise known as mood disorders, and that statistic is higher in female patients (Hooker et al., 2020). Disorders include depression, bipolar disorder, dysthymia, and the related substance-induced mood disorders categorized by mood changes from opioid consumption and while experiencing withdrawal (DSM-5) (Hasin et al., 2013). When measuring emotional affect, both Positive and Negative affect are psychometrics that are significantly displayed when evaluating the OUD patient (St. Marie, 2019). Research on patients with OUD indicates that high scoring of the Negative Affect subcategory of the PANAS is correlated with psychopathy. In contrast, Positive Affect subcategory scores are associated with addiction treatment outcomes (Serafini et al., 2016).

Psychometric results from studies utilizing the Opiate Craving Visual Analogue Scale (OC-VA) Scale assessment provide useful self-report scores in measuring opioid craving severity and prediction of opioid use (Boyett et al., 2021). The scores can be utilized in adjunct with COWS to detect concurrent physiological changes during

withdrawal (Boyett et al., 2021). A Visual Analogue Scale is useful as an instant-measurement instrument, and can be adapted for various, specific research paradigm. Assessing the craving score of patients before and after exposure to opioid cues, in this case before and after cue selection for task cues, and before and after performing the functional task, is proven to be predictive of further opioid use or measure the efficacy of current treatment measures (Boyett et al., 2021). The OC-VAS may also support the identification of sub-components such as tonic (chronic, long term) or phasic (acute/in the moment) craving (Kakko et al., 2019).

Research indicates that conditions will influence the presence of cravings, and whether the patient experiences phasic- or tonic- craving. Individual characteristics and conditions influence tonic craving, and can be predicted based on trait evaluations (Goodyear & Haass-Koffler, 2020). Exposure to cues and changes in contextual conditions will influence phasic craving (Goodyear & Haass-Koffler, 2020).

The OC-VA Scale can assess the patient's tonic and phasic craving. For the sake of this research, the OC-VA Scale is used to assess the phasic craving of patients in response to exposure to opioid cues in four instances. During visit 1, the OC-VA is administered, followed by their selection of preferred drug administration method (IV or IN), then selection of four (4) images of that drug they find the most appealing. Then, the OC-VA Scale is administered a second time. During visit 2, when these personal cues are integrated into the task paradigm, the patient is assessed with the OC-VA Scale prior to the task, they underwent the task, and afterwards the OC-VA Scale is administered a fourth time to assess phasic craving.

1.4 Neurobiology of Addiction

Neurobiological mechanisms underlying opioid addiction are initiated by the activation of μ-opioid receptors within various regions of the mesolimbic system in the brain, resulting in analgesic effects (Kosten & George, 2002). Opioid receptors are predominantly located in areas associated with pain perception, reward circuity, and reinforcement, including the ventral tegmental area (VTA) and the nucleus accumbens (NAc) (Merrer et al., 2009). The neurobiology of opioid addiction (i.e. the Koob cycle) can be elucidated through three primary processes: reward pathway activation, neuroadaptation, and withdrawal/craving (Koob & Volkow, 2010, 2016a).

Opioid receptor stimulation leads to the production and release of dopamine by cells in the ventral tegmental area (VTA), subsequently promoting feelings of euphoria, reinforcement, and pleasure in individuals (Kosten & George, 2002). In a healthy state, feedback from the prefrontal cortex regulates the desire to continue seeking the euphoric effects of dopamine release. However, this regulatory mechanism appears compromised in patients with OUD, as they prioritize the pursuit of pleasure at the expense of their interpersonal relationships and responsibilities, including child-rearing and the development of healthy attachments (Kosten & George, 2002). Concurrently, the neurobiological mechanisms involved in bonding within relationships, such as parent-child bonding, empathy, trust, and attachment, are influenced by the synthesis of oxytocin in the supraoptic nucleus (SON) and paraventricular nucleus (PVN) within the hypothalamus (Walter et al., 2021). In females, the peripheral release of oxytocin induces parturition (childbirth) and milk ejection.

In contrast, central release of oxytocin promotes nurturing behaviors, including the desire and ability to bond with their infant child (Walter et al., 2021). Research indicates that mothers affected by OUD exhibit a heightened affinity for the euphoric effects associated with opioid intake, while displaying a decreased affinity for bonding with their children (Swain & Ho, 2022). The underlying maternal behavior neurocircuit (MBN), such as the supplementary motor area (SMA) that regulates physical responses such as protective cuddling or holding, is "functionally dysregulated" by opioid use (Swain & Ho, 2022). Functional imaging studies utilizing child facial expression visual cues under task indicate reduced response in the SMA in OUD participants, and overall deficits in the MBN response to images of the OUD's child (Swain & Ho, 2022).

Chronic, repeated exposure to addictive substances over long periods alters the mesolimbic system functioning, resulting in the dysregulation of the reward circuitry while reinforcing addictive behavior (Koob & Volkow, 2016). The limbic system is involved in generating cravings and motivating the pursuit of addictive substances. In addition, the normal balance of the limbic system is disrupted, and the brain becomes hypersensitive to cues associated with substance use ((Koob & Volkow, 2016b). These cues can trigger intense cravings and a strong desire to engage in drug-seeking behavior. The involvement of the limbic system in motivation and craving contributes to the persistent and often overwhelming urge to use drugs, even in the face of negative consequences or the need to fulfill a specific role i.e., motherhood responsibilities. Addiction can disrupt the emotional regulation function of the mesolimbic system, leading to emotional dysregulation (A. Murphy et al., 2012). Individuals with addiction may experience heightened emotional

responses, including increased anxiety, irritability, and depression, particularly during periods of withdrawal or when they are unable to access the addictive substance (Koob & Volkow, 2016). This hijack of emotional processing contributes to the cycle of addiction by driving individuals to seek relief or escape from negative emotions through substance use, creating a positive feedback loop of avoidance and drug craving/seeking. The hippocampus and amygdala, involved in memory formation and associative learning, are also activated in addiction and lead to the formation of strong memories and associations between substance use and environmental cues/triggers (Kutlu & Gould, 2016). These associations can persist long after individuals have abstained from use, and contribute to the risk of relapse.

The nucleus accumbens (NAc), a pivotal structure within the brain's reward circuitry, plays a significant role in opioid addiction. The following are features of the NAc's involvement: reward and pleasure, reinforcement of drug-seeking behavior, craving and relapse, and sensitization and tolerance (Harris & Peng, 2020). Increased dopamine release in the NAc during opioid use reinforces drug-seeking behavior and engenders a profound sense of euphoria, contributing to the addictive properties of opioids (Harris & Peng, 2020). When opioids bind to opioid receptors in the NAc, it triggers the release of dopamine, the neurotransmitter associated with pleasure and reward. This release of dopamine in the NAc produces a euphoric effect, reinforcing the use of opioids and contributing to the addictive properties of these substances (Harris & Peng, 2020). The NAc's role in reinforcement is crucial in the development and perpetuation of opioid addiction. Opioids stimulate the NAc, leading to dopamine release and creating a

compelling incentive to seek out and use the drug (Harris & Peng, 2020). This reinforcement of drug-seeking behavior establishes the cycle of addiction, as individuals are driven to repeat the behavior to experience the pleasurable effects associated with opioid use. Prolonged opioid use leads to neuroadaptation, where the brain adjusts its functioning to compensate for the presence of the drug (Kosten & George, 2002). With continued use, the brain becomes tolerant to opioids, necessitating higher doses to achieve the same effects. Neuroadaptation also induces alterations in the reward pathway, rendering it less responsive to natural rewards and more reliant on opioids for dopamine release (Kosten & George, 2002).

Changes in other neurotransmitters and their receptors in the NAc also occur during opioid addiction. For example, there is evidence of alterations in the levels of gamma-aminobutyric acid (GABA), glutamate, and opioid receptors within the NAc (Kosten & George, 2002). These changes further contribute to the neurochemical imbalance and dysregulation observed in the NAc during opioid addiction. Additionally, opioid addiction is associated with neuroadaptive changes in the NAc, such as alterations in gene expression and protein synthesis (Kosten & George, 2002). These changes can affect the functioning of various intracellular signaling pathways and contribute to the long-lasting effects of addiction on the NAc and its associated behaviors (Kosten & George, 2002).

The social neuropeptides oxytocin (OXT) and arginine vasopressin (AVP) serve pivotal roles in regulating social behavior and emotional states (Song & Albers, 2018). These nonapeptides are involved in hormone regulation and a broad range of social behavior. OTX and AVP are synthesized in the hypothalamus within the magnocellular

neurons of the supraoptic and paraventricular nuclei (Chatterjee et al., 2016). The axonal projections of AVP- and oxytocin-producing neurons from supraoptic and paraventricular nuclei mirror AVP and OTX dual activity as hormones and neuropeptides, as they project their axons to many brain locations and the neurohypophysis (Baribeau & Anagnostou, 2015). Oxytocin binds to oxytocin receptors (OXTR), which are located in the hypothalamus, peripheral tissues such as the uterus, testes, and liver, and myoepithelial cells surrounding the alveoli of mammary glands (Chatterjee et al., 2016).

Interestingly, these receptors experience elevated levels of expression during the post-partum lactation period in women (Chatterjee et al., 2016). OXT-OXTR signaling is responsible for stress and social response via hypothalamo-pituitary-adrenal axis regulation. Oxytocin potentiates responses to pro-social behavior, examples including altruism, cooperation, and caregiving. OXT also increases behavioral responses such as evoking contentment, inducing trust, generosity, and bonding between humans (Chatterjee et al., 2016).

Discontinuation of opioids or the waning of their effects will result in withdrawal symptoms, otherwise known as the negative affect category of the Koob cycle. Withdrawal manifests as a collection of physical and psychological symptoms, including intense cravings, anxiety, irritability, muscle aches, and gastrointestinal distress (Harris & Peng, 2020). The NAc is closely linked to the brain's reward pathway. The NAc is also involved in the experience of craving, which is an intense urge or desire to use opioids. Opioid addiction induces changes in the NAc, including alterations in dopamine receptors and other neurochemical processes, contributing to the development of craving (Kosten &

George, 2002). These cravings can persist long after an individual has ceased using opioids and significantly increase the risk of relapse, even after a period of abstinence. Prolonged opioid use can lead to neuroadaptations within the NAc, resulting in sensitization and tolerance (N. C. Christie, 2021, 2021). Sensitization refers to an increased response to opioids, while tolerance refers to a reduced response. Over time, these neuroadaptations can drive individuals to escalate their opioid use to achieve the desired effects, perpetuating the cycle of addiction. Cravings, characterized by intense urges to use opioids, can persist long after withdrawal symptoms subside and contribute to the cycle of addiction.

Moreover, opioid addiction involves other brain regions and neurochemical systems. Chronic opioid use can lead to changes in the prefrontal cortex, which is responsible for decision-making, impulse control, and judgment (Kosten & George, 2002). These changes can impair cognitive functions, making it arduous for individuals to resist drug cravings or engage in rational decision-making regarding drug use.

The three stages of addiction – binge/intoxication, withdrawal/negative affect, and craving – have discrete neurocircuity as revealed via animal and human imaging studies(Koob & Volkow, 2010, 2016b). The ventral tegmental area and the ventral striatum are focal during binges/intoxication, the extended amygdala is indicated in the withdrawal/negative affect stage, and a wider network comprising the orbitofrontal cortex-dorsal striatum, prefrontal cortex, basolateral amygdala, hippocampus, and insular are involved in craving (Koob & Volkow, 2010, 2016b). Disruption to inhibitory control is attributed to the inferior frontal cortices (Koob & Volkow, 2010, 2016b). Neuroadaptive cascades beginning in the mesolimbic – dopaminergic system, as mentioned above, lead to

the dysregulation outlined in the Koob cycle in the prefrontal cortex, cingulate gyrus, and the extended amygdala (Koob & Volkow, 2010, 2016).

The Impaired Response Inhibition and Salience Attribution (iRISA) model posits that drug addiction is characterized by impaired response inhibition and shifts in salience attribution (Zilverstand et al., 2018). This model suggests that individuals with addiction struggle to inhibit impulsive responses, thus allocating excessive attention to drug-related stimuli. The salience network (SN), consisting of nodes in the amygdala, hypothalamus, thalamus, and ventral striatum, is activated when addicted individuals are exposed to drug cues during cognitive tasks (Seeley, 2019). The activation levels in the SN are correlated with self-reported drug-craving scores and drug seeking-behaviors (Zilverstand et al., 2018). OUD patients exhibit increased SN recruitment during drug related processing, including cue exposure; however, they experience a blunted SN recruitment response to non-drug cues (Zilverstand et al., 2018). The SN also experiences an abnormal response in inhibitory control to the drug cues, making it a useful region of interest in further studies in the context of addiction relapse (Zilverstand et al., 2018).

Neuroimaging techniques, including fMRI, have revealed disruptions in social networks when drug users encounter drug-related cues, leading to compromised decision-making and inhibition (Zilverstand et al., 2018). However, the research exploring the shift in salience attribution specific to OUD, and even more targeted to OUD in mothers, is limited. To advance addiction treatment strategies and develop novel interventions, it is crucial to investigate the molecular mechanisms underlying addiction by addressing behavioral and cognitive neuroscience inquiries. One hypothesis is that drug addiction

induces long-term changes in behavior by co-opting normal mechanisms of associative memory (Everitt et al., 2008). Research indicates that as drug-craving and drug-seeking behaviors become compulsory and habitual, neural control shifts from ventral domains to dorsal domains mediated by the dopaminergic circuity changes reinforced by opioid intake (Everitt et al., 2008). Understanding the unique neural mechanisms in individuals with OUD is of utmost importance. It holds the potential for enhancing comprehension and making a positive impact on this population, their families, scientific research, medicine, and society as a whole.

As stated earlier, compulsive drug use leads to the deterioration of normative social attachment, and the underlying neural mechanisms governing social interactions in drug users remain poorly understood. Despite the significance of social support in addiction recovery and its predictive value for abstinence, the neural response to drug-related stimuli in comparison to social attachment stimuli has not been thoroughly examined. The differing neural responses are an important element to understand when devising behavioral interventions for OUD treatment. Comprehending these processes involved in the interplay of hijacking reward pathways, neuroadaptation, and cortex alterations is vital for developing effective treatment strategies and interventions to aid individuals in recovering from opioid addiction. It is noteworthy that research in this field is ongoing, and novel insights continue to emerge as scientists delve deeper into the intricacies of addiction and the brain.

1.5 OUD Treatment Approaches

Addiction interventions encompass a range of approaches, including both pharmacological and behavioral methods (McHugh et al., 2010). Pharmacological interventions involve the administration of medications such as methadone and buprenorphine, which are prescribed according to specific regimens. Behavioral interventions, on the other hand, employ techniques like cognitive-behavioral therapy (CBT) with skill-building components, as well as operant learning strategies and contingency interventions that provide rewards for negative drug test results. For instance, contingency intervention component was implemented in our study, whereby patient participants were required to pass a drug screen. After completing the questionnaires and imaging scans, they were rewarded with a $100 gift card.

Among the available pharmacological treatments for opioid use disorder (OUD), Naltrexone, an opioid antagonist, blocks the μ-opioid receptor, thereby preventing the euphoric effects associated with opioid use and subsequent intoxication. Methadone and buprenorphine, functioning as μ-opioid receptor agonists, are alternative treatment options commonly utilized for the detoxification and maintenance of OUD patients experiencing withdrawal symptoms during treatment. These medications produce analgesic effects. Non-pharmaceutical interventions, such as Contingency Management and Cognitive Behavioral Therapy (CBT), have demonstrated effectiveness when combined with pharmaceutical interventions. It is worth noting, however, that physicians exhibit reluctance to employ Contingency Management, and studies indicate no significant

difference between physician management alone and physician management combined with CBT.

While animal models have contributed significantly to our understanding of addiction, they do not fully encompass the complexities of human drug use and present limitations impeding research advancement. It is important to develop methodologies that capture shifts in salience attribution in human subjects, allowing for a more comprehensive exploration of the behavioral and neurobiological mechanisms affected by opioid use disorder. This research aims to pinpoint exact differences in OUD mothers and identify novel biomarkers that healthcare providers can utilize in a clinical setting and advance both fundamental and translational addiction research by investigating disruptions in social attachment within the OUD population. Moreover, the findings and conclusions from this pilot study may positively impact the genetic and molecular basis of OUD research.

1.6 Multimodal Hypotheses

Our overall hypothesis was that mothers with OUD had reduced levels of social cognition concerning attachment, metacognition and social network quality and size. These differences will be observed at the trait, state,and behavioral levels.

Trait level. We predicted group differences in attachment style, metacognition, and social network breadth. Due to OUD patients experiencing poor attachment histories as either causation of or correlated with their opioid addiction, the OUD will self-report unhealthy attachment styles with their interpersonal/romantic partner relationships. The OUD group will also self-report unhealthy attachment styles and low levels of enmeshment in their relationship with the youngest child who was used as their cue in the study.

Metacognitive abilities will also be significantly different between groups due to maladaptation from addiction to opioids. Due to hijacked impulse control and thought patterns resulting from information processing and actions that fulfill opioid addiction, the OUD group will self-report metacognitive abilities that are more irregular than the control level. Moreover, the quantitative evaluation of social networks will significantly differ for the OUD group. Due to the decreased socialization inherent in opioid addiction and neurochemical changes that affect social attachment and behavior reinforcement, OUD will self-report a lower number of social networks.

State level. We expected differences in the emotional affect wherein the OUD is more likely to display higher levels of emotional affect in both positive and negative categories. This is due to dysregulation and higher sensitivity to strong, overwhelming emotions that are difficult to control.

We predicted significant increases in the OCVA-Scale after exposure to the opioid cue during Phase I of the experiment after the participant selected the appropriate visual cue (IV or IN), and Phase II after completing the matching task. OCVA-Scale score increase prediction is attributed to the craving potential after exposure to each favored opioid cue.

We anticipated significant differences between groups in the post-scan stimuli rating across cue categories, especially in the post-scan stimuli rating specifically for the C and the O cues.

Behavioral level. We forecasted group differences in the behavioral responses to the cues while under task. Due to a lack of impulse control, the OUD will respond faster while under task. Increased speed will foster potential disregard for correct cue choice; OUD will also

have a higher error rate. OUD will also have a faster reaction time to the opioid cue and a higher ER to the opioid cue than the NHC, due to the salient nature of the opioid image and the potential for craving induction.

2. Methods

2.1 Participants

Mothers with OUD (N=15) with an average age of 34.4 (SD±3.9) were recruited from a community residential treatment facility in Arlington, VA. Control mothers without OUD (N=17) with an average age of 38.9 (SD±8.3) were recruited using social media and outreach in the George Mason University (GMU) community in Fairfax, VA. All participants gave written informed consent and the Institutional Review Board at GMU approved the study. The NHC group received a $50 Amazon or VISA gift card, and the OUD group received $100 VISA gift card.

Inclusion criteria. Criteria for inclusion were as follows for participants in both groups: be a biologically distinct female between the ages of 18-50, with a minimum of one child between the age of 1-17 y/o. The OUD group had to meet the following requirements: a current diagnosis of OUD per the DSM-5, and currently taking buprenorphine or methadone while enrolled in the treatment program. Each participant was required to provide four recent photos of their youngest child. The average age of the youngest OUD child was 8.8 years old (±4.3 years), and the average age of the youngest NHC was 6.5 years old (±4.5 y). Across both groups, the average age of the youngest child was 7.8 years old (±4.5 y).

Exclusion criteria. Exclusionary criteria for participants of both groups included meeting one or more of the following conditions: currently pregnant; history of seizures, head injury, or neurological dysfunction as well as a current diagnosis of schizophrenia or schizophrenic disorder; taking any medication known to affect alertness/brain activity

(e.g., Trazodone, Valium, or Xanax); having any permanent physical metal implant including prostheses, braces, valvular transplant, pacemaker or implants, copper IUD, artificial lenses, therapeutic patches (e.g., nicotine), non-removable piercing, and/or recent tattoo in the past six months, as evaluated on a preliminary brief psychological survey. IUD brand Mirena was the only acceptable type of implant per the GMU MRI Lab protocols. Exclusion criteria for the control group included meeting any of the following conditions: previous admission to an alcohol/drug treatment program, or diagnosis of alcohol/drug abuse.

Throughout the study, every participant experienced the same conditions of experimentation, with the exception of the additional questionnaires for the OUD group regarding opioid use and craving.

2.2 Self-Report Questionnaire Battery

Each participant was required to complete a self-report questionnaire battery before the MRI scan using the Qualtrics online platform (https://www.qualtrics.com) and clinical evaluation. The questionnaires included three categories: demographic/ screening, trait, and state.

Questionnaires in this study are used to reveal indicators in the participants that yield information on their inherent traits and current states of being. These reflective indicators are measures that "reflect" underlying constructs, and are determined using rating scales – nominal, ordinal, interval, Likert, etc. The state and trait-based questionnaires in this study utilize unidimensional scales. Unidimensional constructs, i.e. Likert scale rating, begin with the defined construct of interest, the questionnaire title, then

the participant's list of questions. For example, when the aim is to identify metacognition in patients, we administered a unidimensional MCQ30 measuring the participant's singular attribute of metacognitive abilities. The multidimensional measure of the parental attachment to the child may be the observation of scoring from multiple questionnaires in the study coupled with the behavioral results – the AAS, WHOTO, Response Time under task, and Error Rate % under task (Gagliardi, 2022). The study aims to understand further the relationship between the maternal-child bond and opioid addiction using a multidimensional approach in collecting behavioral, emotional-trait, emotional-state, demographic, physiological, and cognitive perspectives as data-points.

Demographic/ screening questionnaires. The first part of the battery was delivered before the MRI scan visit and obtained information including participants' age, sex, racial/ethnic origin, education, menses, birth control, pre-MRI screening, and opioid use onset. The following questionnaires were included: *Telephone Interview Neuroimaging* (TIN, safety screening questions as required for the MRI lab), *Biographical Questionnaire* (BQ, demographic questions regarding race, ethnic origin, education, etc.), and *Edinburgh Handedness Inventory* (EHI, pre-MRI protocol for using the button box determining dominant hand) (Oldfield, 1971).

Trait-based questionnaires. The trait-based questionnaires were delivered before the MRI scan visit. These questionnaires were obtained to identify distinguishing factors inherent to the participant's nature. The following questionnaires (and available subscales) were included: *NEO-Five Factor Inventory* (NEO-PI-R, assessing an individual's

personality traits: neuroticism, extraversion, openness, agreeableness, conscientiousness) (Costa Jr. & McCrae, 2008); *Interpersonal Reactivity Index* (IRI, assessing an individual's empathy facets: fantasy, perspective-taking, empathetic concern, personal distress) (Davis, 1980). *Machiavellianism IV Test* (MACH-IV, assessing an individual's tendency to manipulate others) (R. Christie & Geis, 2013); (*Emotion Contagion Questionnaire* (ECQ, assessing an individual's susceptibility to affect by individuals or groups: sadness, happiness, anger, love, fear) (Doherty, 1997); *State-Trait Anxiety Inventory-Trait Anxiety* (STAI-T, assessing an individual's anxiety levels)(Spielberger, 1985); *Empathy Quotient* (EQ, assessing an individual's empathetic abilities)(Baron-Cohen & Wheelwright, 2004); *Toronto Alexithymia Scale* (TAS, assessing an individual's emotional identification of the self: Difficulty describing feelings, difficulty identifying feelings, ability to identify or describe one's own feelings, externally-oriented thinking)(Bagby et al., 1986); *UCLA Loneliness Scale* (UCLA-LS, assessing an individual's feelings of loneliness and social isolation)(Russell et al., 1978); *Rushton Altruism Scale* (RAS, assessing an individual's tendencies towards altruistic behaviors)(Rushton et al., 1984) ; *Social Value Orientation* (SVO, assessing an individual's self-regarding versus other regarding preferences)(R. O. Murphy & Ackermann, 2014); *Adult Attachment Scale* (AAS, assessing an individual's attachment style: close, anxious, depend) (Collins & Read, 1990); *Relationship Questionnaire* (RQ, assessing an individual's attachment style: secure, fearful, preoccupied, dismissing) (Bartholomew & Horowitz, 1991); *Experiences in Close Relationships Inventory* (ECR, assessing an individual's attachment style related to romantic relationships: anxiety, avoidance)(Wei et al., 2007); *Cambridge Friendship*

Questionnaire (CFQ, assessing an individual's friendship style) (Baron-Cohen & Wheelwright, 2003)*; Social Network Index* (SNI, assessing an individual's number of individuals in social network: high contact, total social network, embedded networks) (Cohen et al., 1997); *Social Provisions Scale* (SPS, assessing an individual's perceived availability of social support based on views of current relationships: social integration, attachment, opportunity for nurturance, reassurance of worth, reliable alliance, guidance)(Gottlieb & Bergen, 2010); *Trust Self Report* (TSR, assessing an individual's trust in strangers, friends, neighbors, family) (*Lee, 2021); *Metacognitions Questionnaire* (MCQ-30, assessing an individual's self-regulatory executive function: lack of cognitive confidence, positive beliefs about worry, cognitive self-consciousness, negative beliefs about uncontrollability and danger, need to control thoughts)(Wells & Cartwright-Hatton, 2004); and *WHOTO-Parent Child Attachment* (WHOTO, assessing an individual's attachment toward child and romantic partner: proximity seeking, safe haven, separation distress, and secure base; attachment subscales: romantic partner enmeshment, child enmeshment) (Fraley et al., 2011; Fraley & Davis, 1997).

The OUD group completed one additional trait-based questionnaire: *Metacognitions Questionnaire* (MCQ-OUD, assessing an individual's belief regarding their drug of choice: positive cognitive regulation, positive emotional regulation, negative uncontrollability, negative cognitive interference) (adapted from Wells & Cartwright-Hatton, 2004).

State-based questionnaires. The state-based questionnaires were delivered during the MRI scan visit (pre- and post-scan) to obtain information on participants' current physical,

emotional, and mental states, their mood, and symptoms of opioid addiction. The following questionnaires were included: *Profile of Mood States* (POMS, assessing an individual's emotional status) (McNair et al., 1971); *Positive and Negative Affect Schedule* (PANAS, assessing an individual's emotional state over the past seven days) (Thompson, 2007); *Neuromotor Examination* (CDW, assessing an individual's physiological assessment of respondent) (**Lee, 2021); *Clinical Opiate Withdrawal Scale* (COWS, assessing an individual's physiological assessment of opioid withdrawal symptoms) (Wesson & Ling, 2003). Note that the NHC group did not have to complete the COWS.

The OUD group completed one additional state-based questionnaire: *Opiate Craving Visual Analogue Scale* (OC-VAS, assessing an individual's rating on craving for opioids, Visit 2, Part 1 and Visit 2 Part 2) (Boyett et al., 2021).

2.3 Experimental Paradigm – fMRI task

We adjusted the previously published matching task paradigm (Hariri et al, 2000). We developed the Incentive Cue Task (ICT) as a block-design, where individuals were asked to match one of two pictures shown side by side to a third one on the top of the screen. Blocks of different stimuli categories were (i) OP: cue of *drugs (opioids)* in both intravenous (IV) and intranasal (IN) form, (ii) FC: cues of *nondrug appetitive food* (i.e., control for drug stimuli), (iii) OC: cues *of subjects' youngest child* to whom they feel attached, (iv) FD: cues of *familiar face* cues matched by gender and race to personalized photos (i.e., control for attachment stimuli), (v) NC: *cues* of *common household objects*

similar in shape/color to the drug cues, and (vi) SC: cues of *shapes* (i.e., control for sensorimotor response).

Before the scan date, participants provided four (4) pictures of their youngest child. The average age of the youngest OUD child was 8.8 years old (±4.3 years), and the average age of the youngest NHC was 6.5 years old (±4.5 y). Across both groups, the average age of the youngest child was 7.8 years old (±4.5 y).

Participants identified a child similar to their own such as an actor/actress or singer, who fell within the guidelines listed for the FC cue selection. Participants selected their top four favorite foods from a common comfort food list, then selected the one food they craved the most from the top four. Based on substance use history and methodology of drug administration (IV, IN), the OUD group chose four images from a visual library of either IV cues or IN opioid cues. The OP cues for the NHC group were chosen randomly from the IV image library, due to the onset of discomfort likely caused from the visual cue of IV drug paraphernalia, thus inducing a stronger neural response displayed via behavioral and fMRI data. The participant-specific images for all categories (OC, FC, FD, NO, OP, and SP) were formatted to the same dimensions (scale 480 x 360, resolution 96 x 96, formatted to a solid black background) (Appendix X) (**Fig. 1**).

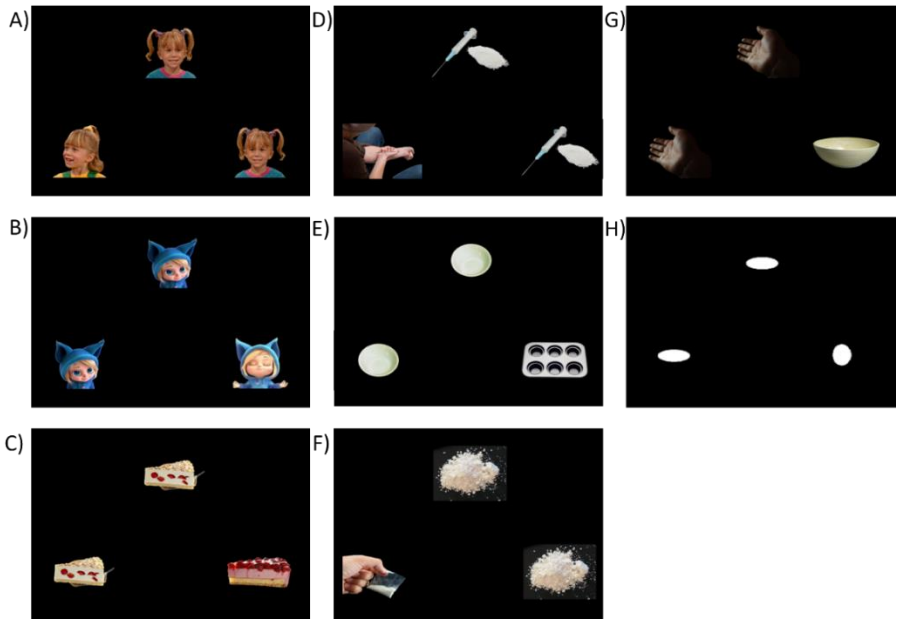


Figure 1. **Example paradigm cue images across categories** A) FC: familiar child cues selected based on similarity to the own child in gender, age, race, ethnicity, appearance, B) OC: own child (cues changed for the sake of this paper to protect the privacy of the patient and their family, C) FD: non-drug appetitive food cues as a control for experiencing craving, D) OP: Intravenous opioid cues, E) NC: neutral objects corresponding in shape/size to the Intravenous cue, F) OP: intranasal Opioid cues, and H) SP: shape cues.

The IC task was presented with the E-Prime 2.0 software (Psychology Software Tools, Inc) to collect participants' response times (RT in ms) and error rates (ER in %) with a button box selection tool, held by the participant in the MRI scanner while under task. Each participant completed one run lasting about 13.36 minutes consisting of four blocks, each lasting 3.40 minutes. Each block was divided between the two alternating cue conditions: "Shape" the sensorimotor control, or "Image" consisting of the curated cues. First shown was the Shape cue repeating six times at two seconds each. This was followed by one of the five stimuli cues (OC, FC, FD, NO, OP) 6 times at two seconds each. Between each task cue, the fixation cross was shown for one second each. This repeats five times

during each block. The paradigm was coded so that the presentation of the "Image" cue was randomly assigned during the task. There is no pattern in the presentation of the "Image" cue by the category.

This repeats continuously until four blocks are complete, wherein each of the five cue categories is presented a total of four times within the run. The participant ideally utilized the button box to select the proper cue 240 times – 120 for the shape cues, and 120 for the curated cues.

Both groups completed a post-scan stimuli rating scale after the ICT, representing a sliding scale rating (1-100) for the participant-specific stimuli (n=4) per category (OC, FC, FD, NO, OP) utilized in the IC task.

2.4 Procedure

During the study, participants completed three phases: pre-scanning, scanning, and post-scanning, lasting a five hours and thirty minutes.

Pre-scanning phase (3 hours). Participants selected cues, provided the photos of their child, and completed the questionnaire battery. Prior to selecting the opioid cues that were most appealing they rated their craving before and after drug cue exposure.

The control group was contacted via phone, text, and email to confirm all requirements, and were given the address of the Peterson Hall – MRI Laboratory. This group was also given the option to complete the questionnaires either in person on the scan date prior to scanning, or at home with a researcher on standby via Zoom, FaceTime, or phone call. If selected to complete the questionnaires at home, the researcher confirmed

via monitoring Qualtrics and checking in with the participant before, during, and after the questionnaires were complete.

Scanning Phase (2 hours). Participants arrived at the GMU MRI laboratory on the scheduled date/time of the exam and completed the mandatory COVID health check screening as directed by university protocols. BAC was administered and was required to be 0. UDS was administered and was required to be negative except for the presence of buprenorphine or amphetamine (if patients were prescribed this) for the OUD group.

The state-based questionnaires measured current physiological and emotional states: POMS, PANAS, COWS, and OC-VAS scale. Then, a practice run for the IC task was administered on a laptop using dissimilar but relevant cues to mimic the requirements for the real IC task during the scan. Each participant was given a button box tutorial instructing them how to hold the button box in their right hand and select the proper button corresponding with the correct answer. The MRI technologist administered a pre-MRI safety screening and directed participants to change into scrubs in the Peterson Hall restroom. During this time, the researcher queues the IC task with the participant cues onto the E-Prime program on the MRI lab desktop to use during the IC task. The researcher ran a "test" E-Prime run with the participant cues on the MRI Lab desktop, confirming that each edited image displays homogeneity in visual specifications and that no errors would occur during the IC task. When the participant returned to the lab having changed into scrubs, a final pre-scan metal detection protocol took place with the participant, and the participant was guided into the MRI scan room.

Participants were guided into the scanner with assistance from the researcher and MRI technologist. Each participant was given a pair of ear plugs and instructed on how to place them for maximum safety. Then, they were eased into a supine position of comfort in the scanner. Safety measures were followed: the appropriate protective pads were placed around the participant, and the mirror-lens headpiece was placed on their head. The researcher placed the button box into the participant's right hand and guided them on finger placement to correctly respond to task cues, as previously explained during the button box tutorial in the lab atrium. The technologist and researcher moved into the control room. Using the MRI scan room loudspeaker from the control room, the researcher asked the participant to press each response button individually on the button box as if responding to the task, confirming the technical viability of the task response. The MRI technologist then began the MRI scan series (between 35-40minutes): (i) anatomical MRI scan for measuring gray matter volume brain structure (6 min, 38 sec), (ii) resting-state BOLD fMRI scan for measuring resting-state functional connectivity (8 min), (iii) task-based BOLD fMRI scans for completing the IC task (13 minutes, 50 sec), and (iv) anatomical DTI scan for measuring white matter brain structure (6 min, 30seconds). Between each scan in the series, the researcher would speak to the participant through the loudspeaker to confirm relative comfort, remind the participant to remain still, and convey instructions as required.

Following completion of all scanning portions, the researcher and technologist enter the scan room. The participant was reassured, safety pads and helmet were removed, and they were instructed to sit up slowly from the cot. Upon completing these post-scan measures, the participant was led from the scan room to await further instruction.

Post-Scanning Phase (30 minutes). After being led into the MRI laboratory waiting area from the scan room, participants were instructed to change from the scrubs into their normal clothing in the Peterson Hall restroom. During this time, the researcher downloaded the behavioral data collected with the IC task onto a secure flash drive for the statistical analysis and confirmed with the MRI technologist that all neuroimaging data were uploaded to the appropriate participant folder associated with the study. All images stimuli containing the participant's child were permanently removed from the MRI lab desktop. After the participant returned to the lab lobby, only the OUD group completed a fourth time the OC-VAS scale (Visit 2 / Part 2) to measure post-scan/post-task opioid craving, Both groups completed the post-scan stimuli assessment rating (1-100 on the sliding scale) on the laboratory laptop, wherein they rated the stimuli of the five categories presented during the IC task; both groups were given their gift card compensation ($50 for the NHC group, $100 for the OUD group), and signed the form confirming receipt. Participant involvement was then complete, and participants left the MRI laboratory and Peterson Hall.

2.5 Statistical Data Analyses

The statistical analyses for the questionnaire (demographic/ screening, trait-based, and state-based) and behavioral data (RT in ms, ER in % from the IC task, post-scan stimuli assessment ratings) were carried out using SPSS Version 23 (Statistical Package for the Social Sciences, IBM Corp, 2020) with a statistical threshold of $p<0.05$ (two-tailed). The descriptive statistics (mean, range, median, standard deviation, standard error) for all data were calculated and Shapiro-Wilk ($n < 2,000$) tests were performed to test for normal distribution. If individual measures were not normally distributed, non-parametric testing

(i.e., two-sample Mann-Whitney tests) was applied. Otherwise parametric testing (i.e., independent sample t-tests, and analysis of variance [ANOVA], analysis of covariance [ANCOVA]) was utilized. Post-hoc follow-up dependent and independent t-tests were performed for significant main or interaction ANOVA/ ANCOVA effects.

Questionnaire data analysis. The questionnaire data were downloaded from Qualtrics and questionnaire scores were calculated according to questionnaire manuals.

Demographic/ screening questionnaires. Non-parametric testing (e.g., Chi-square test, Mann-Whitney tests) was performed to compare demographic/ screening data (e.g., race, ethnic origin, birth control use, and gender of youngest child) between groups (NHC, OUD). Questionnaire scores that survived group comparison were selected as covariates for the behavioral data analysis (IC task), but only if this measure was relevant to the outcome parent-child attachment. For the intent of this study, education was selected as the only demographic covariate. The significant differences between groups in the age at which the participant had their first child are further elaborated in the Discussion section.

Trait- and state-based questionnaires. Since the trait-based measures included 50 subcategories and the state-based measures included four categories, Bonferroni corrections (Trait-based: $p<0.05/50<0.001$, State-based: $p<0.05/4<0.0125$) were applied to account for multiple comparisons. Trait- and state-based questionnaire measures that survived Bonferroni correction were selected as covariates for the behavioral data analysis (ICT), but only if the measure was relevant to the outcome of measuring parent-child attachment. Due to the focus of this study, the dependent attachment style (AAS-Dependent) and the Metacognition about Negativity and Worry (MCQ30-Negative) were

the only survey measures selected as covariates. The Social Network Index-High Contact Role was not selected as a covariate, as this measure was irrelevant to the parent-child attachment outcome measure. Note that further discussion on demographic and questionnaire subcategories that were significant and not included in the behavioral and fMRI analysis are elaborated on in the discussion section.

WHOTO questionnaire. The parent-child attachment WHOTO questionnaire was arguably the most relevant to the main outcome measure of assessing the attachment between the mother and child for both groups. This questionnaire was a multi-level assessment of attachment experienced between participant and their romantic partner, and participant and their child. Due to the complexity of the survey, this questionnaire was analyzed independent of the other questionnaires. Group comparison did not survive Bonferroni correction (50 subcategories, $0.05/50 = 0.001$, $p < 0.001$); and, therefore, those measures were not used as covariates in the behavioral data analysis.

OC-VA scale. Only the OUD group completed the OC-VA scale and a 2 x 2 ANOVA on those scale measures was performed with Visit (1, 2) and Part (pre, post) as within-subjects factors.

Behavioral Data Analysis. Behavioral data analysis included measures from the ICT and post-scan stimuli assessment ratings.

ICT measures. Participants who encountered button box malfunction (NHC: 3 out of 17, OUD: 3 out of 15) were removed from the data analysis. Data were aggregated into the five experimental categories (OC, FC, FD, NO, OP) and one control category (SP) used as a covariate to control for participants' sensorimotor responses. A 5 x 2 ANCOVA on

behavioral data was performed with Category (OC, FC, FD, NO, and OP) as a within-subjects factor, Group (NHC, OUD) as between-subjects factor, and years of education, dependent attachment style, and metacognition about negativity, and SP cue measures (RT, ER) as covariates.

Post-scan stimuli assessment ratings. A mixed ANCOVA on post-scan stimuli assessment ratings was performed with Category (OC, FC, FD, NO, and OP) as a within-subjects factor, Group (NHC, OUD) as a between-subjects factor, and years of education, dependent attachment style, and metacognition about negativity as covariates.

3. Results

3.1 Demographic Data

The descriptive and inferential statistics for participant demographics are presented in Table 1. Significant differences were found between the OUD and NHC in years of education ($p < 0.001$) and Age at first pregnancy ($p < 0.001$).

***Table 1**. Descriptive and inferential statistics on participant demographics for OUD and NHC groups.*

OUD Group (M±SD)	**NHC Group (M±SD)**	**Significance (p)**
Age		
34.00±3.89	39.00±8.33	$t(30)=1.98$, p=0.057
Years of Education		
12.00±2.60	17.60 ±3.52	$t(30)=5.16$, p<0.001
Age first pregnancy		
21.60±4.06	30.10±4.58	$t(30)=3.49$, p=0.002
Age of child used in the study (youngest child)		
8.82±4.32	6.53±4.49	$t(30)=-1.47$, p=0.150
Race (White/AA/Asian)		
White: 15.00	White: 12.00	χ^2 (2)= 2.56, p = 0.300
African American: 2.00	African American: 1.00	
Asian: 0.00	Asian: 2.00	
Ethnicity (Hispanic/Not Hispanic)		
Hispanic/Latino: 0.00	Hispanic/Latino: 2.00	χ^2 (1)= 2.60, p = 0.110

Not Hispanic/Latino: 17.00	Not Hispanic/Latino: 12.00	
Birth Control (BCP/no BCP)		
BCP: 0.00	BCP: 1.00	χ^2 (1)= 1.28, p = 0.260
No BCP: 17.00	No BCP: 14.00	
Child Gender (son/daughter)		
Daughter: 9.00	Daughter: 5.00	χ^2 (1)= 1.25, p = 0.27
Son: 8.00	Son: 10.00	
Age 1st opioid use		
20.XX±4.47	N/A	Range:
Years of opioid use		
14.XX±8.01	N/A	Range:
Last opioid use (days) before participant consent		
376.XX±1238.43	-	Range: 1.00 - 5,120.00

3.2 Questionnaire Data

Trait questionnaires. Descriptive and inferential statistics for the trait-based questionnaire data are presented in Table 2. Questionnaire results are scored by subcategory. Significant differences were found between NHC and OUD in the following subcategories: Dependent Attachment style (AAS-Dependent), negative metacognition about uncontrollable thoughts (MCQ30-Negative Beliefs about Uncontrollability and Danger), and high contact roles within their social network (SNI-High Contact). Looking at the WHOTO – region enmeshment for the parent-child dyad, the subcategory is significant when evaluated irrespective of the other subcategories in all Trait questionnaires (p=0.035). The possible

connection between this and the SNI results will be exlaborated on further in the discussion section.

Table 2. *Descriptive statistics on the trait questionnaires that were administered to all participants. "+" indicates the data is normally distributed, "*" indicates the data is not normally distributed.*

	OUD	**NHC**	**Significance (Bonferroni correction, p<0.001)**
Trait Subcategories	M±SD	M±SD	P value
Adult Attachment Scale (AAS)			
Close+	3.15±0.82	3.39±0.66	0.360
Anxious+	3.04±0.88	2.2±0.84	0.010
Dependent*	2.52±0.86	3.53±0.77	0.002
Cambridge Friendship Questionnaire (CFQ)			
Total+	80.88±11.52	85.4±12.41	0.290
Emotional Contagion Questionnaire (ECQ)			
Sadness+	10.41±2.67	10.2±3.10	0.840
Happiness+	12.94±1.89	11.47±2.70	0.080
Anger+	9.18±2.43	9.8±2.01	0.440
Love+	12.65±2.87	10.33±2.97	0.033
Fear+	11.47±2.53	10.27±2.69	0.200
Total+	56.65±7.69	52.07±8.79	0.130
Experiences in Close Relationships (ECR)			
Anxiety*	26.35±6.56	20.00±6.80	0.012
Avoidant*	19.29±8.01	12.67±7.05	0.019
Emotional Quotient (EQ)			
Total+	58.41±9.01	58.67±7.05	0.930
Interpersonal Reactivity Index (IRI)			
Fantasy+	2.3±0.83	2.25±.071	0.840
Perspective-Taking +	2.95±0.68	2.72±0.54	0.300

Empathy Concern *	3.42±0.60	2.98±0.44	0.027
Personal Distress *	2.03±0.75	1.43±0.71	0.026
Machiavelli – IV (MACH-IV)			
Total +	3.98±1.14	4.25±0.42	0.390
Metacognition Questionnaire – Opioid (MCQ-OUD)			
Positive Cognitive Regulation+	12.24±5.44	-	-
Positive Emotional Regulation+	13.88±4.90	-	-
Negative Uncontrollability+	13.00±4.50	-	-
Negative Cognitive Interference+	12.06±5.06	-	-
Total+	51.18±15.35	-	-
Metacognition Questionnaires 30 (MCQ-30)			
Lack of Cognitive Confidence+	12.59±5.30	11.07±4.77	0.400
Positive Beliefs about Worry+	9.24±3.29	9.93±2.76	0.520
Cognitive Self-Consciousness+	15.71±4.27	14.33±4.50	0.380
Negative Beliefs about Uncontrollability and Danger*	14.59±6.04	8.73±2.25	0.001
Need to Control Thoughts*	11.24±2.86	9.13±3.16	0.058
Total+	63.35±12.85	53.2±10.15	0.020
NEO Five Factor Inventory (NEO)			
Neuroticism+	3.41±0.66	2.91±0.75	0.051
Extraversion+	3.63±0.44	3.36±0.43	0.085
Openness+	3.48±0.54	3.48±0.67	0.990
Agreeableness+	3.71±0.52	3.75±0.51	0.830
Conscientiousness+	3.60±0.73	3.73±0.69	0.610
Rushton Altruism Scale (RAS)			
Score+	58.29±9.06	62.33±7.18	0.180
Relationship Quotient (RQ)			
Numeric Score – self identification +	2.12±0.93	1.67±1.05	0.210
Social Network Index (SNI)			
Total High Contact role*	4.18±2.19	6.47±1.03	0.001
Total Social Network *	9.00±10.21	22.53±12.26	0.002
Social Provisions Scale (SPS)			
Total+	71.18±20.24	84.27±9.18	0.028

Social integration *	11.41±3.39	14.00±2.07	0.016
Attachment +	12.41±3.62	14.20±1.66	0.090
Opportunity for nurturance *	11.76±3.55	14.73±2.09	0.008
Reassurance of worth +	11.24±3.53	12.87±1.92	0.120
Reliable Alliance+	12.29±4.04	14.27±1.83	0.093
Guidance +	12.06±3.83	14.2±1.86	0.059
State-Trait Anxiety Inventory – Trait Anxiety			
Total +	49.06±9.59	41.20±8.35	0.020
Social Value Orientation (SVO)			
Angle *	34.47±8.04	40.22±6.81	0.038
Toronto Alexithymia Scale (TAS)			
Difficulty describing feelings +	12.53±4.24	10.93±3.86	0.277
Difficulty identifying feelings+	17.00±5.50	12.60±4.56	0.021
Externally-oriented thinking+	17.70±5.02	19.33±2.99	0.280
Total +	47.47±10.75	42.87±9.47	0.210
Trust Self Report (TSR)			
Careful+	0.88±0.33	0.67±0.49	0.150
Trust+	0.35±0.49	0.67±0.49	0.081
Total+	9.06±2.46	10.73±2.09	0.048
UCLA – Loneliness Scale (UCLA-LS)			
Total*	28.59±15.19	14.07±13.06	0.007
WHOTO			
Safe Haven +	2.89±0.86	3.12±0.67	0.420
Separation Distress +	2.61±1.07	3.01±0.69	0.230
Secure Base +	3.04±0.75	3.10±0.59	0.780
Proximity Seeking +	3.01±0.75	3.27±0.42	0.250
Attachment- Romantic Partner			
Scale 1 +	3.95±1.52	4.77±0.41	0.054
Scale 2 +	3.69±1.27	4.30±0.78	0.120
Region Enmeshment +	4.88±2.39	5.13±1.64	0.730
Scale 3 +	5.25±2.01	6.13±1.43	0.170
Scale 4 +	4.31±1.81	3.15±1.27	0.049
Scale 5 +	6.75±2.98	6.71±2.45	0.970
Scale 6+	3.31±1.47	3.07±0.91	0.600

Attachment - Child			
Scale 7 +	4.33±0.99	4.82±0.27	0.076
Region Enmeshment +	4.00±2.42	5.60±1.45	0.035

State questionnaires. Descriptive and inferential statistics for the state questionnaire data are presented in Table 3. Significant differences were found between the OUD and NHC in the emotional experience they had over the past week (PANAS - Positive and PANAS – Negative).

Table 3. *State report questionnaire descriptive and inferential statistics T30. "+" indicates the data is normally distributed, "*" indicates the data is not normally distributed .*

	OUD	**NHC**	**Significance (Bonferroni correction, p < 0.010)**
State Subcategories	M±SD	M±SD	P value
Positive and Negative Affect Schedule (PANAS)			
Positive *	39.29±6.80	27.73±10.70	<0.001
Negative*	21.82±7.15	14.60±5.21	0.003
Profiles of Mood States (POMS)			
Total Mood Disturbance+	13.53±20.68	17.14±21.75	0.647
Clinical Opioid Withdrawal Scale (COWS)			
Total +	0.18±0.53	0.73±0.88	0.036

OC-VA scale. The OUD group completed the OC-VA scale, and the craving evaluation was administered pre- and post- visit 1 and visit 2, for four (4) data pieces for each participant. Figure 2 displays the OC-VA scale ratings (means [M] ± standard error of the

mean [SEM]) on which a 2 x 2 ANOVA was performed with Visit (1, 2) and Timing (pre-task, post-task) as within-subjects factors. There were no main effects of Visit and Timing, neither a Visit x Part interaction effect. Paired sample t-testing indicate that the OC-VA ratings between the pre-and post- visit One evaluation are significant ($p = 0.0170 \pm 19.02$); however there is no significant increase in OC-VA scoring between the pre- and post- visit two evaluation ($p > 0.001$).

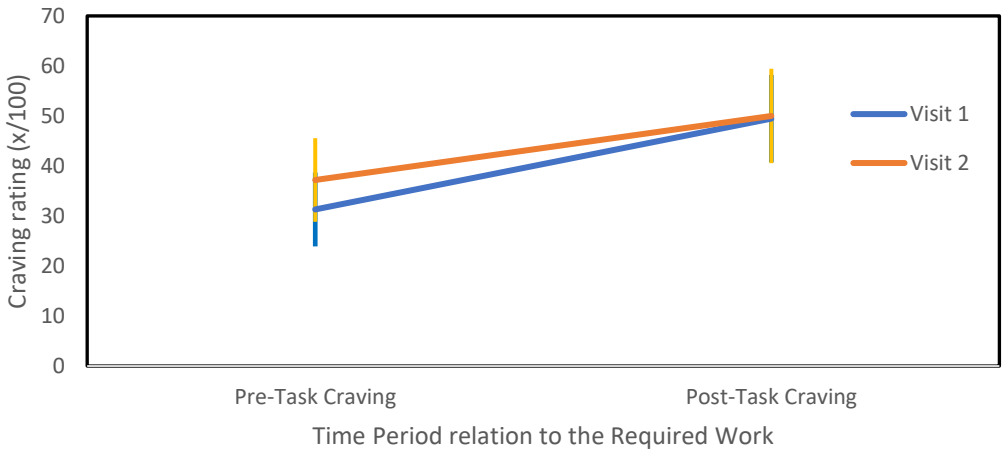


Figure 2. *Comparison of OCVA-S ratings by the OUD group during Visit 1 and Visit 2, pre-task and post-task, $p<0.05$.*

3.3 Behavioral Data

Response Time. Normality testing on the Response Time (ms) revealed the data is normally distributed. Independent sample t-testing revealed significant difference between

groups for RT to the opioid cue (p=0.040). Figure 3 displays the adjusted means for response times (M±S.E.M) for the five individually curated cues utilized in the matching task: own child, familiar child, food, neutral, and opioid controlled for SP error rate, years of education, dependent attachment style, and meta-cognition about negativity/danger as covariates.

A mixed ANCOVA on the Response Time (ms) was performed with cue Category (OC, FC, FD, NO, and OP) as a within-subjects factor, Group (NHC, OUD) as a between-subjects factor, and years of education, dependent attachment style, and meta-cognition about negativity/danger, and the RT for the sensorimotor control cue Shape as covariates. Dependent attachment style (p=0.008) and shape response time (p=0.007) mainly affected the RT for participants across cue categories. Dependent attachment style and shape response time were predictive factors for the RT. No interaction effects were observed.

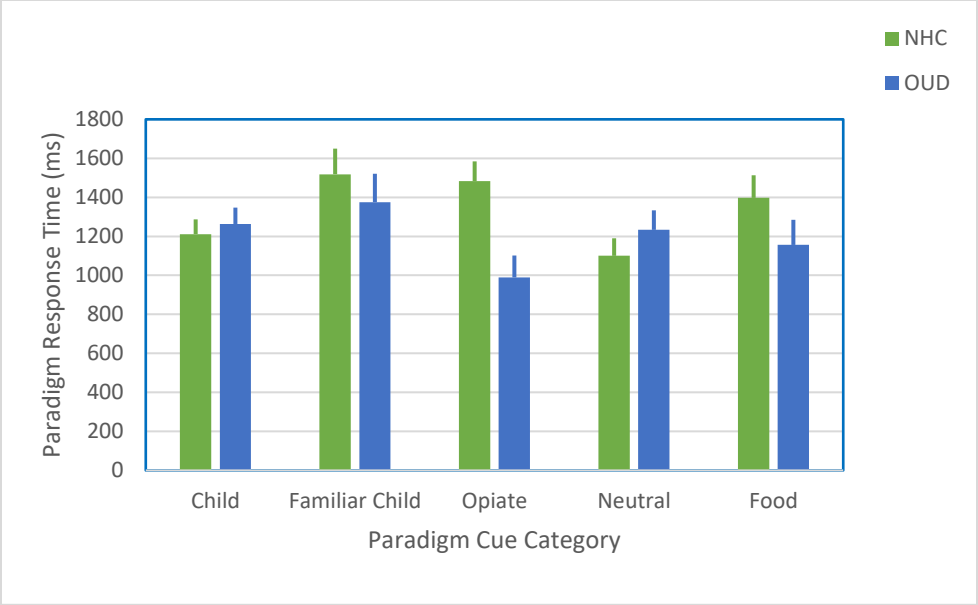


Figure 3. *Response Time for Matching Task. Adjusted means for response time (RT, ms) and standard error of the mean for the cue categories controlled for SP response time, education, attachment style (dependent), and meta-cognition (negative beliefs), and SP cue as covariates*

Error Rate. Normality testing on the ER revealed the data were not normally distributed. Nonparametric testing revealed a significant difference between groups for ER in response to the opioid cue (p=0.049).

Figure 4 displays the adjusted means for the error rate (%) (M±S.E.M) for the five individually curated cues utilized in the matching task: own child, familiar child, food, neutral, and opioid, controlled for SP error rate, years of education, dependent attachment style, and meta-cognition about negativity/danger as covariates.

Figure 4. Average Task Error Rate as a percentage (%) per group by paradigm cue category: Child (own child), familiar child, Opioid (IV/IN, IV for NHC), Neutral item, and Food. Error bars indicate standard error mean. Results controlled by covariates: Years of Education, Attachment Style- Dependent, MCQ30-Negative, and SP cue.

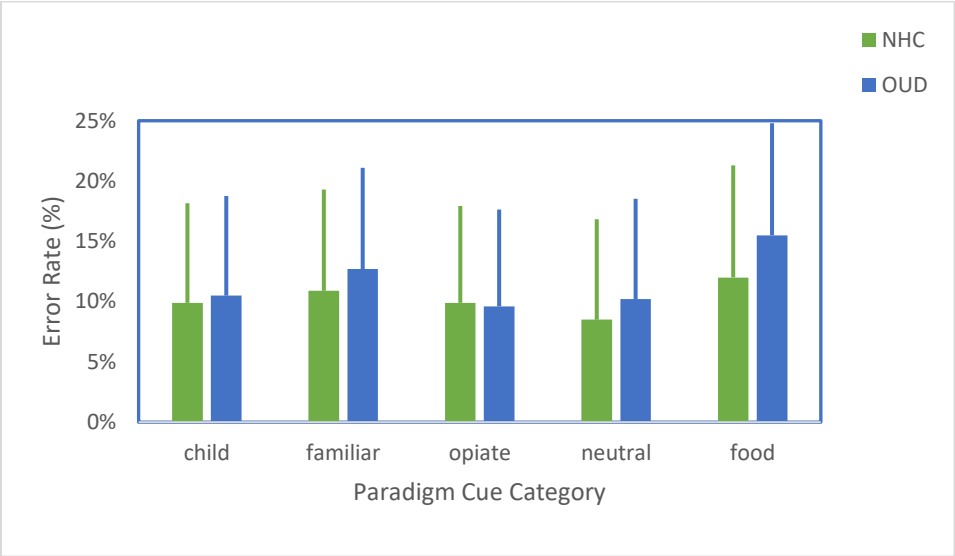


Figure 4. *Average Task Error Rate as a percentage (%) per group by paradigm cue category: Child (own child), familiar child, Opioid (IV/IN, IV for NHC), Neutral item, and Food. Error bars indicate standard error mean. Results controlled by covariates: Ye ars of Education, Attachment Style- Dependent, MCQ30-Negative, and SP cue.*

Post-Scan-Stimuli. Normality testing on the post scan stimuli cues (scale score 1-100) revealed the data was normally distributed. Independent sample t-testing revealed significant differences between groups for the rating in response to the opioid cue ($p<0.05$, $p=0.00$). Figure 5 displays the adjusted means for the post-scan stimuli (M±S.E.M) for the five individually curated cues utilized in the matching task: own child, familiar child, food, neutral, and opioid, controlled for SP error rate, years of education, dependent attachment style, and meta-cognition about negativity/danger as covariates. A mixed ANCOVA on the Post Scan Stimuli was performed with cue Category (OC, FC, FD, NO, and OP) as a within-subjects factor, Group (NHC, OUD) as a between-subjects factor, and years of

education, dependent attachment style, and meta-cognition about negativity/danger, and the SP Error Rate as covariates. Group (p =0.048) had a main effect on the post-scan stimuli for participants across all cue categories. The group is a predictive factor for the stimuli rating. No interaction effects or within subject contrasts were observed. [pairwise comparisons are all significant].

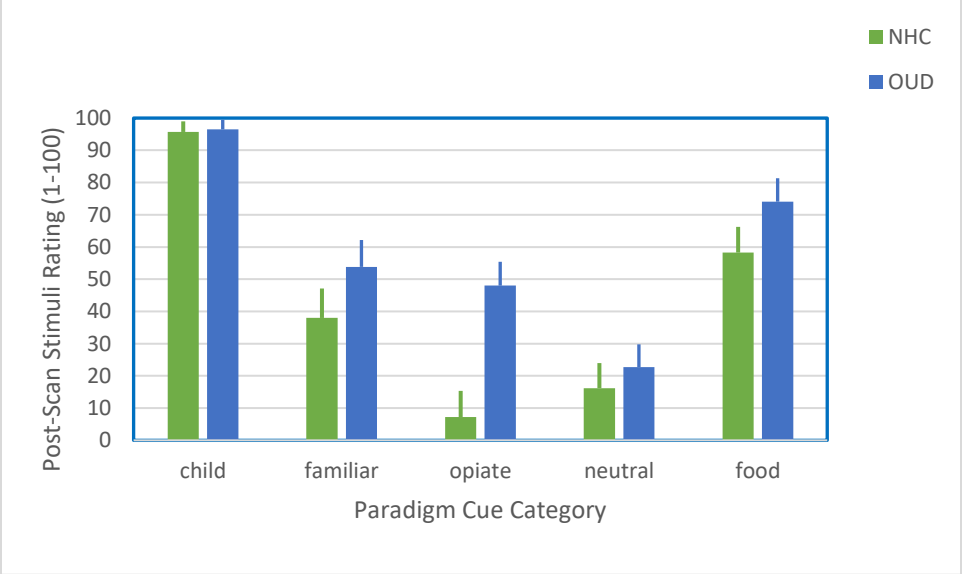


Figure 5. The Post Scan Stimuli Rating Sliding scale (1-100) of the stimuli for each participant while under task. Error bars account for the standard error mean, with a confidence interval of 95%. They were displayed per grou[by paradigm cue category: Child (own child), familiar child, Opioid (IV/IN, IV for NHC), Neutral household item, and Food. Results controlled by covariates: Years of Education, Attachment Style- Dependent, MCQ30-Negative.

4. Discussion

4.1 Overall Summary

In this study, we examined maternal attachment and the maternal-child bond in women affected by opioid use disorder. Our objective in the study was to investigate the effect of OUD on the parent-child bond, attachment, and metacognitive abilities/thought processing abilities in affected mothers; investigate the relationship between drug cue salience and subsequent drug craving; and examine the relationship between OUD and maternal behavior. Data points of interest included the following: visual salience towards cues of the participant's youngest child, behavioral choices in response to visual cues under task, tonic/phasic craving of opioids, parent-child enmeshment, and self-report evaluations across emotional trait and state categories. Overall, we hypothesized that the alteration in the system of attachment by OUD would manifest via adverse thought processes and behavior in the patients, culminating with detrimental treatment of their child. These alterations were tested at the demographic level, the self-report trait level, the self-report state level, and finally at the behavioral level. Tools utilized in the study included clinical diagnostics, self-report questionnaires, task-based cues in a functional imaging paradigm, and functional MRI scanning (which was not the focus of this thesis). By exploring these research objectives, we aimed to deepen our understanding of the impact of addiction on maternal attachment and neural functioning. Ultimately, this study may contribute to the development of targeted interventions and treatments to support women with addiction and promote healthy attachment relationships with their youngest children.

Questionnaires Measures. First, we discuss the results from the self-report measures, including demographic, trait-based, and state-based questionnaires.

Demographic level. We predicted that women who have children at a younger age have statistically fewer years of education than women who have children older We also predicted the OUD group would be significantly younger at the age of their first pregnancy.

Trait level. Due to patients experiencing poor attachment histories caused by or correlated with addiction, we predicted the OUD will self-report unhealthy attachment styles with their interpersonal/romantic partner relationships. The OUD group will also self-report unhealthy attachment styles and low levels of enmeshment in their relationship with the youngest child, the same child who was used as their cue in the study. We predicted adverse metacognitive differences in the OUD due to maladaptation from opioid addiction. Due to the hijacked impulse control, altered thought patterns, and lack of metacognitive strength resulting from addiction patterns in behavior and information processing, the OUD group will self-report metacognitive abilities at a below-control level. Lastly, quantitative evaluation of social networks will yield a lower number in size of their social networks due to decreased socialization inherent in opioid addiction and neurochemical changes that affect social attachment and behavior reinforcement.

Our study identified significant differences in various psychological factors assessed via a self-report questionnaire. These differences encompassed the dependent attachment style, metacognitive beliefs regarding negative occurrences and worry about the future, the number of high-contact individuals within the social network, and levels of parent-child enmeshment. These factors were employed as covariates in statistical

evaluation of the behavioral results. These factors are also key in generation of future hypotheses and research on opioid addiction.

State level. We predicted differences in the emotional affect wherein the OUD experiences dysregulation and higher sensitivity to strong and overwhelming emotions that are difficult to control. Therefore, the OUD will be more likely to display higher levels of emotional affect in both positive and negative categories. We predicted significant increases in the OCVA-Scale after exposure to the opioid cue during Phase I of the experiment after the participant selects their salient visual cue (IV or IN), and after Phase II of the experiment during which the participant completed the matching task. OCVA-Scale score increases are attributed to the craving potential after exposure to each favored opioid cue. Other contributing factors in this craving increase may be stress, performance anxiety, and desire to mitigate discomfort from participation in an unfamiliar environment, i.e a clinical research study under task during a fMRI scan.

Behavioral Measures. Second, we discuss the results from the behavioral measures (RT, ERT) collected with the ICT. We predicted group differences in the response speed and error rate to the cues while under task. Due to a lack of impulse control, OUD will respond faster while under task. With this speed and potential disregard for correct cue choice, OUD will also have a higher error rate. Specific to the cue category, OUD will have a faster reaction time to the opioid cue and a higher error rate to the opioid cue than the NHC, due to the salient nature of the opioid image to the OUD patient. Finally, there will be significant differences between groups in the post-scan stimuli rating across cue categories.

We expected significant differences in the post-scan stimuli rating specifically for the C and the O cues.

First, we evaluated the self-report results from the demographic, trait-based, and state-based questionnaires. Second, we evaluated the behavioral response results collected while the patients were under task while scanning. Statistical analysis identified significant distinguishing factors in the OUD group. This identifies the potential effects of the hijacked dopaminergic limbic pathways in the reward system influenced by years of opioid use. We hypothesized that neurobiological changes would impact their behavioral response to varying cues during the task, and their self-report evaluations.

At the demographic level, regarding the educational background, there was a significant difference between the OUD and NHC groups regarding years of education, with the OUD group having a lower mean. This finding is consistent with the global demographic theory, which suggests that increased years of education lead to a delayed childbearing age in women. It is observed that women with 12 years of education or less tend to have higher Total Fertility Rates. In contrast, the TFR rates decline as women acquire higher levels of education, in order from associate's, bachelor's, master's, and doctoral degrees. These demographic disparities may have implications for understanding the influences and experiences related to addiction and maternal roles.

At the trait level, the study identified significant differences in various psychological factors assessed via a self-report questionnaire. These differences encompassed: the dependent attachment style, metacognitive beliefs regarding negative occurrences and worry about the future, the number of high-contact individuals within the

social network, and levels of parent-child enmeshment. These factors were employed as covariates in evauating the behavioral results. These factors are also key in the generation of future hypotheses and research on opioid addiction.

At the state level, the study found significant differences in both negative and positive emotional affect. Some differences approached significance in craving pre- and post- task as evaluated by the OCVA-Scale.

At the behavioral level, when controlling for the significant traits (AAS, MCQ30), our findings revealed OUD patients demonstrated residual salient qualities in response to the opioid category task cues, indicating a comparatively heightened response. This suggests that cues associated with opioids still hold significant salience for patients, reflecting the enduring impact of addiction on cognitive and emotional processing. No differences were detected in response to cues associated with the participants' children, implying that patients exhibit similar levels of salience and responsiveness to cues related to their child compared with healthy mothers. These findings highlight the importance of exploring the complexities of salience and emotional processing within the context of addiction and maternal attachment.

The significant qualities identified in our self-report measures were used as covariates in the statistical processing of the behavioral response data. Adult Attachment Scale and the MCQ30-Negative results were used as covariates in the behavioral analysis to account for the ubiquitous influence of opioid addiction on the mesolimbic pathway and changes in attachment attribution among OUD patients. The Social Network Index provided a count of high-contact individuals within the participant's social network,

including individuals outside the family. Although the SNI results were significant, and relevant in assessing broader concepts of addiction, it is not directly relevant to studying the specifics of the mother-child relationship at this level. Therefore, the SNI was eliminated as a covariate in behavioral analysis.

Overall, these findings provided valuable insights into the demographic, psychological, and behavioral aspects related to addiction and maternal roles. Understanding these factors can contribute to the development of targeted interventions and support systems aimed at promoting healthy maternal attachment and addressing the unique challenges faced by individuals with addiction. New avenues for research direction in addiction studies were illuminated based on these results.

Regarding the fMRI scan results, it is important to acknowledge that data was collected but not used in this research. The results were underpowered, meaning the sample size may not have been large enough to detect significant neural markers.

Individual differences of metacognition and self-awareness inherent in the OUD patients may have influenced self-report measure results. The control group may have had stronger metacognitive abilities and self-awareness as a result of consistent practice in their daily life, which could have impacted their self-report responses. In contrast, the OUD patients may have exhibited a lack of metacognitive strength, potentially affecting their self-report measures. Acknowledging these limitations is important for a understanding the study's outcomes. Future research with larger sample sizes, refined paradigms, and diverse assessment tools could further explore these complex dynamics

and improve our understanding of addiction's influence on maternal attachment and cognitive processes.

The participant recruitment for this study was constrained by the study location, which was the recovery center of NCTR for individuals with opioid use disorder (OUD), as well as the social networks of the researchers who recruited participants from the NHC (non-OUD control) group. Among the participants from both groups, 27 were White, three (3) were African American, and two (2) were Asian. Expanding the recruitment web outside of the DC-Metro area into variegated socioeconomic regions may provide more information on demographic indications of OUD in motherhood.

One of the objectives was to develop a comprehensive set of questionnaires for assessing the addiction recovery status and remission of OUD patients. Additionally, building a Theory of Mind model specific to OUD patients is a broader goal in the field of addiction psychology. Including specific questionnaires is crucial due to significant mean score differences in the OUD cohort. The following questionnaires are essential for evaluating OUD patients and studying attachment: Adult Attachment Scale, Metacognitions Questionnaire, Social Network Index, and Positive and Negative Affect Schedule.

The WHOTO measurement of parent-child enmeshment was identified as a significant subcategory that does not pass Bonferroni correction for use as a covariate. The first category of the WHOTO has potential as a comparative list evaluated with the roles identified in the SNI evaluation. There is potential for the identification of crossovers in evaluating the roles that individuals play via the SNI, and then observing

how those same individuals are scored within the WHOTO. This questionnaire has the potential to be modified for further use in OUD self-report evaluation, however does posess limitaitons. It is a one-dimensional questionnaire that can be used to exclusively report on the parent-child bond, however it reauires an increase in sensitivity to detect of maternal-child bond differences. In the WHOTO utilized, only two subcategories out of thirteen reported on the parent-child bond, and expanding the scope of quesitoning to include more measures regarding parent-child bonding would be beneficial. Measuring the enmeshment, attachment, and WHOTO subcategories (safe haven, separation, secure base, proximity) utilized in this questionnaire as applied to maternal-child bond could improve the self-report results with more distinct differences between experimental groups.

OC-VAS assessments are necessary to establish pre- and post-cue exposure craving scores for each OUD participant, particularly focusing on the "Opioid" cue in the Post-Scan stimuli subcategory. One addition to the questionnaire battery is the inclusion of a pre and post-scan assessment requesting the emotional desire of the participant to see their child (C). This may be useful in establishing a comparison to the OC-VAS and the COWS assessments in assessing opioid withdrawal, in parallel or against the strength of the maternal-child bond.

The OUD exhibited significant behavioral differences in response to the opioid cues. Notably, the OUD group exhibits a significantly faster reaction time (RT) to the opioid cue. This finding supports the initial hypothesis, that the lack of impulse control would yield a significantly faster RT across all cue categories. However, the only

significantly fast RT was identified in response to the opioid cue – all other behavioral responses were within normal range. The significance of RT to the opioid cue may be attributed to the OUD participants' familiarity with the IV/IN drug of choice, and the salient nature of the cue as stimulated in the visual cortex. The role of craving Another explanation may be that the control participants' experienced surprise or discomfort in reaction to the intravenous opioid cues (IV), and required additional time to evaluate the stimuli and respond using the button box.

Among the selected covariates, the AAS-Dependent subcategory is the only covariate with a significant main effect on RT by group. This subcategory assesses the participant's self-perceived ability to depend on others and have others depend on them. The NHC group scored significantly higher than the OUD group, indicating a main effect on response time between the control and OUD groups. When considering both the self-report measure and the behavioral results, it can be inferred that a more dependent attachment style leads to a slower response time in the control group. This suggests a more thoughtful approach to cues, in contrast to a reactive response observed in the OUD group.

The study contributes to the theoretical understanding of the maternal bond by demonstrating its resilience in the face of opioid addiction, as demonstrated by unremarkable differences in the OUD behavior responses. It challenges the notion that addiction pathways completely hijack the maternal bond, and provides evidence that the bond can endure despite the impact of addiction. This finding adds nuance to our understanding of the complex interplay between addiction and maternal attachment,

contributing to the broader theoretical literature on bonding. The study also contributed to theories related to salience attribution and craving response within the context of addiction. By differentiating cues and examining responses to opioid cues versus child-related cues, the study provides insights into the mechanisms underlying salience attribution and the subsequent craving response. This contributes to theories on cue reactivity, reward processing, and the role of neurobiological pathways in addiction. Further, the findings of this study can contribute to attachment theory, particularly in the context of maternal attachment. Further functional research in support of the self-report and behavioral data is ideal, and can be utilized in the style of previous addiction studies. Studies on nicotine addiction, for example, target the insula, NAc, and amygdala in observing the inability of participants to quit a smoking habit. Cue exposure and subsequent functional imaging have identified cortical activation during cue exposure, and this can be segued into opioid addiction functional imaging research to optimize imaging results via heightened cue valence.

The study's methodology, including the differentiation of cues and the integration of functional imaging and self-report measures, contributes to the field of addiction research. By employing these methods, the study provides a template for future research examining the neural and behavioral correlates of addiction and maternal bonding. This methodological contribution advances our ability to investigate complex phenomena and contributes to the refinement of research tools and techniques in addiction and maternal health studies.

The findings from this graduate thesis have significant practical implications for various stakeholders involved in addiction treatment, maternal support, and policy-making. Firstly, recognizing that the maternal bond can endure despite the impact of opioid addiction highlights the importance of incorporating and preserving the mother-child relationship in addiction treatment programs. By understanding the resilience of this bond, clinicians and treatment providers can develop interventions that capitalize on the inherent strength of the maternal bond to support recovery and improve outcomes for both the mother and child.

Moreover, the identification of differences in the response to opioid cues among individuals with opioid addiction emphasizes the need for tailored approaches to craving management and relapse prevention. Clinicians can use this knowledge to develop personalized treatment plans that specifically address the unique challenges and triggers faced by individuals with opioid addiction. Strategies that aim to strengthen the maternal bond and reinforce positive parenting behaviors can be integrated into addiction treatment programs, fostering a supportive environment for both mother and child.

4.2 Strength and Limitations

Our study possessed several strengths that contribute to its robustness. One notable strength was the ability to differentiate cues, enabling a clear contrast and behavioral response between the child cue, opioid cue, and other cues while controlling for visual recognition and sensorimotor reaction. This differentiation enhances the validity and reliability of the study findings. However, certain limitations need to be acknowledged.

First, a small number of participants in the cohort is one limitation. With a limited sample size, the generalizability of the findings to the broader population may be compromised, and the study's statistical power could be reduced. To address these limitations, future study directions should consider conducting two runs of the imaging paradigm. This approach will increase the viability and robustness of the paradigm itself by providing more data points and replication of results. Additionally, it will allow for the verification of the efficacy of the stimuli in eliciting the desired behavioral and neural network responses. By expanding the sample size and conducting multiple runs, the study will enhance its internal validity and strengthen the generalizability of the findings.

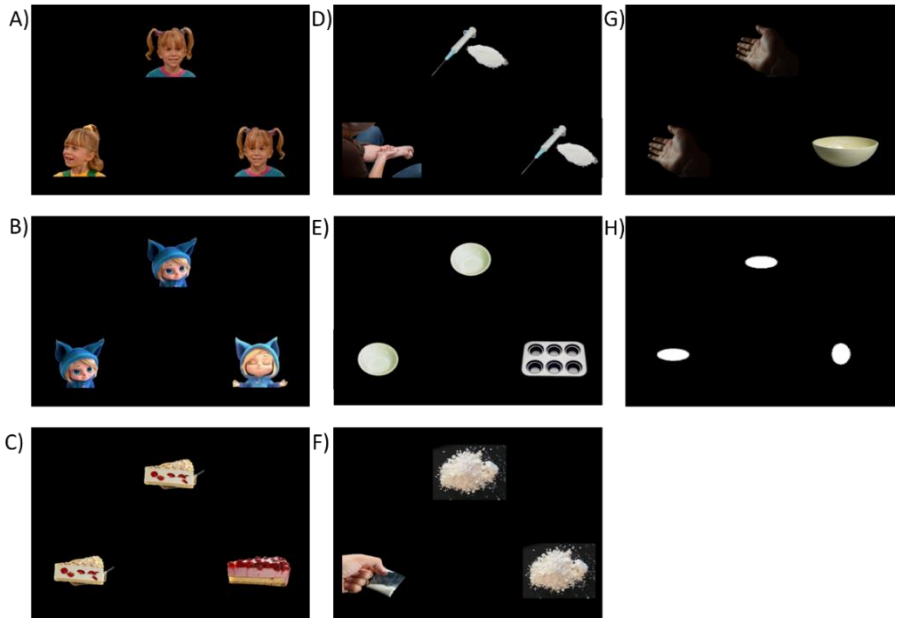
Another limitation is the reliance on self-report measures for certain constructs, which may introduce response biases and subjective interpretations. The study's focus on OUD participants housed in the NCTR may limit the generalizability of the findings to other settings or populations. Additionally, excluding certain demographic groups or comorbid conditions could be a delimitation, potentially impacting the sample representativeness. These factors should be considered when interpreting the results and drawing conclusions. In light of these considerations, future directions of the study could involve exploring the longitudinal effects of addiction treatment on maternal attachment and the neurobiological mechanisms involved. Additionally, investigating the influence of contextual factors, such as social support and stress, on maternal attachment and addiction recovery could provide valuable insights. Further research could also delve into potential interventions or therapeutic approaches aimed at enhancing maternal attachment and recovery outcomes in individuals with OUD.

4.3 Summary and Conclusion

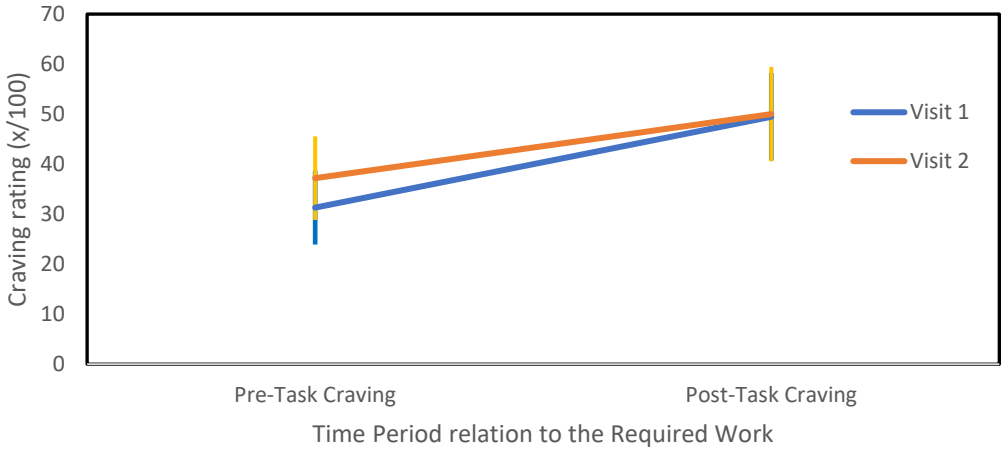
In summary, our study provided insights into the impact of opioid addiction on salient attribution and craving response to opioid cues, utilizing a multidimensional approach with both self report and behavioral measures. Our findings reveal that while opioid addiction influences the response to opioid cues, there are no significant differences in attribution to cues related to one's own child between the groups. This unexpected result challenges the initial hypotheses regarding the potential hijacking of the maternal bond by addiction pathways. Instead, it suggests that the maternal bond may possess inherent strength, enabling it to persevere through the mechanisms of addiction. Furthermore, this study emphasizes the need for the development of strategies that can further explore the neurobiology of addiction in conjunction with maternal bonding and their interconnected effects. Future research can examine potential differences and delve deeper into the underlying mechanisms at play by employing alternative paradigms involving functional imaging tasks and self-report measures.

Appendix A: Figures Guide from the Text

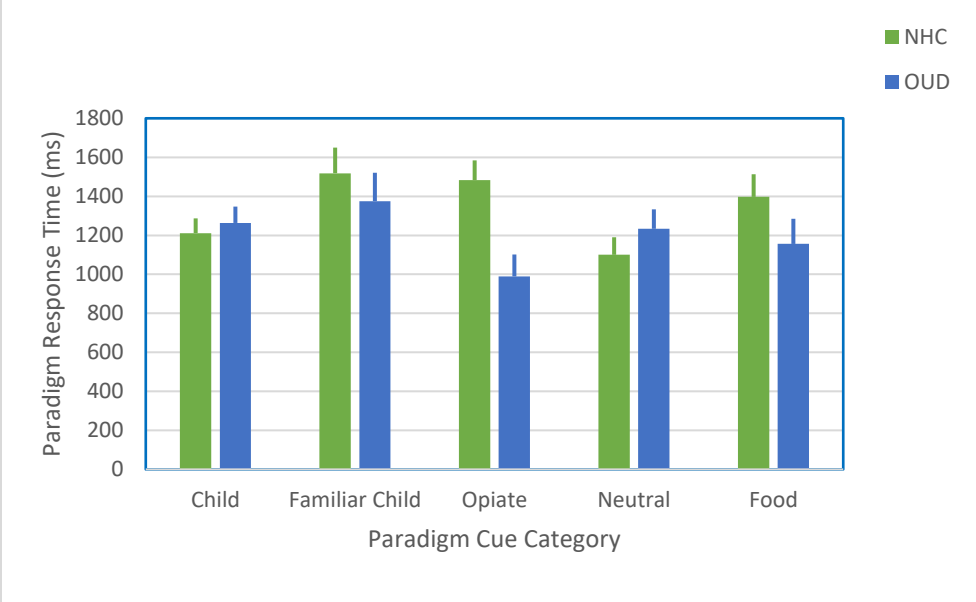
A1: Figure 1



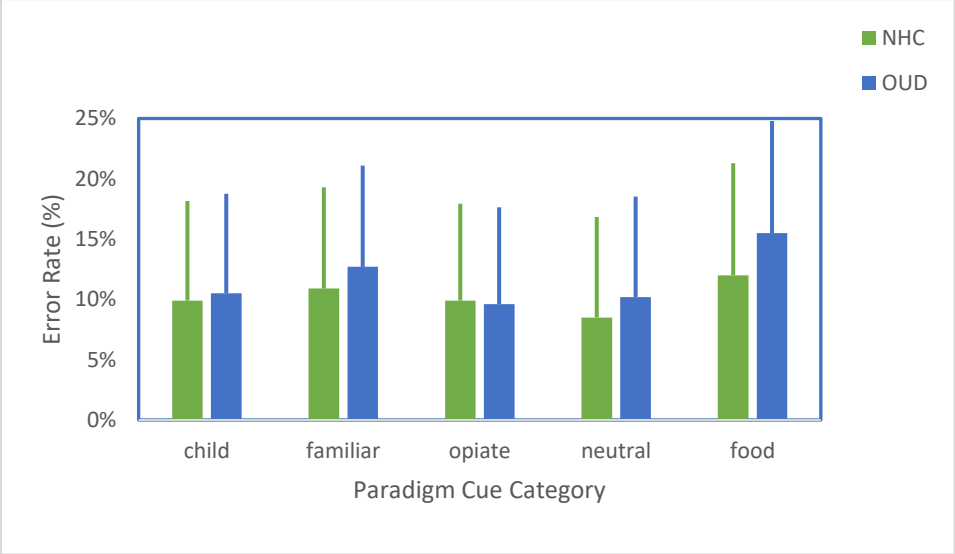
A2: Figure 2



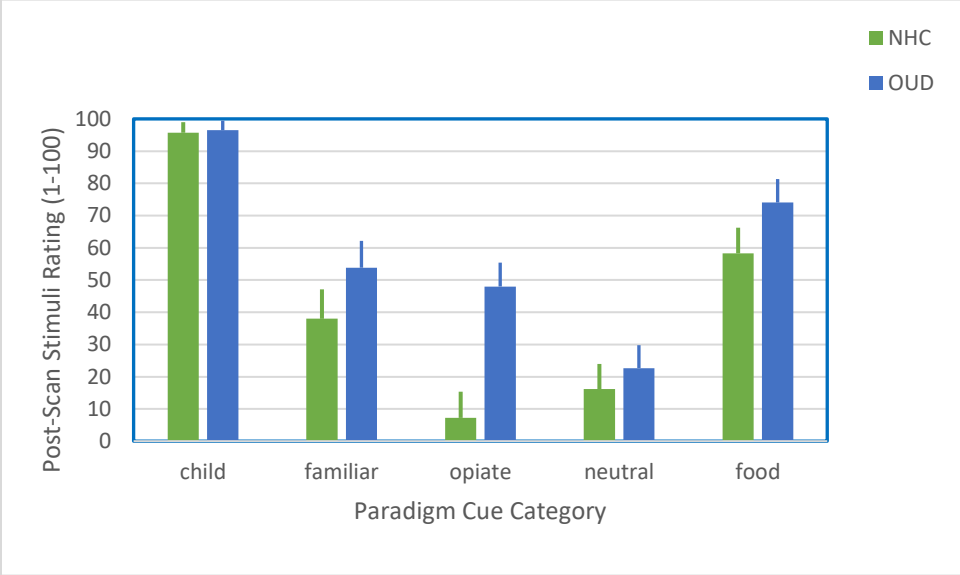
A3: Figure 3



A4: Figure 4



A5: Figure 5

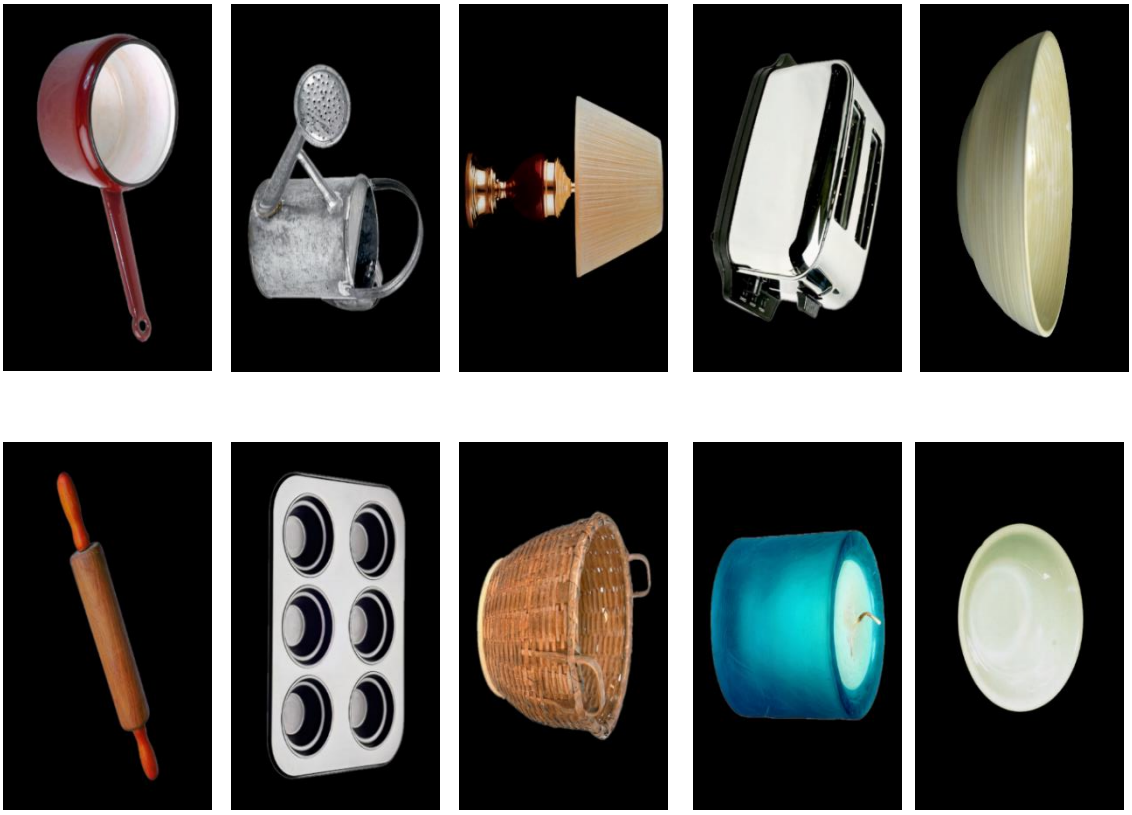

NHC
OUD
Post-Scan Stimuli Rating (1-100)
100
90
80
70
60
50
40
30
20
10
0
child
familiar
opiate
neutral
food
Paradigm Cue Category

Appendix B: Task Cue Library

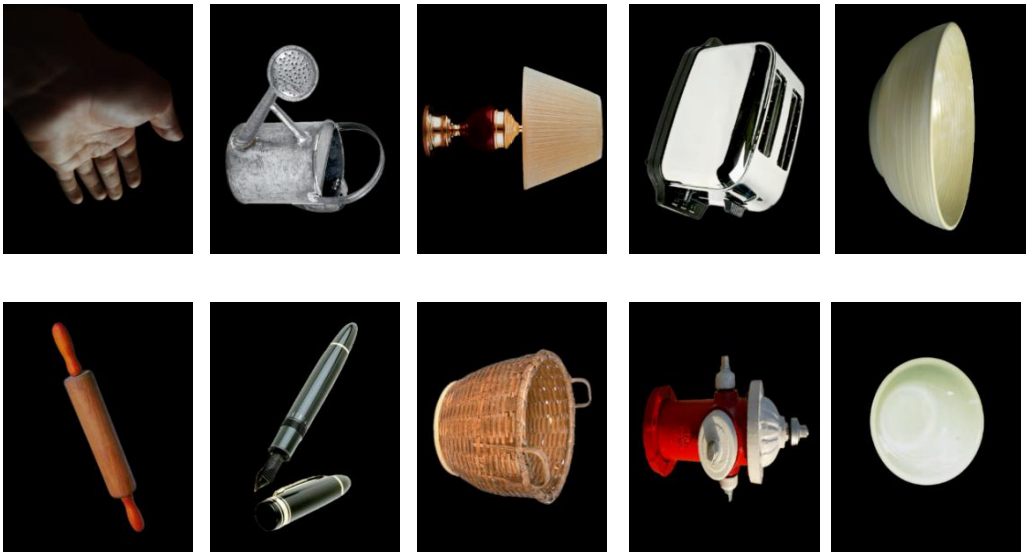
B1. Intravenous Opioid (IV) Cue Library

B2. Intranasal Opioid (IN) Cue Library

B3. Intravenous Opioid Neutral Object (N)



B4. Intranasal Opioid Neutral Object (N)



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Biography

Gwendolyn Kennedy received her Bachelor's in Environmental Studies from Dickinson College in 2015. She worked as an outdoor science educator in San Gorgonio, California after undergrad, before returning to Virginia to pursue a Master's Degree. She has studied at George Mason for a Master's in Biology since 2020, and is a volunteer EMT-B for the Falls Church Fire Department outside of school.