12-2022

Prenatal Opioid Use and Neonatal Abstinence Syndrome: A Review of the Neurophysiological, Neuropsychological, and Behavioral/Emotional/Social Impacts in the Pediatric Population

Candice Gore
National-Louis University

Prenatal Opioid Use and Neonatal Abstinence Syndrome: A Review of the Neurophysiological, Neuropsychological, and Behavioral/Emotional/Social Impacts in the Pediatric Population

Candice Y. Gore, LPC, MAMFT, MA

Florida School of Professional Psychology at National Louis University

Elizabeth Lane, PhD
Chair

Kathie Bates, PhD
Member

A Clinical Research Project submitted to the Faculty of the Florida School of Professional Psychology at National Louis University in partial fulfillment of the requirements for the degree of Doctor of Psychology in Clinical Psychology.

Tampa, Florida
December, 2022

The Doctorate Program in Clinical Psychology
Florida School of Professional Psychology
at National Louis University

CERTIFICATE OF APPROVAL

Clinical Research Project

This is to certify that the Clinical Research Project of

Candice Yvonne Gore

has been approved by the
CRP Committee on December 17, 2022
as satisfactory for the CRP requirement
for the Doctorate of Psychology degree
with a major in Clinical Psychology

Examining Committee:

Elizabeth Lane, PhD

Committee Chair: Elizabeth Lane, PhD

Kathie Bates, Ph.D.

Member: Kathie Bates, PhD

Abstract

The opioid epidemic over the past two decades has raised concerns regarding the developmental fetal impact of prenatal opioid use. Research in this area continues to grow, but largely has focused on treatment for neonates experiencing withdrawal symptoms postnatally. Long term clinical implications for this at-risk population have not been studied extensively leaving many gaps in research and highlighting the need for future empirical studies. This literature review will examine the neurophysiological, neuropsychological, and the behavioral/social/emotional impacts on infants, toddlers, and school aged children who were prenatally exposed to opioids with or without the diagnosis of neonatal abstinence syndrome. Providing a deeper understanding of the possible short- and long-term impacts of these children will better inform physicians, clinicians, teachers, and caregivers on the importance of implementing early interventions with children in this at-risk population.

Keywords: neonatal abstinence syndrome, prenatal opioid exposure, neurophysiological, neuropsychological, behavioral, social, emotional

DEDICATION

This paper is dedicated to my family for the unwavering love, support, and sacrifice they provided me during this journey.

TABLE OF CONTENTS

Page

CHAPTER I: OPIOIDS AND PRENATAL USE

Introduction and History

Opioids are a class of drugs, which include both legal prescriptions and illegal drugs that are frequently used for pain management but can also be used recreationally. Williams (2008) describes the three classes of opioids as natural, semi-synthetic, and synthetic compounds. Commonly prescribed opioids include oxycodone, hydrocodone, codeine, and morphine, with the most used illegal opioid being heroin. Synthetic opioids are also used such as fentanyl, methadone, and tramadol (Williams, 2008). All types of opioids are chemically similar and interact with opioid receptors in the brain and body (National Institute on Drug Abuse, n.d.) and are widely distributed throughout the central nervous system (Chaves et al., 2017). According to Patel and Rushefshy (2022) the history of the opioid epidemic has occurred in three waves: First, as a product of Civil War soldiers being treated for pain with opioids; second, during the war on drugs era from 1960-2000, which focused on illegal drugs such as heroin; and lastly, from 2000-2020 after OxyContin was introduced as a pain reliever. The third wave of the opioid epidemic is associated with pharmaceutical companies reassuring medical providers that opioid pain relievers would not lead patients to become addicted (Patel & Rushefshy, 2022). Therefore, prescription opioid rates increased. After a rampant misuse of prescribed and non-prescribed opioids demonstrated the highly addictive component of opioids, the U.S. Department of Health and Human Services declared a public health emergency in 2017 (U.S. Department of Health and Human Services, 2021). During this twenty-year period there has been a rapid increase in addiction to prescribed opioids, fentanyl, and heroin, as well as an increase in overdose deaths.

The opioid epidemic has impacted people from all walks of life. American Psychiatric Association's (2013) *Diagnostic and Statistical Manual of Mental Disorder* (5th ed.; DSM-5)

explains that addiction to opioids can be found across social economic status, as well as across racial and ethnic groups. The misuse of opioids can lead to a diagnosis of opioid use disorder (OUD; American Psychiatric Association, 2013). The 2019 National Survey on Drug Use and Health indicates that in the past year, over 10 million individuals, 12 years of age and older, misused opioids. Of those individuals, around 9.3 million misused prescribed opioids for pain relief, over 340,000 used heroin only, and a little over 400,000 misused prescribed opioids and used heroin (Substance Abuse and Mental Health Services Administration, 2020). Although the statistics related to the use, abuse, and dependence of opioids have risen and fallen at different times over the past two decades, the epidemic still has an astounding impact on the population within the United States. According to the *DSM-5* (American Psychiatric Association, 2013), opioid use disorder is defined as a destructive pattern of opioid use resulting in substantial impairment or suffering over a period of at least one year. The Substance Abuse and Mental Health Services Administration (2020) found that the diagnosis of opioid use disorder has decreased for individuals 12 years and older from 2.4 million in 2015 to 1.6 million in 2019.

This paper will focus on how the opioid epidemic has impacted the pediatric population due to intrauterine exposure to opioids leading to neonates being diagnosed with neonatal abstinence syndrome (NAS). This syndrome identifies neonates who are experiencing withdrawal symptoms after delivery due to the cessation of opioids they were receiving prenatally. As the rapid rise of the opioid epidemic has occurred over the past two decades, an increase in neonatal abstinence syndrome has also been observed. Examining the maternal, neonate, and pediatric impacts will allow for a greater understanding of how children who were diagnosed with NAS as neonates could possibly experience neuropsychological deficits and neurophysiological alterations, as well as behavioral, social, and emotional difficulties.

Opioid Impact on Maternal Women

Maternal Screening. Ko et al. (2020b) conducted a survey, in 2017, of obstetricians and gynecologists (OBGYNs) that revealed, although almost 80% of OBGYNs frequently screen their patients for maternal substance use, only 11% reported utilizing a validated assessment. The most frequently reported screening method was asking the patient if they were using substances. Regarding opioid screening, more than half of the physicians indicated that it is a high priority for them to screen for prescription and non-prescription opioid medications. Additionally, approximately 75% of physicians indicated that screening for illicit substances was a high priority in their practice (Ko et al., 2020b). This indicates that although most OBGYNs endorse substance screening as a high priority, standardized universal screening for substance use/abuse is not currently the typical practice during prenatal visits. There are several substance use/abuse assessments that can easily be utilized and scored by providers or their medical team during routine prenatal visits. The American College of Obstetricians and Gynecologists Committee on Obstetric Practice (ACOG; 2017) identifies the following as validated prenatal substance use/abuse screening tools: 4 Ps Plus (parents, partner, past, pregnancy; Chasnoff & Hung, 1999), the National Institute on Drug Abuse Quick Screen (National Institute on Drug Abuse, n.d.), and CRAFFT (car, relax, alone, forget, friends, trouble; Knight & Boston Children's Hospital, 2016), used for adolescents and young adults. Each assessment consists of four to six elements to assess for substance abuse. Pregnant women have a better chance of being screened for substance use/abuse if the obtain prenatal care. However, prenatal care was obtained later and less frequently from pregnant women diagnosed with OUD when compared to pregnant women diagnosed with another substance use disorder (Clemans-Cope et al., 2018), suggesting that women with OUD are less likely to receive early intervention and treatment.

Direct patient self-report is the method typically being used in most OBGYN offices today to assess maternal substance use (Ko et al., 2020a) and is most likely not a reliable method among all patients. A barrier for a pregnant woman to honestly disclose her substance use may include being fearful of child protective services involvement, legal involvement, the possibility of losing their child, and/or social judgement (Gressler et al., 2017). These barriers are linked to pregnant women struggling with opioid use/abuse who are not receiving medication assisted treatment. Therefore, their neonate is at a greater risk for being diagnosed with neonatal abstinence syndrome (Gressler et al., 2017). Jarlenski et al. (2017) explained that in 2017, twenty states had mandated laws regarding reporting pregnant women who were using substances and four states only required reporting if the healthcare provider deemed the substance use as being associated with child maltreatment (Jarlenski et al., 2017). The remaining states had no identified perinatal substance use laws. States utilize a variety of reporting indicators such as positive toxicology results, a medical provider knowing the pregnant woman is actively using substances, and/or the neonates demonstrating withdrawal symptoms after delivery (Jarlenski et al., 2017). Faherty et al. (2019) found that states who do not civilly or criminally prosecute pregnant women with a diagnosis of OUD, not only demonstrate a higher prevalence of OUD diagnoses, but also have a higher rate of patients receiving treatment for their opioid use. A cross sectional study examined the live hospital birth records of eight states and found there were significantly greater odds for NAS neonates to be born in states with punitive policies (i.e., criminalizing substance use during pregnancy); however, no associations were found between NAS incidence and reporting policies (Faherty et al., 2019). This data may suggest that enacting punitive state policies with the hopes to deter substance use during pregnancy is not having the desired effect lawmakers intended.

Preventative measures have been examined to help reduce the rise in opioid use/abuse, which would inadvertently lead to reduced intrauterine opioid exposure and decrease neonates being diagnosed with neonatal abstinence syndrome. The Centers for Disease Control and Prevention (CDC) posted guidelines in 2016 for physicians who are prescribing opioids to patients suffering from chronic pain, excluding those receiving active oncology treatment, palliative care, or hospice. They recommended utilizing the scientific evidenced based method framework, GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) to identify the effectiveness, risks, and benefits involved for each long-term (≥1 year) opioid therapy patient. Recommendations are divided into three areas: determining when to start or continue opioid treatment for pain, opioid selection and treatment regimen, and assessing the level of risk (Dowell et al., 2016). The ACOG recommendations include utilizing universal screening and obstetric care at the initial visit, psychoeducation, referrals for maternal substance use treatment, utilizing validated screening measure, use of non-opioid pain management when appropriate, opioid agonist pharmacotherapy, and discussing the risks and benefits of taking opioids during pregnancy (American College of Obstetricians and Gynecologists, 2017). Madsen et al. (2018) conducted a national survey regarding the knowledge and prescribing practices of opioids among obstetricians and gynecologists. It revealed that almost all OBGYNs prescribed opioids as an outpatient pain reliever after surgery and less than 30% typically prescribe for non-surgical reported pain; however, less than 20% of these OBGYNs reported following at least three of the four ACOG recommended prescribing practices. The recommended prescribing practices include screening for opioid dependence, providing a minimal number of pills, individualize the opioid prescription to each patient, and provide each patient with education on how to properly dispose of unused medications (Madsen et al., 2018). This data suggests the

importance of increasing OBGYNs overall knowledge of opioid use and adherence to the ACOG recommendations. Prenatal exposure to opioids may occur during unplanned pregnancies prior to the woman knowing she was pregnant. Promoting, educating, and providing easy access to contraceptive services to women prescribed opioids and/or receiving substance abuse treatment is one risk reducing approach to unplanned pregnancies (American College of Obstetricians and Gynecologists, 2017).

Maternal Factors. Several studies have identified maternal factors that have been found among women who utilized opioids during pregnancy. Whiteman et al. (2014) found significantly higher rates of depression, anxiety, and insomnia in women who utilized opioids during the gestational period when compared to non-opioid using pregnant women. Expected mothers with opioid dependence endorsed a history of physical/emotional/sexual abuse and/or a criminal history (Tabi et al., 2020). Mothers with neonates diagnosed with NAS are at a greater risk to struggle with depression than those with neonates without NAS. Additionally, mothers who had neonates that experienced long-term prenatal opioid exposure and did not exhibit withdrawal symptoms demonstrated similar depression risks as those mothers who had neonates diagnosed with NAS (Faherty et al., 2018).

Demographically, Whiteman et al. (2014) reported there is an increased likelihood of a woman using opioids during pregnancy related to increased maternal age and women who are white and non-Hispanic. Additionally, there is a decreased likelihood of a woman using opioids during pregnancy with increased household income (Whiteman et al., 2014). An association has also been found with women utilizing opioids during pregnancy being more likely to be insured by Medicaid than non-using pregnant women (Gressler et al., 2017; Patrick et al., 2012). Mothers of neonates with NAS are also more likely to have Medicaid insurance (Patrick et al.,

2015b) and neonates diagnosed with NAS are more likely to be covered by Medicaid when compared to late preterm neonates and term neonates born without complications (Patrick et al., 2015a). Medically, persistent medical conditions (i.e., hypertension, diabetes) were observed more frequently in pregnant women using opioids compared to those who did not use opioids during pregnancy. Additionally, a woman's hospital death rate after delivery increased by almost four times if she used opioids during her pregnancy compared to non-users (Whiteman et al., 2014).

Prenatal and Postpartum Opioid Use Treatment. Pregnant women choosing or needing to use full, semi-synthetic, or synthetic opioids for pain should be provided with the opportunity to have a thorough medical consultation with their physician when deciding what treatment is best for them as well as their fetus. Treating pregnant women for opioid use can be approached through pharmacology, also known as medication assisted treatment, or through non-pharmacologic methods, with pharmacologic methods including the use of methadone, buprenorphine, and naltrexone (Fullerton et al., 2014). A survey of over 460 obstetricians and gynecologists revealed that 33% of the OBGYN respondents usually or always recommended medication assisted treatment to expected mothers with opioid use disorder, although less than 25% of OBGYN respondents felt confident in prescribing medication assisted treatment to opioid dependent expectant women. However, most respondents indicated almost always discussing the fetal impacts of maternal opioid use (Ko et al., 2020a). Detoxification is a treatment approach that can utilize pharmacologic or non-pharmacologic methods conjunctly (Bell et al., 2016). Lastly, some patients choose to not utilize medication assisted treatment and prefer to only obtain counseling or psychotherapy (Jones et al., 2011).

Medication assisted treatment typically involves methadone, buprenorphine, and naltrexone, either independently or in combination (Fullerton et al., 2014). Overall, utilizing methadone as a medication assisted treatment for opioid use yields positive results regarding reduction of illicit opioid use, criminal acts, mortality, and patients remaining in treatment. Research consistently demonstrates that if methadone maintenance treatment is dosed above 60 mg there are more positive outcomes for opioid addicted pregnant women regarding longer treatment engagement, reduced illicit opioid use, and fewer pregnancy complications (Fullerton et al., 2014). However, research has demonstrated that prenatal methadone medication assisted treatment may impact the neonate (Fullerton et al., 2014; Wiegard et al., 2016; Wouldes et al., 2010). One study conducted by Wouldes et al. (2010), examined neonatal outcomes regarding maternal methadone dosage during pregnancy. Researchers found that mothers treated with a higher dose of methadone ($\geq$ 59 mg/day) prenatally, had neonates that were at a greater risk for being born prematurely, having a reduced height, a smaller head circumference, a lower birth weight, and having a longer length of hospital stay (Wouldes et al., 2010). Another study found that neonates born to women participating in methadone maintenance treatment were at a greater risk of developing NAS (Fullerton et al., 2014). Although, a meta-analysis of 29 studies of pregnant women receiving methadone treatment revealed that there were inconsistent findings regarding low versus high methadone dose in relation to the incidence of infants being diagnosed with NAS, with some finding significant differences and others finding no differences (Cleary et al., 2010).

Buprenorphine is an alternative pharmacologic method to utilize when treating pregnant women with opioid use/abuse (Wiegand et al., 2016). Jansson et al. (2017) examined fetal neurobehavioral development with women receiving buprenorphine medication assisted

treatment. Fetal monitoring took place during gestational weeks 24, 28, 32, and 36. Researchers found that prenatal exposure to buprenorphine was linked with reduced fetal heart rate and movement, and the magnitude of these impacts increased with gestational age (Jansson et al., 2017). However, when compared to maternal methadone assisted treatment, Jones et al. (2012) found that fetal heart rate and movement was less physiologically suppressed with fetus' of mothers receiving buprenorphine medication assisted treatment. A sub-study of the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study examined 39 full term infants and found that according to the neonatal intensive care unit (NICU) Network Neurobehavioral Scale (Lester & Tronick, 2005), neonates prenatally exposed to buprenorphine displayed fewer stress-abstinence indicators and lower excitability, arousal, and hypertonia when compared to those who experienced intrauterine methadone exposure. Additionally, neonates exposed to buprenorphine did not need to be held as often as those exposed to methadone in order to maintain a calm alert state, which is also reflected in higher NICU Network Neurobehavioral Scale (Lester & Tronick, 2005) scores regarding self-regulation (Coyle et al., 2012). Research has demonstrated more positive neonate outcomes, when mothers were treated with buprenorphine compared to methadone, in the following areas: neonates had a decreased risk of being born prematurely, had a larger birth weight, required a lower morphine dose to treat NAS symptoms, shorter length of NAS pharmacological treatment, reduced length of hospital stay, and had a greater head circumference (Jones et al., 2010; Metz et al., 2011; Pritham et al., 2012; Zedler et al., 2016). Additionally, prenatal exposure to buprenorphine did not produce adverse effects in infant development (Jones et al., 2012).

A study conducted by Wiegand et al. (2016), examined neonate outcomes when comparing mothers who received methadone medication assisted treatment during pregnancy to

mothers who received treatment with buprenorphine and naloxone. Researchers found that approximately 25% of the neonates born to the mothers who were prenatally treated with both buprenorphine and naloxone were diagnosed with NAS compared to approximately 50% of the neonates whose mothers received methadone monotherapy. Additionally, mothers prenatally treated with buprenorphine and naloxone had neonates that demonstrated significantly lower peak NAS scores and had a significant shorter length of hospital stay than the prenatally methadone exposed neonates. Significant differences were not detected between the neonates of the two maternal treatment groups regarding morphine dose used to treat NAS symptoms, length of NAS treatment, birth weight, birth length, head circumference, NICU admissions, preterm birth, or Apgar score (Wiegand et al., 2016). Naltrexone monotherapy has also been examined and compared to methadone and buprenorphine medication assisted treatment for opioid dependent pregnant women (Towers et al., 2019b). Approximately 8% of neonates born to mothers receiving naltrexone medication assisted treatment experienced NAS symptoms compared to approximately 75% of neonates whose mothers were treated with methadone or buprenorphine. Additionally, neonates who were prenatally exposed to naltrexone were significantly less likely to be admitting to the NICU and had a significant shorter length of hospital stay (Towers et al., 2019b).

Medical providers have also utilized buprenorphine and naltrexone together as a treatment approach. Buprenorphine and naltrexone treatment has been found to be safe during pregnancy, and research has demonstrated that neonates whose mothers received the treatment weighed significantly more at birth than neonates exposed to other narcotics with no medication assisted treatment (Dooley et al., 2016). In another study, mother-neonate dyads who were treated with buprenorphine and naloxone resulted in approximately 25% of neonates being

diagnosed with neonatal abstinence syndrome compared to approximately 51% who were treated with methadone (Wiegand et al., 2016).

Detoxification of opioids can be utilized during pregnancy without directly causing adverse fetal outcomes (Bell et al., 2016). Detoxification is an option that patients can utilize if they want to stop using opioids and do not want to utilize a synthetic opioid such as methadone or semi-synthetic buprenorphine. Approaches to detoxification can include a patient deciding to abruptly discontinue the use opioids or deciding to discontinue use with clinical and/or medical assistance. Bell et al. (2016) conducted a study that examined the following levels of detoxification: acute detoxification while incarcerated (no opioid medication assisted treatment), inpatient detoxification with buprenorphine medication assisted treatment (with and without follow up with behavioral health programs), and with slow buprenorphine (maintenance and then taper) in an outpatient setting. Approximately 30% of women who underwent detoxification had neonates who were diagnosed and treated for NAS with the vast majority of incidences occurring from the cohort who received inpatient detoxification but did not receive continued follow-up management at the outpatient level (Bell et al., 2016). Another study, Stewart et al. (2013), found that women who remained in an inpatient methadone detoxification treatment longer were successfully opioid free at the time of delivery and were more likely to comply with treatment and not terminate prematurely. Neonates born to detoxified mothers also demonstrated shorter length of hospital stay, lower peak NAS scores, and were more likely not to be treated for opioid withdrawal symptoms (Stewart et al., 2013). Due to the benefits and possible adverse effects of each type of medication assisted treatment, physicians should be adequately equipped to provide the pros and cons of each treatment option to allow patients to make an informed decision.

Patients can also choose to have clinical support through individual or group therapy, independently or in conjunction with medication assisted treatment or detoxification (Kahn et al., 2017). Many therapeutic support groups focus on the educational aspects of maternal care and child rearing to facilitate support for opioid addicted pregnant women and mothers of young children (≤5 years of age) who were receiving medication assisted treatment (Kahn et al., 2017). Some therapeutic approaches have integrated reward and contingency aspects of the approach to treatment. Tabi et al. (2020) conducted a small cohort study of 25 opioid dependent expected mothers who participated in Drug Use Targeted Therapy (DUST). Treatment initiation varied with participants entering during their first trimester (n = 10), second trimester (n = 10), or third trimester (n = 5). DUST is a theoretical-empirical approach that includes psychoeducation, therapeutic processing, and buprenorphine medication assisted treatment to help patients achieve abstinence. The frequency of psychotherapy sessions was determined by their success in abstaining from all addictive substances. Sessions decreased with abstinence and increased with detected substance use. Data was analyzed for 20 women, as four discontinued treatment and one had a spontaneous miscarriage. DUST resulted in all the pregnant women achieving tobacco cessation and a 95% sobriety rate of addictive drugs by the time of their delivery (Tabi et al., 2020). A meta-analysis completed by Terplan et al. (2016) revealed that patients participating in contingency management interventions had neonates with shorter length of stay after delivery compared to the control group. However, no differences were indicated regarding opioid abstinence during pregnancy when comparing women who received psychosocial interventions with women who did not (Terplan et al., 2016). Some research has also found that integrating reinforcement-based treatment into a typical comprehensive care treatment approach may be

beneficial in extending opioid dependent pregnant women's length of treatment which could result in positive neonatal impacts, such as shorter length of hospital stay (Jones et al., 2011).

Pregnant women struggling with opioid use, abuse, or dependence have several treatment options depending on their needs and treatment desires (Benningfield et al., 2012). Unfortunately, not all pregnant women who are using opioids decide to obtain treatment for a variety of reasons. Ko et al. (2020a) found that OBGYNs report that a patient's denial and resistance is the leading barrier for them to receive treatment with additional barriers including minimal available treatment programs, financial restraints, and physicians having limited time with the patient during office visits. Researchers found that fewer than 20% of pregnant women using opioids identified state reporting laws or confidentiality concerns as a barrier (Ko et al., 2020a). Regarding mental health, opioid addicted women who endorsed only symptoms of anxiety were more likely to discontinue opioid agonist treatment than those endorsing either depression or neither anxiety nor depressive symptoms, suggesting that pregnant women who are receiving medication assisted treatment and are suffering with anxiety would benefit from additional services to encourage treatment compliance (Benningfield et al., 2012).

The postpartum period is an important time for women struggling with opioid use/abuse in their treatment and recovery. ACOG (2017) recommends that women should continue to obtain support during the postpartum stage through substance use treatment and additional psychosocial support services. In a study conducted by Ko et al. (2020a), most of the OBGYN respondents recommended postpartum mothers with OUD to receive opioid cessation, to breastfeed if receiving medication assisted treatment, and stated they would refer them to a substance abuse treatment program or addiction specialist. Additionally, during the postpartum

period almost all the respondents indicated discussing contraceptive methods to reduce unplanned pregnancies (Ko et al., 2020a).

Neonatal Abstinence Syndrome

NAS is a syndrome present in neonates who are displaying drug withdrawal symptoms after delivery due to prenatal opioid exposure, either from licit or illicit drug use, followed by an abrupt discontinuation of the drug (Reddy et al., 2017). NAS is also referred to as neonatal opioid withdrawal syndrome by some medical and clinical professionals (Kocherlakota, 2014). The *International Statistical Classification of Diseases and Related Health Problems* (11th ed.; ICD-11; World Health Organization, 2019) uses the code KD35 to medically diagnose neonates who were exposed to drugs intrauterine and are experiencing withdrawal symptoms. Withdrawal symptoms are neurological in nature, impacting the neonate's autonomic functions, and can have a variable presentation resulting from drug type, frequency, and metabolic rate (World Health Organization, 2019). Neonates diagnosed with NAS display a variety of signs and symptoms including neurobehavioral dysregulation initiated by the opioids they were receiving gestationally being discontinued. Genetic, epigenetic and environmental factors can also impact the neonate's presentation (Jansson & Velez, 2012). Three main systems involved with NAS are the central nervous system, the autonomic nervous system, and the gastrointestinal tract. Withdrawal signs and symptoms could include but are not limited to hyperirritability, tremors/seizures, high-pitched cry, difficulty sleeping and/or remaining calm, changes in vital signs, sweating, nasal congestion, excessive sneezing, feeding difficulties, diarrhea, vomiting, and dehydration (Jansson et al., 2012; Kocherlakota, 2014).

Patrick et al. (2015b) utilized national databases from 2009 to 2012 to determine the national prevalence of NAS. Researchers found that nationally, the NAS incidence rose to 5.8

per 1,000 births in a hospital in 2012 from 3.4 in 2009. Additionally, they examined 9 regions in the United States and found that the highest incidence, 16.2 per 1,000 hospital births, occurred in the east south central region (Alabama, Tennessee, Kentucky, and Mississippi; Patrick et al., 2015b). One study examined 299 NICUs across 33 states in the United States from 2004 through 2013 and found that NICU admissions due to NAS increased from seven per 1,000 births in 2004 to 27 per 1,000 hospital births in 2013, with the average length of hospital stay increasing from 13 to 19 days (Tolia et al., 2015). Another study conducted by Hirai et al. (2021) completed a cross-sectional analysis of national and state data bases to examine the NAS rates over 47 states and the District of Columbia. They found that NAS rates have risen from 4.0 per 1,000 hospital births in 2010 to 7.3 per 1,000 hospital births in 2017. The state of West Virginia had the highest rate at 53.5 per 1,000 hospital births in 2017 (Hirai et al., 2021).

Neonatal Abstinence Syndrome Screening. Medical professionals can utilize screening tools to facilitate diagnostic determination for neonates with neonatal abstinence syndrome. Current screening tools include the Finnegan Neonatal Abstinence Scoring tool (Finnegan et al., 1975a), the NICU Network Neurobehavioral Scale (Lester & Tronick, 2005), and/or toxicology. The Finnegan Neonatal Abstinence Scoring tool allows hospital caregivers the ability to assess the severity of infant withdrawal symptoms based on 21 items examining common signs and symptoms in order to facilitate pharmacologic dosing (Finnegan et al., 1975b). One study found the administration of the Finnegan Neonatal Abstinence Scoring tool to be effective and reliable for assessing NAS, when analyzing data across two hospitals for a year that did not produce any significant extraneous influences (i.e., day/night shift, census, day of the week, number of assessments completed) on scores (Gomez-Pomar et al., 2017a). However, due to the subjective nature of the screening tool, scoring variability among medical professionals maybe a factor. A

study examining NICU and neonatal nurses who participated in a training regarding the Finnegan Neonatal Abstinence Scoring tool nearly doubled in consistency and accuracy when pre- and post-training results were compared; unfortunately, when follow up assessments were obtained the nurse's scores were closer to the pre-training level (Timpson et al., 2018). These results emphasize the importance of training and accuracy because the scores from the Finnegan Neonatal Abstinence Scoring tool are what dictates the trajectory of the neonate's pharmacological intervention.

A study examining the Finnegan Neonatal Abstinence Scoring tool (Finnegan et al., 1975a) found that 8 of the 21 items were each associated with neonates receiving pharmacologic treatment, suggesting that the Finnegan Neonatal Abstinence Scoring tool can be simplified (Devlin et al., 2020). A simplified version of the Finnegan Neonatal Abstinence Scoring tool can be utilized to save time and is highly correlated ($r^2 = .914$) with the Finnegan Neonatal Abstinence Scoring tool (Gomez-Pomar et al., 2017b). Finnegan et al. (1975b) suggests the decision for pharmacologic treatment should be determined by using either three consecutive scores of eight or higher or two consecutive scores of 12 or higher; therefore, establishing the pharmacological cut off values of ≥ 8 or ≥ 12 when utilizing the original the Finnegan Neonatal Abstinence Scoring tool. The simplified Finnegan Neonatal Abstinence Scoring System has been proven to be a valid measure for assessing infants with NAS with the cut off values of ≥ 8 and ≥ 12 from the Finnegan Neonatal Abstinence Scoring tool (Gomez-Pomar et al., 2017b). Another instrument, the NICU Network Neurobehavioral Scale (Lester & Tronick, 2005), is utilized to assess a neonate behaviorally, neurologically, and their stress/abstinence response (Coyle et al., 2012). Objective measures are also utilized by medical providers to determine the amount of opioids currently in the neonates system. Murphy-Oikonen et al. (2010) demonstrated that

medical urine toxicology screening and meconium screening for neonates showed a more reliable detection of substance exposure than the mother's self-report. A meconium positive screening for opioids was statistically more likely to be found in premature neonates and was also associated with a long length of hospital stay, although it was not associated with a neonates need for pharmacological therapy to treat NAS symptoms (Gray et al., 2010).

Treatment for Neonatal Abstinence Syndrome. Neonates diagnosed with NAS can be treated for withdrawal symptoms with pharmacologic and/or non-pharmacologic methods (Peacock-Chambers et al., 2019). Medical care providers can utilize primary pharmacotherapy including morphine, methadone, or buprenorphine, as well as adjunctive pharmacotherapy including phenobarbital and/or clonidine (Backes et al., 2012; Kelly et al., 2015; Kraft et al., 2017; Surran et al., 2013). Non-pharmacologic approaches include rooming-in, bedside presence, breast feeding, and/or swaddling (Howard et al., 2017; MacMillan et al., 2018; Welle-Strand et al., 2013). Hospital collaboration and utilizing a standardization of care regarding pharmacologic intervention with neonates diagnosed with NAS has resulted in reduced duration in both treatment and length of hospital stay, as well as fewer neonates being discharged from the hospital with medications for NAS symptoms (Backes et al., 2012). One example of a standardized intervention is the Vermont Oxford Network NAS toolkit which focuses on the assessment, treatment, and discharge of NAS neonates; measuring and reporting rates of NAS; and delivering treatment to mother-infant dyads with compassion, healing, and understanding (Patrick et al., 2016).

Morphine was found to be the pharmacotherapy used most frequently from 2004-2013 (Tolia et al., 2015). Morphine is typically administered based on two protocols, symptom only and weight based (Kelly et al., 2015). In a study by Chisamore et al. (2016), neonates with NAS

who received the symptom only protocol, were treated with morphine significantly more frequently and had a greater length of hospital stay when compared to neonates who received the weight-based protocol. The morphine dose in neither protocol produced differences regarding the neonate's length of hospital stay (Chisamore et al., 2016). Morphine treated neonates had higher baseline Finnegan scores than those treated with methadone (Burke & Beckwith, 2017). However, a study found that utilizing methadone as an intervention is linked with statistically significant reduced length of hospital stay and duration of pharmacotherapy treatment compared to morphine (Davis et al., 2018).

Buprenorphine is a narcotic medication that is also utilized in treating prenatally opioid exposed neonates suffering from withdrawal symptoms (Kraft et al., 2017). Treatment with sublingual buprenorphine in term neonates ($\geq$ 37 weeks) who were prenatally exposed to opioids showed a significant reduced length of treatment and hospital stay when compared to neonates receiving oral morphine (Kraft et al., 2017). Adjunctive therapies are often included in treatment for neonates with NAS who are not responding adequately to monotherapy (Isemann et al., 2011; Surran et al., 2013). When examining neonates treated with methadone monotherapy and neonates treated with methadone and with phenobarbital, Isemann, et al. (2011) found that neonates treated with methadone monotherapy had a reduced length of hospital stay compared with neonates requiring adjunctive therapy. Phenobarbital and clonidine are additional medications utilized adjunctively. In one study, no differences were noted when supplementing phenobarbital versus clonidine with morphine treatment for NAS neonates regarding morphine dose; however, phenobarbital was prescribed for a longer total duration of treatment including after hospital discharge (Surran et al., 2013). In sum, neonates who are diagnosed with NAS can

receive pharmacological treatment with monotherapy or adjunctive therapy, both supporting the reduction of withdrawal symptoms.

Medication dosage and titration are also taken under consideration when treating intrauterine opioid exposed neonates (Davis et al., 2018). Ibach et al. (2016) compared neonates diagnosed with NAS being treated with methadone versus being treated with morphine. The methadone initial dose (*Mdn* = 0.09 mg/kg) and most common administration interval (every 8 hours) were higher than the initial morphine dose (*Mdn* = 0.04 mg/kg) and administration interval (every 3 hours). Researchers did not find differences between the two treatment groups regarding number of adjusted doses, duration to symptom relief, or tapering complexity score (Ibach et al., 2016). This suggests that although they are both effective treatments, methadone may be easier to manage on an outpatient basis, compared to morphine, because it requires less frequent dosing administrations. Hall et al. (2014) examined 547 infants (417 with a weaning protocol and 130 with no weaning protocol) who were treated pharmacologically for NAS symptoms. Protocol driven approaches included morphine-based weaning and methadone-based weaning, no differences were found between the two protocols regarding length of hospital stay or treatment duration; however, the morphine-based weaning protocol required neonates to receive longer supplemental phenobarbital than the methadone-based weaning protocol. Overall, the weaning protocol approach resulted in a reduced length of opioid exposed treatment and length of hospital stay compared to the non-protocol treatment (Hall et al., 2014). In another study, Backes et al. (2012) compared methadone weaning in an inpatient only setting to a combined inpatient and outpatient setting and found that less than 20% of neonates receiving combined inpatient and outpatient treatment required an increase dose of methadone to treat NAS symptoms. Additionally, neonates who were weaned from methadone in the combined

inpatient and outpatient setting had less duration of hospitalization than those who only received inpatient treatment (Backes et al., 2012). Regarding the discontinuation of morphine as a pharmacologic treatment, Kelly et al. (2015) found that neonates who were weaned off morphine at home experienced a longer weaning period (average of 12 days) than those being weaned in a hospital setting. However, the extended intervention period with oral morphine at home resulted in fewer rehospitalizations due to rebound withdrawal symptoms, than the neonates weaned at the hospital (Kelly et al., 2015). In sum, methadone and morphine are both effective treatments and weaning can take place in the hospital, an outpatient facility, or in the home environment.

Non-pharmacologic interventions are often utilized in conjunction with the pharmacologic approaches discussed above. These approaches include rooming in, bedside presence, swaddling, and breastfeeding (Coyle et al., 2012; Howard et al., 2017; MacMillan et al., 2018; Peacock-Chambers et al., 2019; Reece-Stretan et al., 2015). A meta-analysis comparing a rooming-in approach to the typical NICU admission found that rooming-in was more favorable for neonates with NAS, indicated by a reduced need for pharmacotherapy and shorter length of hospital stay (MacMillan et al., 2018). Another study found that the duration of time that a mother spent at her infant's bedside was associated with shorter length of hospital stay, reduced days of pharmacologic intervention, and lower NAS severity (Howard et al., 2017). Swaddling and low lighting are standard comfort interventions provided to NAS neonates (Coyle et al., 2012). ACOG (2017) recommends breastfeeding of the infant by women who have obtained stability through opioid agonists. Researchers have revealed that breastfed opioid exposed infants had shorter stays at the hospital when compared to formula fed or a combination of formula and breastfed (Isemann et al., 2011; Pritham et al., 2012). Additionally, breastfed neonates with NAS who were treated with methadone or buprenorphine both indicated a

reduction in pharmacotherapy intervention duration when compared to non-breastfed infants (Welle-Strand et al., 2013). These findings suggest that regardless of receiving methadone medication assisted treatment or buprenorphine medication assisted treatment, breastfeeding produces more favorable outcomes for NAS neonates regarding medication intervention duration than non-breastfed neonates diagnosed with NAS. Women are advised not to breastfeed if they are not actively engaged in treatment, are positive for substances at delivery, have relapsed/actively using within a 30-day period prior to delivery, are not planning to receive postpartum substance abuse treatment, or are engaged in chronic alcohol consumption (Reece-Stremtan et al., 2015).

Post Hospital Discharge. After being treated for symptoms of opioid withdrawal post-delivery, neonates diagnosed with neonatal abstinence syndrome may be readmitted to the hospital (Patrick et al., 2015a; Uebel et al., 2015). Patrick et al. (2015a) found that NAS neonates who stayed in the hospital for 8-28 days had a decreased rate of hospital readmission. Regarding the first 30 days post-delivery and the first year of life, neonates diagnosed with NAS had more rehospitalization admissions than those without NAS (Patrick et al., 2015a; Uebel et al., 2015). Patrick et al. (2015a) indicated that drug withdrawal was the most common reason for readmission from birth to 30 days old. One study demonstrated that rebound withdrawal leading to rehospitalization is associated with a reduced intake of their mother's breast milk (Isemann et al., 2011). Research has also found that fewer neonates diagnosed with NAS will be rehospitalized for withdrawal symptoms if they receive extended morphine weaning at home (Kelly et al., 2015). However, rehospitalization rates regarding NAS symptoms were similar between neonates receiving methadone weaning through inpatient only and those receiving methadone weaning through inpatient and outpatient treatment (Backes et al., 2012). Regarding

later in child development, children (ages 2-13 years) who were diagnosed with NAS as neonates were more likely to experience rehospitalization for the following: respiratory disease and infections, as well as injuries including burns, poisoning, maltreatment, accidents, and assault (Uebel et al., 2015).

Healthcare Costs

The healthcare system in the United States has also been impacted by the increase of opioid use/abuse, especially with pregnant women and their exposed neonate (Clemans-Cope et al., 2018; Strahan et al., 2020; Whiteman et al., 2014; Winkelman et al., 2018). Pregnant women who are diagnosed with OUD accrue higher medical costs than those diagnosed with a different substance use disorder (Clemans-Cope et al., 2018) and the total annual calculation of national hospital costs due to maternal opioid use is approximately 30 million dollars (Whiteman et al., 2014). Hospital expenses are significantly higher for neonates diagnosed with NAS compared to non-NAS neonates (Winkelman et al., 2018). From 2009 to 2012, the national costs attributed to NAS treatment increased from over $730 million to almost $1.5 billion (Patrick et al., 2015b). National hospital data in 2016 indicated the total hospital cost associated with NAS neonates was over $570 million or over $22,500 per neonate, with Medicaid covering over $470 million of the care (Strahan et al., 2020). During the period spanning from 2004 to 2014, Medicaid coverage accounted for approximately 73% - 82% of neonates diagnosed with NAS, increasing the total hospital cost from approximately $65 million in 2004 to over $460 million in 2014 (Winkelman et al., 2018). Healthcare costs are not only impacted during early life, but also later in life due to the lasting impacts of prenatal opioid exposure. Deficits caused by NAS may lead to the need for special education in school aged children who were exposed to opioids prenatally, resulting in an average cost of over $500,000 a year reported by one state (Morgan & Wang, 2019). Children

who were diagnosed with NAS had higher inpatient, outpatient, and emergency room visits in later childhood than those not diagnosed with NAS. Overall, the United States has seen a rise in healthcare costs due to opioid use/abuse for both pregnant women and neonates born with NAS (Liu et al., 2019).

Caregiver Custody

Neonates diagnosed with NAS post-delivery can be discharged in the care of their biological parents or be placed in the care of another caregiver such as a family member or foster family if Child Protective Services is involved (Jansson & Velez, 2012). Hall et al. (2016) conducted a cohort study in Kentucky that examined the caregiver families of children diagnosed with NAS after birth. The study found that families who had a caregiver who received at least 1 month of medication assisted treatment for opioid use were significantly more likely to maintain custody of their children than those who did not receive medication assisted treatment once their child welfare case was closed. Overall, parental custody retention was significantly associated with every additional month the opioid user obtained medication assisted treatment, at the rate of a 10% increase in odds. The researchers demonstrated that families with two or more adult opioid users in the household were significantly less likely to maintain custody of their children than those families with one opioid user (Hall et al., 2016).

Statement of Problem

The *DSM-5* explains that the prevalence of opioid use disorder is over 35% for adults and the onset can be seen as early as the late teens, with opioids being obtained both legally and illegally (American Psychiatric Association, 2013). The National Survey on Drug Use and Health data from 2005-2013 indicated that more than half of individuals with a diagnosis of

OUD were found in adults ranging in age from 18 to 34 years (Wu et al., 2016) which encompasses a large majority of childbearing years. This leaves women with OUD at risk for prenatally exposing their baby to opioids if they become pregnant. The Centers for Disease Control and Prevention reviewed state inpatient databases of 30 states and the District of Colombia spanning from 1999-2014 and found that during this time the prevalence of OUD rose to approximately 6.5 females out of 1,000 presenting at the hospital during the time of delivery (Haight et al., 2018). Maternal transmission of opioids to the fetus through the placenta is easily achieved due to opioids being water soluble and having a low molecular weight with synthetic opiates crossing more easily. As the fetus progresses through develop during gestation, the transmission across the placenta increases (Kocherlakota, 2014).

The opioid epidemic has led to an increase in the diagnosis of neonatal abstinence syndrome among neonates with recognizable impacts being present throughout different stages of development. Winkelman et al. (2018) described how national hospital data indicated that the number of neonates diagnosed with NAS, who were covered by Medicaid, increased over five times from 2004 to 2014, resulting in approximately 14 out of 1,000 births. Neonates with NAS who were covered by private insurance also increased from less than one in 1,000 births to two in 1,000 births during this time period (Winkelman et al., 2018). Although the current research is limited in nature, research regarding the neurophysiological, neuropsychological, behavioral, social, and emotional impacts of prenatal opioid exposure with or without the diagnosis of neonatal abstinence syndrome continues to expand. However, the research is not as exhaustive as the data that has been collected regarding the impacts of fetal alcohol spectrum disorders. Opioids and alcohol are both harmful substances that when consumed prenatally can have lasting impacts throughout the child's development including neurologically, cognitively, behaviorally,

socially, and emotionally. The extensive research obtained regarding the impacts of fetal alcohol spectrum disorders can help guide the future direction of prenatal opioid exposure and NAS research. This literature review will explore the neurophysiological, neuropsychological, behavioral, social, and emotional impacts of prenatal opioid exposure, and supplementarily examine the impacts of prenatal alcohol exposure to increase the support of what researchers have demonstrated within the opioid exposed population.

Prenatal opioid exposure may lead to a variety of medical problems. Opioid use during pregnancy is associated with an increased risk of going into labor and/or delivering prematurely, poor embryonic development, and having a still born infant (Whiteman et al., 2014). Neonates with NAS are at higher risk of postnatal complications such as low birth weight, jaundice, problems related to feeding, meconium aspiration syndrome, seizures, and respiratory distress syndrome (Patrick et al., 2012, 2015b). Neonates with NAS compared to neonates without NAS and are also more likely to need resuscitation at birth, have lower Apgar scores at 5 minutes, are more likely to be admitted to the hospital nursery, and have a longer hospital duration (Uebel et al., 2015). The average hospital stay for neonates diagnosed with NAS is approximately 16 days (Patrick et al., 2012; Strahan et al., 2020). Neonates diagnosed with NAS displayed a longer post-delivery hospital stay (approximately 15 days) compared to late preterm (i.e., 34-37 weeks) neonates (5 days) and term neonates (i.e., 38+ weeks) born without complication was (2 days; Patrick et al., 2015a). However, neonates born in late preterm (i.e., 34-37 weeks) are more likely to have a lower birth weight than either NAS neonates or term neonates born without complication (Patrick et al., 2015a).

Toddlers and school aged children diagnosed with NAS as a neonate may require intervention services as they progress through development. Merhar et al. (2018) looked at

retrospective evaluations at a children's hospital and found that less than 50% of opioid exposed toddlers were receiving early intervention services, and of those children, many were receiving one or more services at the hospital such as speech and language therapy, occupational therapy, and physical therapy. Peacock-Chambers et al. (2019) conducted a retrospective cohort study to examine factors linked with early intervention referrals and enrollment of infants who were diagnosed with neonatal abstinence syndrome between 2006-2013 (n = 256) by utilizing hospital birth records and records from the Department of Public Health Early Intervention. Infants who were discharged to their biological parents were more likely to be referred for early intervention services than those discharged to foster care (81% versus 66%), with approximately 50% of infants with NAS being enrolled in services and approximately 38% staying enrolled for 6 months or longer. Peacock-Chambers et al. concluded that greater aims to improve developmental supports for this at-risk population should focus on providing services for infants going into foster care and for infants with shorter hospital stays to decrease the gap between when early intervention referrals are made.

Purpose of the Study

Animal and human research has indicated that in-utero exposure to opiates can have an impact on fetal brain development (Boggess & Risher, 2022; Kongstorp et al., 2020; Merhar et al., 2019; Sanchez et al., 2008; Schlagal et al., 2022; Vishnubhotla et al., 2022). These impacts can result in structural neurological changes in the basal ganglia, thalamus, and cerebellar white matter, possibly leading to difficulties with motor learning, executive functioning, alertness, social judgement, and regulating emotions and behaviors. Deficits in neurodevelopmental, behavioral, and cognitive functioning has also been associated with opiate exposure during the gestational period (Arter et al., 2021; Azuine et al., 2019; Beckwith & Burke, 2015; Hunt et al.,

2008; Levine & Woodward, 2018; McGlone & Mactier, 2015; Miller et al., 2020; Yeoh et al., 2019). The purpose of this study is to identify the neuropsychological, behavioral/social/emotional, and neurophysiological impacts found in the pediatric population who were diagnosed with neonatal abstinence syndrome postnatally.

A thorough examination of the neuropsychological, behavioral/social/emotional, and neurophysiological impacts found among the pediatric NAS population will help support efforts to reduce the barriers for early intervention and treatment for these children. Most individuals with OUD do not utilize treatment and those who do seek alcohol/drug treatment tend to access self-help groups more often than other treatment settings such as outpatient or inpatient (Wu et al., 2016). Additionally, the 2015 National Survey on Drug Use and Health found the most common demographics reported among adults in the United States misusing opioid prescriptions and/or are diagnosed with OUD were those with mental/behavioral health concerns, who were unemployed, and/or from a low socioeconomic status, and those who were medically uninsured (Han et al., 2017), indicating the strong need for active outreach in a variety of settings and within unprivileged populations. National hospital records indicated that NAS rates were highest among those living in a rural area, being in a low SES classification, and being American Indian/Native Alaskan or white (Strahan et al., 2020).

The findings indicated by this research could facilitate early intervention for this at-risk prenatally opioid exposed with or without neonatal abstinence syndrome population. Services provided by neuropsychologists and individual/family psychotherapists include interventions such as serial neuropsychological or psychological evaluations, social skills training, behavioral/emotional management, and parent/caregiver skills. Early intervention is important

when deficits are indicated in order to reduce further developmental stagnation, minimal/slowed progress, or decline.

Research Questions

Specific research questions regarding the pediatric population that have been diagnosed with neonatal abstinence syndrome allow for a more thorough examination into the impacts that prenatal opioid exposure can have on children. For the purpose of this paper, the following research questions will be explored:

1. What neurophysiological and neuroanatomical impacts have been found in children prenatally exposed to opioids with or without a diagnosis of NAS?
2. What neuropsychological deficits have been found in the pediatric population with a history of being prenatally exposed to opioids with or without a diagnosis of NAS?
3. What behavioral, social, and/or emotional impacts have been found among children prenatally exposed to opioids with or without a diagnosis of NAS?

Research Procedure

Studies of infants, toddlers, and school aged children, both male and female, who were diagnosed with neonatal abstinence syndrome postnatally due to intrauterine exposure to opioids were examined. Inclusion criteria consisted of infants who were diagnosed with NAS postnatally and/or experienced opioid exposure during the gestational period. Extraneous variables excluding children from being eligible for this research review included those born $\leq$ 36 weeks gestation, children with early onset leukemia, intraventricular hemorrhage, epilepsy, significant chronic medical conditions (i.e., cardiovascular, pulmonary, or renal), physical congenital anomalies, genetic disorders (i.e., Downs Syndrome, Phenylketonuria), and other neurological

diagnoses and/or a congenital or acquired medical disorder that could negatively impact neuropsychological, behavioral, and social/emotional deficits separately from the impacts of prenatal opioid exposure. Research from the prenatally opioid exposed population with or without NAS, as well as research from fetal alcohol spectrum disorders was utilized to thoroughly evaluate each of the aforementioned research questions.

CHAPTER II: NEUROPHYSIOLOGICAL AND NEUROANATOMICAL IMPACTS

Research Question #1

What neurophysiological and neuroanatomical impacts have been found in children prenatally exposed to opioids with or without a diagnosis of NAS?

Neurological Impacts of Prenatal Opioid Use and NAS

Opioids are a group of analgesic agents that act in both the central nervous system and the peripheral nervous system (Pathan & Williams, 2012). The three primary receptors associated with opioid use are the μ opioid receptor (mu), the δ opioid receptor (delta), and the κ opioid receptor (kappa; Pathan & Williams, 2012). The μ opioid receptor and δ opioid receptor both play a role in regulating the feeling of pain relief, numbness, and euphoria, whereas the κ opioid receptor is involved in regulating the dysphoric and aversive effects associated with opioid use (Preedy, 2016). For the opioid to achieve the analgesic response in the central nervous system, it first must cross the blood brain barrier. The blood brain barrier is a selectively permeable physical and biochemical barrier that protects the neuronal function in the central nervous system. Opioids can cross the blood brain barrier by being transported by the P-glycoprotein (Schaefer et al., 2017). Regarding fetal impact, opioids are able to easily cross the placenta; however, the neuropathology of opioids in the fetal brain are still poorly understood due to the mechanisms of the developing central nervous system differing from the mature adult system (Kocherlakota et al., 2014). Researchers have begun to reveal neurophysiological and neuroanatomical impacts associated with prenatal exposure to opioids.

Using opioids while pregnant can negatively impact fetal central nervous system development (Schaefer et al., 2017). Endogenous opioids and their receptors are necessary for

the development and functioning of a healthy central nervous system, which may be disrupted by prenatal prescription and/or illegal opioids (Boggess & Risher, 2022). Therefore, non-organic opioids being consumed, especially in large doses, could produce adverse impacts on fetal central nervous system development. Several studies have examined the neuroanatomical impacts of prenatal opioid use, revealing both consistent and inconsistent findings.

Subedi et al. (2017) completed a prospective cohort study of NAS infants (n = 34) and non-NAS infants (n = 33), to examine plasma brain-derived neurotrophic factor (BDNF) in the infant's blood within 48 hours after birth. Researchers explain that BDNF is a growth factor that supports neuronal growth and survival and is highly expressed in the central nervous system and the peripheral nervous system. Additionally, BDNF has been shown to have a neuromodulatory effect on learning and memory. They found that mean BDNF level in the NAS group was significantly higher than the non-NAS group (252.2 $\pm$ 91.6 ng/ml vs. 211.3 $\pm$ 66.3 ng/ml, p = 0.04), although BDNF levels did not significantly correlate with the severity of NAS symptoms (Subedi et al., 2017). Researchers concluded that prenatal opioid exposure may be linked to increased upregulation of BDNF gene expression in the central nervous system, which could impact nervous activity regulation in infants who are experiencing early opioid withdrawal symptoms.

A cohort study conducted in Australia examined the neuroanatomical volumetric impacts of in-utero opioid exposure, by assessing magnetic resonance imaging (MRI) scans of 16 infants and comparing them to the normative values of the population (Yuan et al., 2014). Five mothers endorsed only using one opioid during pregnancy, and eleven mothers reported poly-opioid use. Due to opioid withdrawal symptoms, more than 87% of the infants were diagnosed and treated for NAS with morphine. Opioid exposed infants showed significantly smaller basal ganglia

volume (mean difference = -2.6, p = .01) and whole brain volume (mean difference = -68.0, p = .001) when compared to the population means. Opioid exposed infants also demonstrated significantly larger lateral ventricular volumes (mean difference = 1.4, p = .008; Yuan et al., 2014).

In another study, neuroimaging was compared between 20 term infants prenatally exposed to opioids and 20 term control infants within the ages of 4-8 weeks to examine the presence of structural injury or brain malformations (Merhar et al., 2019). All of the mothers in the exposed group endorsed smoking tobacco during the pregnancy, all except one of the mothers were positive for hepatitis C, and almost half of the mothers were receiving medication assisted treatment (Merhar et al., 2019). Structural MRI indicated white matter lesions or signal abnormalities in eight of the opioid exposed infants (40%), and septopreoptic fusion anomalies were found in two of the infants in the exposed group. Sixty-three percent of the exposed infants who showed white matter injury were treated for NAS and 58% of the exposed infants who showed no white matter injury were treated for NAS. Fifty percent of infants who demonstrated white matter injury were born to mothers who were receiving medication assisted treatment with methadone prenatally and 50% were born to those who received buprenorphine. The percentages of infants born to mothers receiving medication assisted treatment who did not show white matter injury were methadone (33%) and buprenorphine (67%). No infants in the control group showed any neurological malformations. White matter fetal development may have been interrupted by in-utero opioid exposure during gestation although the etiology is unclear (Merhar et al., 2019). More research involving imaging and neurodevelopmental assessments will provide further information about the impact of white matter lesions during later development in children with a history of prenatal opioid exposure.

Radhakrishnan et al. (2021) conducted a study using resting state MRI, to identify how prenatal exposure to opioids can impact the developing brain networks. They examined the neuroimaging of term infants exposed to opioids prenatally (n = 10) and non-substance exposed infants (n = 22), at less than 48 weeks old. Maternal opioid use was determined by self-report and medical records. Nine of the opioid using mothers were participating in medication assisted treatment, with seven receiving buprenorphine and two receiving methadone. Four of the opioid using mothers endorsed polysubstance use and seven reported smoking tobacco during pregnancy. All mothers of the control infants reported no substance or tobacco use during pregnancy (Radhakrishnan et al., 2021). All participants were fed, swaddled, and provided ear protection during neuroimaging which took place during natural sleep and lasted approximately 22 minutes. One area of the brain that was examined was the amygdala which is important for emotional regulation, such as fear, stress, and aggression. The regions of significantly correlated connectivity with the amygdala were expressed in false discovery, rate cluster-corrected z-score values. The prenatal opioid exposed infants showed significantly higher connectivity (ranging from z = 2.48 to z = 4.74) for the left amygdala and the following regions compared to controls: the right medial prefrontal, left inferior temporal gyrus, right anterior temporal, bilateral paracentral lobule, left inferior parietal lobule, bilateral precuneus, and the right superior temporal gyrus. Additionally, the opioid exposed group demonstrated significantly higher connectivity (ranging from z = 2.35 to z = 2.71) for the right amygdala and the bilateral medial prefrontal, left dorsal prefrontal, left inferior parietal lobule, right precuneus, and left middle temporal gyrus. Overall, Radhakrishnan et al. (2021) concluded that imaging of the opioid exposed group, compared to the non-substance exposed control group, demonstrated altered connectivity of the amygdala to several cortical regions. Including the frontal, temporal, parietal,

and occipital lobes, and the cerebellum. Additionally, the opioid exposed group showed overlapping regions of increased connectivity in the medial prefrontal cortex, which involves executive functioning and working memory (Radhakrishnan et al., 2021).

A study compared neuroimaging scans (MRIs) between neonates who were prenatally exposed to methadone (n = 20) and non-exposed controls (n = 20) that were taken at the postmenstrual age (gestational age plus chronological age) of approximately 39 to 41 weeks (Monnelly et al., 2018). Mothers were recruited from a substance abuse clinic for pregnant women and were being prescribed methadone to treat OUD. Nineteen of the neonate's mothers reported smoking tobacco, drinking excessively (approximately 4 units per day), and illicit and/or prescribed polysubstance use (Monnelly et al., 2018). The data indicated that across the white matter skeleton, the median fractional anisotropy in the methadone-exposed infants was 12% lower. Additionally, the exposed neonates demonstrated a decreased fractional anisotropy in the inferior longitudinal fasciculi and the internal capsule ($p < .05$) even after adjusting for head circumference. No abnormalities were detected in the brainstem, cerebellum, or deep or cortical grey matter areas. Researchers suggest that neonates prenatally exposed to methadone are at risk of having altered microstructures in major white matter tracks that are not related to head growth (Monnelly et al., 2018).

Vishnubhotla et al. (2022) compared global brain structural connectivity of infants exposed to opioids prenatally (n = 11) and nonexposed infants (n = 18) through MRI including diffusion tensor imaging at less than 3 months corrected postmenstrual age. Participants were recruited and assessed at Indiana University Health. Mothers of the exposed infants received medication assisted opioid treatment during pregnancy, with 10 mothers receiving buprenorphine and one mother receiving methadone. Three of the mothers additionally endorsed the use of

heroin and five of the mothers endorsed the use of other illicit drugs including marijuana, methamphetamines, and cocaine. Neuroimaging assessment included tractography on the whole brain, pairwise connectivity analysis, and network measures for fiber count and fractional anisotropy. Overall, Vishnubhotla et al. found that pairwise connectivity showed significant alterations based on fiber count and fractional anisotropy for 32 and 24 connections, respectively, for uncorrected *p*-values. Network measures showed significant alterations based on fiber count and fractional anisotropy values for 15 and 22 networks, respectively, for uncorrected *p*-values. Significance was not maintained in these areas after the researchers corrected for multiple comparisons. Connectivity based on fiber count was significantly higher ($p < .05$) for the connections between the right superior frontal gyrus and right paracentral lobule ($t(8.77)$, p-corrected $< .001$) and significantly lower between the right superior occipital gyrus and right fusiform gyrus ($t(-7.06)$, p-corrected $= .003$), compared to controls and after adjusting for multiple comparisons. Researchers concluded that compared to non-exposed infants, the opioid exposed infants demonstrated significantly higher fractional anisotropy-based fiber tracts connecting the right superior frontal gyrus and right paracentral lobule, as well as significantly lower fractional anisotropy based fiber count for the connection between the right superior occipital gyrus and the right fusiform gyrus (Vishnubhotla et al., 2022). The superior frontal gyrus has demonstrated associations with response inhibition and motor urgency (Hu et al., 2016) and the paracentral lobule carries out motor and sensory functions in the lower limbs (Johns, 2014). The right superior occipital gyrus and the right fusiform gyrus are regions that have been associated with visual processing, as well as object and facial recognition (Weiner & Zilles, 2016). Thus, results suggested higher response inhibition, lower motor urgency, and reduced visual processing with potential deficits in object and facial recognition.

A study examined adolescents (ages 17-22 years) with a history of prenatal opioid and polysubstance exposure (n = 38) compared to a non-exposed group (n = 44; Nygaard et al., 2018). All of the infants in the exposed group experienced tobacco exposure and almost 50% were exposed to heroin prenatally. Alcohol, benzodiazepines, and amphetamines were used by 13% or less of the mothers of the exposed infants, with a total average of substances used being approximately 3.5 substances each (Nygaard et al., 2018). Seventy-four percent of the exposed infants were diagnosed with NAS postnatally. Neuroimaging was taken with a 3-T MRI scanner and showed that MRIs taken of exposed adolescents revealed significantly smaller cortical surface areas and neuroanatomical volumes as well as thinner cortices. Specifically, significant differences between the exposed group and the comparison group were found regarding volumes within the following areas, after controlling for age and sex and adjusting for multiple analyses: whole brain (b = 0.70, p = .004), cerebral cortex (b = 0.82, p = .003), cerebral white matter (b = 0.52, p = .036), accumbens (b = 0.54, p = .036), basal ganglia (b = 0.79, p = .004), thalamus (b = 0.74, p = .004), and the cerebellar white matter (b = 0.59, p = .03). Thinner cortices were found in the exposed group for left precentral gyrus, in the inferior parietal cortex, and the precentral and postcentral gyri in the right hemisphere, after adjusting for sex and age, with a significance of $p \leq .004$ (Nygaard et al., 2018).

Sirnes et al. (2017) conducted a small cross-sectional study which compared T1 weighted MRI scans of children, ages 10-14 years, with prenatal opioid exposure (n = 16) and unexposed controls (n = 16), matched by sex and age. Results indicated that the children who were prenatally exposed to opioids had statistically significant ($p < .05$) reduced regional brain volumes in the following areas: cerebellar white matter (10.3% smaller than controls, mean difference = 3, 95% CI [0.57, 5.44], p = .018), thalamus (7.6% smaller than controls, mean

difference = 1.21, 95% CI [0.10, 2.32], p = .035), and the basal ganglia (6.5% smaller than controls, mean difference = 1.60, 95% CI [0.20, 3.01], p = .027). No statistical significance was indicated regarding global brain measures including total brain (mean difference = 24.66, 95% CI [-22.10, 71.43], p = .285), cerebral cortex (mean difference = 11.50, 95% CI [-22.52, 45.52], p = .488), or cerebral white matter volumes (mean difference = -0.78, 95% CI [-23.50, 21.94], p = .944; Sirnes et al., 2017). Researchers concluded that MRI scans demonstrate a statistically significant association between in-utero opioid exposure and decreased regional brain volumes in the basal ganglia, thalamus, and cerebellar white matter (Sirnes et al., 2017).

Overall, current research has demonstrated that prenatal exposure to opioids can have neurological impacts on the developing fetal brain. Significant differences have been detected for neuroanatomical volumes, cortical surface areas, and thinner cortices (Nygaard et al., 2018; Sirnes et al., 2017; Yuan et al., 2014). Decreased fractional anisotropy in white matter and increased radial diffusion have also been identified (Monnelly et al., 2018). Research has also indicated altered connectivity involving the amygdala and regions involving executive function and working memory (Radhakrishnan et al., 2021). Altered fractional anisotropy was indicated for prenatally exposed infants for areas involving response inhibition, visual processing, as well as motor and sensory functions (Vishnubhotla et al., 2022). These findings highlight that children prenatally exposed to opioids are at a greater risk of experiencing neurophysiological and neuroanatomical alterations that may impact development.

Relationships Between Neurological and Neuropsychological Findings

A study examined healthy non-prenatally drug exposed infants (n = 58) and prenatally drug exposed infants (n = 75) to assess the brain and behavioral impacts of gestational drug exposure on infant development (Salzwedel et al., 2020). Researchers analyzed the impacts of

whole-brain functional connectivity for prenatal exposure to nicotine, alcohol, marijuana, cocaine, selective serotonin reuptake inhibitors (SSRIs), and/or opiates, and five critical non-drug variables including: age at birth, age at scan, sex, birth weight, and maternal depression. Pregnant women were recruited for this study during their third trimester from inpatient and outpatient substance abuse programs in North Carolina. More than 82% of infants in the drug exposed group experienced prenatal polysubstance exposure (Salzwedel et al., 2020). Regarding non-drug characteristics, when comparing the control versus the drug exposed group, the drug exposed group demonstrated lower birth weight ($t(131) = 2.79$, $p = .006$) and had mothers who on average were more depressed ($t(131) = -2.91$, $p = .004$). Neuroimaging was collected when infants were between 2 and 6 weeks old and behavioral outcomes were completed at approximately 3 months old. Prior to neuroimaging, the infants were fed, swaddled, and fitted for ear protection. Images were taken while the infants were sleeping, and their head position was secured with a vacuum-fixation device. Structural images and rsfMFIs were collected and assessed. Salzwedel et al. (2020) utilized an intersubject variability model to determine the impacts of prenatal drug exposure on neonatal brain functional connectivity at the regional and network levels. Regarding whole-brain connectivity, they found over 24,500 connections of which over 2,500 connections were significantly associated with at least one drug ($n = 1,206$) or non-drug ($n = 1,184$) individual characteristic. Researchers examined 12 functional networks that were categorized as primary (i.e., primary visual, secondary visual, sensorimotor, and auditory) or higher order (i.e., cingulo-opercular, dorsal attention, language, frontoparietal, default-mode, posterior multimodal, ventral multimodal, and orbital affective). Heat maps were created to show the number of significant effects that were found between functional connections and the six drug variables, which demonstrated spatial distributions associated with higher-order regions and

networks in the drug exposed infants. The prenatal drug exposed group demonstrated significantly greater odds of drug-related effects overlapping high-order networks (*OR*: 1.27, 95% CI [1.12,1.44], $p < .001$). The heat maps showing the whole-brain distribution effects indicated the infants with prenatal opioid exposure specifically showed high levels of regional significant effects in the middle frontal and angular gyrus (Salzwedel et al., 2020). A subset of 80 participants were assessed with the Bayley Scales of Infant and Toddler Development, third edition (BSID-3; Bayley, 2006), for cognitive, language, and motor domains. Data revealed that when comparing the control group with the drug exposed group, the prenatally drug exposed infants demonstrated significantly lower scores for language ($t(78) = 2.43$, $p = .018$) and motor domains ($t(78) = 2.58$, $p = .012$), and slightly lower scores, although not significant, for the cognitive domain ($t(78) = 1.84$, $p = .069$; Salzwedel et al., 2020). Regarding associations between the neuropsychological domains and drug/non-drug individual characteristics, eight significant positive associations were detected. Two significant relationships were determined for the cognitive domain including maternal depression score on the Edinburgh Postnatal Depression Scale (Cox et al., 1987; $e = 0.19$, $SE = 0.06$, $t = 3.33$, $p = 00.1$) and SSRIs ($e = 2.35$, $SE = 0.69$, $t = 3.42$, $p = .001$). Nicotine ($e = 0.76$, $SE = 0.21$, $t = 3.69$, $p < .001$) and SSRIs ($e = 1.47$, $SE = 0.50$, $t = 2.94$, $p = .004$) were significant for the language domain. Four significant relationships were identified for the motor domain including birth age ($e = 0.13$, $SE = 0.03$, $t = 4.53$, $p < .001$), cocaine (e = 2.05, SE = 0.36, t = 5.61, $p < .001$), nicotine ($e = 1.20$, $SE = 0.32$, $t = 3.71$, $p < .001$), and SSRIs ($e = 3.66$, $SE = 0.79$, $t = 4.65$, $p < .001$). No significant relationships were identified regarding prenatal opioid exposure and cognitive ($p = .509$), language ($p = .588$), or motor domains ($p = .823$). Further analysis was conducted to determine if relationships of individual drug and non-drug characteristics and brain functional connectivity was linked to

behavioral outcomes. Researchers constructed individual functional connectivity-behavior models for each behavior measure (i.e., cognitive, language, and motor domains), and each connection demonstrating significant effects between drug/non-drug characteristics and functional connectivity. Salzwedel et al. found 85 overall connections (42 drug related and 26 non-drug related) after correcting for false discovery rate at a significance of $q = .05$. The eight significant relationships were further analyzed to determine if the relationship was mediated by brain functional connections. The mediation analyzes included the detected connection in the corresponding functional connection-behavioral model and identified that the relationships only remained significant for cocaine ($p < .001$) and nicotine ($p < .001$) regarding the motor related relationship. All other significant individual drug/non-drug characteristics and behavior relationships became insignificant (Salzwedel et al., 2020). Overall, researchers concluded that their study resulted in three important findings: prenatal drug exposure affected approximately 5% of whole brain functional connections, prenatal drug exposure showed concentrated distributions on high-order functional networks, and lastly, prenatal drug related functional connections that were associated with behavioral outcomes demonstrated a mediation role on the relationship between prenatal drug exposure and both cognitive and language outcomes. Regarding prenatal exposure to opioids specifically, heat maps illustrating the number of affected connections demonstrated the highest concentration of effects in the right angular gyrus and the left middle frontal gyrus. The angular gyrus is involved in language, number processing, theory of mind, and spatial attention (Seghier, 2013), and the left middle frontal gyrus is involved with literacy, language, and executive control (Koy et al., 2017; Sierpowska et al., 2018). These findings are important for understanding the possible neurodevelopmental impacts that may be observed in children with a history of prenatal opioid exposure.

A small Norwegian study examined the neuroanatomical impacts on children whose mothers underwent opioid and polysubstance detoxification during pregnancy (Walhovd et al., 2015). Mothers of the exposed children were recruited from residential treatment institutions and the substance free control group was recruited from child health centers. The substance abusing women received medical and psychological care to support them during the detoxification process which included abstinence or tapering until abstinence was achieved. Treatment initiation varied for the women: three of the women began in their first trimester, four during the second trimester, and four during the third trimester. At 4.5 years of age, the children in the opioid exposed group (n = 12) and the substance free controls (n = 12), completed neurocognitive testing, visual acuity testing, and received an MRI (Walhovd et al., 2015). Cognitive testing was administered with the Wechsler Preschool and Primary Scale of Intelligence, Third Edition (WPPSI-III; Wechsler, 2008). No significant differences ($p < .05$) were found when comparing the substance exposed group to the comparison group regarding overall IQ (M = 94.9, SD = 7.2 vs. M = 99.4, SD = 8.0, p = .163) performance IQ (M = 95.6, SD = 10.2 vs. M = 100.7, SD = 9.1, p = .210), or verbal IQ (M = 98.2, SD = 8.8 vs. M = 100.0, SD = 10.0, p = .639). Visual acuity testing was conducted with the Lea Symbols 10-line folding distance chart. Researchers found that children with opioid and/or polysubstance exposure prenatally had significantly lower visual acuity when compared to non-exposed children. Significant differences ($p < .05$) were found with the substance exposed group showing poorer left eye acuity (M = 0.60, SD = 0.20 vs. M = 0.80, SD = 0.19, p = .029) and a trend towards poorer binocular acuity (M = 0.65, SD = 0.22 vs. M = 0.80, SD = 0.09, p = .063; Walhovd et al., 2015). Univariate analyses of variance were performed for subcortical volumes and separate general linear models were run for MRI cortical analyses. Maternal opioid detoxification during

pregnancy did not result in differences regarding neuroanatomical volumes when comparing the opioid exposed infants to the non-exposed controls for hippocampus (M = 7585, SD = 851 vs. M = 7640, SD = 935, p = .478), amygdala (M = 2571, SD = 360 vs. M = 2634, SD = 241, p = .769), accumbens (M = 1436, SD = 145 vs. M = 144, SD = 220, p = .969), thalamus (M = 13,544, SD = 1265 vs. M = 13,646, SD = 1164, p = .726), cerebellar cortex (M = 109,845, SD = 13,797 vs. M = 109,610, SD = 10,695, p = .726), or corpus callosum (M = 2332, SD = 320 vs. M = 2497, SD = 237, p = .445). Additionally, analysis of variance did not indicate significant differences ($p <$ .05) for cortical thickness, volume, or area when compared to non-substance exposed children after controlling for age and sex (Walhovd et al., 2015). Overall, the substance exposed group demonstrated significantly lower left eye visual acuity, although no significant differences were found regarding neurocognition, neuroanatomical volumes, or cortical thickness, area, or volume.

A small study examined how prenatal substance use impacts white matter of the brain using diffusion tensor imaging of school aged children (ages 8-13 years; Walhovd et al., 2010). They compared imaging of 14 adopted children who were prenatally exposed to opioids and polysubstance use and 14 non-exposed children who served as the control group. Walhovd et al. (2010) used tract-based spatial statistics to create a white matter skeleton to represent tracts common to the group as a comparison. Ten clusters, of $\geq$ 100 voxels, for the contrast of the control group being greater than the exposed group, were identified. These clusters demonstrated significant group differences ($p <$ .05) with the prenatal exposed group showing lower fractional anisotropy for the following areas: right occipital/lingual gyrus, left deep temporal, right deep temporal, left lateral occipital/angular, left inferior temporal gyrus, right occipital fusiform temporal gyrus, left middle temporal gyrus, right postcentral/supramarginal gyrus, left projection

from splenium corpus callosum, and right frontal pole, with all p-values falling at $p \leq .001$. Regarding tract-wise percentages, the only tract that showed group differences in mean fractional anisotropy was the right inferior longitudinal fasciculus ($F(4.327)$, $p = .048$; Walhovd et al., 2010). Additionally, participants were administered the Wechsler Intelligence Scale for Children, Revised (WISC-R; Wechsler, 1974), which is a general abilities measure consisting of 12 subtests. The full-scale intelligence quotient score and the freedom from distractibility factor score were analyzed to determine brain-behavior relationships. The full-scale intelligence quotient (FSIQ) score is derived from all 12 subtests, and the freedom from distractibility factor score is comprised of the Arithmetic, Digit Span, and Coding subtests. The freedom from distractibility factor (FFD)measures concentration and short-term attention, as well as executive and short-term memory processes involving evaluating and monitoring task performance and planning. Regarding the entire sample, Walhovd et al. found that five clusters significantly correlated with cognitive function including the right deep temporal white matter, superior division of the left lateral occipital areas, left inferior temporal gyrus, the right occipital/fusiform temporal gyrus, and the right prefrontal part of the forceps minor. However, after analyzing these significant correlations among the groups, the only significance ($p < .05$) identified was within the control group, with a negative correlation ($r = -.058$, $p = .048$) between radial diffusion and FSIQ in the forceps minor. Overall, the substance exposed group showed lower fractional anisotropy in white matter areas within the central, inferior, and posterior regions. Myelination takes place in these regions during early development within the central nervous system although no impacts were seen in the early-myelinating brain stem (Walhovd et al., 2010). Therefore, links between prenatal substance use and timing of myelination are not clear and warrant further

examination. Confounding variables possibly influencing early myelination should also be considered such as genetics and maternal health (Walhovd et al., 2010).

Sirens et al. (2018) conducted a small hospital-based study which compared the functional magnetic resonance imaging (fMRI) results of school-age children (ages 10-14 years), with (n = 11) and without (n = 12) prenatal opioid exposure during working memory-selective attention tasks (i.e., n-back task and Stroop color-word task; Golden, 1978). Opioid exposed participants were recruited from a university hospital in Norway with exposure history consisting of heroin and/or opioid assisted medication treatment. Additionally, 72% of the opioid exposed children were also reportedly exposed to prenatal polysubstance use and six of the exposed children experienced NAS symptoms postnatally (Sirens et al., 2018). The non-drug exposed control group was matched for gender and born on the same day and at the same hospital as the exposed group. Demographically, it is notable that a high prevalence of attention-deficit/hyperactivity disorder (ADHD) was observed in the opioid exposed group compared to the control group, at 64% vs. 8% respectively. The n-back and Stroop color-word task measured processing speed, focused attention, inhibition, and task switching. Sirens et al. found that after adjusting for birth weight, no significant differences were found between the groups regarding response pace and accuracy (HR = 1.29, 95% CI [.90, 1.83], p = .164). In general, within group analysis showed similar patterns of blood oxygen level dependent activation within the parietal and prefrontal regions for both the exposed and control groups. Between group analysis demonstrated that the exposed group showed increased activation during both the word 2-back task and the color 2-back task, which are more cognitively demanding conditions. The exposed group showed greater blood oxygen level dependent activation than the control group for three significant clusters, at a significance of $p < .05$, and after corrections for multiple comparisons.

The color 2-back showed two significant clusters, the left middle frontal gyrus (BOLD activation cluster size = 277, $t = 5.78$, $p < .05$) and the right middle frontal gyrus (BOLD activation cluster size = 186, $t = 5.17$, $p < .05$), and the word 2-back task demonstrated a significant cluster in the left precentral gyrus (BOLD activation cluster size = 148, $t = 5.00$; Sirens et al., 2018). Sirnes et al. concluded that fMRI revealed that opioid exposed children, compared to the control children, showed increased activation in the prefrontal cortical areas during the more cognitively demanding aspects of the working memory-selective attention task, indicated by blood oxygen level dependent activation. These findings suggests that brain functioning of children exposed to opioids prenatally can be impacted during child development and exposed children may require more effort for motivation and attention during more cognitive demanding tasks.

Schweitzer et al. (2015) conducted a study examining the neural activation of adolescents (ages 12-15 years) with a history of prenatal drug exposure ($n = 27$) and non-exposed controls ($n = 20$), during a visuospatial working memory task versus a control task. Exposed participants experienced intrauterine exposure to cocaine and/or heroin and were from a larger longitudinal study at the inner-city University of Maryland hospital examining drug using mothers and their infants. Twelve of the participants were exposed to both heroin and cocaine, and two were exposed to heroin only. Control group participants were born in the same hospital as the exposed group. The majority of the participants were African American, and none of the study participants were diagnosed with a psychiatric disorder and were not taking psychotropic medications. Participant's neural activation was examined with a fMRI while completing a computerized two-back visuospatial working memory task and a control task. Data was collected for the percentage of correct responses, as well as the reaction time for the target and control conditions. Behaviorally, Schweitzer et al. found that both the drug exposed group ($r(27) = -$

.408, p = .034) and the control group (r(19) = -.673, p = .002) demonstrated a negative correlation of intra-individual variability in reaction time to accuracy on the visuospatial working memory task, with better accuracy being associated with less variability in response time. Between group differences were not indicated for accuracy, reaction time, or intra-individual variability in reaction time. Neural activation on the whole brain analysis showed main effects of condition for all of the participants in the frontal parietal attention network, although overall, no main effect of group was indicated. Regarding brain-behavioral relationships, the control group demonstrated a significant group by condition interaction between the left medial frontal gyri activation during the visuospatial working memory task. The control group also demonstrated a significant correlation between activation in the right culmen (visuospatial working memory task-control task) and reaction time (r(19) = -.471, p = .042), although the exposed group did not demonstrate significance (r(27) = .003, p = .989). Resting state neuroimaging, showed that the drug exposed group demonstrated significantly less integrated global efficiency on the visuospatial working memory task compared to the control group (F(1,39) = 6.206, p = .017). Additionally, group by condition interaction for integrated nodal efficiency and degree for the node corresponding to the medial frontal gyri were significantly reduced in the drug exposed group (integrated node efficiency: F(1,39) = 4.139, p = .049; integrated node degree: F(1,39) = 4.568, p = .039). Schweitzer et al. concluded that behaviorally, the control group demonstrated expected relationships on the visuospatial working memory task between reaction time, intra-individual variability in reaction time, and accuracy. Specifically, slower responders in the control group demonstrated less accuracy and great variability. Even though the overall performance for the two groups was equivalent, the drug exposed group did not show any relationship between reaction time and behavioral measures (i.e., accuracy and variability).

Additionally, when compared to the control group, the drug exposed group demonstrated a reduced extent of activation associated with the left medial frontal gyri and working memory performance. Lastly, drug exposure may impact the culmen region, as the drug exposed group demonstrated deactivation in this region during the visuospatial working memory task and activation during the control task, which contrasted with the control group's response. Overall, these findings demonstrate subtle differences experienced by the drug exposed group regarding attentional and response preparation challenges linked with network related functioning and decreased activity in the cerebellar and frontal regions, specifically in the medial frontal gyri (Schweitzer et al., 2015).

Overall, research examining brain-behavioral relationships has revealed some associations with children who have a history of prenatal opioid exposure, although these findings are limited. Currently, research has indicated opioid and substance exposed children and adolescents show reduced activation in the left medial frontal gyri and deactivation in the culmen region during a visuospatial working memory task (Schweitzer et al., 2015). This suggests a link between attentional and response preparation challenges and decreased activity in the cerebellar and frontal regions. Additionally, exposed children and adolescents demonstrated increased activation in the prefrontal cortical area during the more cognitive demanding aspects of the working memory-selective attention task (Sirens et al., 2018). Research in this area is needed to contribute to the growing knowledge of how prenatal opioid exposure impacts child development. Current challenges in the research are small sample sizes, limited longitudinal studies, and high probability of prenatal polysubstance exposure, which could explain the limited findings.

Animal Studies

Animal studies can provide further knowledge in how opioids impact the developing brain and can support the rationale for future studies on infants and children with a history of prenatal opioid exposure. Although animal research can help support the expanding knowledge in this area, the neurodevelopment and mechanisms of a rodent and a human are not directly correlated; however, animal findings are important for the growing research needed in the prenatal opioid exposed pediatric population.

Kongstorp et al. (2020) examined the brain tissue of rat pups that were prenatally exposed to methadone or buprenorphine revealing that both exposed groups demonstrated reduced binding of the μ-opioid receptor in the cerebrum up to 2 weeks post-delivery, although binding of the N-methyl-D-aspartate receptor was not impacted. Pups exposed to methadone or buprenorphine also displayed decreased activation of Ca^{2+}/calmodulin-dependent protein kinase II and/or extracellular signal-regulated kinase during development which are important for the downstream signaling of μ-opioid receptor and N-methyl-D-aspartate receptor. Additionally, young adult pups demonstrated increased extracellular signal-regulated kinase activation in the hippocampus. Findings imply that prenatal opioid exposure can negatively impact the developing endogenous opioid system and neurological proteins important for cognitive functioning, which can suffer long-term effects (Kongstorp et al., 2020).

Grecco et al. (2022) examined the cerebral microstructural differences between prenatal methadone exposed (n = 15) and prenatal saline exposed (n = 15) male mice pups at 8 weeks old. Diffusion tensor imaging was utilized to characterize brain microstructures. Researchers found that the mice prenatally exposed to methadone showed significantly higher fractional anisotropy, mean diffusivity, and axial diffusivity across cortical and subcortical regions including the

hippocampus, dorsal amygdala, thalamus, septal nuclei, dorsal striatum and nucleus accumbens, when compared to the saline exposed mice. Grecco et al. concluded that prenatal exposure to methadone is associated with microstructural alterations across cortical and subcortical regions. These findings may provide further insight into the developmental mechanisms involved in the cognitive and behavioral impacts that have been observed in the prenatally opioid exposed pediatric population, specifically regarding memory, emotional regulation, learning, decision making, and motivation (Grecco et al., 2022).

Vestal-Laborde et al. (2014) also looked at prenatal methadone exposure by examining the impacts of rat pups prenatally. Researchers found that exposed rat pups demonstrated elevated brain levels of splicing variants of myelin basic protein, myelin proteolipid protein, and myelin-oligodendrocyte glycoprotein. Oligodendrocytes are the myelinating cells in the central nervous system that express opioid receptors in a developmentally regulated manner. Vestal-Laborde et al. concluded that prenatal exposure to methadone is associated with alterations in early myelination which could disrupt the sequential synchronization of brain development. Specifically, these findings illuminate accelerated oligodendrocyte maturation and myelination due to the involvement with the opioid system; therefore, opioid use or medication assisted treatment with opioids could interfere with typical brain development and myelin formation.

Sanchez et al. (2008) examined the impacts of prenatal exposure and dosing levels of buprenorphine in rat pups by administering either 0.3 or 1 mg/kg per day. Researchers found that rats pups exposed to the 0.3 mg/kg of buprenorphine per day showed an acceleration and significant increase of all myelin basic protein expression, although those exposed to the higher dose (1 mg/kg/day) of buprenorphine, demonstrated a developmental delay of myelin basic protein expression. Additionally, when the corpus callosum was examined at 26 days old, both

dosing levels indicated a significant increase in myelinated axons and thinner myelin sheath. Researchers concluded that exposure to buprenorphine prenatally is associated with alterations at the level of axon-glial interactions. This finding demonstrates the important role that opioid signaling plays in regulating myelination (Sanchez et al., 2008).

Neurological and behavioral relationships have also been examined through animal research. Schlagal et al. (2022) examined the possible neurodevelopmental impacts of prenatal opioid use and management by conducting a study with mice. Researchers emulated human opioid use disorder by giving female mice oxycodone prior to mating, and medication assisted opioid treatment was mimicked by giving the mice buprenorphine after they became pregnant. Mice in the experimental group (ages 2 to 4 months) received 10 mg/kg injections of oxycodone, twice a day for 7 days. On day eight, males were placed in the cages and once pregnancy was confirmed they began receiving a liquid diet which included buprenorphine. Dosing began at 0.5 mg/kg per day and increased 0.5 mg/mg every day, until a maximum dose of 4 mg/kg was reached and given for the remaining gestational period. The control group mice (ages 2-4 months) did not receive oxycodone or buprenorphine and were only given the liquid diet. Schlagal et al. collected the brains of pups at either embryonic day 18.5 or during late adolescence (approximately 70 days postnatal). A significant reduction of cortical thickness, altered corticogenesis, and a significant increase in ventricle width was observed in opioid exposed embryos at day 18.5, when compared to controls. The late adolescent offspring group underwent an assessment of motor activity and a forced swim test, prior to brain sample collection. The results of the open field motor activity assessment demonstrated that opioid exposed offspring showed significantly greater total distance travelled and increased travel velocity, compared to non-exposed mice. The forced swim test is a measure of depressive-like

behavior, which did not produce any significant findings. These results indicate that adolescent exposed mice showed greater hyperactivity, but depressive-like behavior was not observed. Additionally, brain collections showed that the exposed adolescents demonstrated increases in dopamine neuron ontogenesis within the ventral tegmental area. Schlagal et al. concluded that opioid exposed embryos showed reduced cortical thickness, altered carcinogenesis, and enlarged ventricles, which have been linked to neurodevelopmental and psychological disorders. Adolescent mice who were prenatally exposed to opioids demonstrated increased hyperactivity and increased generation of dopaminergic neurons, which align with ADHD behaviors in humans. These findings are consistent with behavioral research for children with a history of prenatal opioid exposure (Schlagal et al., 2022).

Gamble et al. (2022) conducted an animal study with rats to determine the neurological and behavioral impacts of prenatal methadone exposure. During gestational days 3-20, the experimental group pregnant rats received methadone injections twice a day, the control group received water injections, and a naïve group was undisturbed. At approximately 70 days postnatal, the offspring from all three groups underwent behavioral tests to assess recognition memory, with the Novel Object Recognition task, or working spatial memory with Spontaneous Alteration. The adolescent female exposed rats demonstrated impaired working spatial memory, and both male and female exposed rats showed impaired behavior during the recognition memory task compared to both the non-exposed and naïve rats. Hippocampal dentate granule cell function was also examined and showed that compared to the non-exposed and naïve offspring, the methadone exposed female rats had decreased excitability and increased inhibition of dentate granule cells, although this was not seen in males (Gamble et al., 2022).

Jantzie et al. (2020) examined the impacts of methadone receiving rat dames and their exposed pups to examine the possible impacts on the developing brain, neurologically and behaviorally. Data revealed that prenatal methadone exposure increases neuroinflammation through chemokines and cytokines and alters microglia morphology which corresponds with reduced myelin basic protein, reduced structural coherence, and decreased fractional anisotropy (Jantzie et al., 2020). Researchers concluded that these findings suggest prenatal exposure to methadone is associated with neurological alterations in rat pups. Additionally, adult rats who received prenatal exposure to methadone demonstrated deficits in associative learning and executive control when assessed with a touchscreen task (Jantzie et al., 2020).

Overall, animal research regarding the neurological impacts of prenatal opioid exposure allows for potential areas of vulnerability to be highlighted. Studying the impacts of methadone and buprenorphine in animals is particularly important because they are common medication assisted treatment options for pregnant women who are addicted or struggling with opioid use/misuse. Current animal research indicates that prenatal exposure to opioids can impact the developing brain by observed alterations in the opioid system, myelination, and microstructural alterations in the cortical and subcortical regions (Grecco et al., 2022; Sanchez et al., 2008; Vestal-Laborde et al., 2014). Brain-behavioral relationships in animals have demonstrated that prenatal opioid exposure is linked with increased hyperactivity and increased generation of dopaminergic neurons, as well as decreased excitability and increased inhibition of hippocampal dentate granule cells in females and impaired working spatial memory (Gamble et al., 2022; Schlagal et al., 2022).

Fetal Alcohol Spectrum Disorders

Fetal alcohol spectrum disorders (FASDs) is an umbrella term that represents several conditions resulting from prenatal exposure to alcohol (American Academy of Pediatrics, 2018). These conditions include the following: fetal alcohol syndrome, partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder, neurobehavioral disorder associated with prenatal alcohol exposure, and alcohol-related birth defects. Ranging in severity, fetal alcohol syndrome is at the most severe end of the spectrum and consists of facial abnormalities, growth deficits, and central nervous system abnormalities (American Academy of Pediatrics, 2018). The impacts of prenatal alcohol exposure have been heavily studied and researched and have demonstrated the negative impact alcohol can have on fetal brain and organ development. Alcohol and opioids are both able to cross the placenta during pregnancy leaving the fetus vulnerable to adverse developmental impacts (Bjorkquist et al., 2010; Kocherlakota et al., 2014). The research involved in fetal alcohol spectrum disorders is important to include in this review to demonstrate the overlapping impacts, as well as to guide the future direction of research for the opioid prenatally exposed pediatric population.

Roos et al. (2021) examined the white matter integrity of 83 toddlers (ages 30-37 months) with prenatal alcohol exposure who were a part of the Drakenstein Child Health Study birth cohort. During a natural sleep cycle, infants prenatally exposed to alcohol (n = 25) and non-exposed controls (n = 58), underwent diffusion MRI. Roos et al. found that results from the alcohol exposed group compared to the non-exposed control group demonstrated a medium effect size after the false discovery rate correction (q = 0.05) in brain stem and limbic tracts. Specifically, regarding the brain stem tract, mean diffusivity and radial diffusivity were lower in the exposed group in the right corticospinal tract. In the limbic tract, the exposed group

demonstrated lower fractional diffusivity and higher radial diffusivity in the right uncinate fasciculus, and lower mean diffusivity and radial diffusivity in the right fornix stria terminalis. The fornix stria terminalis and uncinate fasciculus have been associated with externalizing behavior and uncinate fasciculus has also been associated with internalizing behavior in typically developing children, suggesting possible risk for emotional and behavioral dysregulation. Roos et al. concluded that altered white matter microstructural integrity that has been found in neonates prenatally exposed to alcohol persists in toddlers ages 2-3 years.

Lebel et al. (2008) conducted a small study using diffusion tensor imaging to evaluate the microstructural differences of white and deep gray matter in children with fetal alcohol spectrum disorder. Participants included children diagnosed with fetal alcohol spectrum disorder (n= 24) and healthy controls with no prenatal alcohol exposure (n = 95), ranging in age from 5 to 13 years. Fractional anisotropy was utilized as an indicator of white matter integrity, and the average water diffusion was measured by mean diffusivity. A total of 14 brain structures were examined, 10 major white matter tracts and four deep gray matter structures. Lebel et al. found that children in the fetal alcohol spectrum disorders group demonstrated reduced total brain volume, white matter volumes, and gray matter volumes. Significant differences were also observed in the front and posterior portions of the corpus callosum, cingulum, corticospinal tracts, inferior fronto-occipital fasciculus, inferior and superior longitudinal fasciculi, globus pallidus, putamen, and thalamus. Researchers concluded that children with a fetal alcohol spectrum disorder are at a greater risk of having diffusion abnormalities in white matter and deep gray matter areas of the brain.

Bjorkquist et al. (2010) examined the neuroimaging of children who experienced heavy fetal alcohol exposure (n = 21) and demographically matched non-exposed, typically developing

children (n = 10), between the ages of 8-16 years. The alcohol exposed children were selected from a retrospective cohort of children who experienced heavy prenatal alcohol exposure and were participating in a study at the Center for Behavioral Teratology at San Diego State University. Ten of the children in the alcohol exposed group met criteria for fetal alcohol syndrome. Researchers focused on the cingulate gyrus due to this region's role in cognitive control, attention, and emotion regulation, all of which have demonstrated being impacted by fetal alcohol spectrum disorders. Bjorkquist et al. found that compared to the control group, all of the children and adolescents in the alcohol exposed group demonstrated significantly smaller raw cingulate gray matter, white matter, and tissue volumes. However, only cingulate white matter volumes remained significantly reduced after adjusting for respective cranial tissue constituents. Reductions were identified in both fetal alcohol syndrome and fetal alcohol spectrum disorder participants. Researchers concluded that volumetric reductions observed in the cingulate gyrus region may contribute to emotional and behavioral deficits that have been recognized in children with fetal alcohol spectrum disorders (Bjorkquist et al., 2010).

Alcohol and opioids are both teratogens that can negatively impact the developing fetus and result in neurodevelopmental deficits (American Academy of Pediatrics, 2018; Kocherlakota et al., 2014). Research has demonstrated some overlapping neurological findings regarding these two at risk populations, such as reduced whole brain volumes, reduced white matter volumes, and altered white matter microstructural integrity (Lebel et al., 2008; Nygaard et al., 2018; Roos et al., 2021; Sirnes et al., 2017; Yuan et al., 2014). Utilizing the extensive research that has been conducted for the fetal alcohol spectrum disorders population can facilitate future research to examine the neuroanatomical and neurophysiological impacts of prenatal exposure to opioids.

The links between neurological and neuropsychological impacts of prenatal alcohol exposure have also been studied. Donald et al. (2016) examined the brain structure and cognitive abilities of infants who experienced prenatal alcohol exposure (n = 28) and demographically matched healthy controls (n = 45). Neuroimaging was conducted between the ages of 2-4 weeks, and at 6 months of age. The Bayley Scales of Infant and Toddler Development, Third Edition (BSID-3; Bayley, 2006) was utilized to assess early developmental outcomes. Results indicated that the alcohol exposed infants showed significantly lower total gray matter volume. After correction for overall gray matter volume, the left hippocampus, bilateral amygdala, and left thalamus regions demonstrated lower volume compared to controls, even after controlling for age, gender, ethnicity, and maternal smoking status. Additionally, Donald et al. found significant brain-behavior relationships in the alcohol exposed group. These relationships occurred between the motor and adaptive domains on the BSID-3 with regional corrected gray matter volumes, primarily in the temporal and frontal lobes. Specifically, significant associations were found for the right middle orbitofrontal cortex and the right superior orbitofrontal cortex for the motor composite. The adaptive behavior composite was significantly associated with the right medial orbitofrontal gyrus, the right middle frontal gyrus, and the left middle temporal pole. The prenatally exposed group also demonstrated deficits on the socio-emotional scale on the BSID-3 compared to the non-exposed control group. The researchers concluded that prenatal alcohol exposure can negatively impact brain growth early in development.

Andre et al. (2020) examined the neurological and mental health impacts of prenatal exposure to alcohol and postnatal adversity. Postnatal adversity included one or more of the following: abuse, neglect, caregiver changes, and witnessing domestic violence or substance abuse. They examined 66 children (ages 7-16 years) in the following three groups: prenatal

alcohol exposure and postnatal adversity (*n* = 21), prenatal alcohol exposure without postnatal adversity (*n* = 12), and non-exposed age and gender matched controls (*n* = 33). Neuroimaging was assessed with diffusion MRI, and parents of the participants were given the Behavioral Assessment System for Children, Second Edition (BASC-2; Reynolds & Kamphaus, 2004) to assess behavior. The prenatal alcohol exposed group without adverse postnatal exposures indicated lower fractional anisotropy in bilateral cingulum and left uncinate fasciculus as well as smaller volumes in left anterior cingulate cortex than the two other groups. The prenatal alcohol exposed group with adverse postnatal exposure(s) demonstrated similar fractional anisotropy values as controls. Additionally, the alcohol exposed group without adverse postnatal exposure demonstrated higher mean diffusivity in the left uncinate compared to the exposed group with adverse postnatal exposure(s), as well as smaller right anterior cingulate and superior frontal gyrus volumes than the non-exposed control group. Regarding behavior, Andre et al. found that both the prenatal alcohol exposed groups demonstrated higher ratings of externalizing behaviors (i.e., hyperactivity, aggression, and conduct problems) compared to controls. No significant brain-behavior interactions were detected for internalizing or externalizing behavior. Researchers concluded that children and adolescents prenatally exposed to alcohol are at a greater risk of experiencing externalizing symptoms compared to non-exposed controls. Overall, children who experienced prenatal alcohol exposure and experienced or did not experience postnatal adverse exposure(s), demonstrate different brain structures, suggesting that the interaction of prenatal and postnatal exposure can impact brain development in a variety of ways (Andre et al., 2020).

Gautam et al. (2014) assessed 41 participants (ages 6-17 years), who had either fetal alcohol spectrum disorders (*n* = 25) or were non-exposed age matched controls (*n* = 16), with structural MRI and an executive functioning battery at two time points. The mean interval

between scans for the FASD group was 2.46 years and the control group mean interval was 2.36 years. They wanted to examine age-related changes in white matter volume and determine if these changes are associated with executive function change over time. Researchers specifically investigated the frontal and parietal regions, as well as the corpus callosum. The FASD group demonstrated significantly smaller regional volumes when compared to the control group for the corpus callosum, middle frontal, supramarginal, and inferior parietal regions. Regarding cognitive functioning, *t*-tests showed that the FASD group performed significantly poorer than the non-exposed group on the Trail Making Test-B (Reitan & Wolfson, 1985), digit-forward span and digit-backward span from the Wechsler Intelligence Scale for Children (WISC-IV; Wechsler, 2003), and the California Verbal Learning Test-C (CVLT-C; Delis et al., 1994). Overall, these cognitive measures assessed for mental flexibility, attention, verbal working memory, and free recall. Both groups showed increases over time in white matter volume, which was related to an improvement in performance on all cognitive measures. Additionally, Gautam et al. found that children with FASD showed significant associations between age-related increases in callosal, frontal, and parietal white matter volume and cognitive improvements over time that were not indicated in the non-exposed controls. Researchers concluded that children with a fetal alcohol spectrum disorder could cognitively benefit from interventions focused on enhancing white matter plasticity (Gautam et al., 2014).

Gautam et al. (2015) examined the volumes of white matter and subcortical gray matter, as well as areas of cognitive development in children and adolescents (ages 7-15 years) exposed prenatally to alcohol (n = 75) and non-exposed controls (n = 64). Measures included two structural magnetic resonance scans (approximately 2 years apart), Wechsler Intelligence Scale for Children, fourth edition (WISC-IV; Wechsler, 2003), the Child Behavior Checklist

(Achenbach, 1991), and the Behavior Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000). Gautam et al. found that the group exposed to alcohol prenatally demonstrated smaller volumes across the brain compared to the control group. Results also indicated that prenatally alcohol exposed children who demonstrated worse behavior and/or executive functioning tended to show larger volume increases over time. Increases were particularly found in the frontal and temporal-parietal regions compared to those alcohol exposed children with fewer behavioral concerns and/or executive function deficits (Gautam et al., 2015).

Examining longitudinal scans can provide insight into structural abnormalities and the trajectories of neurodevelopment with the fetal alcohol spectrum disorders population. Treit et al. (2013) conducted a small study of children, ages 5-15 years, with a fetal alcohol spectrum disorder (n = 17) and a non-substance exposed control group (n = 27). The children and adolescents underwent serial neuroimaging approximately 2 to 4 years apart, totaling 92 scans in all. Researchers evaluated diffusion tensor imaging and volumetric MRIs. Both groups demonstrated increases in fractional anisotropy and decreases in mean diffusivity, which aligns with the changes expected during typical development. However, significant age-by-group interactions were demonstrated for three major white matter tracts after conducting a mixed-models analysis, including: superior longitudinal fasciculus, superior fronto-occipital fasciculus, and inferior fronto-occipital fasciculus. Treit et al. explained that the greater reduction of mean diffusivity observed in the fetal alcohol spectrum disorders group, indicates altered developmental progression in the above named frontal-association tracts. No significant volumetric differences were observed regarding total brain, white matter, cortical gray matter, or deep gray matter when analyzing age-by-group interactions. Participants additionally underwent a neuropsychological battery to examine if any significant correlations occurred between

neuroimaging and cognitive scores between scans. Researchers revealed that greater reductions in mean diffusivity was correlated with larger gains in reading and vocabulary between scans for the fetal alcohol spectrum disorder group, but not for the control group. Specifically, neuroimaging showed sharper reductions of mean diffusivity in the superior fronto-occipital fasciculus and superior longitudinal fasciculus for reading, and in the superior fronto-occipital fasciculus for receptive vocabulary. Overall, Treit et al. concluded that longitudinal diffusion tensor imaging indicates that children and adolescents with a fetal alcohol spectrum disorder are at a greater risk for experiencing delayed white matter development.

Summary of What We Know

Research regarding the neurophysiological and neuroanatomical impacts of prenatal opioid exposure has provided insight into the possible changes that can occur to the brain structure and function. Many of the studies have been conducted with small cohorts examining pediatric neuroimaging of participants who experienced gestational exposure to opioids and/or polysubstance use with or without a diagnosis of NAS. Possible volumetric impacts on neuroanatomy have revealed findings with some inconsistencies. The basal ganglia have been demonstrated to be significantly smaller in exposed infants and school aged children when compared to the normative population mean and non-exposed controls (Sirnes, et al., 2017; Yuan et al., 2014). Regional brain volumes in the thalamus and cerebellar white matter areas were also statistically reduced for school aged children with a history of prenatal opioid and polysubstance exposure (Sirnes et al., 2017). Infant's whole brain volumes were also significantly smaller (Yuan et al., 2014), although the MRIs of school-aged children did not indicate a significant difference regarding whole brain volumes (Sirnes et al., 2017). Additionally, neuroimaging of exposed infants showed lateral ventricular volumes that were significantly larger than those of

the population mean (Yuan et al., 2014). At 4.5 years old, toddlers who had opioid and polysubstance exposure in utero did not demonstrate MRIs with significant differences regarding neuroanatomical volume or cortical thickness, volume, and/or area (Walhovd et al., 2015); however, neuroimaging of exposed adolescents showed significantly smaller neuroanatomical volumes and cortical surface areas, as well as thinner cortices (Nygaard et al., 2018). School aged children prenatal exposed to opioids did not demonstrate significant differences examining global brain measures for cerebral cortex and cerebral white matter volumes (Sirnes et al., 2017). Spatial distributions examining whole-brain functional connections, from rsfMRIs, demonstrated associations in higher-order regions and networks in drug exposed infants (2 to 6 weeks old). These findings were not found in non-exposed control group. Neuroimaging heat maps illustrated that the infants, specifically exposed to opioids prenatally, showed higher levels of regional significant effects in the middle frontal and angular gyrus (Salzwedel et al., 2020).

White matter integrity in the brain can be measured using diffusion tensor imaging methodology (Treit et al., 2013). Studies have indicated lower fractional anisotropy in white matter when comparing neuroimaging of exposed infants, toddlers, and school-aged children to non-exposed controls (Monnelly et al., 2018; Walhovd et al., 2010). One study demonstrated that infants exposed to opioids prenatally showed significantly higher fractional anisotropy based fiber tracts connecting the right superior frontal gyrus and right paracentral lobule, and significantly lower fractional anisotropy based fiber count for the connection between the right superior occipital gyrus and the right fusiform gyrus (Vishnubhotla et al., 2022).Toddlers and school-aged children with opioid and polysubstance prenatal exposure additionally demonstrated higher radial diffusion in white matter. Differences in fractional anisotropy and radial diffusion in white matter were found in the central, inferior, and posterior regions, which is where

myelination in the central nervous system takes place during early development (Walhovd et al., 2010), suggesting that infants, toddlers, and school-aged children exposed to opioids, methadone, and/or polysubstance use have a greater risk of having white matter alterations compared to non-exposed children. Altered connectivity has been observed in prenatally exposed infants (< 48 weeks old), regarding the connectivity of the amygdala and several cortical regions including the frontal, temporal, parietal, occipital, and the cerebellum (Radhakrishnan et al., 2021).

The examination of infant's blood, 48 hours postnatally, showed that neonates diagnosed with NAS had significantly higher levels of plasma brain derived neurotrophic factor compared to non-exposed infants without NAS, which plays an important role is supporting neuronal growth and survival (Subedi et al., 2017). These results suggest that prenatal opioid exposure might be linked with an increase in upregulation of brain derived neurotrophic factor gene expression in the central nervous system during the early stages of opioid withdrawal. An examination of structural injury or brain malformations in 20 exposed infants demonstrated that eight of the infants showed white matter lesions or signal abnormalities and two of the infants had septopreoptic fusion anomalies when neuroimaging was examined at 4-8 weeks old (Merhar et al., 2019). These findings suggest that prenatal exposure to opioids may disrupt white matter fetal development during gestation.

Research demonstrating brain-behavioral relationships is limited. Increased activation in the prefrontal cortical areas during the more cognitive demanding aspects of a working memory-selective attention task was indicated for children and adolescents who were prenatally exposed to opioids (Sirens et al., 2018). During a visuospatial working memory task, substance exposed children and adolescents demonstrated reduced activation in the left medial frontal gyri and deactivation in the culmen region. Attentional and response preparation challenges were linked

with decreased activity in the cerebellar and frontal regions (Schweitzer et al., 2015). Other studies did not find significant correlations between neuropsychological performance and neurological activation (Walhovd et al., 2015; Walhovd et al., 2010). This area of research needs to be vastly expanded to identify how the neurological impacts of prenatal opioid exposure are associated with neuropsychological and neurodevelopmental deficits that have been observed in this at-risk pediatric population.

Animal studies provide helpful information in supporting future human studies, although limitations of animal research must be considered due to the differences that exist between human and animal development. Animal research has demonstrated that prenatal opioid exposure may impact neurological proteins (Jantzie et al., 2020; Kongstrop et al., 2020; Sanchez et al., 2008). Rat pups prenatally exposed to methadone showed reduced myelin basic protein (Jantzie et al., 2020) whereas pups prenatally exposed to buprenorphine showed an acceleration and significant increase in all basic protein expression. Conversely, higher exposure doses of buprenorphine demonstrated a delayed expression of myelin basic protein (Sanchez et al., 2008). Additionally, pups exposed to methadone showed a disruption in sequential synchronization of brain development due to elevated levels of splicing variants of myelin (Vestal-Laborde et al., 2014). Significantly higher fractional anisotropy, mean diffusivity, and axial diffusivity across cortical and subcortical regions have been observed in prenatally methadone exposed mice (Grecco et al., 2022). Animal studies, regarding prenatal opioid exposure, have yielded similar findings to human studies. Specifically, they have indicated that prenatal exposure to opioids can impact the developing brain by observed microstructural alterations in cortical regions and possible impacts on myelination (Grecco et al., 2022; Sanchez et al., 2008).

Research conducted with the pediatric fetal alcohol spectrum disorders population also can help guide research regarding the prenatal opioid impacts on the brain. Regarding brain volumes, studies have indicated that infants and children who were prenatally exposed to alcohol showed decreased total gray matter volumes, smaller left anterior cingulum cortex volumes, and generally smaller volumes across the brain (Andre et al., 2020; Donald et al., 2016; Gautam et al., 2015; Lebel et al., 2008). White matter microstructural integrity, as evidenced by altered radial diffusivity and axial diffusivity, has been observed in neonates and toddlers prenatally exposed to opioids, and decreased fractional anisotropy in opioid exposed neonates, toddlers, and school aged children (Andre et al., 2020; Roos et al., 2021, Lebel et al., 2008). Neuroimaging examining school-aged children demonstrated significant differences in fractional anisotropy and mean diffusivity in several regions, suggesting diffusion abnormalities in white matter and deep gray matter areas of the brain (Lebel et al., 2008). Two- to four-week-old infants showed significant differences in subcortical regions such as the amygdala and left thalamus and hippocampus when compared to infants not exposed to alcohol prenatally (Donald et al., 2016). MRIs of children and adolescents prenatally exposed to heavy alcohol consumption, showed significantly reduced cingulate white matter volumes (Bjorkquist et al., 2010). Overall, neurological research regarding prenatal exposure to alcohol and opioids has demonstrated similar findings regarding reduced whole brain volumes, reduced white matter volumes, and altered white matter microstructural integrity.

Neuroanatomical and neurophysiological research can facilitate a deeper understanding of the possible neurodevelopmental impacts that may be observed within the prenatally exposed pediatric population. Highlighting the neuropsychological, behavioral, social, and emotional functions of brain regions and structures discussed above can provide further insight to the

impacted child's family, medical, clinical, educational, and other involved support systems. An overview of the functions involved in these regions demonstrate that the basal ganglia are very important for motor control and motor learning during developmental stages. It has also been linked with executive functioning, allowing/inhibiting actions, executive decision making, and emotions (Lanciego et al., 2012; Riva et al., 2018; Young et al., 2022). The thalamus is responsible for relaying sensory and motor signals and additionally plays a role in alertness, sleep, prioritizing attention, learning, and memory (Fama & Sullivan, 2015). Cerebellar white matter allows for communication between the gray matter neuronal processes and the rest of the body, particularly regarding fine tuning motor activity. Neuroimaging has indicated a cerebellar sensorimotor-cognitive dichotomy, with cognitive activation being observed in language and verbal working memory, spatial tasks, executive functions (Schmahmann, 2019) as well as reading and reading disabilities (Travis et al., 2015). The cerebellum has also been linked with social deficits regarding appropriate sequencing of social actions involving the understanding of social norm violations (Van Overwalle et al., 2019). A meta-analysis demonstrated that cerebellar activity during the judgement of social situations is linked with action understanding and mentalizing functionality (Van Overwalle et al., 2015).

Regarding connectivity, higher fractional anisotropy-based fiber tracts connecting the right superior frontal gyrus and right paracentral lobule and significantly lower fractional anisotropy based fiber count for the connection between the right superior occipital gyrus and the right fusiform gyrus have been observed in infants who were prenatally exposed to opioids (Vishnubhotla et al., 2022). The superior frontal gyrus has demonstrated associations with response inhibition and motor urgency (Hu et al., 2016) and the paracentral lobule carries out motor and sensory functions in the lower limbs (Johns, 2014). The right superior occipital gyrus

and the right fusiform gyrus are regions that have been associated with visual processing, as well as object and facial recognition (Weiner & Zilles, 2016). Additionally, altered connectivity of the amygdala to several cortical regions have been observed in infants prenatally exposed to opioids (Radhakrishnan et al., 2021). The amygdala is important for emotional regulation such as fear, stress, and aggression. The prenatally opioid exposed group also showed overlapping regions of increased connectivity in the medial prefrontal cortex, which involves executive functioning and working memory (Radhakrishnan et al., 2021). Alterations in any of these neurological regions due to opioid exposure might have a developmental impact on a young child and is important for their support system and treatment teams to recognize and understand in order to provide appropriate interventions and supports.

Summary of What We Do Not Know

Neurological imaging examining the neurophysiology and neuroanatomy of infants, children, and adolescents who experienced prenatal opioid exposure provides some insight into how this pediatric population is impacted; however, many aspects are still unknown. Research has indicated differences in regions where myelination takes place when comparing the neuroimaging of exposed children to non-exposed children (Walhovd et al., 2010), although there are not clear associations between prenatal opioid and polysubstance use and the timing of myelination. Further research is needed in order to examine the impacts of myelination during different times of fetal development and the links to later deficits during childhood.

The etiology of the neurophysiological and neuroanatomical differences found between pediatrics with a history of prenatal opioid exposure and pediatrics with no history of opioid exposure is still largely unknown. Although differences have been observed, the direct causes of alterations with white matter, neuroanatomical volumes, and neuronal connectivity cannot be

confirmed as a direct cause of gestational opioid exposure during fetal development (Merhar et al., 2019; Monnelly et al., 2018; Vishnubhotla et al., 2022). In addition, most maternal participants endorse using an average of 3.5 substances during their pregnancy, making it difficult to isolate the direct fetal neurological impact of each individual substance (Nygaard et al., 2018; Salzwedel et al., 2020).

Maternal opioid use during pregnancy can negatively impact the developing fetus; however, current research does not explain how the frequency, duration, and/or dose of opioids affects the fetus' brain in utero. Understanding these aspects of prenatal opioid impacts could lead to further knowledge regarding the short- and long-term impacts that have been observed during childhood development. Additionally, research regarding the timing of prenatal opioid use (first, second, or third trimester) on the neurological development of the fetus and impacts during child development are unknown. Emphasis in this area could provide insight into the importance of physicians providing thorough education regarding opioid use and recommending treatment, detoxification, or pharmacological alternatives in order to protect the developing fetus.

Examining associations between prenatal opioid exposure and the neurophysiology and/or neuroanatomy is challenging. The studies reviewed above only utilized small cohorts, with the median score of the exposed cohorts being 27 participants, making it difficult to make associations generalizable to the prenatal opioid exposed population. Controlling for confounding variables with this at-risk population also creates barriers for solid research findings. Women's physical health, mental health, nutritional intake, and overall prenatal care could also have a neurological impact on the developing fetus. This area of research needs to continue to grow to support more reliable findings with this population.

Future Hypotheses

Research is lacking regarding the associations of neurophysiological and neuroanatomical differences with the long-term impacts on neuropsychological, behavioral, social, and emotional functioning. Infants prenatally exposed to alcohol were examined at 6 months old with the BSID-3 (Bayley, 2006) and demonstrated that deficits found in motor, language, cognitive, and adaptive domains were significantly associated with regional volumes in both the temporal and frontal lobes (Donald et al., 2016). Infants with a history of prenatal opioid exposure have shown significant lower cognitive scores (Beckwith & Burke, 2015; Hunt et al., 2008; Merhar et al., 2018; Salo et al., 2010; Yeoh et al., 2019), as well as language and motor scores (Beckwith & Burke, 2015; Merhar et al., 2018). A future study can examine the neuroimaging and neurocognitive outcomes of infants with a history of prenatal opioid exposure to infants without prenatal opioid exposure to determine if associations exist between neuroanatomical volumes and cognitive functioning. A supported hypothesis would be that altered neuroanatomical volumes found in the temporal and frontal lobes of infants exposed to opioids in utero will be positively correlated to lower language and motor scores on the Bayley III. Research has also shown that children 3-6 years of age with a history of prenatal opioid exposure have demonstrated significantly lower scores when compared to normative data and non-exposed children regarding cognition, motor (Hunt et al., 2008; Yeoh et al., 2019), and speech and language (Hunt et al., 2008; Rees et al., 2020). A longitudinal study with the same above hypothesis could demonstrate associations between neuroanatomical volumes and neuropsychological findings with toddlers and early school aged children.

Research studies have been conducted regarding the associations between neuroimaging, cognition, and executive function. Findings indicated that children and adolescents with a fetal

alcohol spectrum disorder demonstrated significantly poorer performance on cognitive tests measuring mental flexibility, attention, verbal working memory, and free recall (Gautam et al., 2014). The FASD group has also demonstrated significantly smaller regional volumes when compared to the control group for the corpus callosum, middle frontal, supramarginal, and inferior parietal regions. Significant associations between age-related white matter volume increases, over two time points, were found in callosal, frontal, and parietal regions and cognitive and executive function improvement for the alcohol exposed group (Gautam et al., 2014). Prenatally exposed children and adolescents who demonstrated higher levels of executive function deficits tended to have neuroimaging that showed larger volume increases in the frontal and temporal-parietal regions over time than those who demonstrated lower levels of deficits regarding executive function (Gautam at al., 2015). Executive function deficits have also been indicted for toddlers with a history of prenatal opioid exposure (Levine et al., 2018). Further research is needed to determine if there is a link between executive function deficits and neuroanatomical volumes for children with a history of prenatal opioid exposure with or without a diagnosis of NAS. A future hypothesis could be that deficits in executive function with toddlers who experienced prenatal opioid use will be associated with increased white matter volumes in the frontal lobe.

Future studies are needed regarding the associations between the neurological impacts and behavioral, social, and emotional impacts within the pediatric population of those who experienced prenatal opioid exposure with or without a diagnosis of NAS. Few current studies exist with this population examining the links between brain alterations and observed behavioral, social, and emotional functioning. Infants and school-aged children with prenatal opioid exposure with or without a diagnosis of NAS have demonstrated reduced regional brain volumes,

compared to non-exposed controls and the normative population, in the basal ganglia (Sirnes et al., 2017; Yuan et al., 2014), thalamus, and cerebellar white matter (Sirnes et al., 2017), as well as altered connectivity between the amygdala and several cortical regions including the frontal, temporal, parietal, occipital, and cerebellum (Radhakrishnan et al., 2021). These regional areas have been linked to executive function, initiation/inhibition of action, attention, emotions, regulating alertness, and social abilities (Lanciego et al., 2012; Riva et al., 2018; Van Overwalle et al., 2019; Young et al., 2022). Future studies can compare the neuroimaging of infants, toddlers, and school aged children to determine if associations exist with parent ratings, teacher ratings, and self-report ratings when appropriate on the Behavioral Assessment System for Children, third edition (BASC-3; Reynolds & Kamphaus, 2015) or other similar measures. A proposed hypothesis could be that the prenatally opioid exposed pediatric population will show a link between the reduction in the basal ganglia, thalamus, and/or cerebellar white matter with elevated concerns regarding executive function, attention, emotions, and social skills on the BASC-3 or other similar measures.

CHAPTER III: NEUROPSYCHOLOGICAL IMPACTS

Research Question #2

What neuropsychological deficits have been found in the pediatric population with a history of being prenatally exposed to opioids with or without a diagnosis of NAS?

Literature Review

The neuropsychological impacts of neonatal abstinence syndrome have been found throughout pediatric development (Hunt et al., 2008; Levine & Woodward, 2018; McGlone & Mactier, 2015; Nygaard et al., 2017; Tronnes et al., 2021). Neuropsychological functioning can be further broken down into domains including attention, executive function, sensory, memory, language, motor function, and visuospatial (Lezak, 2011). Researchers examining the neuropsychological impacts of prenatal opioid exposure have revealed deficits in the following areas: non-verbal cognition, general cognitive function, language, motor, executive functioning, and attention. Understanding the possible neuropsychological impacts that can occur in the pediatric population due to intrauterine exposure to opioids and neonatal abstinence syndrome can provide caregivers, clinicians, physicians, and teachers the knowledge needed to recommend and/or provide intervention services. Early identification of deficits and early implementation of interventions allows for this at-risk population to obtain the services they need.

Neuropsychological Impacts of Infants and Toddlers. Studies examining the general cognition, language, and motor abilities of infants and toddlers have highlighted differences found among children who were prenatally exposed to opioids with or with a diagnosis of neonatal abstinence syndrome. The Bayley Scales of Infant and Toddler Development (BSID; Bayley, 2006) is a common assessment tool utilized to assess five different areas of development

including cognitive functioning (non-verbal problem-solving skills), motor (fine and gross), language (receptive and expressive), social-emotional, and adaptive behavior. The Griffiths Mental Development Scales (Griffiths & Huntley, 1996) for babies also assesses areas of cognitive development in infants. Additional measures of cognitive development for toddlers through young children include the Wechsler Preschool and Primary Scale of Intelligence (Wechsler, 2012) and the McCarthy Scales of Children's Abilities (McCarthy, 1972).

McGlone and Mactier (2015) conducted a study, in Scotland, to examine the neurodevelopmental impacts of medication assisted methadone treatment on infants (age 6 months). Participants included, infants born to opioid dependent mother receiving treatment with methadone (n = 81) and non-exposed healthy controls (n = 26). Exposed infants were recruited 3 days after birth. Substance exposure was confirmed by maternal urine toxicology, meconium samples, and maternal report. Identified substances included one or more of the following: opiates, cannabis, benzodiazepines, and other drugs including stimulants. Controls were matched for birth hospital, gestational age, birth weight, and region of residence at birth. At age 6 months, infants' neurodevelopment was assessed with the Griffiths Mental Development Scales (Griffiths & Huntley, 1996). Areas assessed included locomotor, personal-social, language-hearing, eye-hand, performance, and a general quotient. Infants' whose mothers received methadone medication assisted treatment scored significantly lower than non-exposed controls on all areas. Results from McGlone and Mactier, after adjusting for maternal smoking status and excess alcohol use during pregnancy, are as follows: locomotor (M = 102 vs. M = 111, p = .006), personal-social (M = 94 vs. M = 99, p = .001), language-hearing (M = 105 vs. M = 109, p = .007), eye-hand (M = 94 vs. M = 104, p = .001), performance (M = 96 vs. M = 101, p = .002), and general quotient (M = 97 vs. M = 105, $p < .001$). Further analyses demonstrated that infants

who received any pharmacological treatment for NAS symptoms performed more poorly than infants who did not require treatment (*Mdn* general quotient = 95 vs. 99, $p = .008$; McGlone & Mactier, 2015). Researchers concluded that infants born to opioid dependent mothers who received methadone assisted medication treatment during pregnancy scored significantly lower when compared to matched controls. Even though opioid exposed infants scored significantly lower than controls on neurodevelopmental tasks, no deficits were indicated as median scores still fell within the average range. This demonstrates that significant differences in neurocognitive performance maybe observed in opioid exposed children as early as age 6 months (McGlone & Mactier, 2015).

Hunt et al. (2008) conducted a longitudinal case control study from May 1979 to January 1984, of 133 infants born to opiate dependent mothers and 103 control infants born during the same time period with no prenatal exposure to substances. Exposed infants were born to mothers who participated in a methadone program during pregnancy and had a mean gestational age of approximately 37 weeks. Seventy-four (56%) of the opioid exposed infants received morphine to treat their NAS symptoms. Neurocognitive skills were assessed at 18 months old with the Bayley Scales of Infant and Toddler Development, second edition (BSID-2; Bayley, 1969), measuring general cognition and motor development. At 3 years old, general cognition was assessed with the Stanford-Binet Intelligence Scales (Roid, 2003), motor development with the McCarthy Motor Scale (McCarthy, 1972), and language with the Reynell Expressive Language Scale (Edwards et al., 1997) and Verbal Comprehension A Scale. At age 18 months, Hunt et al. found a significant difference on the Bayley Mental Developmental Index (MDI), assessing general cognition, with the opiate exposed group scoring significantly lower, in thelow average range, than the non-exposed control group who scored in the average range ($M = 88.2$, $SD = 16.4$ vs. *M*

= 105.02, *SD* = 23.0, $p < .001$). At age 3 years, the opiate exposed group continued to perform significantly lower than the control group for general cognition, as assessed with the Standard Binet Intelligence Scale (*M* = 99.9, *SD* = 15.1 vs. *M* = 107.5, *SD* = 13.4, $p < .01$). Language skills were significantly lower for the opioid exposed group, at 3 years of age, when assessed with the Reynell Expressive Language Scale (*M* = 35.5, *SD* = 7.9 vs. *M* = 42.8, *SD* = 12.6, $p < .05$) and Verbal Comprehension A Scale (*M* = 42.4, *SD* = 11.6 vs. *M* = 49.2, *SD* = 11.4, $p < .05$). Motor skills were significantly lower on the McCarthy Motor Scale, at age 3 years (*M* = 49.5, *SD* = 8.7 vs. *M* = 53.9, *SD* = 8.3, $p < .05$), although at age 18 months, a difference was not detected regarding motor abilities as assessed by the Bayley Psychomotor Developmental Index (*M* = 107.5, *SD* = 16.8 vs. *M* = 110.13, *SD* = 14.7; Hunt et al., 2008). This data suggests that lower general cognition scores found in toddlers with a history of prenatally opioid exposure persisted throughout toddlerhood, although fine and gross motor difficulties were not detected until age 3 years. Researchers demonstrated that infants exposed to opiates in utero are at a greater risk of having neurodevelopmental deficits including general cognition, language, motor, and verbal comprehension in early childhood when compared to non-exposed children (Hunt et al., 2008).

A meta-analysis examined cognitive data and compared children born between 1970 and 2004 with prenatal opioid exposure and children who were not exposed prenatally to opioids across 3 age groups: (infant/toddler [$\leq$ 24 months], preschool [ages 3-6 years], and school-aged [ages 7-18 years]; Yeoh et al., 2019). Only published articles that examined cohorts comparing cognitive and motor development between prenatally opioid exposed children and non-exposed controls, ages 0-18 years, were utilized. The most frequently utilized assessments for cognitive ability, found in the 26 eligible studies, were the Bayley Scales of Infant and Toddler Development (Bayley, 2006) for ages 6-24 months and the McCarthy Scales of Children's

Abilities (McCarthy, 1972) and the Stanford-Binet Intelligence Scales (Roid, 2003) for ages 3-6 years. The most common tests utilized to assess the motor abilities of children age 6-24 months were the Bayley Scales of Infant and Toddler Development and the McCarthy Scales of Children's Abilities. The meta-analysis for general cognition compared 1,455 prenatally opioid exposed children to 2,982 non-exposed control children, and motor development compared 688 opioid exposed children with 1,500 non-exposed control children (Yeoh et al., 2019). The mean age at cognitive testing was 13 months for the infant/toddler group, age 4.5 years for the preschool group, and age 13 years for the school-aged group. In the articles obtained, motor development was assessed up to age 6 years and the mean age at testing was age 2 years. Yeoh et al. (2019) examined the standardized mean differences between the opioid exposed group and the non-exposed controls for both general cognition and motor development. Results for general cognition with the infant/toddler group ($p < .001$, $d = -0.52$, 95% CI [-0.74, -0.31]) and the preschool aged group ($p < .001$, $d = -0.38$, 95% CI [-0.69, -0.07]), both demonstrated significantly lower general cognitive scores than the non-exposed control group. No differences were found between the groups regarding cognition for the school-aged group ($p = .23$, $d = -0.44$, 95% CI [-1.16, 0.28]; Yeoh et al., 2019). Motor data were also compared among exposed and non-exposed children $\leq$ 6 years of age and revealed that young children who were prenatally exposed to opioids scored significantly lower regarding motor development when compared to children who had no prenatal substance exposure ($p < .001$, $d = -0.49$, 95% CI [-0.74, -0.23]). Overall, prenatal exposure to opioids is negatively associated with cognitive and motor performance and is detected as early as age 6 months. These differences persist into preschool and early school age, 3-6 years. Further, Yeoh et al. concluded that approximately 6% of children with a history of prenatal opioid exposure had an intelligence quotient two standard

deviations below the mean, suggesting that these at-risk children are three times more likely than typically developing children to be diagnosed with a moderate to severe intellectual disability.

A small study conducted by Beckwith and Burke (2015) included 28 infants (16 males and 12 females) who were treated for NAS post-delivery. Infants were assessed with the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-3; Bayley, 2006) between the ages of 21-98 days (M = 55 days). Researchers wanted to examine the developmental impacts of in-utero exposure to heroin, methadone, and other opioids. Participants were infants who were admitted to an inpatient rehabilitation program to address and treat opioid withdrawal symptoms. Treatment included a progressive tapering of pharmacotherapy (i.e., morphine, methadone, phenobarbital, and Ativan), guided by the results of the Finnegan scales (Finnegan et al., 1975a), which assesses the severity of withdrawal symptoms. Prior to being discharged from the program, the infants were assessed for non-verbal cognition, language, and motor skills with the BSID-3. Beckwith and Burke utilized a history control group based on the normative population established with the BSID-3 (N = 1700, ages 1-42 months), as well as an additional normative population data subsample of the BSID-3 (N = 300, ages 30-90 days) granted by the test provider, Pearson Assessments. This subgroup provided the researchers a data set more closely aligned to the participant sample they were examining. Independent-sample t test showed that the NAS infants with prenatal exposure to opioids scored significantly lower than the BSID-3 whole sample (N = 1700) regarding composite scores for non-verbal cognition (M = 90.14, SD = 11.43 vs. M = 100, SD = 15; $t(28) = -4.48$, $p < .001$), language (M = 82.12, SD = 12.53 vs. M = 100, SD = 15; $t(28) = 7.46$, $p < .001$), and motor skills (M = 96.25, SD = 8.64 vs. M = 100, SD = 15; $t(28) = -2.24$, $p < .05$; Beckwith & Burke, 2015). The utilization of chi-square tests of independence identified if associations, in terms of qualitative descriptions, were present between the samples,

and indicated significantly different distribution scores for language ($\chi^2(6) = 43.4$, $p < .001$) and non-verbal cognition ($\chi^2(6) = 14.8$, $p = .022$) between the NAS study group and the historical control groups. A statistically similar distribution was detected for motor abilities ($\chi^2(6) = 6.8$, $p = .338$). These results were consistent with the findings when the opioid exposed NAS group was compared to the BSID-3 subsample ($N = 300$), showing significantly different distributions for language ($\chi^2(6) = 32.9$, $p < .001$) and cognition ($\chi^2(6) = 14.39$, $p = .026$), but not motor skills ($\chi^2(6) = 6.0$, $p = .421$; Beckwith & Burke, 2015). Researchers concluded that possible deficits in language and non-verbal cognition of NAS infants are reflective of a critical period of fetal development being adversely impacted by prenatal opioid exposure (Beckwith & Burke, 2015).

Merhar et al. (2018) conducted a retrospective study at Cincinnati Children's Hospital of 87 infants who were born between 2011 and 2015, treated for NAS, and later were evaluated around 2 years of age with the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-3; Bayley, 2006). Demographically, all participants were Caucasian, and the maternal median age was 26 years. Regarding prenatal exposure, 57% experienced polysubstance use, including more than one of the following: heroin, cocaine, benzodiazepines, marijuana, amphetamines, and other opioids including oxycodone. Thirty-eight percent of the mothers were receiving medication assisted treatment with methadone and 24% were receiving buprenorphine. Findings indicated that when compared to the normative data, toddlers who were treated for NAS had significantly lower scores, although still in the average range, on the BSID-3 for non-verbal cognition ($M = 96.5$, $SD = 10.6$ vs. $M = 100$, $SD = 15$, $p < .03$), language ($M = 93.8$, $SD = 13.3$ vs. $M = 100$, $SD = 15$, $p < .03$), and motor subscales ($M = 94.0$, $SD = 9.4$ vs. $M = 100$, $SD = 15$, $p < .03$). Birth weight ($Mdn = 2.78$ kg), gestational age ($Mdn = 38$weeks), and hospital length of stay ($Mdn = 18$ days) did not produce significant correlations with the BSID-3 scores (Merhar

et al., 2018). It is important to note that although the majority of the exposed toddlers performed in the average range across all three domains, many toddlers also scored at least one standard deviation below the mean in at least one domain. In the cognitive domain nine toddlers scored < 85 and three toddlers scored < 70, in the language domain 17 toddlers scored < 85 and five toddlers scored < 70, and in the motor domain 11 toddlers scored < 85. Overall, this regional cohort study demonstrated that infants who were diagnosed and treated for NAS showed significantly lower scores for non-verbal cognition, language, and motor development, assessed at age 2 years, and compared to the normative data of the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley, 2006).

Baldacchino et al. (2014) demonstrated contrasting findings in a meta-analysis. Researchers reviewed 200 studies related to prenatal opioid use from 1995 to 2012, but only found five studies that quantitatively examined the neurobehavioral functioning of children, during infancy and pre-school periods, who were exposed to opioids during gestation. Sample sizes of the opioid exposed subjects ranged from $n = 33 – 143$, and non-exposed controls ranged from $n = 45 – 85$. Gestational age was approximately 37 weeks and testing ages for infants was between 12 and 19 months ($M = 14$ months), and for pre-school children between 38 and 60 months ($M = 50$ months; Baldacchino et al., 2014). Regarding cognition, researchers did not find significant differences between the opioid exposed and non-exposed infants ($z = 1.41$, $p = .16$) or pre-school age children ($z = 0.75$, $p = .46$). Additionally, no significant differences were found when assessing psychomotor abilities for infants ($z = 1.67$, $p = .09$) or pre-school age children ($z = 1.00$, $p = .32$). Overall, while results indicated that in-utero opioid exposed infants (ages birth-2 years) and preschool aged children (ages 3-5 years) showed a trend of poorer performance

regarding cognition and psychomotor abilities when compared to non-exposed controls, no significant differences were found between the groups (Baldacchino et al., 2014).

Salo et al. (2010) examined 87 mother-infant dyads (15 opioid use/exposure, 15 mothers with depression with no substance use, and 57 non-opioid exposed infants with no maternal opioid use) at a university hospital to assess the relationship between mothers who used opioids during pregnancy and who received buprenorphine medication assisted treatment and their infant's cognitive development. All opioid using mothers also smoked tobacco during pregnancy and 40% endorsed using other substances including alcohol, benzodiazepines, cannabis, and/or amphetamines. Most mothers entered treatment during their second trimester (M = 14 months pregnant). Maternal depression was assessed by the Edinburgh Postnatal Depression Scale (Cox et al., 1987; M = 13.9, SD = 1.1). Mothers with depression and mothers from the non-opioid exposed group, endorsed no substance use throughout pregnancy. The infants from the dyads ranged in age from approximately 5 months to 11 months. Salo et al. utilized the BSID-2 (Bayley, 1969) Mental Development Index (MDI), which assesses cognition by examining several areas including sensory-perception, memory, early language, problem solving, and knowledge. Results indicated that prenatally opioid exposed infants scored significantly lower on the Mental Development Index when compared to non-exposed infants (M = 92.33, SD = 10.73 vs. M = 105.11, SD = 7.61, F = 4.43, $p < .001$), and infants with mothers who endorsed symptoms of depression (M = 92.33, SD = 10.73 vs. M = 102.33, SD = 10.62, F = 4.43, $p < .001$; Salo et al., 2010). These results remained significant, even after controlling for covariates including birth weight ($F(2, 85) = 0.32$, $p = ns$), gestational age ($F(2, 85) = 0.43$, $p = ns$), maternal age ($F(2, 85) = 0.98$, $p = ns$), and maternal years of education ($F(2, 85) = 0.01$, $p = ns$). Overall, infants who were exposed to opioids and medication assisted buprenorphine treatment,

showed significantly lower developmental skills as assessed by the BSID-2 MDI when compared to non-exposed controls and infants with mothers endorsing depression (Salo et al., 2010). It is important to note that the Mental Development Index (MDI) should be interpreted cautiously because by measuring both cognitive and language abilities, it can be difficult to differentiate which area is impacted. This issue was rectified with the BSID-3 (Bayley, 2006) by having separate domains (Bayley, 2006).

In addition to identified differences in cognition, language, and motor skills, researchers have discovered significant differences regarding executive function, memory, and attention with infants and toddlers who were prenatally exposed to opioids. Levine and Woodward (2018) conducted a study examining the executive function abilities of children whose mothers' received methadone assisted treatment during pregnancy (n = 68) and non-methadone exposed children (n = 88) at 2 years of age. They utilized the Snack Delay task to assess the toddler's inhibition control by asking them to wait until the examiner rings a bell prior to retrieving a snack from underneath a cup. Levine and Woodward found that methadone-exposed children had poorer inhibitory control when compared to the non-methadone exposed group (percentage of successful inhibitory control: 32.3 vs. 57.3, $\chi^2 = 8.91$, $p < .003$) displaying significantly less ability to wait for the treat by inhibiting their behavior by taking the treat prior to hearing the bell almost twice as often as the non-exposed group. Significant differences were also found between the groups for overall inhibitory control (mean difference = -2.10, $p < .001$, 95% CI [-3.07, -1.12]) and overall total waiting scores (mean difference = -14.08, $p < .001$, 95% CI [-20.84, -7.33]; Levine & Woodward, 2018). Levine and Woodward also examined the working memory abilities of these children by utilizing the Three Boxes task, which involved treats being placed under each box, the boxes being shuffled behind a screen, and then represented to the child who

was instructed to find a treat. After a treat was located, it would not be replaced and the boxes were reshuffled, and the child was asked again to locate a treat. Trials would continue until the child was able to successfully retrieve all three treats. Overall, no significant differences were detected among the two groups for block one trials completed ($M = 5.04$, $SD = 1.82$ vs. $M = 5.27$, $SD = 2.09$, $p = .532$) and perseverative errors ($M = 2.09$, $SD = 1.91$ vs. $M = 2.38$, $SD = 2.24$, $p = .469$) or for block two trials complete ($M = 4.82$, $SD = 1.91$ vs. $M = 4.36$, $SD = 1.53$, $p = .168$) and perseverative errors ($M = 1.83$, $SD = 1.89$ vs. $M = 1.43$, $SD = 1.58$, $p = .225$; Levine & Woodward, 2018). Researchers did find that toddlers in the non-exposed group were able to complete the task with fewer errors and fewer trials compared to the toddlers exposed to methadone prenatally; therefore, further analysis was conducted across the two trial blocks. Levine & Woodward revealed that compared to the methadone exposed toddlers, the non-exposed toddlers retrieved all treats more frequently ($p = .008$), required fewer trials to complete the task (block 1: $M = 5.27$, $SD = 2.09$ and block 2: $M = 4.36$, $SD = 1.53$ vs. block 1: $M = 5.04$, $SD = 1.82$ and block 2: $M = 4.82$, $SD = 1.91$, $p = .005$), and made less perseverative reaches to the same box (block 1: $M = 2.38$, $SD = 2.24$ and block 2: $M = 1.43$, $SD = 1.58$ vs. block 1: $M = 2.09$, $SD = 1.91$ and block 2: $M = 1.83$, $SD = 1.89$, $p = .005$), in block two compared to block one. These results suggest that exposed children may have difficulties with sustained attention, learning, and/or working memory.

Neuropsychological Impacts of School-Aged Children. Neuropsychological deficits have also been discovered for school-aged children who were diagnosed with NAS post-delivery, although the current literature for children aged 7 years and older is sparse. Research regarding school-aged children will likely continue to grow as children impacted by the current opioid epidemic enter into older age ranges. In a meta-analysis, Yeoh et al. (2019) found that

within the school-aged group (ages 7-18 years), cognitive results indicated no significant differences regarding cognition (d = -0.44, p = .23, 95% CI [-1.16, 0.28]) when comparing the cognitive data of children with prenatal opioid exposure and children who were not exposed prenatally to opioids (Yeoh et al., 2019). These findings indicate that the impact of prenatal opioid exposure relative to cognitive functioning varies across age cohorts and periods of development when compared to non-exposed children.

A longitudinal prospective study in Oslo, Norway, compared children with prenatal exposure to heroin (primary) and poly-substances (n = 45) with children who had no prenatal exposure to any substances (n = 48) to examine the neuropsychological impacts of gestational opioid and poly-substance exposure during adolescence (age 17-21 years; Nygaard et al., 2017). Children in the drug exposed group were recruited from an inpatient infant and family clinic from 1992-1996 between the ages of 0 to 3 years (Nygaard et al., 2017). More than 75% of the mothers of the exposed children were enrolled in a perinatal risk project at a hospital by their second or third trimester, with the remaining children being born at a different hospital and enrolling in the program after delivery. The non-exposed children living with their biological parents were recruited from a non-clinical maternal and child health center with parents of similar socioeconomic status as the families of the exposed group. 62% of the children in the exposed group were adopted or placed in permanent foster care prior to age 6 months and by age 1 year 87% of the group was adopted or in foster care. Maternal drug use during pregnancy was determined by self-report, medical records, and social records and indicated the mother's drug of choice as heroin (44%), benzodiazepine (13%), alcohol (11%), and psychopharmacology (11%), with the mean amount of poly-substance exposure being 3.5 drugs (range of 2-6 substances), including tobacco. Post-delivery, 78% of the neonates exposed to substances prenatally

experienced neonatal withdrawal symptoms (Nygaard et al., 2017). Descriptively, the exposed group had significantly lower birthweight (M = 3142.6 grams, SD = 676.7 vs. M = 3761.7 grams, SD = 461.2), gestational age (M = 38.5 weeks, SD = 2.2 vs. M = 40.6 weeks, SD = 1.2), and head circumference (M = 34.2 cm, SD = 1.8 vs. M = 35.7 cm, SD = 1.2) when compared to the non-exposed controls. Thirty-six percent of the exposed group had been diagnosed with attention-deficit/hyperactivity disorder, compared to 2% of the non-exposed group (chi-square = 17.9, $p <$ .001; Nygaard et al., 2017). During adolescence, the youths (ages 17-21 years) were assessed with the Wechsler Abbreviated Scale of Intelligence (WASI; Zhu, 1999), the Lafayette Grooved Pegboard (Lafayette Instrument, 2015), the Rey Complex Figure Test (RCFT; Meyers & Meyers, 1995), the California Verbal Learning Test-Second Edition (CVLT-II; Delis et al., 2000), the digit span subtest from the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III; Wechsler, 1997), the Plus-Minus task, Color-Word Interference Test from the Delis-Kaplan Executive Function System (D-KEFS; Delis et al., 2001), a letter memory task, and a N-back task (i.e., a continuous performance task measuring visuospatial working memory). Prenatally opioid and polysubstance exposed adolescents in their late teens and early twenties did not demonstrate any significant differences regarding cognitive functioning when compared to the normative population. However, they performed significantly lower than the non-exposed group in a variety of areas. Regression analysis ($p \leq .05$) of group differences revealed that the prenatally exposed group scored significantly lower than the non-exposed group on general cognitive abilities on the Wechsler Adult Intelligence Scale, third edition (b = 0.75, $p <$ .001), on fine motor abilities as assessed on the Groove Pegboard (b = 0.58, p = .008), visual long-term memory assessed with the Rey Complex Figure Test (b = .092, $p <$ .001), number short-term memory (b = .073, p = .004), and on their ability to continuously monitor and update information

for working memory on the letter memory task ($b = 0.69$, $p = .009$). These results were established after controlling for gender, age at testing, and caregiver education. Nygaard et al. (2017), also examined the number of different types of drugs used during pregnancy. They found that the lower number of substances used prenatally were significantly related to better scores on the letter memory task ($b = 0.38$, $p = 0.009$) and on short-term memory for numbers ($b = 0.22$, $p = .05$), after controlling for gender, age, and caregiver education. Overall, when compared to non-exposed controls, prenatally opioid exposed adolescents performed significantly lower on several cognitive areas including general cognition, fine motor, visual long-term memory, number short-term memory, and monitoring during working memory. These results indicate that neuropsychological differences that have been found in earlier ages do persist over time but may or may not reflect deficits given the lack of significant differences from normative samples (Nygaard et al., 2017).

Rees et al. (2020) conducted a meta-analysis to identify childhood health and educational outcomes of children with a history of NAS, age 0-16 years. Regarding mental health impacts, researchers found that there was a significant association with children diagnosed with NAS and a diagnosis of attention-deficit/hyperactivity disorder later in development ($OR = 3.21$, 95% CI [1.29, 7.97], $I^2 = 94\%$). Lower scores in speech and language development, indicating impairment, were found for children diagnosed with NAS ages 2-4 years ($OR = 2.81$, 95% CI [1.82, 4.33], $I^2 = 26\%$) and a higher probability of being diagnosed with a speech and language impairment was found for NAS children ages 3-8 years ($OR = 1.26$, 95% CI [1.04, 1.52]; Rees et al., 2020). Another study identified as a birth cohort study, utilized data collected from several Norwegian national health registries from 73,480 children born between 1999-2008. Tronnes et al. (2021) wanted to examine if there was an association between time (first trimester or

second/third trimester) and/or duration (≥ 5 weeks or ≤ 4 weeks) of opioid pain reliever use during pregnancy and a diagnosis of ADHD or experienced symptoms of ADHD without a diagnosis, in children who were exposed prenatally. Codeine was the opioid pain reliever most reportedly used by these women. The Conners' Parent Rating Scale-Revised, short form (Conners, 1997) was utilized to assess children (at age 5 years) who were having difficulties with ADHD symptoms but did not meet the full diagnostic criteria for ADHD. National records indicated the highest incidence rate of exposed children who were diagnosed with ADHD occurred between the ages of 7 and 11 years. Data indicated no associations regarding the timing of opioid exposure and an ADHD diagnosis or for experienced ADHD symptoms without a diagnosis; however, children who were exposed to opioids for ≥ 5 weeks during gestation demonstrated a slightly elevated risk of being diagnosed with ADHD compared to children exposed to ≤ 4 weeks of opioids during gestation (*HR* = 1.60, 95% CI [1.04, 2.47]; Tronnes et al., 2021).

Nygaard et al. (2016) performed a prospective longitudinal cross-informant study to compare general cognition as well as attention problems of children with prenatal opioid exposure (n = 72) compared to children with no prenatal substance exposure (n = 58). The children in the exposed group were born to a mother who used an average of 3.5 substances during pregnancy including tobacco, opiates, alcohol, and benzodiazepines, with tobacco (100%), with opiates (54%) being the substances most reportedly used. Due to prenatal substance exposure, almost 80% of infants were diagnosed with NAS. Researchers examined general cognitive functioning as assessed by the McCarthy Scales of Children's Abilities (McCarthy, 1972) and the Wechsler Intelligence Scale for Children, Revised (Wechsler, 1974). Freedom from distractibility, from the Wechsler scale, was specifically examined as a measure

of short-term attention and concentration by utilizing the scores from arithmetic, digit span, and coding subtests. Nygaard et al. found that at age 4.5 years, general cognition was significantly lower for the exposed group compared to the non-exposed group (d = -0.73, p = .04, 95% CI [-0.39, -1.08]), after controlling for multiple covariates including birth weight, gestational age, socioeconomic status, gender, and age at assessment. At age 8.5 years, the opioid exposed group demonstrated significantly lower scores for general cognition (b z-value = -1.03, 95% CI [-1.37, -0.70], p = .002) and freedom from distractibility (b z-value = 0.93, 95% CI [-1.27, -0.58], p = .002) compared to the non-exposed group, even after controlling for multiple covariates (Nygaard et al., 2016). Behaviorally, the participants were assessed at 4.5 years and 8.5 years old by the caregiver rated Child Behavior Check List/4-18 version, the Child Behavior Check List Teacher's Report Form (Achenbach, 1991), and the ADHD Rating Scale (DuPaul et al., 1998). The behavior checklist and the teacher's report examine emotional, behavioral, social, and attention problems. The ADHD scale focuses on symptoms of ADHD diagnostic criteria. Higher ratings on these assessments indicate greater difficulty. Regarding attention, children in the exposed group were rated significantly higher for attention difficulties by their caregiver on the behavior checklist (b z-value = 0.88, 95% CI [0.52, 1.23], p = .005) and ADHD scale (b z-value = 0.91, 95% CI [0.56, 1.26], p = .004), as well as by their teacher on the teacher report (b z-value = 0.66, 95% CI [0.27, 1.04], p = .01) and the ADHD scale (b z-value = 0.68, 95% CI [0.27, 1.08], p = .003), compared to non-exposed children (Nygaard et al., 2016). All differences remained significant after controlling for multiple covariates. The attention domain produced the largest difference with 25% of the exposed children compared to 2% of the non-exposed children scoring at or above the 95th percentile. Additionally, caregivers indicated that 25% of exposed children and teachers indicated that 17% of the exposed children met diagnostic criteria for

ADHD, but no children in the non-exposed group were indicated as meeting diagnostic criteria by either caregivers or teachers (Nygaard et al., 2016). Lastly, differences over time, from age 4.5 to 8.5 years, were analyzed and revealed that no significant differences were found on the ADHD rating scale for caregivers (d = 0.53 vs. d = 0.87, p = .31) or teachers (d = 0.90 vs. d = 0.66, p = .36; Nygaard et al., 2016). Overall, this data indicates that children prenatally exposed to opioids are at risk of having deficits in general cognition during pre-school and early school ages and are also at a greater risk of experiencing attention difficulties.

Gender Differences. Researchers examining the neuropsychological differences between infants, toddlers, and school-aged children who were diagnosed with NAS as a neonate or experienced prenatal opioid exposure have also found differences between the males and females. Skumlien et al. (2020) conducted a historical cohort study, spanning 7 years, of 378 infants and toddlers (girls, n = 194 and boys, n = 184) ranging from 1.2 months to 42.8 months of age recruited from a family outpatient clinic and examined how prenatal opioid exposure impacts cognitive and language development. The family outpatient clinic provides medical care and support primarily to pregnant women, who are currently struggling with substance abuse or have struggled within 2 years of their pregnancy, and their children. This study compared children who were prenatally exposed to opioids (n = 94), alcohol (n = 131), tobacco (n = 115), and those with no prenatal substance exposure (n = 38). Substance exposure was determined by verbal maternal report and/or urine analysis. The BSID-3 (Bayley, 2006) was utilized to assess the toddler's cognitive and language development with most children being tested at least twice. Researchers presented an analysis with age-corrected standardized scores. An interaction effect was detected for opioid exposure and sex for both the cognitive domain (mean difference = $\pm$ 5.78, p = .05, 95% CI [-11.64, 0.07]) and the language domain (mean difference = $\pm$ 6.63

[girls/boys], p = .02, 95% CI [-12.41, -0.86]), with opioid exposed males producing lower scores than opioid exposed females (Skumlien et al., 2020). Additionally, males prenatally exposed to opioids had lower scores on the cognitive domain than non-exposed males (mean difference = -5.82, p = .05, 95% CI [-9.92, -1.47]). Researchers revealed that males exposed to opioids prenatally are at a greater risk of having deficits regarding cognitive and language development during infancy and early toddlerhood (approximately age 1 month-3.5 years) when compared to nonexposed males and opioid exposed females, suggesting the importance of children in this at-risk population to be routinely monitored during the early stages of development (Skumlien et al., 2020).

Similarly, a retrospective study at Cincinnati Children's Hospital evaluated toddlers age 2 years (n = 87), age 2 years, for non-verbal cognition, language, and motor development with the BSID-3 (Bayley, 2006). These toddlers had a history of prenatal opioid exposure and/or polysubstance use and were diagnosed and treated for NAS postnatally (Merhar et al., 2018). Researchers examined if gender differences existed between subscales for cognition, language, and motor skills. Merhar et al. (2018) found that toddler girls who were diagnosed and treated for NAS postnatally, scored significantly higher than the boys with NAS on non-verbal cognition (Mdn = 100 vs. Mdn = 95, p = .002) and language subscales (Mdn = 97 vs. Mdn = 94, p = .04). Significant gender differences did not exist for the motor subscale (Mdn = 97 vs. Mdn = 94, p = .16). This data suggests that gender may play a role in neuropsychological outcomes for toddlers with a history of prenatal opioid exposure who were diagnosed and treated for NAS symptoms.

A longitudinal study examined the cognitive functioning of 72 children who were prenatally exposed to opioids or polysubstance use and 58 children with no prenatal substance exposure (Nygaard et al., 2015). The participants were assessed at the ages of 1 year, 2 years, 3

years, 4.5 years, and 8.5 years. The BSID-II (Bayley, 1969) was utilized for ages 1, 2, and 3 years of age; the McCarthy Scales of Children Abilities (McCarthy, 1972) were used for the 4.5-year-old time frame, and the Wechsler Intelligence Scale for Children, Revised (Wechsler, 1974) was used for the children at 8.5 years old with a general cognitive ability score being calculated. Overall, the exposed group demonstrated significantly lower general cognition scores when compared to the non-exposed children across all age time frames: age 1 year (mean difference = 6.5, $p < .01$, 95% CI [2.2, 10.8]), age 2 years (mean difference = 8.0, $p < .01$, 95% CI [2.8, 13.2]), age 3 years (mean difference = 6.8, $p < .01$, 95% CI [2.8, 10.9]), age 4.5 years (mean difference = 12.0, $p < .01$, 95% CI [7.0, 16.9]), and age 8.5 years (mean difference = 18.3, $p < .01$, 95% CI [12.3, 24.2]); however, significant group differences were found (Nygaard et al., 2015). Group differences were analyzed and showed that exposed boys scored significantly lower than non-exposed boys for all assessments given during each age assessed; however, after controlling for socioeconomic status, gestational age, and birth weight, general cognition scores only remained significant at 4.5 years ($M = 98.9$, $SD = 14.3$ vs. $M = 114.3$, $SD = 11.8$, $p < .001$, 95% CI [9.2, 21.7]) and at 8.5 ($M = 98.9$, $SD = 14.8$ vs. $M = 113.7$, $SD = 14.4$, $p < .001$, 95% CI [7.3, 22.4]). After controlling for the same covariates, the exposed girl's general cognition score was significantly lower than the non-exposed girl controls when assessed at age 8.5 years ($M = 96.6$, $SD = 17.6$ vs. $M = 119.8$, $SD = 13.3$, $p < .001$, 95% CI [13.4, 33.1]). Nygaard et al. (2015) then analyzed the effect between time and group and found no effect for boys ($F(4) = 0.40$, $p = .81$), although the group and time effect was highly significant for the girls ($F(4) = 4.14$, $p = .003$), with the cognitive score differences between the exposed and non-exposed groups at age 8.5 years being significantly ($p < .01$) higher than all other assessment time periods. However, given that a different assessment was used at 8.5 years old, the implication of these results is

unclear. Researchers concluded that overall, differences in general cognition scores between the exposed and non-exposed groups was not reduced over time. However, exposed girls did not demonstrate differences in general cognition until age 8.5 years, whereas exposed boys scores were significantly lower at age 4.5 years and 8.5 years when compared to non-exposed controls potentially reflecting some sex differences in the expression of group differences (Nygaard et al., 2015).

A retrospective study utilized the Maternal Lifestyle Study data to conduct descriptive analyses of 234 children who were diagnosed with NAS postnatally (Miller & Anderson, 2022). The Maternal Lifestyle Study collected data from multiple sites to examine mother-infant dyads in order to investigate possible impacts of children (1-16 years old) born to a mother who used substances during pregnancy. The current study utilized data examining children who were 10 years old. Variables selected by the researchers for the current study included intrauterine exposure, home environment, and neurodevelopmental outcomes (Miller & Anderson, 2022). Demographic results indicated approximately 74% were African American, and approximately 63% were male. Approximately 79% of the children experienced prenatal polysubstance exposure. Neurodevelopmental data of the exposed children indicated approximately 15% were diagnosed with ADHD, 23% with a learning disorder, 24% with language delays, and 26% demonstrated abnormal cognitive development (Miller & Anderson, 2022).

Overall, neuropsychological research has demonstrated that prenatally opioid exposed children perform significantly lower than non-exposed children. Infants and toddlers have specifically demonstrated significantly lower abilities regarding locomotor, fine/gross motor, general cognition, non-verbal cognitive abilities, and language, compared to non-exposed children. Significant differences for school-aged children were found regarding general

cognition, working memory, fine motor skills, attention, auditory short-term memory, and visual long-term memory. Although this area of research is limited, understanding that the prenatally exposed pediatric population is vulnerable to potential neuropsychological difficulties allows for caregivers and involved professionals to be equipped with resources, recommendations, and interventions to support these children.

Caregiver Relationship. Neonates diagnosed with NAS postnatally may experience changes in their environments, as well as have different qualities of relationships with their caregiver (Konijnenberg et al., 2016; Merhar et al., 2018). A retrospective study at Cincinnati Children's Hospital examined how a child's cognitive development is linked with their living environment. Merhar et al. (2018) looked at 87 infants born between 2011 and 2015 who were treated for NAS. These infants were later assessed for general cognition, language, and motor development around 2 years of age with the Bayley Scales of Infant and Toddler Development, Third edition (BSID-3; Bayley, 2006). During the neuropsychological assessment, demographic information was also obtained including the child's current living environment. Forty-four percent were living with adoptive/foster families, 22% with their biological mother, and 34% with a biological relative. Researchers revealed that children who were living with foster or adoptive families scored significantly higher on the cognitive domain measuring non-verbal problem-solving skills when compared to the children who were living with their biological mother or a family member (Mdn = 100 vs. Mdn = 95, p = .03). Similarly, lower motor scores < 85 (p = .02) were significantly more likely to occur in NAS children who lived with their biological relatives compared to foster care or adoptive caregivers. No differences for language were indicated regarding living environment. Researchers concluded that the differences in living environments suggest that socioeconomic factors such as poverty, poor nutrition, and

lower levels of education often found in families of children with NAS, may play a significant role regarding neuropsychological performance (Merhar et al., 2018).

Konijnenberg et al. (2016) conducted a study to examine if the nature of mother-child interactions with children who experienced prenatal opioid exposure impacted their cognitive development. Participants were born between January 2005 and January 2007 and included 35 children prenatally exposed to opioids and medication assisted treatment with methadone or buprenorphine, and 32 non-prenatally exposed controls. Mothers of the exposed children were recruited from opioid medication assisted treatment programs and all endorsed smoking tobacco during pregnancy. Control mothers were recruited from medical clinics and reported no substance use during pregnancy. The children from both groups were assessed at two different time points, age 1 year and age 4 years. A 15-minute free play mother-child interaction was video recorded at age 1 year, which included age-appropriate toys. Interactions were rated on a five-point Likert scale and assessed the following maternal behaviors: positive/negative affect, sensitivity, detachment, animation, intrusiveness, and stimulation of development. The child's behavior was rated for positive/negative mood, activity, and sustained attention. Dyadic scales rated degree of shared experience and synchronism of the interaction. Konijnenberg et al. found that mothers of the exposed infants demonstrated significantly lower sensitivity ($M = 3.40$, $SD = 0.68$ vs. $M = 5.0$, $SD = 0.80$, $p < .001$), less positive affect ($M = 3.17$, $SD = 0.70$ vs. $M = 3.75$, $SD = 0.92$, $p = .007$), and were engaged in fewer developmentally stimulating activities ($M = 3.43$, $SD = 0.78$ vs. $M = 3.84$, $SD = 0.85$, $p = .05$) when compared to the substance free mothers. At age 1 year, exposed children demonstrated less positive mood ($M = 2.60$, $SD = 0.72$ vs. $M = 3.16$, $SD = 0.85$, $p = .007$) and less sustained attention ($M = 3.60$, $SD = 0.77$ vs. $M = 4.13$, $SD = 0.79$, $p = .01$), compared to the non-exposed children. Dyadic mutuality was also significantly

lower for exposed mother-child dyads compared to substance free dyads (M = 3.23, SD = 0.68 vs. M = 4.13, SD = 0.91, $p < .001$). During the follow up 15-minute mother-child interaction, at age 4 years, the mother was instructed to play with a standard set of toys including hand puppets, a puzzle, and a toy farm. Behaviors were rated on a seven-point Likert scale and assessed the mothers on hostility, confidence, respect for the child's autonomy, support, quality of assistance, and stimulation of cognitive development. Children were rated on negativity, overall experience of the session, agency, and persistence. Dyadic scales rated affective mutuality and goal-directed partnership. At follow up, mothers of the exposed children demonstrated a less supportive presence (M = 4.13, SD = 1.38 vs. M = 5.33, SD = 1.21, $p < .001$), less respect for their child's autonomy (M = 4.77, SD = 1.46 vs. M = 5.70, SD = 1.09, p = .007), engaged in fewer cognitive stimulating activities (M = 4.17, SD = 1.15 vs. M = 5.37, SD = 1.27, $p < .001$), provided less effective instructions (M = 3.90, SD = 1.45 vs. M = 5.40, SD = 1.25, $p < .001$), and were less confident in their interactions with their child (M = 5.03, SD = 1.43 vs. M = 5.90, SD = 1.24, p = .02), compared to substance free mothers. Exposed children demonstrated less agency (M = 4.70, SD = 1.15 vs. M = 5.77, SD = 1.01, $p < .001$), less persistence (M = 5.10, SD = 1.24 vs. M = 6.13, SD = 0.68, $p < .001$), and lower experience of the session (M = 4.53, SD = 1.31 vs. M = 5.77, SD = 1.14, $p < .001$). Although significant differences were found between the exposed and non-exposed groups, mean scores of the exposed mother-child dyads indicated generally positive interactions and did not indicate that the exposed mothers had poor parenting skills. Cognitively, select subtests from the Wechsler Preschool and Primary Scale of Intelligence, revised (WPPSI-R; Wechsler, 1989) and the NEPSY (a neuropsychological assessment; Korkman et al., 2007) were selected to measure verbal and nonverbal abilities as well as memory, inhibition, and attention. Cognitive assessments were only given to both groups at age 4 years and indicated that

all mean scores fell in the average range for both groups. However, the exposed children scored significantly lower than the non-exposed children on the NEPSY narrative memory ($M = 6.91$, $SD = 3.75$ vs. $M = 9.03$, $SD = 4.32$, $p = .04$), NESPY statue ($M = 16.23$, $SD = 7.86$ vs. $M = 22.48$, $SD = 7.08$, $p = .001$), NEPSY imitating hand position ($M = 9.09$, $SD = 4.07$ vs. $M = 12.16$, $SD = 4.35$, $p = .004$), WPPSI-R block design ($M = 8.14$, $SD = 2.14$ vs. $M = 9.90$, $SD = 3.65$, $p = .02$), WPPSI-R animal pegs ($M = 8.31$, $SD = 3.22$ vs. $M = 10.42$, $SD = 2.78$, $p = .006$), WPPSI-R sentences ($M = 8.29$, $SD = 2.80$ vs. $M = 11.61$, $SD = 2.86$, $p < .001$), and WPPSI-R vocabulary ($M = 11.74$, $SD = 1.88$ vs. $M = 12.68$, $SD = 1.66$, $p = .04$; Konijnenberg et al., 2016). Lastly, Konijnenberg et al. examined the effects of group status and mother-child interaction on the child's cognitive development scores. Analysis indicated a significant effect of group status on cognitive development ($F(1,54) = 5.65$, $p = .02$, $\eta^2 = 0.10$) as well as mother-child interaction and cognitive development ($F(1,54) = 5.26$, $p = .03$, $\eta^2 = 0.09$). Significant interactions were found for group and cognitive measures including statue, which measures behavioral inhibition ($F(1,54) = 4.10$, $p = .048$, $\eta^2 = 0.07$), imitating hand positions, which measures sensorimotor function ($F(1,54) = 4.45$, $p = .04$, $\eta^2 = 0.08$), and sentences, which measures short-term memory ($F(1,54) = 9.29$, $p = .004$, $\eta^2 = 0.15$). Mother-child interaction had a significant effect on narrative memory ($F(1,54) = 5.45$, $p = .02$, $\eta^2 = 0.09$) and vocabulary ($F(1,54) = 7.41$, $p = .009$, $\eta^2 = 0.12$; Konijnenberg et al., 2016). No significant interaction effects ($p = .93$) were found between mother-child interaction and group status. Researchers concluded that mother-child interaction may be linked with language related skills, whereas as group-related factors may be associated with cognitive skills involving sensorimotor response control. Additionally, the researchers suggested that the exposed mother-child dyads could participate in interventions to strengthen or improve their relationship (Konijnenberg et al., 2016).

Academic Performance. Neuropsychological deficits in early development can be reflected in a child's academic performance. Fill et al. (2018) compared 1,815 children (ages 3-8 years) who were diagnosed with NAS to a matched control group of 5,441 children (ages 3-8 years) without NAS. The data sample was collected by utilizing health and education databases from Tennessee. Medicaid and birth certificate information identified infants who were diagnosed with NAS at birth from 2008 to 2011. The control group was matched for sex, race/ethnicity, gestational age, enrollment in Tennessee Medicaid, and home region. Demographically, children with a history of NAS were more likely to have a lower birth weight (< 2500 grams, 24% vs. 9.2%, $p < .001$), to be born prematurely (<37 weeks, 21.6% vs. 11.5%, $p < .001$), and were more likely to have a NICU admission (20.9% vs. 5.8%, $p < .001$) when compared to the control group (Fill et al., 2018). Data analyses showed that children born with NAS were significantly more likely to receive a disability evaluation referral (19.3% vs. 13.7%, $p < .001$), meet diagnostic criteria for a disability (15.6% vs. 11.7%, $p < .001$), and require classroom interventions or services at school (15.3% vs. 11.4%; $p < .001$) at a rate significantly higher than children who were not postnatally diagnosed with NAS (Fill et al., 2018). Autism spectrum disorder, developmental delay, other health impairment, specific learning disability, and speech or language impairment accounted for more than 95% of the educational disabilities identified. The NAS group was significantly more likely to be diagnosed with developmental delay (5.3% vs. 3.5%; $p = .001$) and speech and language impairment (10.3% vs. 8.3%; $p = .009$), compared to controls. Lastly, Fill et al. found that children in the NAS group, compared to the control group, were significantly more likely to receive school services or therapies including classroom accommodations (5.4% vs. 4.1%; $p = .02$) and speech therapy (14.0% vs. 10.8%; $p < .001$). Researchers concluded that children diagnosed with NAS postnatally are at a greater risk

of having an educational disability and requiring specific interventions at school or within the classroom (Fill et al., 2018).

A study conducted in Australia examined data from a curriculum-based test for literacy and numeracy (from 2000 to 2006) for 3rd, 5th, and 7th grade, to look at possible educational outcomes of children who were exposed with opioids prenatally and diagnosed with NAS. Researchers compared children with NAS (n = 2,234) to matched controls (n = 4,330), and other children born in the same area (n = 598,265; Oei et al., 2017). The control group was matched for sex, gestational age, year of birth, and socioeconomic status. The NAS group, compared to the control group and population group, had significantly more primary parents with education below 9th grade or no education levels reported (44% vs. 18.4% and vs. 17.1%, $p < .001$) and had significantly fewer primary parents with a bachelor's degree (4.3% vs. 19.5% and vs. 23.3%, $p < .001$; Oei et al., 2017). Standardized testing covered five testing domains including: reading, numeracy, writing, grammar, and spelling. In 3rd grade, NAS children compared to the other two groups scored significantly lower in reading ($F(2, 452{,}450) = 63.4$, $p < .001$), numeracy ($F(2, 452{,}450) = 83.9$, $p < .001$), writing ($F(2, 452{,}450) = 110.6$, $p < .001$), grammar ($F(2, 452{,}450) = 89.3$, $p < .001$), and spelling ($F(2, 452{,}450) = 92.6$, $p < .001$). In 5th grade, the NAS also scored significantly lower than the other two groups for reading ($F(2, 303{,}442) = 85.3$, $p < .001$), numeracy ($F(2, 303{,}442) = 96.2$, $p < .001$), writing ($F(2, 303{,}442) = 125.2$, $p < .001$), grammar ($F(2, 303{,}442) = 97.6$, $p < .001$), and spelling ($F(2, 303{,}442) = 98.7$, $p < .001$). In 7th grade, the NAS group also scored significantly lower than both groups in all domains, reading ($F(2, 161{,}645) = 109.8$, $p < .001$), numeracy ($F(2, 161{,}645) = 110.5$, $p < .001$), writing ($F(2, 161{,}645) = 182.1$, $p < .001$), grammar ($F(2, 161{,}645) = 95.8$, $p < .001$), and spelling ($F(2, 161{,}645) = 100.0$, $p < .001$). Children with a history of NAS, in 7th grade, were significantly more likely to

not meet national minimal standards for one or more testing domain than both the control group and the population group (37.7% vs. 18.4% and vs. 14.5%, $p < .001$; Oei et al., 2017). The risk of not meeting the minimal national testing standards was independently linked with NAS (aOR = 2.5, $p < .001$, 95% CI [2.2, 2.7]). Overall, children and adolescents with a history of prenatal opioid exposure and a diagnosis of NAS demonstrated significantly lower academic test scores across every domain and in every grade level examined. Oei et al. (2017) concluded that children born with NAS are at a greater risk of having a lower academic performance than their peers regarding standardized tests. These deficits may require remedial services and accommodations in school.

Fetal Alcohol Spectrum Disorders. The neuropsychological impacts of prenatal opioid exposure and NAS is a growing research area, although it has not been vastly studied. Examining the neurodevelopmental impacts of FASD can help facilitate further understanding of how the prenatally opioid exposed population may be impacted. Rasmussen et al. (2006) examined the neurobehavioral functioning of 50 Canadian children (ages 6-15 years) from a clinically referred sample with a diagnosis of fetal alcohol spectrum disorders. The Wechsler Intelligence Scale for Children, Third Edition (WISC-III; Wechsler, 1991), the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989), the Children's Memory Scale (CMS; Cohen, 1997), the Behavioral Rating Inventory of Executive Functioning (BRIEF; Gioia et al., 2000), and Parent and Teachers Conners' Rating Scales-Revised (CRS-R; Conners, 1997) were the assessments utilized to measure the children's intelligence, memory, executive functioning, and attention. Regarding intelligence, Rasmussen et al. found that mean scores for full scale intelligence quotient, verbal intelligence quotient, and performance intelligence quotient fell in the low average to borderline range. Mean memory performance fell in the borderline range on

indices assessing attention/concentration and verbal delay (i.e., stories and word pairs) and performance fell in the low average range for verbal immediate recall. Regarding executive functioning, they found that the majority of both parent and teacher's ratings were abnormally elevated, with the greatest difficulty being indicated on planning/organizing and working memory. Parent and teacher ratings on the Conners Rating Scales-Revised endorsed clinically elevated scores (at least 1 standard deviation above the mean) for the inattentive and hyperactive/impulsive scales (Rasmussen et al., 2006). Overall, the children diagnosed with FASD demonstrated varied deficits in intelligence, memory, attention, and executive functioning. Rasmussen et al. concluded that children with FASD showed the greatest difficulties with tasks measuring auditory attention, information processing speed, aspects of visual memory, planning/organizing, working memory, attention, and hyperactivity/impulsivity.

McGee et al. (2008) compared the performance of concept formation and conceptual set shifting with children (age 8-18 years) with heavy prenatal exposure to alcohol (n = 47) and typically developing children (n = 60). Concept formation is considered one component of executive functioning. Children were assessed using the Wisconsin Card Sorting Test (Heaton et al., 1993) and the California Card Sorting Test from the Delis-Kaplan Executive Functioning System (Delis et al., 2001). A full scale intelligence quotient score (FSIQ) was also obtained and the control group had significantly higher FSIQ scores than the alcohol exposed group (F(1, 105) = 63.69, p < .001). McGee et al. found that children with or without a diagnosis of fetal alcohol syndrome who experienced heavy alcohol use in utero demonstrated lower scores regarding overall performance on the Wisconsin Card Sorting Test (M = 97.25, SD = 12.13 vs. M = 107.97, SD = 15.25, ES = 0.78, F = 15.51, p < .001) and the California Card Sorting Test (M = 83.39, SD = 14.92 vs. M = 97.81, SD = 6.06, ES = 1.21, F = 12.86, p = .001) compared to controls. The

children and adolescents in the alcohol exposed group had significantly fewer conceptual level responses (M = 96.02, SD = 12.60 vs. M = 108.95, SD = 16.32, ES = 0.89, F = 20.10, p < .001), greater perseverative responses (M = 99.89, SD = 12.80 vs. M = 106.10, SD = 14.39, ES = 0.46, F = 5.40, p = .02), and fewer confirmed correct perceptual sorts (M = 7.04, SD = 3.47 vs. M = 10.82, SD = 1.74, ES = 1.38, F = 16.93, p < .001; McGee et al., 2008). McGee et al. concluded that children and adolescents who were prenatally exposed to heavy alcohol are at a greater risk of having deficits in executive function, specifically with concept formation and conceptual set shifting when compared to typically developing controls. Researchers suggested that deficits in these areas can impact adaptive functioning and problem-solving abilities.

Fuglestad et al. (2015) examined the executive functioning of children (age 3-5.5 years), to see if the well-researched executive functioning deficits found in school-aged children and adolescents with fetal alcohol spectrum disorders is present during this critical developmental period. They evaluated preschool children with FASD (n = 39) and non-exposed age-matched children (n = 50) by utilizing the Executive Functioning Scale for Early Childhood (Carlson & Schaefer, 2012) and a Delay of Gratification task (Mischel et al., 1989). Fuglestad et al. found that the young children with FASD demonstrated greater executive functioning deficits (F(1, 84) = 29.00, p < .001, η^2 = 0.14) and more impulsivity (F(1, 68) = 14.85, p < .001, η^2 = 0.16) compared to the non-exposed comparison group. Lower scores were presented for the children diagnosed with fetal alcohol syndrome (t(4) = -4.00, p = .016) and partial fetal alcohol syndrome (t(17) = -2.60, p = .019), compared to the normative data, although children diagnosed with alcohol-related neurobehavioral disorder did not have significantly different executive functioning scores (t(15) = -1.78, p = .096) compared to normative data. Children with fetal alcohol syndrome had the largest deficits when compared to the normative data compared to

those with partial fetal alcohol syndrome and alcohol-related neurobehavioral disorder (Fuglestad et al., 2015).

Vaurio et al. (2011) conducted a multivariate analysis to determine if neurobehavioral deficits are present in children (6-16 years old) with heavy prenatal alcohol exposure ($\geq$ 4 drinks per occasion at a frequency of at least once per week or $\geq$ 14 drinks per week throughout pregnancy), even when intelligent quotient differences are controlled for. Children in the alcohol exposed group (n = 55) were recruited by professional referrals and self-referrals, and the non-exposed intelligence quotient matched children (n = 55) were recruited from the community through advertisements in child venues and agencies. Vaurio et al. assessed the children on the following neuropsychological tests: Peabody Picture Vocabulary Test-Third Edition (Dun & Dun, 1997), Boston Naming Test (Kaplan et al., 1983), Controlled Oral Word Association Test (Goodglass & Kaplan, 1983), Wisconsin Card Sorting Test (Heaton, 1993), Beery Visual Motor Integration (Berry, 1997), Grooved Pegboard (Lafayette Instrument, 2015), Wide Range Achievement Test-Third Edition (Wilkinson, 1993), California Verbal Learning Test-Children's Version (Delis et al., 1994), Test of Variables of Attention (visual subtest; Leark et al., 1999), and the Child Behavior Checklist (Achenbach, 1991). Prenatally exposed children scored significantly lower than matched controls for executive functioning (p = .03), visual motor integration (p = .022), arithmetic (p = .009), and verbal learning for words learned (p = .003), short term delay free recall (p = .009), and long delay free recall (p = .002). Vaurio et al. found that lower scores in the areas of verbal learning held even when controlling for the full-scale intelligence quotient, suggesting that these differences could not be explained simply by these children having a lower full scale intelligence quotient.

Group differences by gender were demonstrated from a historical cohort study of infants and toddlers (N = 378) ranging from age 1 month to 42 months (Skumlien et al., 2020). This study found that females prenatally exposed to alcohol produced lower cognitive scores (mean difference -3.24, 95% CI [-6.03, -0.44]) and language scores (mean difference -2.69, 95% CI [-5.42, 0.04]) when compared to opioid exposed females, although no differences were identified between the boys in the alcohol exposed vs. opioid exposed groups (Skumlien et al., 2020).

Summary of What We Know

Research examining the neuropsychological impacts of fetal opioid exposure and/or neonates who have been diagnosed with NAS during early development have focused on infancy, toddlerhood, and pre-school aged children. The Bayley Scales of Infant Development (Bayley, 2006) has been utilized to assess the non-verbal cognitive, language, and motor abilities of infants and toddlers from birth to 2 years of age. Several empirical studies have demonstrated that children who experienced prenatal opioid exposure score significantly lower than non-exposed children or when compared to the normative test population regarding general cognitive abilities (Hunt et al., 2008; McGlone & Mactier, 2015, Salo et al., 2010; Yeoh et al., 2019), non-verbal cognitive abilities (Beckwith & Burke, 2015; Merhar et al., 2018), language abilities (Beckwith & Burke, 2015; McGlone & Mactier, 2015; Merhar et al., 2018), motor abilities (Merhar et al., 2018), and locomotor abilities (McGlone & Mactier, 2015). One meta-analysis, however, found that exposed infants and toddlers from birth to 2 years of age did not demonstrate a difference in cognitive or psychomotor abilities when compared to non-exposed children (Baldacchino et al., 2014). Young children, birth to 2 years of age, who experienced opioid exposure during gestation have also demonstrated significantly poorer inhibitory control on an executive functioning task than non-exposed children. On a working memory task,

compared to non-exposed children, no differences were found regarding trials completed and preservative errors, although further analysis indicated that exposed children made more errors and required more trials to complete the task (Levine & Woodard, 2018). This research indicates potential deficits regarding executive functioning and possible difficulties regarding attention, learning, and memory. Children prenatally exposed to opioids from 3-6 years of age scored significantly lower than non-exposed children and/or the normative test population for cognitive abilities, motor abilities (Hunt et al., 2008; Yeoh et al., 2019), and speech and language (Hunt et al., 2008; Rees et al., 2020), although Baldacchino et al. (2014) did not find differences between opioid exposed children and non-exposed children for cognitive or psychomotor abilities. Researchers concluded that possible deficits in language and cognition of NAS infants are reflective of a critical period of fetal development being adversely impacted by prenatal opioid exposure (Beckwith & Burke, 2015). Evidence of children aged 0-6 years of age demonstrating significantly lower cognitive abilities, language abilities, motor abilities, and executive function relative to their non-exposed peers or the normative test population highlights the importance of young children in this at-risk group being assessed throughout early development in order to identify and implement needed interventions to support any identified deficits. Early identification of their needs can also facilitate the implementation of remedial services that may be required during school.

Fewer experimental research studies have been conducted for school-aged children and beyond who were exposed prenatally to opioids with or without a postnatal diagnosis of NAS. Children at 8.5 years of age who were prenatally exposed to opioids and polysubstance use had significantly lower Full Scale Intelligence Quotient (FSIQ) scores on the WISC-R (Wechsler, 1974) compared to the non-exposed group even after controlling for birth age/weight, SES, sex,

and age (Nygaard et al., 2015). Similarly, adolescents 17-21 years old were found to have significantly lower scores regarding general cognition, fine motor skills, working memory, visual long-term memory, and auditory short-term memory (Nygaard et al., 2017), although no significant differences were found for general cognition when compared to the normative population of the Wechsler Abbreviated Scale of Intelligence (Zhu, 1999). An examination of middle childhood and adolescents (7-18 years old) also did not indicate significant differences when comparing the neurocognitive abilities children who experienced prenatal opioid exposure and those children with no substance exposure during the gestational period (Yeoh et al., 2019). A decline in speech and language abilities have been indicated for children between the ages of 3-8 years (Rees et al., 2020).

Children with prenatal opioid exposure have a greater risk of developing ADHD than non-exposed children, with one study finding the highest incidence rate of diagnosis occurring from 7 to 11 years of age (Nygaard et al., 2016, 2017; Rees et al., 2020; Tronnes et al., 2021). An association between time (1^{st} trimester or $2^{nd}/3^{rd}$ trimester) and/or duration ($\geq$ 5 weeks or $\leq$ 4 weeks) of an opioid pain reliever during pregnancy and a diagnosis of or symptoms of ADHD in children who were exposed prenatally has also been examined. No association was found regarding the timing of the opioid during the gestational period for ADHD diagnosis or ADHD symptoms, although an elevated risk was indicated for the duration of exposure, with children prenatally exposed to 5 or more weeks having a greater risk of receiving an ADHD diagnosis compared to children who were exposed to opioids for 4 or less weeks during gestation (Tronnes et al., 2021). Caregivers and teachers indicated exposed children meeting diagnostic criteria for ADHD on the ADHD Rating Scales (DuPaul, 1998) more frequently than children with prenatal substance exposure when assessed at age 4.5 and 8.5 years. Additionally, when assessed by the

Child Behavior Checklist/4-18 (Achenbach, 1991), both age groups demonstrated a significant difference regarding the attention domain compared to non-exposed children with 25% of exposed children scoring at or above the 95th percentile compared to 2% of non-exposed children (Nygaard et al., 2016). Exposed children, 10 to 14 years of age, showed similar patterns as detected by fMRI on a working memory-selective attention task when compared to non-exposed children, although the exposed children demonstrated an impaired task performance and showed increased activation in the prefrontal cortical areas during aspects of the task that were more cognitively demanding (Sirens et al., 2018). Neurodevelopmental data obtained by a descriptive analysis of 234 children, 10 years of age, who were diagnosed with NAS postnatally indicated approximately 15% were diagnosed with ADHD, 23% with a learning disorder, 24% with language delays, and 26% demonstrating abnormal cognitive development (Miller & Anderson, 2022). Overall, minimal research has been conducted regarding the neuropsychological impacts of prenatal opioid exposure for children in middle childhood and adolescence. The preliminary findings discussed above demonstrated the need for continued research in these areas in order to learn about and support these children.

Differences between males and females have been discovered in this population. Researchers revealed that males exposed to opioids prenatally are at a greater risk of having decreased scores on tasks of cognitive and language development in infant and early toddlerhood (approximately 1 month to 3.5 years of age) when compared to nonexposed males and opioid exposed females (Skumlien et al., 2020). Similarly, 2-year-olds who were diagnosed and treated for NAS as neonates were assessed and showed that the boys scored lower for cognition and language when compared to the girls (Merhar et al., 2018). Exposed boys scored significantly lower for general cognition across multiple age ranges (i.e., 1-3 years, 4.5 years, and 8.5 years)

when compared to non-exposed boys, but when assessed at 8.5 years old full scale intelligence quotient scores were significantly lower for both boys and girls compared to non-exposed children (Nygaard et al., 2015).

Children diagnosed with NAS postnatally have demonstrated a significantly higher rate of being referred for a disability evaluation, being diagnosed with a disability, and actively receiving intervention services within the school system when compared to children who do not have a history of being diagnosed with NAS (Fill et al., 2018). The examination of curriculum-based test scores indicated that children with a history of a NAS diagnosis could struggle with lower and/declining academic performance and risks may be reduced for those children who have parents with a higher education (Oei et al., 2017).

The caregiver relationship and home environment has also been explored. An examination of mother-infant dyads of children exposed to opioids and whose mother received medication assisted treatment demonstrated that these mothers score lower for maternal sensitivity, structuring, and non-intrusiveness. They showed overall low involvement with their infant when compared to mothers endorsing depression and mothers with no opioid dependence history (Salo et al., 2010). Infants treated for NAS were assessed at 2 years of age and demonstrated that children who are living with their biological mother or family member scored significantly lower for general cognition and were more likely to score < 85 for motor abilities than those who were adopted or living with a foster family, although no differences were detected regarding language abilities (Mehar et al., 2018). Descriptively, 71% of 10-year-old children diagnosed with NAS as a neonate were living with a biological parent and 68% were living in an environment with active substance use out of 234 children (Miller & Anderson, 2022). These findings illustrate the importance of these children being consistently followed

throughout childhood development and for education to be provided to caregivers despite whether the child is living with their biological parent(s), family member, adopted family, or foster family.

Summary of What We Do Not Know

The past twenty-two years encapsulates the current opioid epidemic wave which exploded after the falsified claims from the pharmaceutical companies that although opioids are effective pain relievers, they do not contain an addictive component (Patel & Rushefshy, 2022). Due to research being in its infancy, there has not been an adequate amount of experimental research studies conducted in order to make confident and consistent associations between prenatal opioid exposure and neuropsychological deficits. Currently, much of the research has been conducted with small cohorts, retrospective data, and/or with women and children who have received treatment. Research examining how this epidemic has impacted fetal development leading to neuropsychological deficits is only beginning, leaving many aspects of unknown.

One area that is largely unknown at this time is the independent impact of substances. The majority of women examined in these studies endorsed polysubstance use during pregnancy, including tobacco and alcohol, making it difficult to isolate which substance is negatively impacting these children throughout development. Even if a pregnant woman was only using one opioid during pregnancy and decides to get treatment, the fetus would still be exposed to the original opioid and the medication used for medication assisted treatment such as methadone or buprenorphine. Additionally, depending on the severity of withdrawal symptoms, the neonate may be exposed to one or more substances utilized to treat their symptoms such as morphine, methadone, or buprenorphine. All of these factors make it challenging to fully understand the neuropsychological impacts of prenatal opioid use. Researchers concluded that comparison

groups that do not consider maternal tobacco use during recruitment could be negatively influencing associated findings when looking at cognitive development and prenatal opioid exposure. Women who are using and/or are opioid dependent during pregnancy should also be participating in smoking cessation due to the comorbidity and high-risk population of children with in-utero exposure to substances (Nelson et al., 2020).

Another area that is largely unknown is the long-term neuropsychological impacts based on the timing of opioid exposure during gestational developmental periods. Understanding how fetal development is impacted differently during each trimester would provide beneficial knowledge of the associations between timing and deficits observed later in the child's development. Many studies only obtained maternal opioid dependent/using women late in their pregnancy and who were receiving medication assisted treatment. Data in this area would be challenging to find because it would not be ethical to have pregnant women using opioids or receiving opioid medication assisted treatment only during certain gestational trimesters; therefore, data can only be obtained by women reporting the timing of their opioid use. Many women receiving treatment would have exposed their neonates to opioids and opioids through medication assisted treatment making it difficult to find isolated timing of exposure. A cohort of opioid dependent women who only used during the first trimester would be difficult to find because they would have to acutely detox without medication assisted treatment for the second and third trimester. Analyzing gestational timing cohorts would likely involve a large national collaboration of physicians and researchers to gather an adequate number of participants.

Infants, toddlers, and school-aged children are unique individuals with different genetic factors, life experiences, caregiver relationships, home environments, and possible mental health and medical predispositions. Any one of the aforementioned could possibly have an impact on

their neuropsychological abilities and can be difficult to isolate during research studies, making pure findings related to the impacts of prenatal opioid use challenging. Obtaining a pure sample may not be possible but having the knowledge and understanding of how additional variables can impact children with a history of opioid exposure can facilitate more informed decisions regarding their needs. A child's heredity, caregiver relationship, and home environment could have an impact on their neuropsychological functioning allowing for physicians, clinicians, and/or teachers to take a more systemic approach for recommendations to encompass multiple areas in their lives.

In order to thoroughly understand the impacts of prenatal opioid use/abuse, researchers need to continue to gather more data on this population. Efforts need to be made to collect data from multiple hospitals across the nation to make results more generalizable to the population. Longitudinal studies will allow researchers to follow and assess children who were exposed prenatally to opioids throughout their development allowing for different periods of development to be examined. Currently the most researched age groups have been infants and toddlers, indicating that there is a growing need for data to be analyzed with school-aged children which, will be possible with longitudinal studies.

Future Hypotheses

Future research and hypotheses can help facilitate the understanding of clinically significant findings related to the neuropsychological impacts of prenatal opioid exposure with or without a diagnosis of NAS. An abundance of research data has demonstrated decline or deficits of executive function in children with fetal alcohol syndrome or a fetal alcohol spectrum disorder (Fuglestad et al., 2015; McGee et al., 2008; Rasmussen et al., 2006). Additionally, Levine and Woodard (2018) demonstrated that children whose mothers received methadone medication

assisted treatment during pregnancy due to opioid dependence showed poorer inhibitory control on a task compared to non-exposed children at age 2 years. These findings can support the hypothesis that school-aged children who experienced opioid exposure during gestation and received a diagnosis of NAS postnatally will demonstrate significantly lower executive function scores when compared to non-exposed children. The independent variable (predictor) is children who experienced prenatal opioid exposure with or without a diagnosis of NAS. The dependent variable (criterion) could be the executive functioning performance on subtests from the Delis-Kaplan Executive Functioning System (D-KEFS; Delis et al., 2001), including Towers, Color-Word Interference, and Trails, and caregiver and teacher ratings on the Behavior Rating Inventory of Executive Function (BRIEF-2; Gioia et al., 2015).

Children with a history of prenatal opioid or opioid and polysubstance exposure have been associated with a greater risk of being diagnosed with ADHD compared to children who did not experience gestational substance exposure (Azuine et al., 2019; Nygaard et al., 2016, 2017; Rees et al., 2010) as well as having significantly lower scores or demonstrating an impaired task performance on working memory tasks (Levine & Woodward, 2018; Nygaard et al., 2007; Sirens et al., 2018). A hypothesis that would help contribute to the growing knowledge of this population is that children who experienced prenatal opioid exposure will demonstrate significantly lower working memory and processing speed scores on the Wechsler Intelligence Scales for Children, fifth edition (WISC-V; Wechsler, 2014) when compared to children born without prenatal substance exposure. This hypothesis combines the current findings of a higher incidence rate of ADHD in exposed children with the knowledge that children with ADHD tend to demonstrate relative and/or normative weaknesses on the working memory index and the processing speed index on the WISC-V. The independent variable (predictor) is children who

were prenatally exposed to opioids. The dependent variable (criterion) is the cognitive performance on the WISC-V.

CHAPTER IV: BEHAVIORAL, SOCIAL, AND/OR EMOTIONAL IMPACTS

Research Question #3

What behavioral, social, and/or emotional impacts have been found among children prenatally exposed to opioids with or without a diagnosis of NAS?

Literature Review

Infants, toddlers, and school-aged children who were prenatally exposed to opioids might be at risk for behavioral, social, and/or emotional difficulties during childhood development. Research in these areas is not exhaustive and needs to continue in order to make more solidified associations among children who experienced opioid exposure during gestation. The current studies have examined small cohorts or are based on large retrospective databases, producing findings that have demonstrated some inconsistencies. Although the aspects being examined below are in the early stages of examination, these preliminary studies help provide insight into this at-risk population as well as pave the way for future studies.

Impacts with Infant and Toddlers. Neonates born with NAS are classified as at-risk and often require additional assessment and monitoring (Reddy et al., 2017). Neonates can be assessed with the Neonatal Intensive Care Unit (NICU) Network Neurobehavioral Scale (Lester & Tronick, 2005) and/or the Finnegan Neonatal Abstinence Scoring Tool (Finnegan et al., 1975a). Lester et al. (2014) explained that the NICU Network Neurobehavioral Scale is utilized to assess the neurobehavioral integrity of at-risk neonates who are at a greater risk for poorer developmental outcomes. The NICU Network Neurobehavioral Scale assesses a variety of neurobehavioral performances including signs of stress/abstinence, neurological integrity, and behavioral functioning (Lester et al., 2014). The Finnegan Neonatal Abstinence Scoring Tool

assesses the severity of NAS symptoms and is often utilized to determine if pharmacologic treatment is continued or discontinued (Finnegan et al., 1975a). These tools play an important role in assessing and guiding intervention services for this at-risk population.

A longitudinal study across multiple sites examined 1 month old, substance exposed infants (n = 658) compared to non-exposed group (n = 730) to determine if neurodevelopmental impacts of prenatal opioid use and/or cocaine use exists (Lester et al., 2002). The substance exposed group was separated into mothers who endorsed cocaine use during pregnancy and those who endorsed opiate use. The non-exposed comparison group was matched with gestational age, race, and gender. The exposed group was identified through meconium testing and maternal self-report. Alcohol, marijuana, and tobacco use were endorsed within both the exposed and non-exposed comparison group. Researchers utilized the NICU Network Neurobehavioral Scale (Lester & Tronick, 2005) and adjusted for covariates (type of substance exposure, birth weight, social economic status, and site location) for both the exposed and non-exposed groups. Findings demonstrated that opioid exposed infants, at 1 month of age, displayed higher orientation/attention scores (measuring inanimate and animate visual and auditory responses) and greater signs of experiencing stress and symptoms related to abstinence when compared to non-opioid exposed infants. However, after adjusting for covariates, no differences were found for orientation/attention (M = 5.42, SD = $\pm$ 0.15 vs. M = 5.33, SD = $\pm$ 0.05, p = .536) or stress/abstinence (M = 0.19, SD = $\pm$ 0.01 vs. M = 0.17, SD = $\pm$ 0.01, p = .195; Lester et al., 2002).

A small study conducted at the Eastern Maine Medical Center examined the neurobehavior displayed by 6-week-old infants born to mothers who received pharmacologic treatment with methadone. Exposed participants with a diagnosis of NAS were divided into two

groups: required pharmacological treatment postnatally (n = 23) and did not receive postnatal pharmacologic treatment (n = 16). The control group (n = 21) was unexposed and matched for age, gestational period, hospital delivery, and social economic status (Heller et al., 2017). The NICU Network Neurobehavioral Scale (Lester & Tronick, 2005) was utilized to assess neurobehavioral development and the Finnegan Scale (Finnegan et al., 1975a) was used postnatally to determine NAS severity and need for pharmacological treatment. Significantly higher stress/abstinence scale scores were found among 6-week-old infants with NAS who did or did not receive pharmacological treatment when compared to healthy non-opioid exposed infants ($F(2, 55) = 4.8$, $p < .05$). These results suggest that prenatally methadone exposed infants may experience neurobehavioral effects involving stress/abstinence (negative affect/withdrawal symptoms) that lasts until at least age 6 weeks. Infants with NAS who received pharmacologic treatment additionally scored significantly lower than the control group for regulation measuring the ability to organize motor activity and physiological state ($F(2, 56) = 7.9$, $p < .01$) and quality of movement measuring motor control (($F(2, 56) = 7.7$, $p < .01$). No group mean differences were found for habituation (ability to stop responding to visual/auditory stimuli), attention, excitability, asymmetrical reflexes, arousal, handling (physical interventions required to achieve a calm state), non-optimal reflexes, hypertonicity (muscle tightness), and hypotonicity (decreased muscle tone), all falling above $p > .05$; Heller et al., 2017). Researchers concluded that these findings will guide medical and clinical staff in recommending or providing parent/caregiver interventions to support a positive caregiver-infant dyad, specifically regarding how to respond to infants experiencing withdrawal symptoms (Heller et al., 2017).

A multi-site study examined the neurobehavioral impacts of full-term infants (n = 39) whose opioid dependent mothers either received buprenorphine or methadone medication

assisted treatment during pregnancy. The study is called the Maternal Opioid Treatment: Human Experimental Research (MOTHER) study and is a double blind, randomized clinical trial. Infants were assessed with the NICU Network Neurobehavioral Scale (NNNS; Lester & Tronick, 2005) throughout the first 30 days postnatally (Coyle et al., 2012). Overall, infants who were exposed to methadone or buprenorphine prenatally both showed improved neurobehavior during the first month after delivery. Specifically, linear effects demonstrated increased attention ($F(1, 51) = 47.7$, $p < .001$), quality of movement ($F(1, 71) = 90.6$, $p < .001$), and self-regulation ($F(1, 48) = 36.2$, $p < .001$), as well as decreased need for handling ($F(1, 43.5) = 17.5$, $p < .001$), and decreased arousal ($F(1, 68) = 24.6$, $p < .004$), excitability ($F(1, 68) = 39.3$, $p < .001$), depression ($F(1, 115) = 29.3$, $p < .001$), and hypertonia ($F(1, 72) = 18.0$, $p < .001$). Researchers found that women who received buprenorphine had infants who had fewer stress-abstinence signs ($df = 168.46$, $F = 12.94$, $p < 0.001$), less excitability ($df = 184.57$, $F = 12.70$, $p < 0.001$) and less hypertonia ($df = 114.99$, $F = 7.50$, $p = 0.007$), greater ability to self-regulate ($df = 175.07$, $F = 4.21$, $p = 0.042$), and required less holding in order to maintain a quiet alert state ($df = 172.30$, $F = 11.40$, $p = 0.001$), when compared to the infants whose mothers received methadone medication assisted treatment during pregnancy. Additionally, after controlling for medication condition, infants who were older when they started receiving morphine for withdrawal symptoms demonstrated a higher mean for self-regulation ($r = .39$, $df = 22$, $p < .01$) as well as lower excitability ($r = -.48$, $df = 22$, $p < .02$) and lower hypertonia ($r = -.51$, $df = 22$, $p < .02$). Researchers concluded that maternal buprenorphine medication assisted treatment for opioid dependency during pregnancy produced less severe withdrawal symptoms for infants compared to infants exposed to methadone medication assisted treatment (Coyle et al., 2012).

A longitudinal study assessing mother-child dyads (n = 96), from the MOTHER study, examined the neuropsychological, growth, and temperament impacts on children from birth to 3 years of age, to determine if differences exist between maternal buprenorphine or methadone assisted treatment during pregnancy (Kaltenbach et al., 2018). Additionally, the study compared children who were treated for NAS with children who were not treated for NAS. Demographically, the mothers were relatively young (M = 26.1, SD = 5.4), Caucasian (94%), did not graduate high school education (41%, M = 11.5 years of education, SD = 2.1), were unemployed (76%), and never married (74%). Infants were generally healthy (5-minute Apgar score: M = 9.1, SD = .9), gestational age (M = 38.8 weeks, SD = 2.0), and 56% were treated for NAS. Children were assessed at 3, 6, 12, 24, and 36 months of age with a variety of well-established tests. A significant medication condition and time interaction effect was found for the Receptive-Expressive Emergent Language Test, Third Edition (REEL-3; Bzoch et al., 2003), with the percentile rank being significantly lower for the buprenorphine group compared to the methadone group when assessed at age 12 months (M = 28.8, SD = 5.9 vs. M = 45.9, SD = 5.0, p < .03). A NAS treatment group and time interaction effect was found for the Distress and Limitation scale on the Infant Behavior Questionnaire, Revised (IBQ-R; Garstein & Rothbart, 2003), with the infants who received NAS treatment being significantly higher compared to those who did not require treatment when assessed at age 6 months (M = 3.9, SD = 0.2 vs. M = 3.3, SD = 0.3, p < .05; Kaltenbach et al., 2018). Physical increases were observed for weight, head, and height over time. Neurodevelopmentally, improvements were seen for overall cognitive development, language, and sensory processing. Temperament also showed gains overtime. Researchers concluded that overall findings show that over time, from ages 3 to 36 months, children whose mothers receive medication assisted treatment with buprenorphine or

methadone do not demonstrate a developmental decline in growth, cognitive, language, sensory processing, or temperament. Lastly, receiving NAS treatment postnatally due to prenatal opioid exposure does not have a negative impact on overall early childhood growth and development (Kaltenbach et al., 2018).

A study out of the University of New Mexico with the Ethanol, Neurodevelopment, Infant and Child Health (ENRICH) birth cohort was initiated in 2013 to examine 78 mother-infant pairs. Researchers compared prenatal exposure to methadone medication assisted treatment to healthy non-exposed control group, and they also examined treatment for NAS and NAS severity with behavioral and neurodevelopmental outcomes (Bakhireva et al., 2019). Four different time periods were assessed: prenatal, delivery, 5-8 months postpartum, and 20 months postpartum. Neurodevelopmental assessments for behavioral and social/emotional abilities included the Parenting Stress Index-Short Form (PSI-SF; Abidin, 1995), the Infant Behavioral Questionnaire-revised (IBQ-R; Garstein & Rothbart, 2003), the Infant/Toddler Sensory Profile (Dunn, 2002) and the Still Face Paradigm (SFP; Tronick et al., 1978). No differences were found for scores on the PSI-SF or the IBQ-R when comparing the methadone exposed group with the healthy controls and when comparing the treated for NAS group and the not treated for NAS group, with all p-values falling above .05. Bakhireva et al. (2019) reported that the medication assisted treatment exposed group was significantly lower than the non-exposed comparison group on the Still Face Paradigm, self-regulation, (ß = -18.9, $p = .01$) and on Infant/Toddler Sensory Profile, sensation seeking ($OR = 4.87$, $p < .01$, 95% CI [1.55, 15.30]), even after adjusting for covariates. Additionally, longer length of hospital stay was linked with a higher ratings of parent-child dysfunctional interaction on the Parenting Stress Index ($p = 0.18$). Researchers concluded that parental stress is linked with longer hospital stay and thus it is

important for mothers to receive appropriate intervention recommendations. Parent interventions can provide them with the necessary skills to cope with their stress and to learn how to respond appropriately to their child (Bakhireva et al., 2019).

Metosky and Vondra (1995) explored the behavioral organizational strategies and symbolic representational abilities of prenatally polysubstance exposed toddlers (n = 20) and non-substance exposed toddlers (n = 20), to determine if differences exist. Participants were recruited from an inner-city prenatal clinic that serves a low-income population. All mothers of exposed infants endorsed polysubstance use throughout pregnancy, including legal and illegal substances. The control group was matched for race, gestational age, socioeconomic status, maternal age, maternal marital status, and maternal level of education. Toddlers were assessed around age 18 months during a recorded 15-minute unstructured play session with the Belsky and Most's 14-step developmental play scale (Belsky & Most, 1981), which rates the child on total symbolic play, undifferentiated exploration, functional play, transitional play, simple pretend play, and elaborated pretend play (Metosky & Vondra, 1995). Mothers were present during the play session but were instructed not to initiate engagement or provide any guidance with the play materials. Additionally, maternal ratings of infant coping and self-regulatory behaviors were assessed with the Early Coping Inventory (ECI; Zeitlin, et al., 1988). Regarding play frequency, results revealed that exposed toddlers spent significantly less total time engaged in symbolic play compared to non-exposed toddlers (M = 26.55 seconds, SD = 35.85 vs. M = 69.42, SD = 46.40, z = -2.964, $p < .01$). Play duration was evaluated for total length of time across all symbolic levels as well as individual levels. Exposed toddlers demonstrated significantly less time for total symbolic levels ($t(36) = 3.75$, $p < .001$) and for the simple pretend level ($t(35) = 3.65$, $p < .001$) when compared to controls (Metosky & Vondra, 1995). A

significant difference was also found regarding affect, with the exposed group displaying more negative affect than the non-exposed group (M = 22.70, SD = 31.50 vs. M = 7.95, SD = 19.10, z = -2.50, $p < .01$). Additionally, mothers of the prenatally exposed toddlers rated their child as less adaptable (M = -2.05, SD = 2.17 vs. M = 2.05, SD = 2.44, t = 5.61, $p < .001$), and as having lower ability to organize interactions in their environment (M = -1.42, SD = 2.05 vs. M = 1.42, SD = 1.74, t = 4.73, $p < .001$), fewer self-initiation skills (M = -1.23, SD = 2.29 vs. M = 1.23, SD = 1.96, t = 3.65, $p < .01$), lower ability to self-regulate/persevere (M = -1.45, SD = 2.28 vs. M = 1.45, SD = 1.67, t = 4.58, $p < .001$), fewer reactions to novel experiences (M = -1.19, SD = 2.40 vs. M = 1.19, SD = 1.78, t = 3.58, $p < .01$), lower ability to self-comfort (M = -0.95, SD = 1.75 vs. M = 0.95, SD = 0.93, t = 4.27, $p < .001$), and lower ability to problem solve (M = -0.70, SD = 1.79 vs. M = 0.70, SD = 1.54, t = 2.65, $p < .05$) compared to rating of mothers with non-exposed toddlers on the Early Coping Inventory (Metosky & Vondra, 1995). Impulse control was the only item on the Early Coping Inventory that did not produce a difference between exposed and non-exposed ratings of the toddlers (M = -0.43, SD = 2.39 vs. M = 0.43, SD = 2.51, t = 1.21, $p = ns$). Metosky & Vondra further explored if correlations existed between maternal behavioral ratings and behavioral organization during free play. Results indicated that toddlers who were less engaged during play were rated low for self-regulating/persevering ($r(40) = .29$, $p < .05$) and ability to self-comfort ($r(40) = .33$, $p < .05$). Toddlers who were rated as having a lower frustration tolerance displayed more signs of negative affect ($r(40) = -.47$, $p < .01$) and were more unengaged ($r(40) = -.29$, $p < .05$; Metosky & Vondra, 1995). Overall, researchers concluded that prenatally polysubstance exposed toddlers are at a greater risk of experiencing behavioral organizational deficits and more negative affect when engaging in play compared to non-exposed controls (Metosky & Vondra, 1995). Limited engagement in age-appropriate levels

of play, difficulty self-regulating, and displaying more negative affect such as irritability could all possibly impact social and playful interactions with their peers.

Merhar et al. (2018) conducted a retrospective study at Cincinnati Children's Hospital of 87 toddlers who were treated for NAS and later were evaluated at 2 years of age. Most of the neonates were treated with methadone (72%), while others were treated with buprenorphine or morphine. Researchers mainly focused on neuropsychological outcomes; however, supplementally during the 2 year follow up they asked families about sleep and behavioral difficulties their child may be experiencing. They found that more than 25% of the exposed toddler's families reported sleep and behavioral difficulties. Families endorsed their child had experienced difficulties falling and/or staying asleep and endorsed behavioral issues that included tantrums, sensory issues, and hyperactivity (Merhar et al., 2018).

A secondary data analysis was run with the Maternal and Infant Data Hub which was conducted in the Midwest region of the United States of children born between 2013 and 2019 (Arter et al., 2021). Diagnoses were determined by the International Classification of Diseases (ICD-9 and ICD-10) to examine the social issues and the mental health of two prenatal opioid exposed groups, with NAS (n = 199) and without NAS (n = 455), and a comparison group of unexposed children (n = 13,173; Arter et al., 2021) at ages 1, 2, and 3 years. Researchers found several social issues that were significant for the prenatally exposed opioid groups compared to non-exposed controls. Social issues included that the child was in welfare custody (non-exposed: 0.8% vs. opioid exposed: 7.5% and vs. exposed and NAS: 17.8%, $p < .001$), was in foster care (0.5% vs. 4% and vs. 11.3%, $p < .001$), had other problems related to lifestyle (non-exposed: < 0.1% vs. exposed and NAS: 5%, $p < .001$), and had problems related to social environment (1.2% vs. 7.7% and vs. 21.7%, $p < .001$), all occurring during the first year of life. Significant

differences remained during the 2nd (non-exposed: 0.4% vs. opioid exposed: 2.9% and vs. exposed and NAS: 4.4%, $p < .001$) and 3rd year of life (1.0% vs. 6.2% and vs. 12.9%, $p < .001$) for problems related to social environment. Welfare custody also remained significant when the children were 3 years of age (1.2% vs. 5.7% and vs. 6.1%, $p < .05$). Comparisons between the two exposed groups showed that opioid exposed children with a history of NAS had almost double the rate of diagnosis of social problems compared to exposed children without NAS. At age 3 years, the exposed children who also were diagnosed with NAS had significantly higher rates of being diagnosed with adjustment disorder with mixed disturbance of emotions and conduct than the exposed children without a NAS diagnosis (exposed and NAS: 7.6% vs. opioid exposed: 2.6% and vs. non-exposed: 0.2%, $p < .001$; Arter et al., 2021).

Animal research has also been conducted to study the behavioral, social, and emotional reactions of young rats who were prenatally exposed to opioids. Chen et al. (2015) conducted a study with rats to examine the behavioral effects observed in young rats who were prenatally exposed to methadone, buprenorphine, or morphine. Pregnant rats were administered the medication during embryonic days 3-20 and one group was given saline. The offspring were assessed between 6 and 10 weeks. Researchers found that offspring that experienced prenatal opioid exposure to either methadone, buprenorphine, or morphine showed significant impairment for social interaction by showing increased social withdraw compared to the control group. Young rats in all the treatment groups demonstrated increased anxiety-like behaviors during a light-dark transition test; however, no significant differences were detected compared to controls regarding anxiety (Chen et al., 2015).

Impacts with Pre-school and School-aged children. Similarly, to the research that has been conducted among very young children with prenatal opioid exposure, the research

examining the behavioral, social, and emotional impacts of pre-school and school-aged children is limited and some inconsistencies have been found. Hunt et al. (2008) conducted a case control study at a hospital in Sydney, Australia to examine the neurodevelopmental and social impacts on children who were exposed to opioids prenatally, who were assessed at 18 months and 3 years old. This longitudinal study examined 133 children born to mothers who received methadone assisted treatment and compared them to children born to a substance free mother. Of the 133 exposed children, 74 (56%) received morphine to treat their NAS symptoms postnatally. Social competence was assessed with the Vineland Social Maturity Scale (Sparrow et al., 2005), at 18 months old and at 3 years old. Social competence was significantly lower for the opioid exposed group at 18 months old (M = 113.2, SD = 15.6 vs. M = 119.15, SD = 17.5, $p < .05$) as well as at 3 years old (M = 38.4, SD = 8.1 vs. M = 46.1, SD = 7.7, $p < .05$). This study demonstrated that infants exposed to opiates in utero are at a greater risk of having social difficulties in early childhood when compared to non-exposed children (Hunt et al., 2008).

Levine and Woodward (2018) examined the relationship between executive function and emotional and behavioral adjustments in childhood development when comparing children prenatally exposed to methadone (n = 68) and non-exposed children (n = 88). Children's executive function was assessed at 2 years of age and their behavioral and emotional adjustment was assessed at 4.5 years of age by caregiver ratings on the 25-item Strengths and Difficulties Questionnaire (Goodman, 2001). They found that poorer inhibitory control at age 2 years was significantly associated with greater levels of hyperactivity (M = 4.67, SD = 2.29 and M = 4.29, SD = 2.38, $p < 0.001$), conduct (M = 2.06, SD = 1.60 and M = 2.47, SD = 1.90, $p = 0.001$), peer relationships (M = 1.72, SD = 1.97 and M = 1.59, SD = 1.56, $p = 0.021$), and total behavior difficulties (M = 10.58, SD = 6.27 and M = 10.25, SD = 5.51, $p < 0.001$) when assessed at age

4.5 years (Levine & Woodward, 2018). Researchers concluded that early detection of executive function deficits may indicate the possibility for behavioral challenges later in child development.

Miller et al. (2020) conducted a retrospective, longitudinal design to examine the factors linked with abnormal behavioral development in children with in-uterine substance exposure or who were diagnosed with neonatal abstinence syndrome at ages 1, 5, and 10 years. Data was utilized from the Maternal Life Study dataset, from 1993-2011, originally collected from a multisite (i.e., Rhode Island, Florida, Tennessee, and Michigan) investigation to examine the impact of maternal substance use on children (drug exposed dyad: $n = 658$ and non-exposed: $n = 730$). In this study, abnormal behavioral development was defined as a conclusion from a licensed clinician's examination of the child's development based on behavioral assessments, direct assessment, child's medical history, and child's family history. Miller et al. found that prenatal substance exposure included tobacco, alcohol, opioids, cocaine, and/or marijuana, with over 75% of children having polysubstance exposure and approximately 32% meeting criteria for neonatal abstinence syndrome. Infants who met criteria for NAS were more frequently prenatally exposed to cocaine ($p < .001$), polysubstance use ($p = .002$), and/or opioid exposure ($p = .01$). Descriptive statistics at age 1 year indicated that 90% of the children lived with a biological parent, more than 10% of households had a low socioeconomic status, and 63% of children lived in an active substance use environment. At age 5 years, 82% of children lived with a biological parent, 16% of households had a low socioeconomic status, and 70% of households used Medicaid. At age 10 years, 77% of children lived with biological parent, 18% in a low socioeconomic status. Sixty-six percent of children lived in an active substance use environment, and 70% of households used Medicaid. Prenatal exposure to opioids was associated with

abnormal behavioral development at age 10 years (*OR* = 0.418, $p < .001$). NAS significantly predicted abnormal behavior development at age 10 years (*OR* = 2.077, $p < .001$) although no associations were found at age 1 year (*OR* = .890, $p = ns$) or 5 years (*OR* = .795, $p = ns$; Miller et al., 2020). At age 5 years, the following predicted abnormal behavioral development: biological living situation (*OR* = 0.497, $p < .001$), low socioeconomic status (*OR* = 2.393, $p < .05$), and Medicaid insurance (*OR* = 0.475, $p < .05$). Predictors of behavioral abnormal development found at age 10 years were low socioeconomic status (*OR* = 2.393, $p < .001$), use of child services (*OR* = 0.211, $p < .001$), and low neighborhood safety index (*OR* = 1.318, $p < .001$). Researchers concluded that because prenatal opioid exposure and NAS are linked with behavioral difficulties later in development, it is vitally important for this population to obtain neurodevelopmental and behavioral evaluations throughout childhood and to be supported by appropriate interventions (Miller et al., 2020).

A large birth cohort study from the Boston area of 454 children (birth to 21 years of age) who experienced prenatal opioid exposure examined both the short- and long-term impacts within this population (Azuine et al., 2019). Participants were recruited from the Boston Medical Center after birth and records were also obtained at primary care and subspecialty clinics under the Boston Medical Center. Opioids used during pregnancy included heroin, oxycodone, and/or methadone. Substance use period under examination was defined as 6 months before conception to date of delivery. In general, participants were multiracial, had a low socioeconomic status, and lived in an urban area. Data analysis revealed that prenatal opioid exposure was linked with an increased risk of children (< 6 years) being diagnosed with conduct disorder and/or emotional disturbance (*OR* = 2.13; 95% CI [1.20, 3.77]) and lacking expected physiological development (*OR* = 1.80, 95% CI [1.20, 3.77]), compared to non-exposed children. School-aged children who

were prenatally exposed to opioids demonstrated a significantly greater risk of being diagnosed with attention-deficit/hyperactivity disorder (*OR* = 2.55, 95% CI [1.42, 4.57]), compared to non-opioid exposed children (Azuine et al., 2019). This study highlights the importance of prenatally opioid exposed children being followed by a treatment team and receiving neuropsychological assessments throughout childhood in order to facilitate effective treatment.

A small study examined the social and emotional development of children (ages 6-13 years) who were exposed prenatally to methadone ($n = 20$) with a non-exposed control group ($n = 20$; de Cubas & Field, 1993). Mothers were selected from a methadone medication assisted treatment program and endorsed also drinking alcohol and smoking cigarettes at a moderate level during their pregnancy. Demographics regarding the participants of both groups were low socioeconomic status, the majority were Caucasian, and most of the children lived in two parent homes (de Cubas & Field, 1993). Each child's social and emotional development was assessed with the Roberts Apperception Test for Children (McArthur & Roberts, 1989) and the Achenbach Behavior Checklist (Achenbach, 1991). Children in the methadone exposed group demonstrated significantly higher scores for aggression ($M = 55.0$ vs. $M = 46.2$, $p < .01$), anxiety ($M = 57.0$ vs. $M = 46.0$, $p < .01$), rejection ($M = 60.5$ vs. $M = 52.5$, $p < .01$), and maladaptive outcome ($M = 1.1$ vs. $M = 0.1$, $p < .01$). Significant differences were also found for behavioral and emotional problems including depression ($M = 58.4$ vs. $M = 48.1$, $p \leq .001$), social withdrawal ($M = 56.8$ vs. $M = 50.8$, $p < .05$), somatic complaints ($M = 56.9$ vs. $M = 52.1$, $p \leq .01$), aggression ($M = 56.7$ vs. $M = 48.1$, $p \leq .01$), hyperactivity ($M = 59.2$ vs. $M = 51.0$, $p \leq .001$), delinquency ($M = 63.8$ vs. $M = 56.4$, $p \leq .001$), internalizing behaviors ($M = 59.2$ vs. $M = 46.3$, $p \leq .001$), and externalizing behaviors ($M = 60.4$ vs. $M = 48.6$, $p \leq .001$), with the exposed group scoring significantly higher than the non-exposed group (de Cubas & Field, 1993).

Overall, these results indicate that the opioid exposed pediatric population is vulnerable for experiencing a variety of emotional and behavioral difficulties. Early interventional support could help these children develop appropriate coping skills to manage their experienced struggles.

Uebel et al. (2015) conducted a population-based study from government population databases examining births, hospitalization, and death records that occurred in Australia between July 2000 and December 2011. The study aimed to demonstrate reasons for hospitalizations that occur in children who were diagnosed with NAS at birth. Records indicated during this time frame there were 3,842 infants diagnosed with NAS compared to 1,017,421 infants without NAS. Overall, infants diagnosed with NAS were at a greater risk of rehospitalization, which continued to be higher than non-NAS infants throughout childhood. Adjusted odd ratios demonstrated that NAS children were more likely to have a hospital readmission, after birth hospital discharge, due to assaults (*OR* = 15.2, 95% CI [11.3, 20.6]), maltreatment (*OR* = 21.0, 95% CI [14.3, 30.9]), and poisoning (*OR* = 3.6, 95% CI [2.6, 4.8]). Additionally, mental and behavioral disorder admissions were higher among NAS children for autism, conduct, and adjustment disorders (*OR* = 2.6, 95% CI [2.1, 3.2]; Uebel et al., 2015). Researchers indicated the importance of monitoring and supporting children in the at-risk NAS population throughout childhood due to the increased likelihood of rehospitalization for physical, emotional, and behavioral concerns (Uebel et al., 2015).

Nygaard et al. (2016) performed a prospective longitudinal cross-informant study to compare behavioral and social problems of children with prenatal opioid exposure (*n* = 72) compared to children with no prenatal substance exposure (*n* = 58). Mothers of the exposed group used an average of 3.5 substances during pregnancy. Tobacco use was endorsed by all

mothers and opiates were the second most reportedly used substance (54%). Almost 80% of infants were diagnosed with NAS postnatally. The participants were assessed at ages 4.5 years and 8.5 years by the caregiver rated Child Behavior Check List/4-18 version and the Teacher's Report Form (Achenbach, 1991). The behavior checklist and the teacher's report examine emotional, behavioral, social, and attention problems. Behaviors analyzed were categorized into internalizing and externalizing behaviors. Internalizing behaviors are related to anxiety, depression, withdrawal, and somatic complaints. Externalizing behaviors are related to aggressive and delinquent behaviors. Social and attention behavior difficulties are categorized separately. Higher scores on these assessments indicate greater difficulties. Nygaard et al. (2016) found that at age 4.5 years, exposed children compared to non-exposed children were rated by the teachers as having greater internalizing behavior problems (d = 0.62, p = .03, 95% CI [0.27, 0.97]), externalizing behavior problems (d = 0.76, p = .004, 95% CI [0.42, 1.11]), and greater social difficulties (d = 0.68, p = .02, 95% CI [0.33, 1.03]) after controlling for multiple covariates including birth weight, gestational age, socioeconomic status, gender, and age at assessment. No internalizing problems (d = 0.05, p = .61, 95% CI [-0.31, 0.42]), externalizing problems (d = 0.20, p = .84, 95% CI [-0.12, 0.53]), or social problems (d = 0.37, p = .41, 95% CI [0.03, 0.71]) were indicated as significant by the toddler's caregivers. At age 8.5 years, exposed children compared to non-exposed children were rated by their caregiver as having greater externalizing behavior problems (d = 0.68, p = .02, 95% CI [0.31, 1.05]) and greater social problems (d = 0.70, p = .02, 95% CI [0.33, 1.07]), and the teachers indicated greater externalizing problems (d = 0.55, p = .06, 95% CI [0.15, 0.95]), after controlling for multiple covariates. Overall, this data indicates that prenatally opioid exposed pre-school aged children may experience and display more internalizing, externalizing, and social difficulties in the school environment, whereas

elementary aged children (age 8.5 years) who were prenatally exposed to opioids are at risk of having externalizing behavioral problems at home and school, and social difficulties at home (Nygaard et al., 2016).

Caregiver Relationship. Caregiver relationships and the child's living environment has also been explored with the prenatally opioid exposed populations. Descriptively, a retrospective study of 234 children (aged 10 years) who were diagnosed with NAS and experienced intrauterine exposure to one or more substances indicated approximately 71% of the children lived with at least one biological parent, 68% had households currently using substances (alcohol and/or illicit drugs), and less than 25% of the children lived in poverty (Miller & Anderson, 2022).

A small study examined the caregiver-child relationship of buprenorphine exposed children living with their biological mother (n = 7) or living in foster care (n = 14) compared to non-exposed children (n = 13; Salo et al., 2009). The buprenorphine using mothers also disclosed the use of additional substances during pregnancy including tobacco (95%), benzodiazepines (42%), amphetamines (42%), alcohol (19%), and cannabis (9%). At age 3 years, the mother-child interaction was assessed using the Emotional Availability Scales (EAS-3; Biringen et al., 1998), after participating in a video recorded 5-minute free play session. Play objects included a doll, teddy bear, ball, blocks, and a mirror. Additionally, the Self-Efficacy for Parenting Tasks Index, Toddler Scale (SEPTI-TS; Coleman & Karraker, 2003) was used to measure parental self-efficacy. Results revealed that dyads including exposed children, regardless of living environment, had mothers who scored lower on maternal sensitivity (exposed in parental care: M = 4.57, SD = 1.17 and exposed in non-parental care: M = 5.68, SD = 0.93 vs. non-exposed controls: M = 7.03, SD = 0.69, F = 5.89, $p < .01$) and non-hostility (M = 3.64, SD = 0.85 and M =

4.36, *SD* = 0.72 vs. *M* = 4.96, *SD* = 0.13, *F* = 6.61, *p* < .05). The children in the exposed dyads scored lower on child responsiveness (*M* = 4.0, *SD* = 0.91 and *M* = 4.82, *SD* = 0.82 vs. *M* = 6.0, *SD* = 0.54, *F* = 4.59, *p* < .05) and involvement (*M* = 4.29, *SD* = 1.07 and *M* = 4.61, *SD* = 0.81 vs. *M* = 5.96, *SD* = 0.51, *F* = 4.68, *p* < .05; Salo et al., 2009) when compared to non-exposed children. Lastly, the substance using mothers scored significantly lower for self-reported maternal self-efficacy than non-using mothers (*M* = 200.08, *SD* = 7.02 vs. *M* = 215.77, *SD* = 11.86, *F* = 6.55, *p* < .01; Salo et al., 2009). This study demonstrated the importance of educating and providing these mothers and caregivers with the support they need to develop a healthy developmental bond with their child and reinforced the idea that prenatal opioid and polysubstance exposure not only impacts the child individually, but their relationship with their caregiver (Salo et al., 2009).

Salo et al. (2010) later examined 87 mother-infant dyads at a university hospital to assess mother-infant interactions. Researchers compared three groups of mother-infant dyads: mothers who abused opioids before and during pregnancy (*n* = 15), mothers with depression (*n* = 15), and mothers with no substance abuse history (*n* = 57). All opioid mothers endorsed using opioids as their primary drug of choice for many years and started medication assisted treatment with buprenorphine during their second trimester. Mother-infant interaction were assessed with the Emotional Availability Scales (EAS-3; Biringen et al., 1998), which were rated using a 4-minute non-structured play video recording of the dyad. The effect for group status was significant for maternal sensitivity (*F*(2,85) = 11.40, *p* < .001), maternal structuring (*F*(2, 85) = 9.04, *p* < .001), maternal non-intrusiveness (*F*(2, 85) = 2.09, *p* < .05), and infant involvement (*F*(2, 85) = 8.53, *p* < .001) with the opioid use/exposure dyads scoring significantly lower than the non-using/non-exposed dyads and the maternal depression dyads. Regarding maternal background, opioid-

abusing mothers who had a history of being in the foster care system during childhood displayed mother-infant interactions that were more intrusive ($t(1, 85) = 7.54$, $p < .01$) and hostile ($t(1, 85) = 5.07$, $p < .05$) than the non-substance using mothers and depressed mothers. These findings were similar for opioid abusing mothers who had a criminal record history scoring significantly higher for intrusiveness ($t(1, 85) = 9.17$, $p < .01$) and hostility ($t(1, 85) = 5.99$, $p < .05$) than the other two dyads, who did not have either of these social risk factors in their backgrounds. Regarding the exposed infants with mothers who had a criminal history scored lower in responsiveness ($t(1, 85) = 5.69$, $p < .05$; Salo et al., 2010). Researchers concluded that mother-infant interactions in the opioid using/exposed group may have been impacted by interruption in early emotional bonding due to the infants experiencing withdrawal symptoms. Overall, this study highlights the possible impacts that opioid exposure and social risk factors play on mother-infant interactions.

Attachment styles between caregivers and children with prenatal opioid exposure have also been examined. One study examined the attachment behaviors in full term, 12-month-old children who experienced prenatal methadone exposure ($n = 35$) and their mothers compared to a non-exposed group ($n = 46$; Goodman et al., 1999). Participants were African American mothers and their children from low socioeconomic status who were recruited from a hospital at the University of Chicago. Mothers in the comparison group were matched for age (18-35 years), socioeconomic status, intelligence quotient, education, and marital status (Goodman et al., 1999). Child attachment behaviors to their mother were assessed by observing a videotaped separation-reunion procedure. No significant differences were found between the two groups regarding proximity-seeking during the time of the reunion ($M = 3.83$, $SD = 2.24$ vs. $M = 3.72$, $SD = 2.17$, $F = 0.11$). The methadone exposed group had significantly higher levels of disorganization ($F(1,$

78) = 7.33, $p < .01$), although effects were not found for avoidant behaviors ($F(1, 78) = 3.27$, $p = .074$) or contact-maintaining behaviors ($F(1, 78) = 3.65$, $p = .06$) when compared to children who were not exposed prenatally to substances (Goodman et al., 1999). Researchers concluded that although methadone exposed children were more likely to develop a disorganized-disoriented attachment compared to non-exposed children (11.4% vs. 0.0%), but they were also as likely to develop a secure attachment (71.4% vs. 80.4%; Goodman et al., 1999).

Opioid dependent mothers face new challenges as they enter parenthood. Infants born with prenatal opioid exposure can be difficult to soothe, have difficulties with self-regulation, and exhibit higher stress/abstinence signs (Bakhireva et al., 2019; Coyle et al., 2012; Heller et al., 2017). Difficulties also can emerge in later development with these children such as tantrums, hyperactivity, emotional and behavioral disturbances (Azuine et al., 2019; Merhar et al., 2018; Uebel et al., 2015) making parenting difficult to navigate. An empirically tested intervention known as attachment and behavioral catch-up (ABC) or the modified version (mABC) may be a helpful early intervention for parents to utilize in order to learn effective parenting skills (Martin et al., 2022). The ABC intervention is a 10-week, 1 hour a week, in-home strengths-based intervention that supports parents in learning how to nurture an infant who is difficult to soothe, how to respond sensitively, and how to avoid responding to their infant with intrusive behaviors (Martin et al., 2022). Several randomized trials have shown the ABC intervention to demonstrate higher parental sensitivity when compared to a control group, with both groups having parent-child dyads stemming from vulnerable populations. The modified ABC intervention maintains the core concepts and utilizes flexible manualized content, video clips (illustrated by others and themselves), and provides in the moment feedback to the parent (Martin et al., 2022). In addition to the 10 sessions, the mABC has one prenatal session and one

postnatal session to help prepare parents for the challenges they will face as their infant goes through opioid withdrawal symptoms (Labella et al., 2021). These interventions can support the unique challenges of parenting prenatally exposed infants and promote positive parenting skills, which can facilitate mental and physical health development.

Fetal Alcohol Spectrum Disorders. Research examining children who have been diagnosed with a Fetal Alcohol Spectrum Disorder have been conducted for many years, producing more empirical studies for this population. Below the behavioral, social, emotional, and adaptive findings will be examined that have been demonstrated in order to help identify the possible impacts that could occur with children who experienced prenatal opioid exposure with or without a diagnosis of NAS.

Behavioral, Social, and Emotional Impacts. Molteno et al. (2014) examined infants whose mothers reported alcohol consumption during pregnancy. A total of 85 infants (6.5 months old) were assessed regarding infant emotional withdrawal with the Alarm Distress Baby Scale (Guedency & Fermanian, 2001) and 119 infants (6.5 months old) were assessed regarding temperament with the EAS Temperament Survey (Buss & Plomin, 1984). The researchers found that exposure to alcohol prenatally was associated with an increase in infant emotional withdrawal and a decrease in overall activity. Molteno et al. found that children who were later diagnosed with fetal alcohol syndrome or partial fetal alcohol syndrome at 5 years old demonstrated a greater amount of emotional withdrawal and decreased responsivity and activity as infants (6.5-month-old infants). Additionally, at 9 years of age, infant emotional withdrawal was a significant predictor of poorer IQ on the WISC-IV.

Rasmussen et al. (2010) conducted a study of 60 children (ages 3-8 years) in two groups, prenatal alcohol exposed (n = 37) and non-exposed (n = 23), evaluating their social skills with

the Social Skills Rating System (SSRS; Gresham & Elliott, 1990). This study is involved in a larger project that is evaluating a respite program. Sixty percent of those children in the alcohol exposed groups had a diagnosis of a fetal alcohol spectrum disorder and the remaining children either had a pending diagnosis, suspected diagnosis, or had not been formally assessed during the time of the study. The respite program publicly advertised for volunteer participants. Rasmussen et al. found that caregivers of the children with prenatal alcohol exposure indicated child ratings in the deficit range for responsibility, hyperactivity and internalizing problems as well as lower overall social skills on the Social Skills Rating System when compared to the group of non-exposed children. Most of the children in the alcohol exposed group were not living with a biological parent, although results indicated that home placement was not related to social skills (Rasmussen et al., 2010).

A small study of 45 children (ages 5-12 years) compared 15 children with fetal alcohol syndrome, 15 children with matched verbal IQs to the fetal alcohol syndrome group, and 15 children in the normal control group with overall IQs in the average to above average range (Thomas et al., 1998). Comparison was made between groups in the social skills domain of the Vineland Adaptive Behavior Scale (Sparrow et al., 2005), rated during caregiver interviews. Thomas et al. (1998) found that children with fetal alcohol syndrome were most impaired in the interpersonal relationship skills domain, and a significant correlation was indicated between the children's chronological age and age equivalent score that was not present for the two control groups. The authors concluded that the social deficits identified in the children with fetal alcohol syndrome may be chronic rather than merely delayed (Thomas et al., 1998).

A study of 56 children (6-13 years of age) diagnosed with a fetal alcohol spectrum disorder were recruited from clinics in the State of Washington to determine if the level of

emotional understanding is impacted within this group (Petrenko et al., 2017). Emotional understanding was measured using the Kusche Affective Interview, Revised (KAI-R; Beilke et al., 1988). Results demonstrated that children with FASD have delays in the area of emotional understanding compared with normative data, specifically regarding understanding that someone can experience a variety of emotions at the same time, emotions can be hidden, and understanding that it is acceptable to experience all emotions (Petrenko et al., 2017).

A Canadian study of 58 children (8 to 12-years-old) within two groups, a fetal alcohol spectrum disorder (n = 37) and a control group of typically developing children (n = 21) were examined in the areas of social perspective taking and empathy (Stevens et al., 2015). On the NEPSY-II Theory of Mind subtest (social perspective taking; Korkman et al., 2007), the FASD group scored significantly lower than the control group on the verbal and contextual subtests. On the Test of Social Cognition (TSC; Saltzman-Benaiah & Lalonde, 2007), the control group performed better than the FASD group on the subtests of False Beliefs, Strategic Control of Emotions, and Personalized Emotions. Empathy was measured by the child-completed Index of Empathy and a parent-completed empathy subscale from the Social Skills Improvement System (Gresham & Elliott, 2008). The Index of Empathy indicated lower scores in the FASD group, although sex differences indicated males were lower in both groups. The Empathy subscale within the Social Skills Improvement System indicated that parents rated children in the FASD group lower regarding empathy than parents of the typically developing children in the control group (Stevens et al., 2015).

Lindinger et al. (2016) examined the theory of mind (social perspective taking) ability in 63 children (9-11 years of age) whose mother was recruited during pregnancy in South America. The 63 children were broken down into four groups: fetal alcohol syndrome (n = 8), partial fetal

alcohol syndrome (n = 19), non-syndrome children who were heavily exposed to alcohol in utero (n = 17), and children exposed to no or little alcohol in utero (n = 19). Researchers found that children prenatally exposed to alcohol scored significantly lower than controls on the Reading the Mind in the Eyes test which assesses a child's ability to recognize different expressions of emotions from a series of photographs isolated on the eye region. The Reading the Mind in the Eyes test is considered a higher-order theory of mind measure and could play a role in behavioral impairment (Lindinger et al., 2016).

Doyle et al. (2019) examined if a relationship exists between behavioral concerns including psychopathology often found in children with heavy prenatal alcohol exposure (i.e., oppositional behaviors and conduct behaviors) and executive functioning. They assessed participants (10-17 years old) in three groups: alcohol exposed with oppositional/conduct behaviors, alcohol exposed without oppositional/conduct behaviors, and a control group of typically developing children and adolescents, using the D-KEFS (Delis et al., 2001) and BRIEF, parent report (Gioia et al., 2000). Doyle et al. found that both the alcohol groups (exposed with/without oppositional/conduct behaviors) demonstrated lower levels of executive functioning. Significant main effects were found on the parent reported BRIEF with the alcohol exposed with oppositional/conduct behaviors group being rated the highest for executive functioning problems, then the alcohol exposed without oppositional/conduct behaviors group, and then the control group. Researchers concluded that further investigation is needed regarding those with heavy prenatal exposure due to the fact that oppositional/conduct behaviors related to executive function were only detected by the parent ratings on the BRIEF and not the direct measures of executive function.

Adaptive Impacts. Examining the impacts of adaptive skills are also important because they not only shed light on how children are able to care for themselves independently, but also explore how they are able to interact with others around them. Fagerlund et al. (2012) examined the adaptive abilities of children and adolescents (8-20 years old; *n* = 143) who received a diagnosis of a fetal alcohol spectrum disorder using the Vineland Adaptive Behavior Scales (Sparrow et al, 2005). They compared the FASD group (*n* = 73) with a typically developing control group (*n* = 40) and a group of IQ-matched children who also had a specific learning disorder (*n* = 30). Fagerlund et al. found that the children in the FASD group had lower adaptive scores in all domains (i.e., communication, daily living skills, and socialization) than both the comparison groups. Additionally, the FASD group showed a decline with age in the social skills domain, that is, the older FASD group of children had higher levels of decline. The researchers concluded that early intervention in these areas can decrease maladjustment in these children as they progress through development.

Crocker et al. (2009) wanted to examine alcohol-exposed children and children diagnosed with attention-deficit/hyperactivity disorder due to the overlap of these two groups and adaptive behavior. They utilized the Vineland Adaptive Behavior Scales (Sparrow et al., 2005) to look at the adaptive abilities of children who were heavily exposed to alcohol prenatally (*n* = 22), children diagnosed with ADHD (*n* = 23), and typically developing controls (*n* = 20) within the age range of 6 to 13 years old. Results indicated that compared to the control group, the alcohol exposed group and the ADHD group both demonstrated impairments on all three domains (i.e., communication, daily living skills, and socialization). The alcohol exposed group demonstrated deficits for communication (*M* = 77.23 and *SD* = 22.89) falling in the borderline range and for daily living skills (*M* = 69.41 and *SD* = 19.83) falling in the impaired range. Difficulties were

detected regarding socialization (*M* = 81.50 and *SD* = 20.85) falling in the low average range. The ADHD group demonstrated mean scores in the low average range across all three domains and the typically developing control group demonstrated average scores. Additionally, compared to the ADHD group, the alcohol exposed group was rated significantly lower on daily living skills. Regarding the socialization and communication domains, the alcohol exposed group demonstrated lower scores at older ages, suggesting an arrest in development among this population (Crocker et al., 2009).

Thomas et al. (1998) compared social skills of children (ages 5-12 years) diagnosed with fetal alcohol syndrome (*n* = 15) to two control groups, intelligence quotient matched children (*n* = 15) and children with intelligence quotients in the average to above-average range (*n* = 15). Social skills were assessed by caregiver interviews on the Vineland Adaptive Behavior Scale (Sparrow et al., 2005). The three subdomains of the Vineland Adaptive Behavioral Scale that were assessed were interpersonal relationship skills, use of play and leisure time, and coping skills. Results indicated that the FAS group demonstrated the most deficits in the area of interpersonal relationship skills. Additionally, Thomas et al. examined the chronological age of the child compared to their age equivalent score on the social scale and found a significant correlation with the children in the FAS group that was not present in either of the control groups. This increased discrepancy between chronological age and age equivalent score, particularly found in older children in the FAS group, suggests that social skills with FAS children may be related to arrested versus delayed development (Thomas et al., 1998).

A study conducted by Whaley et al. (2001) of 66 children (20 months to 11 years of age), alcohol-exposed (*n* = 33) and clinic referred (*n* = 33), were assessed on the Vineland Adaptive Behavior Scale (Sparrow et al., 2005) in the following subdomains: communication, daily living

skills, and socialization. Participants were referred from outpatient and inpatient clinic settings with all children in the alcohol-exposed group having heavy prenatal alcohol exposure. Children in the clinic referred group had diagnoses including but not limited to language disorders, adjustment disorders, intellectual disability, ADHD, bipolar disorder, and major depressive disorder (Whaley et al., 2001). Researchers found no significant differences regarding adaptive skills between the alcohol exposed and psychiatric clinical population. However, results indicated that with age, the alcohol exposed group demonstrated a more drastic decline regarding socialization skills compared to the clinic group, suggesting that these declines may become more significant with age (Whaley et al., 2001).

Ware et al. (2012) completed a multisite study which compared three different groups of children, heavy prenatal alcohol exposure (n = 142), non-exposed children diagnosed with ADHD (n = 82), and typically developing children (n = 133) regarding adaptive abilities and executive function. The Vineland Adaptive Behavior Scales-II (Sparrow et al., 2005) was used to assess adaptive functioning and the Delis-Kaplan Executive Functioning System (D-KEFS; Delis et al., 2001) was used to assess executive functioning. The alcohol exposed group and ADHD group demonstrated similar significantly lower scores on all executive functioning tasks compared to the control group. Regarding adaptive behavior the alcohol exposed group demonstrated significantly lower scores tcompared to both the ADHD and typically developing control group. Researchers concluded that increased difficulties in executive functioning can be predictive of poorer adaptive behavior. Specifically, the alcohol exposed group demonstrated a significant relationship between adaptive functioning and non-verbal executive functioning measures from the D-KEFS including the trail making test and design fluency-switching (Ware et al., 2012).

A study was conducted of 46 children (ages 3-14 years) who either had a diagnosis of partial fetal alcohol syndrome, alcohol-related neurodevelopmental disorder, or prenatal alcohol exposure to determine if differences were present regarding adaptive behavior (Carr et al., 2010). All three of these diagnoses fall under the fetal alcohol spectrum disorders umbrella. Results indicated that children diagnosed with alcohol-related neurodevelopmental disorder scored significantly lower on the Adaptive Behavior Assessment System, Second Edition (ABAS-II; Harrison & Oakland, 2003) than those children with prenatal alcohol exposure (Carr et al., 2010). Compared to the normative data, deficits were identified for the partial fetal alcohol syndrome for the general adaptive composite falling in the impaired range (M = 69.9 and SD = 10.7), conceptual domain falling in the borderline range (M = 71.3 and SD = 12.8), social domain falling in the borderline range (M = 71.1 and SD = 8.8), and the practical domain falling in the borderline range (M = 77.5 and SD = 12.4). The alcohol-related neurodevelopmental disorder group also demonstrated deficits compared to the normative data demonstrating scores in the severe impairment range in the general adaptive composite, the mild impairment range in the conceptual and social domains, and scores falling in the borderline range for the practical domain. Children and adolescents in the prenatal alcohol exposed group scored in the borderline range in the general adaptive composite, the conceptual domain, and social domain, and scored in the low average range in the practical domain (Carr et al., 2010). These findings suggest that adaptive behavior deficits are observed in several diagnoses that occur under the FASD umbrella.

Summary of What We Know

Behavioral, social, and emotional abilities can be observed independently, but typically the three areas are observed together due to the impact they have on one another. The research

regarding the behavioral, social, and emotional functioning of children who experienced gestational opioid exposure is currently not extensive, although the findings are contributing to a growing foundation of data. Current research has examined children ranging in age from birth to late adolescence and have found some significant results regarding lower neurobehavior, socialization, attachment, and emotional functioning.

The Neonatal Intensive Care Unit Network Neurobehavioral Scale (Lester & Tronick, 2005) is frequently utilized to assess at-risk infants. One- to two-month-old opioid exposed infants assessed by the NICU Network Neurobehavioral Scale showed significantly higher stress abstinence signs when compared to non-exposed infants (Heller et al., 2017; Lester et al., 2002), although one study found that after adjusting for covariates, no significance was found (Lester et al., 2002). Infants with prenatal opioid exposure who were diagnosed with NAS, with or without being treated with methadone, both demonstrated significantly lower scores for regulation and quality of movement when compared to non-exposed infants at 6-weeks-old (Heller et al., 2017). Research regarding the impacts of infants born to mothers receiving buprenorphine medication assisted treatment while pregnant compared to methadone medication assisted treatment has demonstrated inconsistencies. Two studies utilizing data from the Maternal Opioid Treatment: Human Experimental Research study (MOTHER) exhibited different results regarding the impact on infants whose mother were treated during pregnancy with buprenorphine versus methadone. One study assessed infants during their first 30 days of life with the Neonatal Intensive Care Unit Network Neurobehavioral Scale (Lester & Tronick, 2005), and found that although both groups of infants showed improved neurobehavior during the progression of the first 30 days of life, the infants born to mothers who received buprenorphine medication assisted treatment had fewer stress abstinence signs, were less excitable, had less muscle tension, had a

higher ability to self-regulate, and required less holding in order to achieve a quiet alert state when compared to infants whose mother received methadone (Coyle et al., 2012). In contrast, the other study found that no significant differences were detected when comparing infants whose mothers were treated for opioid dependence with buprenorphine versus methadone when assessed at 3, 6, 12, 24, and 36 months old (Kaltenbach et al., 2018).

Descriptively, one study found that more than 25% of families with children age 2 years, who were diagnosed and treated for NAS as neonates, reported these toddlers as having difficulties with staying and/or falling asleep and also reported behavioral issues such as tantrums and hyperactivity (Merhar et al., 2018). These findings may be related to difficulties with self-soothing and self-regulation found in neonates with prenatal opioid exposure. Children prenatally exposed to opioids who were diagnosed with NAS postnatally demonstrated significantly higher rates of being diagnosed with adjustment disorder with mixed disturbance of emotions and conduct at 3 years of age when compared to opioid exposed children without NAS and non-exposed controls (Arter et al., 2021).

Social difficulties have been identified with young children with prenatal opioid exposure. During early development, 18-month-old children who experienced opioid and polysubstance exposure in utero showed less time engaging in symbolic play and demonstrated more irritability during play when compared to non-exposed children (Metosky & Vondra, 1995). Prenatally exposed infants with or without NAS showed statistically significant differences with clinical significance for the following social issue categories at 12 months old compared to non-exposed controls according to the ICD-9 and ICD-10 codes: child welfare custody, foster care, other problems related to lifestyle, and problems related to social environment. The significance for problems related to social environment remained during the

2nd and 3rd year of life. Opioid exposed children with NAS were diagnosed with social issues at almost double the rate as opioid exposed children without NAS and non-exposed controls (Arter et al., 2021). Animal research examining young rat pups prenatally exposed to methadone, buprenorphine, or morphine at 6 and 10 weeks old found that when compared to the control group, all exposed groups demonstrated significant impairment for social interaction by showing increased social withdrawal. Increased anxiety was also observed among the exposed groups during the light-dark transition, although these differences were not significant (Chen et al., 2015).

Children whose mothers received medication assisted treatment for opioid dependence during pregnancy showed significant differences on the Vineland Social Maturity Scale (Sparrow et al., 2005) at 3 years of age compared to the non-exposed children (Hunt et al., 2008). One study found when examining executive function and behavioral/emotional adjustment that poor inhibitory control detected at 2 years of age was associated with greater levels of hyperactivity, conduct, and total behavior difficulties when assessed at 4.5 years old with the Strengths and Difficulties Questionnaire (Goodman, 2001; Levine & Woodward, 2018). Conduct disorder and/or emotional disturbance was detected for children with prenatal opioid exposure younger than 6 years of age (Azuine et al., 2019) Prenatal substance exposure and a diagnosis of NAS significantly predicted abnormal behavior development at age 10 years, although a significant difference was not detected at 1 and 5 years of age (Miller et al., 2020). Young school aged children and children in early adolescence (6-13 years of age) who experienced opioid exposure and whose mothers received methadone medication assisted treatment showed significantly higher ratings of aggression, anxiety, rejection, and maladaptive behaviors when assessed with the Roberts Apperception Test for Children (McArthur & Roberts, 1989). Exposed

children also demonstrated significantly higher ratings for depression, social withdrawal, somatic complaints, aggression, hyperactivity, and delinquency on the Achenbach Behavior Checklist (Achenbach, 1991; de Cubas & Field, 1993). The findings above demonstrate behavioral, social, and emotional difficulties that can impact a child's development and highlights the importance of these at-risk children receiving early therapeutic intervention so they can development the skills needed to mitigate the possible negative impacts of exposure.

The relationship between caregivers and children with a history of prenatal opioid exposure has also been examined and can support a deeper level of understanding of what these children are experiencing. Interactions between prenatally opioid exposed infants with opioid dependent mothers have demonstrated a lower ability to self-regulate (Bakhireva et al., 2019). Studies examining attachment have shown that children born to opioid dependent mothers have demonstrated a more disorganized attachment style, are more avoidant, showed lower contact-maintaining behaviors, and were less likely to seek out physical contact from their parent during a separation-reunion enactment when compared to non-exposed children (Goodman et al., 1999; Romanowicz et al., 2019). Opioid dependent mothers scored lower on sensitivity, structuring, non-intrusiveness, and self-efficacy when they were observed interacting with their child compared to non-opioid using mothers (Salo et al., 2009, 2010). Exposed children showed lower responsiveness and involvement (Salo et al., 2009) and mothers of exposed children rated them as more difficult and less adaptable (Metoksy & Vondra, 1995).

Infants and children with a fetal alcohol spectrum disorder have also demonstrated reduced behavioral, social, and emotional functioning. Infants who experienced prenatal alcohol exposure have shown greater emotional withdrawal, decreased responsivity, and decreased activity (Molterno et al., 2014). Caregiver ratings regarding social skills have indicated lower

functioning for alcohol exposed children compared to non-prenatally alcohol exposed children for interpersonal relationship skills, overall social skills, and empathy (Rasmussen et al., 2010; Stevens et al., 2015; Thomas et al., 1998). A significant correlation for the alcohol exposed children with fetal alcohol syndrome was detected for chronological age and age-equivalent scores for interpersonal relationship skills (Thomas et al., 1998), suggesting that social skills problems among children with fetal alcohol syndrome may indicate arrested development rather than a delay for school-aged children. Children and those in early adolescence with a fetal alcohol spectrum disorder have demonstrated delays regarding emotional understanding and understanding someone is able to experience a variety of emotions at the same time, it is acceptable to experience all emotions, and emotions can be hidden (Petrenko et al., 2017). Children with fetal alcohol syndrome, partial fetal alcohol syndrome, and non-syndrome with heavy alcohol exposure scored significantly lower on a test assessing a child's ability to recognize different expressions of emotions from the eye region of photographs compared to a non-exposed control group (Lindinger et al., 2016) which could play a role in a child's ability to appropriately interact with others.

Overall adaptive functioning, communication, and socialization difficulties and deficits among children with a fetal alcohol spectrum disorder have also been revealed (Carr et al., 2010; Crocker et al., 2009; Fagerlund et al., 2012). When comparing children with prenatal alcohol exposure and children with a psychiatric diagnosis, no significant differences were detected regarding adaptive functioning, although the alcohol exposed children showed a drastic decline in social skills as they progressed in age (Whaley et al., 2001). Significantly lower scores for adaptive behavior compared to typically developing controls have been linked with heavy prenatal alcohol exposure as well as ADHD. When examining these two groups, both

demonstrated impairments for communication and socialization, and both groups demonstrated similar difficulties with executive function (Crocker et al., 2009; Ware et al., 2012).

Summary of What We Do Not Know

There are still many avenues to be explored regarding how prenatal opioid exposure impacts the behavioral, social, and emotional abilities during child development. Similarly, to the neuropsychological findings among this at-risk population, studies in these areas have produced inconsistencies and have limited data overall. Additionally, studies have involved small participant cohorts and large retrospective data bases making consistent associations regarding the behavioral, social, and emotional impacts of prenatal opioid exposure challenging.

The impacts of prenatal opioid use with or without a diagnosis of NAS on adaptive functioning is an area that has not yet been explored. It is important to understand the possible impacts on adaptive functioning because it not only impacts independent living skills, but also examines at a person's ability to interact with others. Research regarding adaptive functioning can highlight possible difficulties with communication and socialization which could help guide clinicians in providing appropriate interventions.

Another area where there is minimal data is whether there is a relationship between prenatal opioid exposure and certain mental health diagnosis as defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5)*. Several studies have demonstrated associations between prenatal opioid exposure and ADHD, as discussed in Chapter III, but other behavioral, social, and emotional disorders have not been closely examined. The limited available information is based on one study indicating a higher rate of adjustment disorder among exposed 3-year-olds (Arter et al., 2021) and another study finding that children with a history of NAS were at greater risk of being hospitalized for mental and behavioral

disorders such as autism, conduct, and adjustment disorder by age 10, compared to children without NAS (Uebel et al., 2015). No other studies at this time have looked at links between mental health diagnoses with this prenatal opioid exposed population. Understanding if certain diagnoses are more prevalent among children with a history of prenatal opioid exposure with or without NAS could help physicians, clinicians, teachers, and caregivers be more cognizant of certain symptoms allowing for early diagnosis and intervention services.

Lastly, information is limited regarding how an opioid exposed child's living environment impacts behavioral, social, and/or emotional functioning. Living arrangements could include living with a biological parent, family member, friend of the family, in foster care, or with an adopted family. Each of these family living environments could provide challenges independently, making it difficult to determine a solid link between opioid exposure and living environments with a child's behavioral, social, and emotional functioning. Research in this area could increase the knowledge of how to support each caregiver in providing effective behavioral management, positive emotional support, and appropriate social interaction. Increasing caregiver skills arms them with knowledge of how to react and interact with children at risk for behavioral, social, and emotional deficits.

Future Hypotheses

There are many directions future research can explore regarding the impacts of prenatal opioid exposure on behavioral, social, and emotional functioning during childhood development. The minimal research that has been examined among children with a history of gestational opioid exposure with or without a diagnosis of NAS and the research that has been conducted with children with a fetal alcohol spectrum disorder can be utilized to help guide which research avenues would be best explored. Based on the research of the aforementioned at-risk

populations, several areas of focus can contribute to the vital knowledge needed to support and provide intervention services to children experiencing deficits due to prenatal opioid exposure.

Interactions between opioid exposed children and their caregivers have been examined to assess and observe attachment patterns. Opioid exposed children with or without a history of NAS have demonstrated a more disorganized attachment style and more avoidant behaviors and show fewer contact-maintaining behaviors (Romanowicz et al., 2019; Godman et al., 1999). Behavioral, social, and emotional deficits and difficulties have also been explored. Toddlers who experienced prenatal opioid exposure have demonstrated less time engaging in symbolic play, more irritated during play, tantrums, and lower social skills abilities (Hunt et al., 2008; Merhar et al., 2018; Metosky & Vondra, 1995). School aged opioid exposed children have shown greater behavior difficulties, emotional disturbance, aggression, anxiety, rejection, and social withdrawal (Azuine et al., 2019; de Cubas & Field, 1993; Levine & Woodward, 2018). Examining if any associations are detected among a child's attachment style to their caregiver as an infant and their behavioral, social, and emotional functioning during childhood could inform the importance of implementing early parenting skills interventions. The separation-reunion procedure can be utilized to assess the infant's attachment style and children's behavioral, social, and emotional abilities can be assessed with the Behavior Assessment System for Children, third edition (BASC-3; Reynolds & Kamphaus, 2015). A future hypothesis could explore whether, opioid exposed infants identified with a disorganized or avoidant attachment style will have higher caregiver ratings for difficulties regarding internalized behaviors, externalized behaviors, and/or social skills during school-aged years when compared to non-exposed children.

The adaptive functioning skills of children exposed prenatally to opioids has not currently been examined. Although no data for opioid exposed children exists, researchers can utilize the

data with fetal alcohol spectrum disorders to guide future studies. Children diagnosed with a fetal alcohol spectrum disorder have demonstrated lower overall adaptive scores, communication, daily living skills, socialization, and interpersonal relationship skills when assessed with the Vineland Adaptive Behavior Scale (Sparrow et al., 2005) compared to typically developing children (Crocker et al., 2009; Fagerlund et al., 2012; Thomas et al., 1998; Ware et al., 2012). A future study could hypothesize that children with prenatal opioid exposure will demonstrate a greater risk of lower adaptive behaviors when compared to non-exposed children on the Vineland Adaptive Behavior Scale. Early interventions regarding adaptive functioning could support a reduction of deficits in these children as they progress through childhood. Interventions involving communication and social skills could facilitate more positive interpersonal relationships with their peers and others in their lives.

Currently, several studies have indicated that exposed children score significantly lower for general cognition compared to non-exposed children or the normative population of the assessment utilized (Beckwith & Burke, 2015; Hunt et al., 2008; Merhar et al., 2018; Yeoh et al., 2019). Research has also indicated that prenatally opioid exposed children are at a greater risk of developing social and emotional problems (Azuine et al., 2019; Metosky & Vondra, 1995). A hypothesis supported by these findings is, there will be a negative correlation between the parent ratings of social and emotional difficulties and cognitive development in children who were prenatally exposed to opioids and diagnosed with neonatal abstinence syndrome (NAS) postnatally. The independent variable (predictor) is the parent ratings of social and emotional abilities on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III; Bayley, 2006). The dependent variable (criterion) is the cognitive performance on the Bayley Scales of Infant and Toddler Development, third edition (Bayley-III).

CHAPTER V: DISCUSSION

Summary of Research Findings

The opioid epidemic has transitioned across three waves in the United States. Beginning during the Civil War, moving through the war on drugs, and currently due to the pharmaceutical company's false promises of a non-addictive pain reliever, OxyContin, around the year 2000 (Patel & Rushefshy, 2022). The highly addictive OxyContin led to additional opioid pain relievers being prescribed and utilized for pain management such as oxycodone, hydrocodone, codeine, and morphine. Synthetic and semi-synthetic opioids are also being prescribed with all types of opioids having a similar chemical makeup, interacting with the opioid receptors in the brain and body (National Institute on Drug Abuse, n.d.) and being broadly distributed throughout the central nervous system (Chaves et al., 2017). Acting as an effective pain reliever coupled with physicians being unaware of the highly addictive component of the drug led physicians to frequently prescribe opioids to their patients. Heroin is the most commonly used illegal opioid that some prescription opioid dependent individuals may turn to when they are no longer able to obtain or afford legal opioids. By 2017, the U.S. Department of Health and Human Services declared a public health emergency due to the overwhelming amount of opioid misuse and dependency (U. S. Department of Health and Human Services, 2021).

The rise of the use and abuse of opioids in the United States over the past two decades has led to an increase in prevalence of neonates being diagnosed with neonatal abstinence syndrome due to prenatal opioid exposure followed by the abrupt cessation of opioids after delivery (Kocherlakota, 2014; Reddy et al., 2017). Neonates with a history of gestational opioid exposure do not always receive a diagnosis of NAS, although many do. Current research emphasizes the short- and long-term impacts of prenatal opioid use with or without a diagnosis

of NAS within the pediatric population. Prenatal opioid exposure can impact fetal and childhood development neurologically, psychologically, and physically.

Neurologically, brain physiological and anatomical impacts have been found in infants and children with a history of prenatal opioid exposure with or without NAS. Neuroanatomic volumetric impacts have been identified in infants, children, and adolescents with a history of prenatal opioid use, demonstrating reductions in the basal ganglia (Sirnes et al., 2017; Yuan et al., 2014), thalamus and cerebellar white matter (Sirnes et al., 2017), as well as whole brain volumes (Yuan et al., 2014). These regional brain areas can be linked to motor control, motor learning, relaying sensory and motor signals, executive function, behaviors, emotions, regulating alertness, and social skills (Lanciego et al., 2012; Van Overwalle et al., 2019). Contrasting data has indicated no significant differences for global brain volumes for total brain, cerebral cortex, cerebral white matter volumes (Sirnes et al., 2017) or neuroanatomical volumes or cortical volumes (Walhovd et al., 2015). Neuroimaging of adolescents who were prenatally exposed to opioid and polysubstance use demonstrated significantly smaller neuroanatomical volumes and cortical surface areas as well as thinner cortices (Nygaard et al., 2018), although another study of infants with opioid and polysubstance use demonstrated no significant differences regarding neuroanatomical volume or cortical thickness/volume/area (Walhovd et al., 2015). Research growth in this area needs to continue in order to establish more solidified data.

Fractional anisotropy is used to measure connectivity in the brain and studies examining infants exposed to opioids prenatally compared to non-exposed infants have shown decreased fractional anisotropy in white matter (Monnelly et al., 2018; Walhovd et al., 2010) as well as higher radial diffusion in white matter (Walhovd et al., 2010). White matter is in the subcortical part of the brain and consists of millions of myelinated axons that connect neurons to different

areas of the brain. Myelination is involved in high-speech transmission linked to sensory, motor, and cognitive functions (Fields, 2010). Therefore, alterations in white matter tracks and/or disruption in myelination from prenatal opioid use may have an impact on cognition and learning during childhood development. Neuroimaging comparing prenatally opioid and polysubstance exposed infants to non-exposed infants showed exposed infants had spatial distributions associated with higher-order regions and networks as well as higher concentrations in the middle frontal and angular gyrus, indicated by heat maps (Salzwedel et al., 2020). The angular gyrus is involved with several different functions including but not limited to attention, emotion regulation, reading and comprehension, memory retrieval, and social cognition (Seghier, 2013). Although impacts have been discovered, the etiology cannot be inexplicitly attributed to prenatal opioid exposure. The research highlighting the neurological impacts can lead to future studies linking the physiological and anatomical findings to observed neuropsychological, behavioral, social, and emotional functioning observed during childhood development.

Infants aged 21-98 days, who experienced prenatal opioid use have demonstrated significantly lower scores on the BSID-3 (Bayley, 2006) domains for cognition, language, and motor when compared to a normative subsample of infants aged 30-90 days, based on data provided by Pearson (Beckwith & Burke, 2015). Significantly lower scores persisted for opioid exposed toddlers and early school-aged children, 18 months to 6 years old, regarding cognition and motor abilities (Hunt et al., 2008; Merhar et al, 2018; Yeoh et al., 2019) as well as language abilities (Hunt et al., 2008; Merhar et al., 2018) when compared to normative data and non-exposed controls. Studies have also demonstrated that infants, toddlers, and early school aged-children (age birth to 5 years old) exposed to opioids prenatally had lower scores for cognition (Baldacchino et al., 2014; Salo et al., 2010) and psychomotor abilities (Baldacchino et al., 2014)

when compared to normative data and non-exposed controls, although no differences were found to be significant. Some research has found that school aged children with a history of prenatal opioid exposure are at a greater risk of experiencing speech and language deficits (Miller & Anderson, 2022; Rees et al., 2022) and exposed adolescents are at a greater risk of experiencing significant fine motor deficits (Nygaard et al., 2017).

Research examining the neuropsychological impacts of prenatal opioid use has some inconsistent findings. One study indicated that children, at 8.5 years of age, who were exposed prenatally to opioids with or without polysubstance use had full scale intelligence quotient (FSIQ) scores that were significantly lower than non-exposed controls (Nygaard et al., 2015). In contrast, another study did not find significant differences for overall cognition in school-age children or adolescents prenatally exposed to opioids (Yeoh et al., 2019). Adolescents (17-21 years) whose mothers used multiple substances during pregnancy, with heroin as their primary substance, during pregnancy did not show significant differences for cognition when compared to the normative data but did show significantly lower scores when compared to a non-exposed control group assessed by the Wechsler Abbreviated Scale of Intelligence (WASI; Zhu, 1999; Nygaard et al., 2017).

Neuropsychological gender differences reveal that infant and toddler aged opioid exposed boys with or without a diagnosis of NAS scored lower than opioid exposed females for cognition and language abilities (Merhar et al., 2018; Skumlien et al., 2020) and significantly lower than non-exposed boys for cognition (Nygaard et al., 2015; Skumlien et al., 2020). Exposed infant and toddler girls scored lower for general cognition than non-exposed girls, and in childhood (age 8.5 years) the differences became significant (Nygaard et al., 2015). Care giving environments may also have an impact on a child's neuropsychological abilities. One study

found that at 2 years of age, children who were treated for NAS and were living with a foster or adoptive family scored significantly higher for cognition and motor abilities when compared to children with NAS who were living with a biological parent or family member (Merhar et al., 2018).

The impacts prenatal opioid use may be observed within the home and school environments regarding academic performance, executive function, and working memory. Academically, a study indicated that children who were exposed to opioids prenatally and were diagnosed with NAS as neonates scored significantly lower on academic based test during elementary and middle school when compared to non-exposed children, with approximately 45% of the exposed children not meeting the minimal national standards for one or more of the academic domains (Oei et al., 2017). Children with a history of NAS are at a greater risk for being referred for a disability evaluation, being diagnosed with a disability, and requiring intervention services at school (Fill et al., 2018). Executive functioning includes abilities regarding inhibition, cognitive shifting, and working memory, with the prefrontal cortex being the primary region of activation (Moriguchi & Hiraki, 2013). Opioid exposed toddlers demonstrated poorer inhibitory control during a snack delay task and also showed poorer task performance on a working memory task (i.e., more errors and additional trials), although differences were not significant compared to non-exposed children (Levine & Woodward, 2018). Working memory problems have been observed in opioid exposed adolescents (Nygaard et al., 2017), and neuroimaging of children and adolescents indicated impaired task performance during a working memory-selective attention task with increased activation in the prefrontal cortical areas as cognitive demands increased (Siren et al., 2018). Extensive research has been conducted regarding the links between children with fetal alcohol syndrome disorders and deficits found in

executive functioning abilities (Fuglestad et al., 2015; McGee et al., 2008; Rasmussen et al., 2006), which may be mirrored in opioid exposed children; however, more research is needed to fully establish this link.

Deficits in executive function and working memory are often found in children diagnosed with attention-deficit/hyperactivity disorder (ADHD). Poor inhibitory control for opioid exposed toddlers at 2 years of age has been significantly associated with increased levels of hyperactivity at 4.5 years of age (Levine & Woodward, 2018). Prenatal opioid exposure has been linked to children and adolescents having an increased risk of being diagnosed with ADHD (Azuine et al., 2019; Miller & Anderson, 2022; Nygaard, et al., 2017; Rees et al., 2020; Tronnes et al., 2021). No association has been found regarding the gestational timing of opioid exposure regarding ADHD symptoms or an ADHD diagnosis; however, exposure to 5 or more weeks of opioids compared to 4 or less weeks was associated with an elevated risk of being diagnosed with ADHD (Tronnes et al., 2021). Parent and teacher ratings have indicated that opioid exposed children show an increase in attention and hyperactivity compared to non-exposed children (de Cubas & Field, 1993; Merhar et al., 2018; Nygaard et al., 2016). Together these risk factors enhance the possibility of opioid exposed children having difficulties in the areas of executive functioning and working memory.

The behavioral, social, and emotional impacts of prenatal opioid use have also been examined. Research has demonstrated that opioid exposed infants with or without a diagnosis of NAS show higher stress abstinence scores and a significantly lower ability to self-regulate when compared to non-exposed infants (Bakhireva et al., 2019; Heller et al., 2017). Studies have also examined the pediatric impacts of mothers obtaining buprenorphine and methadone medication assisted treatment during pregnancy, although findings have been inconsistent. Coyle et al.

(2012) mothers who received buprenorphine medication assisted treatment compared to methadone medication assisted treatment had infants who demonstrated less stress abstinence signs, less excitability, greater ability to self-regulate, and required less physical holding to maintain a quiet alert state when assessed by the NICU Network Neurobehavioral Scale (Lester & Tronick, 2005). Other studies have indicated no significant neuropsychological or temperament differences for infants and toddlers with or without NAS (Kaltenbch et al., 2018) or infant behavioral differences of those who were exposed to either buprenorphine or methadone (Bakhireva et al., 2019). Opioid exposure has been linked with emotional disturbances and behavioral difficulties in children (Azuine et al., 2019; de Cubas & Field, 1993; Merhar et al., 2018) Opioid exposed children have been found to have significantly higher difficulties with aggression, anxiety, rejection, maladaptive outcome, depression, social withdrawal, and delinquency when compared to non-exposed children (de Cubas & Field, 1993). Toddlers exposed to prenatal opioid use with a diagnosis of NAS demonstrated a significantly higher rating of being diagnosed with adjustment disorder with mixed disturbance of emotions and conduct compared to opioid exposed toddlers who were not diagnosed with NAS (Arter et al., 2021). Socially, difficulties have been identified regarding overall social maturity (Hunt et al., 2008), reduced symbolic play and increased irritability during play (Metosky & Vondra, 1995), problems related to the social environment (Arter et al., 2021), and social withdrawal (de Cubas & Field, 1993). Socially and emotionally, similar findings were discovered regarding difficulties in social interaction, emotional regulation, and overall social skills for children with a history of prenatal alcohol exposure with or with a fetal alcohol spectrum disorder (Molterno et al., 2014; Petrenko et al., 2017; Rasmussen et al., 2010; Stevens et al., 2015; Thomas et al., 1998).

Summary of Proposed Future Hypotheses

Growing data has been emerging regarding the pediatric population that has been impacted by prenatal opioid use with or without a diagnosis of NAS. As the opioid epidemic persisted over the past two decades, the need for research in this area flourished. Current research has revealed insightful data; however, research needs to continue as the pediatric population impacted by the opioid epidemic progress through developmental stages. Based on the current data there are many different avenues that can be explored revealing the neuropsychological, behavioral, social, emotional, neurophysiological, and neuroanatomical impacts. Future research and hypotheses are vital in understanding the developmental impacts prenatal opioid exposure is generating and the knowledge needed to support and provide intervention services to these children. Research for children with a history of prenatal opioid exposure with or without a diagnosis of NAS and the research that has been conducted with children with a fetal alcohol spectrum disorder can be utilized to help guide the future direction of research.

Regarding neuropsychological studies, the first suggested future hypothesis for exploration is that school-aged children who experienced opioid exposure during gestation and received a diagnosis of NAS postnatally will demonstrate significantly lower executive function scores when compared to non-exposed children. This hypothesis is supported by toddlers prenatally exposed to opioids demonstrating poor inhibitory control (Levine & Woodward, 2018) as well as research showing executive function deficits in children with prenatal alcohol exposure leading to a fetal alcohol spectrum disorder (Fuglestad et al., 2015; McGee et al., 2008; Rasmussen et al., 2006). Executive function abilities can be measured by subtests from the Delis-Kaplan Executive Functioning System (D-KEFS; Delis et al., 2001), including Towers, Color-

Word Interference, and Trails, as well as caregiver and teacher ratings on the Behavior Rating Inventory of Executive Function (BRIEF-2; Gioia et al., 2015). A second hypothesis could be that children who experienced prenatal opioid exposure will demonstrate significantly lower working memory and processing speed scores on the WISC-V (Wechsler, 2014) when compared to children born without prenatal substance exposure. This hypothesis is supported by the current findings of prenatally opioid exposed children compared to non-exposed children having a greater risk of being diagnosed with ADHD (Azuine et al., 2019; Nygaard et al., 2016, 2017; Rees et al., 2010) as well as having significantly lower scores or demonstrating an impaired task performance on working memory tasks (Levine & Woodward, 2018; Nygaard et al., 2007; Sirens et al., 2018). Additionally, children with ADHD tend to demonstrate relative and/or normative weaknesses on the working memory and the processing speed indices on the WISC-V. Lastly, a future suggested hypothesis could be that there will be a negative correlation between the parent ratings of social and emotional difficulties and cognitive development in children who were prenatally exposed to opioids and diagnosed with neonatal abstinence syndrome (NAS) postnatally. This hypothesis is supported by data indicating that exposed children have demonstrated significantly lower scores for general cognition compared to non-exposed children or the normative population of the assessment utilized (Beckwith & Burke, 2015; Hunt et al., 2008; Merhar et al., 2018; Yeoh et al., 2019) and that prenatally opioid exposed children are at a greater risk of developing social and emotional problems (Azuine et al., 2019; Metosky & Vondra, 1995).

There are many directions for future research regarding the impacts of prenatal opioid exposure on behavioral, social, and emotional functioning during childhood development. One suggested hypothesis is that opioid exposed infants identified with a disorganized or avoidant

attachment style will have higher caregiver ratings for difficulties regarding internalizing behaviors, externalizing behaviors, and/or social skills during school-aged years when compared to non-exposed children. Data supporting this future research includes findings that opioid exposed children NAS have demonstrated a more disorganized attachment style, more avoidant behaviors, and fewer contact-maintaining behaviors when interactions with their caregiver was observed (Godman et al., 1999; Romanowicz et al., 2019). Behavioral, social, and emotional deficits and difficulties have also been demonstrated (Azuine et al., 2019; de Cubas & Field, 1993; Hunt et al., 2008; Levine & Woodward, 2018; Merhar et al., 2018; Metosky & Vondra, 1995). Examining this data could inform the importance of implementing early parenting skills interventions. Another future hypothesis could be children with prenatal opioid exposure will demonstrate a greater risk of adaptive deficits or lower adaptive functioning when compared to non-exposed children on the Vineland Adaptive Behavior Scale (Sparrow et al., 2005). Although there is no current data for adaptive functioning and opioid exposed children, this hypothesis could be supported by research indicating that children with a fetal alcohol spectrum disorder have demonstrated lower overall adaptive scores, communication, daily living skills, socialization, and interpersonal relationship skills when assessed with the Vineland Adaptive Behavior Scale compared to typically developing children (Crocker et al., 2009; Fagerlund et al., 2012; Thomas et al., 1998; Ware et al., 2012). This information could lead to further understanding of the importance of early interventions regarding adaptive functioning to possibly reduce the deficits or difficulties in these children as they progress through childhood.

The associations of neurophysiological and neuroanatomical differences with the long-term impacts on neuropsychological, behavioral, social, and emotional functioning is another important area that needs to be further studied. Infants who experienced prenatal alcohol

exposure demonstrated a significant association between lower scores on motor, language, cognitive, and adaptive domains and regional volumes in both the temporal and frontal lobes compared to healthy controls (Donald et al., 2016). Given that infants with a history of prenatal opioid exposure have shown significantly lower cognitive scores (Beckwith & Burke, 2015; Hunt et al., 200; Merhar et al., 2018; Salo et al., 2010; Yeoh et al., 2019) as well as language and motor scores (Beckwith & Burke, 2015; Merhar et al., 2018), a future hypothesis could be that altered neuroanatomical volumes found in the temporal and frontal lobes of infants exposed to opioids in utero will be positively correlated to lower language and motor scores on the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley, 2006). Additionally, a longitudinal study with the same above hypothesis could demonstrate associations between neuroanatomical volumes and neuropsychological findings with toddlers and early school aged children. This hypothesis is supported by data showing that prenatally opioid exposed children, 3-6 years of age, have significantly lower scores when compared to normative data and non-exposed children regarding cognition and motor skills (Hunt et al., 2008; Yeoh et al., 2019), as well as speech and language (Hunt et al., 2008; Rees et al., 2020).

Research regarding child and adolescents with fetal alcohol spectrum disorder demonstrated significant associations between age-related increases in callosal, frontal, and parietal white matter volumes and cognitive and executive function improvement (Gautam et al., 2014). Similar FASD research found higher levels of executive function deficits and larger volume increases in the frontal and temporal-parietal regions over time than those FASD individuals who demonstrated lower levels of deficits regarding executive function (Gautam at al., 2015). Reduced scores on executive functioning have been found in toddlers with a history of prenatal opioid exposure (Levine & Woodward, 2018), although further research is needed to determine

if there is a link between executive functioning and neuroanatomical volumes for children with a history of prenatal opioid exposure with or without a diagnosis of NAS. A future hypothesis could be that deficits in executive functioning with toddlers who experienced prenatal opioid use will be associated with increased white matter volumes in the frontal lobe. Lastly, a future proposed hypothesis could be that the prenatally opioid exposed pediatric population will show a link between the reduction in the basal ganglia, thalamus, and/or cerebellar white matter with elevated concerns regarding behaviors, emotions, and social skills on the BASC-3 (Reynolds & Kamphaus, 2015). Although, current data does not exist in this area, research has demonstrated that infants and school-aged children with prenatal opioid exposure with or without a diagnosis of NAS show reduced regional brain volumes, compared to non-exposed controls and the normative population, in the basal ganglia (Sirnes et al., 2017; Yuan et al., 2014), thalamus, and cerebellar white matter (Sirnes et al., 2017) and these regional areas have been linked to behaviors, emotions, regulating alertness, and social abilities (Lanciego et al., 2012; Van Overwalle et al., 2019). Future studies can compare the neuroimaging of infants, toddlers, and school aged children to determine if associations exist with parent ratings, teacher ratings, and self-report ratings, when appropriate, on the Behavioral Assessment System for Children, Third edition (BASC-3; Reynolds & Kamphaus, 2015) or similar measures.

Clinical Implications

The research discussed in this review highlights how prenatal opioids can impact children throughout development, arming clinicians, caregivers, teachers, and physicians with the knowledge to best support this at-risk pediatric population. Opioids can begin to have an impact during fetal development that can be observed through neuroimaging in infancy regarding the central nervous system, white matter, and regional brain volumes (Merhar et al., 2019; Subedi et

al., 2017; Yuan et al., 2014) and this impact may result in neuropsychological, behavioral, social, and emotional deficits or difficulties found in toddlers, children, and adolescents. Early detection and intervention are often the treatment trajectory that will provide children experiencing difficulties with the support they need. Studies have shown that reduced performance in cognitive, language, and motor areas may be found with children who were exposed to opioids prenatally with or without a diagnosis of NAS. Obtaining serial psychological and/or neuropsychological evaluations will not only demonstrate the individual's strengths and weaknesses but show how their abilities compare to their peers as well as themselves. Comparing the individual's evaluations over time will allow their team to see if the child's abilities are progressing, declining, or arrested in certain areas. Evaluations would also inform the child's team of a possible clinical diagnosis and highlight specific areas of intervention often needed for them to obtain remedial services and accommodations in school. Additional services children with prenatal opioid exposure may benefit from are speech and language therapy if language deficits are detected and occupational therapy to address motor deficits.

Children prenatally exposed to opioids are at a greater risk of developing attention-deficit/hyperactivity disorder. Research has also indicated executive function and working memory difficulties that may impact the opioid exposed population, similar to those often identified in individuals diagnosed with ADHD. Children in the public school system who have a diagnosis of ADHD are eligible to receive an Individual Education Plan (IEP) based on the Individuals with Disabilities Education Act or a 504 Plan based on the Section 504 of the Rehabilitation Act of 1973. The IEP and 504 Plan are both individualized approaches implemented by the school to provide the child with specific accommodations, services, and/or

specialized instruction to help support them in progressing through the educational system (Spiel et al., 2014).

Behavioral, social, and emotional interventions can be provided through individual therapy, family therapy, and/or parent training. A toddler, child, or adolescent can work one on one with a therapist to develop and/or strengthen skills such as emotional regulation, social skills, attention/focus, impulsivity, and planning/organizing, to name a few. Family therapy and parent training can provide psychoeducation, behavior management, in-vivo intervention/feedback, positive modeling, and can support improving overall family functioning and communication. Specifically, parent training can be utilized for children with ADHD and/or behavioral challenges that have been identified in the prenatally opioid exposed pediatric population. In general, parent training approaches focus on educating parents on how to respond to their child's behaviors in order to increase desired behaviors and decrease or eliminate maladaptive behaviors.

Early detection and intervention services for pregnant women is also vitally important. Harm reduction can be achieved through medical and/or psychological treatment for opioid use/abuse. Regarding treatment options, pregnant women can receive medication assisted treatment, detoxification, and/or psychotherapy (Bell et al., 2016; Fullerton et al., 2014; Jones et al., 2011). Medication assisted treatment with methadone, buprenorphine, or naltrexone are currently the most widely used (Fullerton et al., 2014; Metz et al., 2011; Towers et al., 2019b). Research comparing medication treatment with buprenorphine and methadone has demonstrated that neonates born to mothers obtaining medication assisted treatment with buprenorphine have more positive outcomes including: lower risk of being born preterm, larger birth weight, lower NAS rate, lower morphine doses to treat NAS symptoms, shorter duration of pharmacologic

treatment for NAS, shorter hospital stay, better ability to self-soothe, and fewer signs of experiencing stress and withdrawal symptoms (Jones et al., 2010; Metz et al., 2011; Pritham et al., 2012; Zedler et al., 2016). Naltrexone medication assisted treatment compared to buprenorphine and methadone demonstrated neonates were significantly less likely to be diagnosed with NAS or being admitted to the NICU (Towers et al., 2019b). Regarding non-pharmacologic treatment, pregnant women can obtain counseling and/or psychotherapy in individual and/or group settings (Jones et al., 2011). A combination of medical and psychological support allows the pregnant woman to obtain both physical and mental health support and healing, which may lead to reduced use or abstinence.

Limitations

Polysubstance use is often found among people who utilize substances, whether illicit or licit, with approximately 50% of people diagnosed with prescription opioid use disorder (OUD) using more than one substance, over 88% of heroin users report polysubstance use (Winkelman et al., 2018), and approximately 80% of individuals with OUD have an additional substance use disorder (Wu et al., 2016). Opioid using research participants reported using an average of 3.5 substances during pregnancy (Nygaard, et al., 2016, 2017, 2018) with a high prevalence of opioid dependent pregnant women using tobacco products (Hoflich et al., 2012; Tabi, et al., 2020). Mothers of infants diagnosed with NAS are more likely to smoke tobacco than mothers of non-NAS infants (Uebel et al., 2015) and overall, neonates diagnosed with NAS are at a higher risk of polysubstance exposure than non-NAS controls (Towers et al., 2019a). Maternal alcohol and tobacco use have been linked to a greater risk of opioid use during pregnancy and/or OUD compared to women who did not use substances (Rajabi et al., 2019; Whiteman et al., 2014). Women who are using and/or are addicted to opiates during pregnancy most likely should also

be participating in smoking cessation and/or substance use treatment due to the high comorbidity rate with this population. Comparison groups that do not consider maternal tobacco use during recruitment could be negatively influencing true associated findings when looking at cognitive development and prenatal opioid exposure (Nelson et al., 2020). All these factors make it challenging to isolate the impacts of opioids making a pure sample difficult to obtain, which is an ongoing limitation for research in this area.

Research to date regarding the impacts of prenatal opioid exposure on the pediatric population comprises of limitations including small cohorts, few longitudinal studies, the utilization of large data bases, confounding variables, and reliance on participant self-report, to name a few. Limitations of small cohorts include challenges of interpretation, limitations with statistical analysis, and the possibility of producing false-positive results or overestimations of the associations found (Hackshaw, 2008). Longitudinal studies provide the opportunity to assess impacts with the same cohort over a long period of time; however, these studies are not without difficulties. Attrition is one of the most challenging aspects of longitudinal studies because patients may drop out of the study for a variety of reasons, creating missing data for different time points (Twisk & de Vente, 2002). Missing data for the prenatal opioid pediatric population can create reduced sample size and missing data during different childhood developmental stages being assessed and/or examined. Large scale databases provide limitations because important data may be missing for individuals that may have an impact on the data being analyzed; therefore, research findings could be misinterpreted and/or may be misrepresented. Most researchers try to control for confounding variables, although it is impossible to control for all possible confounding variables. The prenatal mental and physical health, nutritional intake, and environmental factors all could have elements of impact on fetal development and may be

difficult to control. Further research may help to identify additional factors and can enhance matching for exposed versus control samples, which could be a benefit, yet complex factors may not be able to be controlled for none the less. Lastly, one of the most challenging aspects of many of the studies reviewed is the dependency on participant self-report. Self-reported data is based on the participant's full transparency and honesty. Patients who are reporting on their prenatal substance use may under disclose the frequency, duration, amount, and type of substance(s) used out of fear of judgement.

Overall, limitations in the research examining the impacts of prenatal opioid use are inevitable, although efforts should be made by researchers to uphold the integrity of findings to the best of their abilities.

Recommendations

A multi-systemic approach involving a physician, clinician, caregiver, and teacher would provide the child with the most well-rounded care throughout development. Intervention services should begin as early as prenatally by providing the pregnant woman with medical, psychological, and substance dependency support. Postnatally or possibly toward the end of pregnancy, it is recommended that the mother or caregiver obtain psychoeducation to help them develop the necessary skills involved in caring for an infant who was prenatally exposed to opioids and may experience withdrawal symptoms. Withdrawal symptoms occur due to the sudden cessation of opioids or polysubstance use and can result in difficulty maintaining a calm state, frequent high-pitched crying, poor self-regulation, and difficulty sleeping, which may lead to mothers or caregivers to become frustrated (Jansson et al., 2012; Kocherlakota, 2014). Equipping mothers and caregivers with the appropriate skills may help them approach these symptoms in a more tolerable manner.

Education should be provided to parents and caregivers on how to appropriately interact with and respond to their child in order to support a more secure attachment style and a healthy caregiver-child bond. Discussing the benefits of talking with, reading to, early implementation of basic educational aspects (i.e., letter, numbers, colors), engaging in symbolic and imaginary play, and active play involving motor skills (i.e., balancing, jumping, throwing a ball, picking up cheerios, using scissors) during early stages of development is important and may support language, cognitive, and motor development. Therapeutic approaches should be continually recommended throughout development to support behavioral, social, and emotional difficulties that may arise. Additionally, therapists and/or social workers can support the child and their caregiver in obtaining needed resources and navigating and advocating for services within the school system. Some children with prenatal opioid exposure may be displaced from their home, so it is vitally important that each caregiver be informed of the evaluations, services, and/or treatment that has been provided so the child can continue receiving the support they need with minimal interruption.

Recommendations for physicians are geared towards patient education, connecting to resources, and screening. The impact of the opioid epidemic does not discriminate and has affected people from across educational, economic, racial, and cultural lines. Physicians and other medical care providers have an obligation to provide their patients with a thorough education regarding the possible impacts of opioid use during pregnancy. General education can be provided to patients during prenatal appointments and to childbearing aged women currently prescribed opioids. Physicians can discuss alternative treatments for pain relief during pregnancy and possible medication assisted treatment options. Women prescribed opioids who are not pregnant can be educated on the importance of utilizing birth control practices to prevent

unplanned pregnancies while taking opioid prescriptions. Physicians can provide patients with reputable referrals for opioid abuse and dependency, psychotherapy, and self-help support groups such as narcotics anonymous. Opioids can be detected for 1-7 days when assessed by urinary analysis. Detectability duration can vary among individuals due to the type of opioid used, frequency, duration, and amount of use, as well as specific aspects of each patient such as metabolism, height, and weight (Bhatt, 2019). Consent to consistently screen for substances, via urinary analysis, at every prenatal appointment may increase the likelihood of detecting opioids and therefore, of being able to provide the patient with support.

It is difficult to gauge how much knowledge the general population has on the magnitude of the opioid epidemic and impacts that have accrued. Increasing public awareness through media, social media, and specific flyers in heavily trafficked areas cannot only increase overall awareness, but also provide opioid dependent women with treatment and support resources. Enhancing research efforts to reveal the impacts of prenatal opioid use is also needed. Research involving the impacts of the opioid epidemic on the pediatric population is still in the beginning stages and requires extensive examination to demonstrate the deficits that may occur throughout child development. It is recommended that research continue and should encompass more regions throughout the United States, larger cohorts, and longitudinal studies to help expand the growing knowledge in this area and provide these at-risk children with the best support to thrive through all stages of development.

References

Abidin, R. R. (1995). *Parenting Stress Index, Third Edition (PSI-3)*. Psychological Assessment Resources, Inc.

Achenbach, T. M. (1991). *Manual for the Child Behavior Checklist/4-18 and 1991 Profile*. Lawrence Erlbaum Associates Publishers.

Achenbach, T. M. (1991). *Manual for the Teacher's Report Form and 1991 Profile*. Lawrence Erlbaum Associates Publishers.

American Academy of Pediatrics. (2018, September). *Fetal alcohol spectrum disorders*. https://www.healthychildren.org

American Psychological Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Publisher.

American College of Obstetricians and Gynecologists Committee on Obstetric Practice. (2017). Opioid use and opioid use disorder in pregnancy, *ACOG Committee Opinion No. 711*, *130*, 81-94.

Andre, Q. R., McMorris, C. A., Kar, P., Ritter, C., Gibbard, W. B., Tortorelli, C., & Lebel, C. (2020). Different brain profiles in children with prenatal alcohol exposure with or without early adverse exposures. *Human Brain Mapping, 41*, 4375-4385. https://doi.org/10.1002/hbm.25130

Arter, S., Lambert, J., Brokman, A., & Fall, N. (2021). Diagnoses during the first three years of life for children with prenatal opioid exposure and neonatal abstinence syndrome using a large maternal infant data hub. *Journal of Pediatric Nursing, 61*, 34-39. https://doi.org/10.1016?j.pedn.2021.03.011

Azuine, R. E., Ji, Y., Chang, H., Kim, Y., Ji, H., DiBari, J., Hong, X., Wang, G., Singh, G. K., Pearson, C., Zuckerman, B., Surkan, P. J., & Wang, X. (2019). Prenatal risk factors and perinatal and postnatal outcomes associated with maternal opioid exposure in an urban, low-income, multiethnic US population. *JAMA Network Pediatrics, 2*(6), 1-14. https://doi.org/10.1001/jamanetworkopen.2019.6405

Backes, C. H., Backes, C. R., Gardner, D., Nankervis, C. A., Giannone, P. J., & Cordero, L. (2012). Neonatal abstinence syndrome: Transitioning methadone-treated infants from an inpatient to an outpatient setting. *Journal of Perinatology, 32*, 425-430. https://doi.org/10.1038/jp.2011.114

Bakhireva, L. N., Holbrook, B. D., Shrestha, S., Leyva, Y., Ashley, M., Cano, S., Lowe, J., Stephen, J. M., & Leeman, L. (2019). Association between prenatal opioid exposure, neonatal opioid withdrawal syndrome, and neurodevelopment and behavioral outcomes at 5-8 months of age. *Early Human Development, 128*, 69-76. https://doi.org/10.1016/j.earlhumdev.2018.10.010

Baldacchino, A., Arbuckle, K., Petrie, D. J., & McCowan, C. (2014). Neurobehavioral consequences of chronic intrauterine opioid exposure in infants and preschool children: A systematic review and meta-analysis. *BioMed Central Psychiatry, 14*(104), 1-12. https://doi.org/10.1186/s12888-015-0438-5

Bayley, N. (2006). *Bayley Scales of Infant and Toddler Development, Third Edition (BSID-3).* The Psychological Corporation.

Bayley, N. (1969). *Manual for the Bayley Scales of Infant Development, Second Edition (BSID-2)*. The Psychological Corporation.

Beckwith, A. M., & Burke, S. A. (2015). Identification of early developmental deficits in infants with prenatal heroin, methadone, and other opioid exposure. *Clinical Pediatrics, 54*(4), 328-335.

Beery, K. E. (1997). *Manual for the Beery-Buktenica Developmental Test of Visual-Motor Integration, Fourth Edition (Beery VMI-IV).* Modern Curriculum Press.

Beilke, R. L., Kusche, C. A., & Greenberg, M. T. (1988). *Coding manual for the Kusche Affective Interview—Revised (KAI-R)*. Unpublished manuscript.

Bell, J., Towers, C. V., Hennessy, M. D., Heitzman, C., Smitth, B., & Chattin, K. (2016). Detoxification from opiate drugs during pregnancy. *American Journal of Obstetrics and Gynecology, 215*(5), 670-676. https://doi.org/10.1016/j.ajog.2016.03.015

Belsky, J., & Most, R. K. (1981). From exploration to play: A cross-sectional study of infant free play behavior. *Developmental Psychology, 17*, 630-639.

Benningfield, M. M., Dietrich, M. S., Jones, H. E., Kaltenbach, K., Heil, S. H., Stine, S. M., Coyle, M. G., Arria, A. M., O'Grady, K. E., Fischer, G., & Martin, P. R. (2012). Opioid dependence during pregnancy: Relationships of anxiety and depression symptoms to treatment outcomes. *Addiction, 107*(1), 74-82. https://doi.org/10.1111/j.1360-0443.2012.04041.x

Bhatt, A. (2019, June 11). *How long do opioids stay in your system?* Addiction Center. https://www.additioncenter.com/opiates/how-long-do-opioids-stay-system/

Biringen, Z., Robinson, J., & Emde, R. N. (1998). *The Emotional Availability Scales, Third Edition*. Unpublished manuscript.

Bjorkquist, O. A., Fryer, S. L., Reiss, A. L., Mattson, S. N., & Riley, E. P. (2010). Cingulate gyrus morphology in children and adolescents with fetal alcohol spectrum disorders. *Psychiatry Research: Neuroimaging, 181*, 101-107. https://doi.org/10.1016/j.pscychresns.2009.10.004

Boggess, T., & Risher, W. C. (2022). Clinical and basic research investigations into the long-term effects of prenatal opioid exposure on brain development. *Journal of Neuroscience Research, 100*, 396-409. https://doi.org/10.1002/jnr.24642

Burke, S., & Beckwith, A. M. (2017). Morphine versus methadone treatment for neonatal withdrawal and impact on early infant development. *Global Pediatric Health, 4*, 1-6. https://doi.org/10.1177/2333794X17721128

Buss, A. H., & Plomin, R. (1984). *Temperament: Early Developing Personality Traits*. Lawrence Erlbaum.

Bzoch, K. R., League, R., & Brown, V. L. (2003). *Receptive-Expressive Emergent Language Test, Third Edition (REEL-3): Examiner's Manual*. Pro-ed.

Carlson, S. M., & Schaefer, C. M. (2012). *Executive Function Scale for Early Childhood Test Manual*. University of Minnesota.

Carr, J. L., Agnihotri, S., & Keightley, M. (2010). Sensory processing and adaptive behavior deficits of children across the fetal alcohol spectrum disorder continuum. *Alcoholism: Clinical and Experimental Research, 34*(6), 1022-1032. https://doi.org/10.1111/j.1530-0277.2010.01177.x

Chasnoff, I. J., & Hung, W. C. (1999). *The 4P's Plus*. NTI Publishing.

Chaves, C., Remiao, F., Cisternino, S., & Decleves, X. (2017). Opioids and the blood-brain barrier: A dynamic interaction with consequences of drug disposition in brain. *Current Neuropharmacology, 15*(8), 1156-1173. https://doi.org/10.2174/1570159X15666170504095823

Chen, H., Chiang, Y., Yuan, Z. F., Kuo, C., Lai, M., Hung, T., Ho, I., & Chen, S. (2015). Buprenorphine, methadone, and morphine treatment during pregnancy: Behavioral effects on the offspring in rats. *Neuropsychiatric Disease and Treatment, 11*, 609-618.

Chisamore, B., Labana, S., Blitz, S., & Ordean, A. (2016). A comparison of morphine delivery in neonatal opioid withdrawal. *Substance Abuse: Research and Treatment, 10*(1), 49-54. https://doi.org/10.4137/SART.S34550

Cleary, B. J., Donnelly, J., Strawbridge, J. Gallagher, P. J., Fahey, T., Clarke, M., & Murphy, D. J. (2010). Methadone dose and neonatal abstinence syndrome-systematic review and meta-analysis. *Addiction, 105*, 2071-2084.

Clemans-Cope, L., Lynch, V., Howell, E., Hill, I., Holla, N., Morgan, J., Johnson, P., Cross-Barnet, C., & Thompson, J. A. (2018). Pregnant women with opioid use disorder and their infants in three state Medicaid programs in 2013-2016. *Drug and Alcohol Abuse, 195*, 156-163. https://doi.org/10.1016/j.drugalcdep.2018.12.2005

Cohen, M. J. (1997). *Children's Memory Scale Manual*. Harcourt Brace & Company.

Coleman, P. K., & Karraker, K. H. (2003). Maternal self-efficacy beliefs, competence in parenting, and toddlers' behavior and developmental status. *Infant Mental Health Journal, 24*(2), 126-148.

Conners, C. K. (1997). *Conners' Rating Scales—Revised (CRS-R): Technical Manual*. Multi-Health Systems.

Cox, J. L., Holden, J. M., & Sagovsky, R. (1987). Detection of postnatal depression: development of the 10-item Edinburgh Postnatal Depression Scale. *British Journal of Psychiatry, 150*, 782-786.

Coyle, M. G., Salisbury, A. L., Lester, B. M., Jones, H. E., Lin, H., Graf-Rohrmeister, K., & Fischer, G. (2012). Neonatal neurobehavior effects following buprenorphine versus methadone exposure. *Addiction*, *107*(1), 63-73. https://doi.org/10.1111/j.1360-0443.2012.04040.x

Crocker, N., Vaurio, L., Riley, E. P., & Mattson, S. N. (2009). Comparison of adaptive behavior in children with heavy prenatal alcohol exposure or attention-deficit/hyperactivity disorder. *Alcoholism: Clinical and Experimental Research, 33*(11), 2015-2023. https://doi.org/10.1111/j.1530-0277.2009.01040.x

Davis, C. P., Franklin, L. M., Johnson, G. S., & Schrott, L. M. (2010). Prenatal oxycodone exposure impairs spatial learning and/or memory in rats. *Behavioral Brain Research, 212*(1), 27-34. https://doi.org/10.1016/j.bbr.2010.03.022

Davis, J. M., Shenberger, J., Terrin, M., Breeze, J. L., Hudak, M., Wachman, E. M., Marro, P., Oliverira, E. L., Harvey-Wilkes, K., Czynski, A., Engelhardt, B. E., D'Apolito, K., Bogen, D., & Lester, B. (2018). Comparison of safety and efficacy of methadone vs. morphine for treatment of neonatal abstinence syndrome: A randomized clinical trial. *JAMA Pediatrics, 172*(8), 741-748. https://doi.org/10.1001/jamapediatrics.2018.1307

de Cubas, M. M., & Field, T. (1993). Children of methadone-dependent women: Developmental outcomes. *American Journal of Orthopsychiatry, 63*(2), 266-276. https://doi.org/10.1037/h0079429

Delis, D. C., Kaplan, E., & Kramer, J. H. (2001). *Delis-Kaplan Executive Function System (D-KEFS): Examiner's Manual*. The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (1994). *California Verbal Learning Test-Children's Version (CVLT-C)*. The Psychological Corporation.

Delis, D. C., Kramer, J. H., Kaplan, E., & Ober, B. A. (2000). *California Verbal Learning Test, Second Edition. (CVLT-II).* The Psychological Corporation.

Devlin, L. A., Breeze, J. L., Terrin, N., Gomez-Pomar, E., Bada, H., Finnegan, L. P., O'Grady, K. E., Jones, H. E., Lester, B., & Davis, J. M. (2020). Association of a simplified Finnegan neonatal abstinence scoring tool with the need for pharmacologic treatment for neonatal abstinence syndrome. *JAMA Pediatrics, 3*(4), 1-11. https://doi.org/10.1001/jamanetworkopen.2020.2275

Donald, K. A., Fouche, J. P., Roos, A., Koen, N., Howells, F. M., Riley, E. P., Wood, R. P., Zar, H. J., Narr, K. L., & Stein, D. J. (2016). Alcohol exposure in utero is associated with decreased gray matter volume in neonates. *Metabolic Brain Disease, 31*(1), 81-91. https://doi.org/10.1007/s11011-015-9771-0

Dooley, J., Gerber-Finn, L., Antone, I., Guilfoyle, J., Blakelock, B., Balfour-Boehm, J., Hopman, W. M., Jumah, N., & Kelly, L. (2016). Buprenorphine-naloxone use in pregnancy for treatment of opioid dependence: Retrospective cohort study of 30 patients. *Canadian Family Physician, 62*, 194-200.

Dowell, D., Haegerich, T. M., & Chou, R. (2016). CDC guideline for prescribing opioids for chronic pain—United States, 2016. *Centers for Disease Control and Prevention MMWR, 65*(1), 1-49.

Doyle, L. R., Glass, L., Wozniak, J. R., Kable, J. A., Riley, E. P., Coles, C. D., Sowell, E. R., Jones, K. L., & Mattson, S. N. (2019). Relation between oppositional/conduct behaviors and executive function among youth with histories of heavy prenatal alcohol exposure. *Alcoholism: Clinical and Experimental Research, 43*(6), 1135-1144. https://doi.org/10.1111/acer.14036

Dunn, W. (2002). *Infant/toddler Sensory Profile: User's Manual*. Harcourt Assessment, Inc.

Dun, L. M., & Dun, L. M. (1997). *Examiner's Manual for the Peabody Picture Vocabulary Test, Third Edition (PPVT-II).* American Guidance Service.

DuPaul, G. J., Power, T. J., Anastopoulos, A. D., & Reid, R. (1998). *ADHD Rating Scale-IV: Checklists, Norms, and Clinical Interpretation*. Guilford.

Edwards, S., Fletcher, P., Garman, M., Hughes, A., Lettus, C., & Sinka, I. (1997). *Reynell Developmental Language Scales III: The University of Reading edition*. GL Assessments.

Ennaceur, A., & Meliani, K. (1998). A new one-trial test for neurobiological studies of memory in rats III: Spatial vs. non-spatial working memory. *Behavioral Brain Research, 51*(1), 83-92.

Fagerlund, A., Autti-Ramo, I., Kalland, M., Santtila, P., Hoyme, H. E., Mattson, S. N., & Korkman, M. (2013). Adaptive behavior in children and adolescents with fetal alcohol spectrum disorders: A comparison with specific learning disability and typical development. *European Child & Adolescent Psychiatry, 21*(4), 221-231. https://doi.org/10.1007/s00787-012-0256y

Faherty, L. J., Kranz, A. M., Russell-Fritch, J., Patrick, S. W., Cantor, J., & Stein, B. D. (2019). Association of punitive and reporting state policies related to substance use in pregnancy with rates of neonatal abstinence syndrome. *JAMA Pediatrics, 2*(11), 1-12. https://doi.org/10.1001/jamanetworkopen.2019.14078

Faherty, L. J., Matone, M., Passarella, M., & Lorch, S. (2018). Mental health of mothers of infants with neonatal abstinence syndrome and prenatal opioid exposure. *Maternal and Child Health Journal, 22*, 841-848. https://doi.org/10.1007/s10995-018-2457-6

Fama, R., & Sullivan, E. V. (2015). Thalamic structures and associated cognitive functions: Relations with age and aging. *Neuroscience and Behavioral Reviews, 54*, 29-37. https://doi.org/10.1016/j.neubiorev.2015.03.008

Fields, R. D. (2010). Change in the brain's white matter: The role of the brain's white matter in active learning and memory may be underestimated. *Science, 330*(6005), 768-769. https://doi.org/10.1126/sceince.1199139

Fill, M. A., Miller, A. M., Wilkinson, R. H., Warren, M. D., Dunn, J. R., Schaffner, W., & Jones, T. F. (2018). Educational disabilities among children born with neonatal abstinence syndrome. *Pediatrics, 142*(3), 1-8. https://doi.org/10.1542/peds.2018-0562

Finnegan L. P., Connaughton, J. F., Jr., Kron, R. E., & Emich, J. P. (1975a). Neonatal abstinence syndrome: Assessment and management. *Addictive Diseases, 2*, 141-158.

Finnegan L. P., Kron R. E., Connaughton, J. F., & Emich J. P. (1975b). Assessment and treatment of abstinence in the infant of the drug-dependent mother. *International Journal of Clinical Pharmacology and Biopharmacy*, *12*(1-2), 19-32.

Fuglestad, A. J., Whitley, M. L., Carlson, S. M., Boys, C. J., Eckerle, J. K., Fink, B. A., & Wozniak, J. R. (2015). Executive functioning deficits in preschool children with fetal alcohol spectrum disorders. *Child Neuropsychology, 21*(6), 716-731. https://doi.org/10.1080/09297049.2014.933792

Fullerton, C. A., Kim, M., Thomas, C. P., Lyman, D. R., Montejano, L. B., Dougherty, R. H., Daniels, A. S., Ghose, S. S., & Delphin-Rittmon, M. E. (2014). Medication-assisted treatment with methadone: Assessing the evidence. *Psychiatric Services, 65*(2), 146-157. https://doi.org/10.1176/appi.ps.201300235

Gamble, M. E., Marfatia, R., & Diaz, M. R. (2022). Prenatal methadone exposure leads to long-term memory impairments and disruptions of dentate granule cell function in a sex-dependent manner. *Addiction Biology, 27*, 1-14. https://doi.org/10.1111/adb.13215

Garstein, M. A., & Rothbart, M. K. (2003). Studying infant temperament via the Revised Infant Behavior Questionnaire. *Infant Behavior and Development, 26*, 64-86.

Gautam, P., Lebel, C., Narr, K. L., Mattson, S. N., May, P. A., Adnams, C. M., Riley, E. P., Jones, K. L., Kan, E. C., & Sowell, E. R. (2015). Volume changes and brain-behavior relationships in white matter and subcortical gray matters in children with prenatal alcohol exposure. *Human Brian Mapping, 36*, 2318-2329. https://doi.org/10.1002/hbm.22772

Gautam, P., Nunez, S. C., Narr, K. L., Kan, E. C., & Sowell, E. R. (2014). Effects of prenatal alcohol exposure on the development of white matter volume and change in executive function. *Neuroimage: Clinical, 5*, 19-27. http://doi.org/10.1016/j.nicl.2014.05.010Gioia, G. A., Isquith, P. K., Guy, S., & Kenworthy, L. (2000). *Behavior Rating Inventory of Executive Functioning (BRIEF)*. Psychological Assessment Resource.

Gioia, G. A., Isquith, P. K., Guy, S., & Kenworthy, L. (2015). *Behavior Rating Inventory of Executive Functioning, Second Edition (BRIEF-2)*. PAR, Inc.

Golden, C. (1978). *Stroop Color and Word Test*. Stoelting Co. Gomez-Pomar, E., Christian, A., Devlin, L., Ibonia, K. T., Concina, V. T., Bada, H., &

Westgate, P. M. (2017a). Analysis of the factors that influence the Finnegan neonatal abstinence scoring system. *Journal of Perinatology*, *37*, 814-817. https://doi.org/10.1038/jp.2017.40

Gomez-Pomar, E., Finnegan, L. P., Devlin, L., Bada, H., Concina, V. A., Ibonia, K. T., & Westgate, P. M. (2017b). Simplification of the Finnegan neonatal abstinence scoring system: Retrospective study of two institutions in the USA, *British Medical Journal, 7*, https://doi.org/10.1136/bmjopen-2017-016176

Goodglass, H., & Kaplan, E. (1983). *The Assessment of Aphasia and Related Disorders*. Lea & Febiger.

Goodman, R. (2001). Psychometric properties of the Strengths and Difficulties Questionnaire, *Journal of American Academy of Child and Adolescent Psychiatry, 40*(11), 1337-1345.

Goodman, G., Hans, S. L., & Cox, S. M. (1999). Attachment behavior and its antecedents in offspring born to methadone-maintained women. *Journal of Clinical Child Psychology, 28*, 58-69. https://doi.org/10.1207/s15374424jccp2801_5

Gray, T. R., Choo, R. E., Concheiro, M., Williams, E., Elko, A., Jansson, L. M., Jones, H. E., & Huestis, M. A. (2010). Prenatal methadone exposure, meconium biomarker concentrations and neonatal abstinence syndrome. *Addiction, 105*, 2151-2159. https://doi.org/10.1111/j.1360-0443.2010.03097.x

Grecco, G. G., Shahid, S. S., Atwood, B. K., & Wu, Y. (2022). Alterations of brain microstructures in a mouse model of prenatal opioid exposure detected by diffusion MRI. *Scientific Reports, 12*(17085), 1-11. https://doi.org/10.1038/s41598-022-21416-9

Gresham, F. M., & Elliott, S. N. (1990). *Social Skills Rating System Manual*. American Guidance Service.

Gresham, F., & Elliott, S. (2008). *Skills Improvement System*. Pearson PsychCorp.

Gressler, L. E., Shah, S., & Shaya, F. T. (2017). Association of criminal statutes for opioid use disorder with prevalence and treatment among pregnant women with commercial insurance in the United States. *JAMA Network Open, 2*(3), 1-10. https://doi.org/10.1001/jamanetworkopen.2019.0338

Griffiths, R., & Huntley, M. (1996). *Griffiths Mental Development Scales-Revised: Birth to 2 Years (GMDS 0-2).* APA PsycTests.

Guedency, A., & Fermanian, J. (2001). A validity and reliability study of assessment and screening for sustained withdrawal reaction in infancy: The Alarm Distress Baby Scale. *Infant Mental Health Journal, 22*, 559-575.

Hackshaw, A. (2008). Small studies: Strengths and limitations. *European Respiratory Journal, 32*, 1141-1143. https://doi.org/10.1183/09031936.00136408

Hall, E. S., Wexelblatt, S. L., Crowley, M., Grow, J. L., Jasin, L. R., Klebanoff, M. A., McClead, R. E., Meinzen-Derr, J., Mohan, V. K., Stein, H., & Walsh, M. C. (2014). A multicenter cohort study of treatments and hospital outcomes in neonatal abstinence syndrome. *Pediatrics, 134*(2), 527-534. https://doi.org/10.1542/peds.2013-4036

Hall, M. T., Wilfong, J., Huebner, R. A., Posze, L., & Willauer, T. (2016). Medication-assisted treatment improves child permanency outcomes for opioid-using families in the child welfare system. *Journal of Substance Abuse Treatment, 71*, 63-67. http://doi.org/10.1016/j.jsat.2016.09.006

Haight, S. C., Ko, J. Y., Tong, V. T., Bohm, M. K., & Callaghan, W. M. (2018). Opioid use disorder documented at delivery hospitalization—United States, 1999-2014. *Centers for Disease Control and Prevention MMWR, 67*(31), 1-5.

Han, B., Compton, W. M., Blanco, C., Crane, E., Lee, J., & Jones, C. M. (2017). Prescription opioid use, misuse, and use disorders in U.S. adults: 2015 national survey on drug use and health. *Annals of Internal Medicine, 167*, 293-301. https://doi.org/10.7326/M17-0865

Han, B., Compton, W. M., Jones, C. M., & Cai, R. (2015). Nonmedical prescription opioid use and use disorders among adults aged 18 through 64 years in the United States, 2003-2013. *JAMA, 314*(14), 1468-1478. https://doi.org/10.1001/jama.2015.11859

Harrison, P. L., & Oakland, T. (2003). *Adaptive Behavior Assessment System – Second Edition (ABAS-II).* The Psychological Corporation.

Heaton, R. K., Chelune, G., J., Talley, J. L., Kay, G. G., & Curtiss, G. (1993). *Wisconsin Card Sorting Test Manual*. Psychological Assessment Resources, Inc.

Heller, N. A., Logan, B. A., Morrison, D. G., Paul, J. A., Brown, M. S., & Hayes, M. J. (2017). Neonatal abstinence syndrome: Neurobehavior at 6 weeks of age in infants with or without pharmacological treatment for withdrawal. *Developmental Psychobiological, 59*(5), 574-582. https://doi.org/10.1002/dev.21532

Hirai, A. H., Ko J. Y., Owens, P. L., Stocks, C., & Patrick, S. W. (2021). Neonatal Abstinence Syndrome and Maternal Opioid-Related Diagnoses in the US, 2010-2017. *JAMA, 325*(2), 146-155. https://doi.org/10.1001/jama.2020.24991

Hoflich, A. S., Langer, M., Jagsch, R., Bawert, A., Winklbaur, B., Fischer, G., & Unger, A. (2012). Peripartum pain management in opioid dependent women. *European Journal of Pain, 16*(4), 574-584. https://doi.org/10.1016/j.ejpain.2011.08.0088

Howard, M. B., Schiff, D. M., Penwill, N., Si, W., Rai, A., Wolfgang, T., Moses, J. M., & Wachman, E. M. (2017). Impact of parental presence at infant's bedside on neonatal abstinence syndrome. *Hospital Pediatrics, 7*(2), 63-69. https://doi.org/10.1542/hpeds.2016-0147

Hu, S., Ide, J. S., Zhang, S., & Li, C. R. (2016). The right superior frontal gyrus and individual variation in proactive control of impulsive response. *Journal of Neuroscience, 36*, 12688-12696. https://doi.org/10.1523/jneurosci.1175-16.2016

Hunt, R. W., Tzioumi, D., Collins, E., & Jeffery, H. E. (2008). Adverse neurodevelopmental outcome of infants exposed to opiate in-utero. *Early Human Development, 84*, 29-35. https://doi.org/10.1016/j.earlhumdev.2007.01.013

Ibach, B. W., Johnson, P. N., Ernst, K. D., Harrison, D., & Miller, J. L. (2016). Initial dosing and taper complexity of methadone and morphine for treatment of neonatal abstinence syndrome. *Journal of Pharmacy Technology, 32*(5), 215-222. https://doi.org/10.1177/8755122516657566

Isemann, B., Meinzen-Derr, J., & Akinbi, H. (2011). Maternal and neonatal factors impacting response to methadone therapy in infants treated for neonatal abstinence syndrome. *Journal of Perinatology, 31*, 25-29. https://doi.org/10.1038/jp.2010.66

Jansson, L. M., & Velez, M. (2012). Neonatal abstinence syndrome. *Current Opinion Pediatrics, 24*(2), 252-258. https://doi.org/10.1097/MOP.0b013e32834fdc3a

Jansson, L. M., Velez, M., McConnell, K., Spencer, N., Tuten, M., Jones, H. E., King, V. L., Gandotra, N., Milio, L. A., Voegtline, K., & DiPietro, J. A. (2017). Maternal buprenorphine treatment and fetal neurobehavioral development. *American Journal of Obstetrics and Gynecology, 216*(5), 529-546. https://doi.org/10.1016/j.ajog.2017.01.040

Jantzie, L. L., Maxwell, J. R., Newville, J. C., Yellowhair, T. R., Kitase, Y., Madurai, N., Ramachandra, S., Bakhireva, L. N., Northington, F. J., Gerner, G., Tekes, A., Millio, L. A., Brigman, J. L., Robinson, S., & Allan, A. (2020). Prenatal opioid exposure: The next neonatal neuroinflammatory disease. *Brain Behavior and Immunity, 84*, 45-58. https://doi.org/10.1016/j.bbi.2019.11.007

Jarlenski, M., Hogan, C., Bogen, D. L., Chang, J. C., Bodnar, L. M., & Van Nostrand, E. (2017). Characterization of U.S. state laws requiring health care provider reporting of perinatal substance use. *Womens Health Issues, 27*(3), 264-270. https://doi.org/10.1016/j.whi.2016.12.008

Johns, P. (2014). *Clinical Neuroscience*. Churchill Livingstone.

Jones, H. E., Heil, S. H., Baewert, A., Arria, A. M., Kaltenbach, K., Martin, P. R., Coyle, M. G., Selby, P., Stine, S. M., & Fischer, G. (2012). Buprenorphine treatment of opioid-dependent pregnant women: A comprehensive review. *Addiction, 107*(1), 5-27. https://doi.org/10.1111/j.1360-0443.2012.04035.x

Jones, H. E., Kaltenbach, K., Heil, S. H., Stine, S. M., Coyle, M. G., Arria, A. M., O'Grady, K. E., Selby, P., Martin, P. R., & Fischer, G. (2010). Neonatal abstinence syndrome after methadone or buprenorphine exposure. *The New England Journal of Medicine, 363*(24), 2320-2331.

Jones, H. E., O'Grady, K. E., & Tuten, M. (2011). Reinforcement-based treatment improves the maternal treatment and neonatal outcomes of pregnant patients enrolled in comprehensive care treatment. *American Journal Addictions, 20*(3), 196-204. https://doi.org/10.1111/j.1521-0391.2011.00119.x

Kahn, L. S., Mendel, W. E., Fallin, K. L., Borngraber, E. A., Nochajski, T. H., Rea, W. E., & Blondell, R. D. (2017). A parenting education program for women in treatment for opioid-use disorder at an outpatient medical practice. *Social Work in Health Care, 56*(7), 2-18. https://doi.org/10.1080/00981389.2017.1327470

Kaltenbach, K., O'Grady, K. E., Heil, S. H., Salisbury, A. L., Coyle, M. G., Fischer, G., Martin, P. R., Stine, S., & Jones, H. E. (2018). Prenatal exposure to methadone or buprenorphine: Early childhood developmental outcomes. *Drug Alcohol Dependence, 185*, 40-49. https://doi.org/10.1016/j.drugalcdep.2017.11.030

Kaplan, E., Goodglass, H., & Weintraub, S. (1983). *The Boston Naming Test*. Lea & Febiger.

Kelly, L. E., Knoppert, D., Roukema, H., Rieder, M. J., & Koren, G. (2015). Oral morphine weaning for neonatal abstinence syndrome at home compared with in-hospital: An observational cohort study. *Pediatric Drugs, 71*(2), 151-157. https://doi.org/10.1007/s40272-014-0096-y

Knight, J. R., & Boston Children's Hospital (2016). *The CRAFFT screening interview*. Center for Adolescent Substance Abuse Research at Boston Children's Hospital. https://crafft.org/wpcontent/uploads/2019/02/CRAFFT-2.0_Clinician-Interview.pdf

Ko, J. Y., Tong, V. T., Haight, S. C., Terplan, M., Snead, C., & Schulkin, J. (2020a). Obstetrician-gynecologists' practice patterns related to opioid use during pregnancy and postpartum-United States, 2017. *Journal of Perinatology, 40*(3), 412-421. https://doi.org/10.1038/s41372-019-0535-2

Ko, J. Y., Tong, V. T., Haight, S. C., Terplan, M., Stark, L., Snead, C., & Schulkin, J. (2020b). Obstetrician-gynecologists' practices and attitudes on substance use screening during pregnancy. *Journal of Perinatology, 40*(3), 422-432. https://doi.org/10.1038/s41372-019-0542-3

Kocherlakota, P. (2014). Neonatal abstinence syndrome. *Pediatrics, 134*, 547-561. https://doi.org/10.1542/peds.2013-3524

Kongstorp, M., Bogen, I. L., Steinsland, S., Nerem, E., Salih, T. W., Stiris, T., & Anderson, J. M. (2020). Prenatal exposure to methadone or buprenorphine alters u-opioid receptor binding and downstream signaling in the rat brain. *International Journal of Developmental Neuroscience, 80*, 443-453. https://doi.org/10.1002/jdn.10043

Konijnenberg, C., Sarfi, M., & Melinder, A. (2016). Mother-child interaction and cognitive development in children prenatally exposed to methadone or buprenorphine. *Early Human Development, 101*, 91-97. http://doi.org/10.1016/j.earlhumdev.2016.08.013

Korkman, M., Kirk, U., & Kemp, S. (2007). *NEPSY, Second Edition (NEPSY-II)*. Harcourt Assessment.

Koy, M. S., O'Connor, D., Shehzad, Z., & Milham, M. P. (2017). Differential contributions of the middle frontal gyrus functional connectivity to literacy and numeracy. *Scientific Reports, 7*(17548), 1-13. https://doi.org/10.1038/s41598-017-17702-6

Kraft, W. K., Adeniyi-Jones, S. C., Chervoneva, I., Greenspan, J. S., Abatemarco, D., Kaltenbach, K., & Ehrlich, M. E. (2017). Buprenorphine for the treatment of the neonatal abstinence syndrome. *The New England Journal of Medicine, 376*(24), 2341-2348. https://doi.org/10.1056/NEJMoa1614835

Labella, M. H., Eiden, R. D., Roben, C. K., & Dozier, M. (2021). Adapting an evidenced-based home visiting intervention for mothers with opioid dependence: Modified attachment and biobehavioral catch-up. *Frontiers in Psychology, 12*, 1-15. https://doi.org/10.3389/fpsyg.2021.675866

Lafayette Instrument. (2015). *Grooved Pegboard User's Manual*. Lafayette Instrument Company.

Lanciego, J. L., Luquin, N., & Obeso, J. A. (2012). Functioning neuroanatomy of the basal ganglia. *Cold Springs Harbor Perspectives in Medicine, 2*, 1-20. https://doi.org/10.1101/cshperspect.a009621

Leark, R. A., Dupuy, T. R., Greenberg, L. M., Corman, C. L., & Kindschi, C. L. (1999). *T.O.V.A. Test of Variables of Attention: Professional Guide*. Universal Attention Disorders, Inc.

Lebel, C., Rasmussen, C., Wyper, K., Walker, L., Andrew, G., Yager, J., & Beaulieu, C. (2008). Brain diffusion abnormalities in children with fetal alcohol spectrum disorder. *Alcoholism: Clinical and Experimental Research, 32*(10), 1732-1740. https://doi.org/10.1111/j.1530-0277.2008.00750.x

Lester, B. M., Andreozzi-Fontaine, L., Tronick, E., & Bigsby, R. (2014). Assessment and evaluation of the high risk neonate: The NICU Network Neurobehavioral Scale. *Journal of Visualized Experiments, 90*, 1-9. https://doi.org/10.3791/3368

Lester, B. M., & Tronick, E. Z. (2005). *NICU Network Neurobehavioral Scale (NNNS): Manual*. Paul H. Brooks Pub. Co.

Lester, B. M., Tronick, E. Z., LaGasse, L., Seifer, R., Bauer, C. R., Shankaran, S., Bada, H. S., Wright, L. L., Smeriglio, V. L., Lu, J., Finnegan, L. P., & Maza, P. L. (2002). The maternal lifestyle study: Effects of substance exposure during pregnancy on neurodevelopmental outcome in 1-month-old infants. *Pediatrics, 110*, 1182-1192. https://doi.org/10.1542/peds.110.6.1182

Levine, T. A., & Woodward, L. J. (2018). Early inhibitory control and working memory abilities of children prenatally exposed to methadone. *Early Human Development, 116*, 68-75. https://doi.org/10.1016/j.earlhumdev.2017.11.010

Lezak, M. D. (2011). *Neuropsychological assessment* (5th ed.). Oxford University Press.

Lindinger, N. M., Malcolm-Smith, S., Dodge, N. C., Molteno, C. D., Thomas, K. G., Meintjes, E. M., Jacobson, J. L., & Jacobson, S. W. (2016). Theory of mind in children with fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 40*(2), 367-376. https://doi.org/10.1111/acer.12961

Liu, G., Kong, L., Leslie, D. L., & Corr, T. E. (2019). A longitudinal healthcare use profile of children with a history of neonatal abstinence syndrome. *The Journal of Pediatrics*, *204*(1), 111-117. https://doi.org/10.1016/j.jpeds.2018.08.032

MacMillan, K. D. L., Rendon, C. P., Verma, K., Riblet, N., Washer, D. B., & Holmes, A. V. (2018). Association of rooming-in with outcomes for neonatal abstinence syndrome: A systematic review and meta-analysis. *JAMA Pediatrics, 172*(4), 345-351. https://doi.org/10.1001/jamapediatrics.2017.5195

Madsen, A. M., Stark, L. M., Has, P., Emerson, J. B., Schulkin, J., & Matteson, K. A. (2018). Opioid knowledge and prescribing practices among obstetrician-gynecologists. *Obstetrics & Gynecology, 131*(1), 150-157. https://doi.org/10.1097/AOG.0000000000002407

Martin, C., Chen, H. B., & Dozier, M. (2022). Intervening with opioid-exposed newborns: Modifying an evidenced-based parenting intervention. *Delaware Journal of Public Health, 8*(2), 94-98. https://doi.org/10.32481/djph.2022.05.014

McArthur, D. S., & Roberts, G. E. (1989). *Manual for the Roberts Apperception Test for Children (RAT-C)*. Western Psychological Services.

McCarthy, D. (1972). *Manual for the McCarthy Scales of Children's Abilities*. The Psychological Corporation.

McGee, C. L., Schonfeld, A. M., Roebuck-Spencer, T. M., Riley, E. P., & Mattson, S. N. (2008). Children with heavy prenatal alcohol exposure demonstrate deficits on multiple measures of concept formation. *Alcoholism: Clinical and Experimental Research, 32*(8), 1388-1397. https://doi.org/10.1111/j.1530-0277.2008.00707.x

McGlone, L., & Mactier, H. (2015). Infants of opioid-dependent mothers: Neurodevelopment at six months. *Early Human Development, 91*, 19-21. https://doi.org/10.1016/j.earlhumdev.2014.10.006

Merhar, S.L., McAllister, J.M., Wedig-Stevie, K.E., Klein, A. C., Meinzen-Derr, J., & Poindexter, B. B. (2018). Retrospective review of neurodevelopmental outcomes in infants treated for neonatal abstinence syndrome. *Journal of Perinatology*, *38*(5), 587–592. https://doi.org/10.1038/s41372-018-0088-9

Merhar, S. L., Parikh, N. A., Braimah, A., Poindexter, B. B., Tkach, J., & Kline-Fath, B. (2019). White matter injury and structural anomalies in infants with prenatal opioid exposure. *American Journal of Neuroradiology, 40*, 2161-2165. https://doi.org/10.3174.ajnr.A6282

Metosky, P., & Vondra, J. (1995). Prenatal drug exposure and play and coping in toddlers: A comparison study. *Infant Behavior and Development, 18*, 15-25.

Metz, V., Jagsch, R., Ebner, N., Wurzl, J., Pribasnig, A., Aschauer, C., & Fischer, G. (2011). Impact of treatment approach on maternal and neonatal outcome in pregnant opioid-maintained women. *Human Psychopharmacology, 26*(6), 412-421. https://doi.org/10.1002/hup.1224

Meyers, J. E., & Meyers, K. R. (1995). *Rey Complex Figures Test and Recognition Trial: Professional Manual*. Psychological Assessment Resources.

Miller, J. S., & Anderson, J. G. (2022). Factors in children with a history of neonatal abstinence syndrome at 10 years of age: Evidence from the maternal lifestyle study. *Journal for Specialists in Pediatric Nursing, 27*(1), 1-8. https://doi.org/10.1111/jspn.12358

Miller, J. S., Anderson, J. G., & Lindley, L. C. (2020). Behavioral development in children with prenatal substance exposure and neonatal abstinence syndrome: Associated factors and implications. *Journal of Child and Adolescent Psychiatric Nursing, 33*, 67-76. https://doi.org/10.1111/jcap.12273

Mischel, W., Shoda, Y., & Rodriguez, M. L. (1989). Delay of Gratification in Children. *Science, 244*(4907), 933-938.

Molteno, C. D., Jacobson, J. L., Carter, R. C., Dodge, N. C., & Jacobson, S. W. (2014). Infant emotional withdrawal: A precursor of affective and cognitive disturbance in fetal alcohol spectrum disorders. *Alcoholism: Clinical and Experimental Research, 38*(2), 479-488. https://doi.org/10.1111/acer.12240

Monnelly, V. J., Anblagan, D., Quigley, A., Cabez, M. B., Cooper, E. S., Mactier, H., Semple, S. I., Bastin, M. E., & Boardman, J. P. (2018). Prenatal methadone exposure is associated with altered neonatal brain development. *NeuroImage:Clinical, 18*, 9-14. https://doi.org/10.1016/j.nicl.2017.12.033

Morgan, P. L., & Wang, Y. (2019). The opioid epidemic, neonatal abstinence syndrome, and estimated costs for special education services. *The American Journal of Managed Care, 25*(13), 264-269.

Moriguche, Y., & Hiraki, K. (2013). Prefrontal cortex and executive function in young children: A review of NIRS studies. *Frontiers in Human Neuroscience, 7*(867), 1-9. https://doi.org/10.3389/fnhum.2013.00867

Murphy-Oikonen, J., Montelpare, W. J., Southon, S., Bertoldo, L., & Persichino, N. (2010). Identifying infants at risk for neonatal abstinence syndrome: A retrospective cohort comparison study of 3 screening approaches. *Journal Perinatal & Neonatal Nursing, 24*(4), 366-372.

National Institute on Drug Abuse. (n.d.). *Opioids*. National Institute on Drug: Advancing Addiction Science. Retrieved March 16, 2022, from https://www.nida.nih.gov/reseach-topics/opioids

National Institute on Drug Abuse. (n.d.). *The NIDA Quick Screen*. https://www.nida.nih.gov/sites/default/files/pdf/nmassist.pdf

Nelson, L. F., Yocum, V. K., Patel, K. D., Qeadan, F., Hsi, A., & Weitzen, S. (2020). Cognitive outcomes of young children after prenatal exposure to medications for opioid use disorder: A systematic review and meta-analysis. *The Journal of the American Medical Association Network Open Pediatrics, 3*(3), 1-14, https://doi.org/10.1001/jamanetworkopen.2020.1195

Nygaard, E., Moe, V., Slinning, K., & Walhovd, K. B. (2015). Longitudinal cognitive development of children born to mothers with opioid and polysubstance use. *Pediatric Research, 78*(3), 330-335. https://doi.org/10.1038/pr.2015.95

Nygaard, E., Slinning, K., Moe, V., Due-Tonnessen, P., Fjell, A., & Walhovd, K. B. (2018). Neuroanatomical characteristics of youths with prenatal opioid and poly-drug exposure. *Neurotoxicology and Teratology, 68*, 13-26. https://doi.org/10.1016/j.ntt.2018.04.004

Nygaard, E., Slinning, K., Moe, V., & Walhovd, K. B. (2016). Behavior and attention problems in eight-year-old children with prenatal opiate and poly-substance exposure: A longitudinal study. *PLOS One, 11*(6), 1-21. https://doi.org/10.1371/journal.pone.0158054

Nygaard, E., Slinning, K., Moe, V. & Walhovd, K. B. (2017). Cognitive function of youths born to mothers with opioid and poly-substance abuse problems during pregnancy. *Child Neuropsychology, 23*(2), 159-187. https://doi.org/10.1080/09297049.2015.1092509

Oei, J. L., Melhuish, E., Uebel, H., Azzam, N., Breen, C., Burns, L., Hilder, L., Bajuk, B., Abdel-Latif, M. E., Ward, M., Feller, J. M., Falconer, J., Clews, S., Eastwood, J., Li, A., & Wright, I. M. (2017). Neonatal abstinence syndrome and high school performance. *Pediatrics, 139*(2), 1-10.

Patel, K. B., & Rushefsky, M. E. (2022). *The opioid epidemic in the United States: Missed opportunities and policy failures*. Routledge. https://doi.org/10.4324/9781003215899

Pathan, H., & Williams, J. (2012). Basic opioid pharmacology: An update. *British Journal of Pain, 6*(1), 11-16. https://doi.org/10.1177/2049463712438493

Patrick, S. W., Burke, J. F., Biel, T. J., Auger, K. A., Goyal, N. K., & Cooper, W. O. (2015a). Risk of hospital readmission among infants with neonatal abstinence syndrome. *Hospital Pediatrics, 5*(10), 513-519. https://doi.org/10.1542/hpeds.2015-0024

Patrick, S. W., Davis, M. M., Lehman, C. U., & Cooper, W. O. (2015b). Increasing incidence and geographic distribution of neonatal abstinence syndrome: United States 2009 to 2012. *Journal of Perinatology, 35*, 650-655. https://doi.org/10.1038/jp.2015.36

Patrick, S. W., Schumacher, R. E., Benneyworth, B. D., Krans, E. E., McAllister, J. M., & Davis, M. M. (2012). Neonatal abstinence syndrome and associated health care expenditures: United States, 2000-2009. *The Journal of the American Medical Association, 307*(18), 1934-1940. https://doi.org/10.1001/jama.2012.3951

Patrick, S. W., Schumacher, R. E., Horbar, J. D., Buus-Frank, M. E., Edwards, E. M., Morrow, K. A., Ferrelli, K. R., Picarillo, A. P., Gupta, M., & Soll, R. F. (2016). Improving care for neonatal abstinence syndrome. *Pediatrics, 137*(5), 1-8. https://doi.org/10.1542/peds.2015-3835

Peacock-Chambers, E., Leyenaar, J. K., Foss, S., Feinberg, E., Wilson, D., Friedmann, P., Visintainer, P., & Singh, R. (2019). Early intervention referral and enrollment among infants with Neonatal Abstinence Syndrome. *Journal of Developmental and Behavioral Pediatrics, 40*(6), 441-450. https://doi.org/10.1097/DBP.0000000000000679

Petrenko, C. L., Pandolfino, M. E., Quamma, J., & Olson, H. C. (2017). Emotional understanding in school-aged children with fetal alcohol spectrum disorders: A promising target for intervention. *Journal of Population Therapeutics and Clinical Pharmacology, 24*(2), 21-31. https://doi.org/10.22374/1710-622.24.2.5

Preedy, V. R. (Ed.). (2016). *Neuropathology of drug addictions and substance misuse*. Academic Press.

Pritham, U. A., Paul, J. A., & Hayes, M. J. (2012). Opioid dependency in pregnancy and length of stay for neonatal abstinence syndrome. *Journal of Obstetric Gynecologic and Neonatal Nursing, 41*(2), 180-190. https://doi.org/10.1111/j.1552-6909.2011.01330.x

Radhakrishnan, R., Elsaid, N. M., Sadhasivam, S., Reher, T. A., Hines, A. C., Yoder, K., Saykin, A. J., & Wu, Y. (2021). Resting state functional MRI in infants with prenatal opioid exposure: A pilot study. *Neuroradiology, 63*(4), 585-591. https://doi.org/10.1007/s00234-020-02552-3

Rajabi, A., Dehghani, M., Shojaei, A., Farjam, M., & Motevalian, S. A. (2019). Association between tobacco smoking and opioid use: A meta-analysis. *Addictive Behaviors, 92*, 225-235. https://doi.org/10.1016/j.addbeh.2018.11.043

Rasmussen, C., Becker, M., McLennan, J., Urichuk, L., & Andrews, G. (2010). An evaluation of social skills in children with and without prenatal alcohol exposure. *Child: Care, Health, and Development, 37*(5), 711-718. https://doi.org/10.1111/j.1365-2214.2010.01152.x

Rasmussen, C., Horne, K., & Witol, A. (2006). Neurobehavioral functioning in children with fetal alcohol spectrum disorder. *Child Neuropsychology, 12*(6), 453-468. https://doi.org/10.1080/09297040600646854

Reddy, U. M., Davis, J. M., Ren, Z., & Greene, M. F. (2017). Opioid use of pregnancy, neonatal abstinence syndrome, and childhood outcomes: Executive summary of a joint workshop by the Eunice Kennedy Shriver National Institute of Child Health and Human Development, American Congress of Obstetricians and Gynecologists, American Academy of Pediatrics, Society of Maternal-Fetal Medicine, Centers for Disease Control and Prevention, and the March of Dimes Foundation. *Obstetrics and Gynecology, 130*(1), 10-28. https://doi.org/10.1097/AOG.0000000000002054

Reece-Stretan, S., Marinelli, K. A., & The Academy of Breastfeeding Medicine (2015). ABM clinical protocol #21: Guidelines for breastfeeding and substance use or substance use disorder, revised 2015. *Breastfeeding Medicine, 10*(3), 135-141. https://doi.org/10.1089/bfm.2015.9992

Rees, P., Stilwell, P. A., Bolton, C., Akillioglu, M., Carter, B., Gale, C., & Sutcliffe, A. (2020). Childhood health and educational outcomes after neonatal abstinence syndrome: A systematic review and meta-analysis. *The Journal of Pediatrics, 226*(16), 149-156. https://doi.org/10.1016/j.jpeds.2020.07.013

Reitan, R. M., & Wolfson, D. (1985). *The Halstead-Reitan Neuropsychological Test Battery: Therapy and Clinical Interpretation.* Neuropsychological Press.

Reynolds, C. R., & Kamphaus, R. W. (2004). *Behavior Assessment System for Children, Second Edition (BASC-2).* Pearson.

Reynolds, C. R., & Kamphaus, R. W. (2015). *Behavior Assessment System for Children, Third Edition (BASC-3).* Pearson.

Riva, D., Taddei, M., & Bulgheroni, S. (2018). The neuropsychology of basal ganglia. *European Journal of Pediatric Neurology, 22*(2), 321-326. https://doi.org/10.1016/j.ejpn.2018.01.009

Roid, G. H. (2003). *Stanford Binet Intelligence Scales, Fifth Edition (SB-5).* Western Psychological Services.

Romanowicz, M., Vande Voort, J. L., Shekunov, J., Oesterle, T. S., Thusius, N. J., Rummans, T. A., Croarkin, P. E., Karpyak, V. M., Lynch, B. A., & Schak, K. M. (2019). The effects of parental opioid use on the parent-child relationship and children's developmental and behavioral outcomes: A systematic review of published reports. *Child Adolescent Mental Health, 13*(5), 2-11. https://doi.org/10.1186/s13034-019-0266-3

Roos, A., Wedderburn, C. J., Fouche, J. P., Subramoney, S., Joshi, S. H., Woods, R. P., Zar, H. J., Narr, K. L., Stein, D. J., & Donald, K. A. (2021). Central white matter integrity alterations in 2-3-year-old children following prenatal alcohol exposure. *Drug and Alcohol Dependence, 225*, 1-8. https://doi.org/10.1016/j.drugalcdep.2021.108826

Salo, S., Kivisto, K., Korja, R., Biringen, Z., Tupola, S., Kahila, H., & Kivitie-Kallio, S. (2009). Emotional availability, parental self-efficacy beliefs, and child development in caregiver-child relationships with buprenorphine-exposed 3-year-olds. *Parenting Science and Practice, 9*(3), 244-259. https://doi.org/10.1080/15295190902844563

Salo, S., Politi, J., Tupola, S., Biringen, Z., Kalland, M., Halmesmaki, E., Kahila, H., & Kivitie-Kallio, S. (2010). Early development of opioid-exposed infants born to mothers in buprenorphine-replacement therapy. *Journal of Reproductive and Infant Psychology, 28*(2), 161-179. https://doi.org/10.1080/02646830903219109

Saltzman-Benaiah, J., & Lalonde, C. E. (2007). Developing clinically suitable measures of social cognition for children: Initial findings form a normative sample. *The Clinical Neuropsychologist, 21*, 294-317.

Salzwedel, A., Chen, G., Chen, Y., Grewen, K., & Gao, W. (2020). Functional dissection of prenatal drug effects on baby brain and behavioral development. *Human Brain Mapping, 41*, 4789-4803. https://doi.org/10.1002/hbm.25158

Sanchez, E. S., Bigbee, J. W., Fobbs, W., Robinson, S. E., & Sato-Bigbee, C. (2008). Opioid addiction and pregnancy: Perinatal exposure to buprenorphine affects myelination in the developing brain. *Glia, 56*(9), 1017-1027. https://doi.org/10.1002/glia.20675

Schaefer, C. P., Tome, M. E., & Davis, T. P. (2017). The opioid epidemic: A central role for the blood brain barrier in opioid analgesia and abuse. *Fluids and Barriers of the CNS, 14*(32), 1-11. https://doi.org/10.1186/s12987-017-0080-3

Schlagal, C. R., Dunn, T. J., Xu, P., Felsing, D. E., Merritt, C. R., Manja, S., Fox, R. G., Buffington, S. A., Saade, G., Dineley, K. T., Yu, Y., Cunningham, K. A., & Wu, P. (2022). Maternal opioid exposure culminates in perturbed murine neurodevelopment and hyperactive phonotype in adolescence. *Neuroscience, 463*, 272-287. https://doi.org/10.1016/j.neuroscience.2021.03.014

Schmahmann, J. D. (2019). The cerebellum and cognition. *Neuroscience Letters, 688*, 62-75. https://doi.org/10.1016/j.neulet.2018.07.005

Schweitzer, J. B., Riggins, T., Liang, X., Gallen, C., Kurup, P. K., Ross, T. J., Black, M. M., Nair, P., & Salmeron, B. J. (2015). Prenatal drug exposure to illicit drugs alters working memory-related brain activity and underlying network properties in adolescence. *Neurotoxicology and Teratology, 48*, 69-77. https://doi.org/10.1016/j.ntt.2015.02.002

Seghier, M. L. (2013). The angular gyrus: multiple functions and multiple subdivisions. *The Neuroscientist, 19*(1), 43-61. https://doi.org/10.117/1073858412440596

Sierpowska, J., Fernandez-Coello, A., Gomez-Andres, A., Camins, A., Castaner, S., Juncadella, M., Gabarros, A., & Rodriguez-Fornells, A. (2018). Involvement of the middle frontal gyrus in language switching as revealed by electrical stimulation mapping and functional magnetic resonance imaging in bilingual brain tumor patients. *Cortex, 99*, 78-92. https://doi.org/10.1016/j.cortex.2017.10.017

Sirnes, E., Griffiths, S. T., Aukland, S. M., Eide, G. E., Elgen, I. B., & Gundersen, H. (2018). Functional MRI in prenatally opioid-exposed children during a working memory-selective attention task. *Neurotoxicology and Teratology, 66*, 46-54. https://doi.org/10.1016/j.ntt.2018.01.010

Sirnes, E., Oltedal, L., Bartsch, H., Eide, E. E., Elgen, I. B., & Aukland, S. M. (2017). Brain morphology in school-aged children with prenatal opioid exposure: A structural MRI study. *Early Human Development, 106*, 33-39. https://doi.org/10.1016/j.earlhumdev.2017.01.009

Skumlien, M., Ibsen, I. O., Kesmodel, U. S., & Nygaard, E. (2020). Sex differences in early cognitive development after prenatal exposure to opioids. *Journal of Pediatric Psychology, 45*(5), 475-485. https://doi.org/10.1093/jpepsy/jsaa008

Sparrow, S. S., Cicchetti, D. V., & Balla, D. A. (2005). *Vineland Adaptive Behavior Scales, Second Edition (VABS-2): Survey Forms Manual.* American Guidance Service.

Spiel, C. F., Evans, S. W., & Langberg, J. M. (2014). Evaluating the content of individualized education programs and 504 Plans of young adolescents with attention deficit/hyperactivity disorder. *School Psychology Quarterly, 29*(4), 452-468. https://doi.org/10.1037/spq0000101

Stevens, S. A., Dudek, J., Koren, G., Nash, K., & Rovet, J. F. (2015). Social perspective taking and empathy in children with fetal alcohol spectrum disorders. *Journal of International Neuropsychological Society, 21*, 74-84. https://doi.org/10.1017/S1355617714001088

Stewart, R. D., Nelson, D. B., Adhikari, E. H., McIntire, D. D., Roberts, S. W., Dashe, J. S., & Sheffield, J. S. (2013). The obstetrical and neonatal impact of maternal opioid detoxification in pregnancy. *American Journal of Obstetrics & Gynecology, 209*(267), 1-5. https://doi.org/10.1016/j.ajog.2013.05.026

Strahan, A. E., Guy, G. P., Bohm, M., Frey, M., & Ko, J. Y. (2020). Neonatal abstinence syndrome incidence and health care costs in the United States, 2016. *JAMA Pediatrics, 174*(2), 200-202. https://doi.org/10.1001/jamapediatrics.2019.4791

Subedi, L., Huang, H., Pant, A., Westgate, P. M., Bada, H. S., Bauer, J. A., Giannone, P. J., & Sithisarn, T. (2017). Plasma brain-derived neurotrophic factor levels in newborn infants with neonatal abstinence syndrome. *Frontiers in Pediatrics, 5*(238), 1-7 https://doi.org/10.3389/fped.2017.00238

Substance Abuse and Mental Health Services Administration. (2020). *Key substance use and mental health indicators in the United States: Results from the 2019 national survey on drug use and health* (HHS Publication No. PEP20-07-01-001, NSDUH Series H-55). Rockville, MD: Center for Behavioral Health Statistics and Quality, Substance Abuse and Mental Health Services Administration. Retrieved from https://www.samhsa.gov/data/

Surran, B., Visintainer, P., Chamberlain, S., Kopcza, Shah, B., & Singh, R. (2013). Efficacy of clonidine versus phenobarbital in reducing neonatal morphine sulfate therapy days for neonatal abstinence syndrome: A prospective randomized clinical trial. *Journal of Perinatology, 33*, 954-959. https://doi.org/10.1038/jp.2013.95

Tabi, S., Heitner, S. A., Shivale, S., Minchenberg, S., Faraone, S. V., & Johnson, B. (2020). Opioid addiction/pregnancy and neonatal abstinence syndrome (NAS): A preliminary open-label study of buprenorphine maintenance and drug use targeted psychotherapy (DUST) on cessation of addictive drug use. *Frontiers in Psychiatry, 11*, 1-7. https://doi.org/10.3389/fpsyt.2020.563409

Terplan, M., Ramanadhan, S., Locke, A., Longinaker, N., & Lui, S. (2016). Psychosocial interventions for pregnant women in outpatient illicit drug treatment programs compared to other interventions. *Cochrane Database of Systematic Reviews, 4*, 1-73. https://doi.org/10.1002/14651858.CD006037.pub3

Thomas, S., Kelly, S., Mattson, S., & Riley, E. (1998). Comparison of social abilities of children with Fetal Alcohol Syndrome to those of children with similar IQ scores and normal controls. *Alcoholism: Clinical and Experimental Research, 22*(2), 528-533.

Timpson, W., Killoran, C., Maranda, L., Picarill, A., & Bloch-Salisbury, E. (2018). A quality improvement initiative to increase scoring consistency and accuracy of the Finnegan tool: Challenges in obtaining reliable assessments of drug withdrawal in neonatal abstinence syndrome. *Advanced Neonatal Care, 18*(1), 70-78. https://doi.org/10.1097/ANC.0000000000000441

Tolia, V. N., Patrick, S. W., Bennett, M. M., Murphy, K., Sousa, J., Smith, P. B., Clark, R. H., & Spitzer, A. R. (2015). Increasing incidence of the neonatal abstinence syndrome in U.S. neonatal ICUs. *The New England Journal of Medicine, 372*(22), 2218-2126. https://doi.org/10.1056/NEJMsa1500439

Towers, C. V., Hyatt, B. W., Visconti, K. C., Chernicky, L., Chattin, K., & Fortner, K. B. (2019a). Neonatal head circumference in newborns with neonatal abstinence syndrome. *Pediatrics, 143*(1), 1-7. https://doi.org/10.1542/peds.2018-0541

Towers, C. V., Katz, E., Weitz, B., & Visconti, K. (2019b). Use of naltrexone in treating opioid use disorder in pregnancy. *American Journal of Obstetrics & Gynecology, 222*(83), 83-91. https://doi.org/10.1016/j.ajog.2019.07.037

Travis, K. E., Leitner, Y., Feldman, H. M., & Ben-Shachar, M. (2015). Cerebellar white matter pathways are associated with reading skills in children and adolescents. *Human Brain Mapping, 36*(4), 1536-1553. https://doi.org/10.1002/hbm.22721

Tronick, E., Als, H., Adamson, L. Wise, S., & Brazelton, T. B. (1978). Infants response to entrapment between contradictory messages in face-to-face interaction. J*ournal of the American Academy of Child and Adolescent Psychiatry, 17*, 1-13.

Tronnes, J. N., Lupattelli, A., Handal, M., Skurtveit, S., Ystrom, E., & Nordeng, H. (2021). Association of timing and duration of prenatal analgesic opioid exposure with attention-deficit/hyperactivity disorder in children. *JAMA Network Open, 4*(9), 1-14. https://doi.org/10.1001/jamanetworkopen.2021.24324

Twisk, J., & de Vente, W. (2002). Attrition in longitudinal studies: How to deal with missing data. *Journal of Clinical Epidemiology, 55*(4), 329-337. https://doi.org/10.1016/S0895-4356(01)00476-0

Uebel, H., Wright, I. M., Burns, L., Hilder, L., Bajuk, B., Breen, C., Abdel-Latif, M. E., Feller, J. M., Falconer, J., Clews, S., Eastwood, J., & Oei, J. L. (2015). Reasons for rehospitalization in children who had neonatal abstinence syndrome. *Pediatrics, 136*(4), 812-820. https://doi.org/10.1542/peds.2014-2767

U.S. Department of Health and Human Services. (2021). *What is the U.S. opioid epidemic?*. https://www.hhs.gov/opioids/about-the-epidemic/index.html

Van Overwalle, F., D'aes, T., & Mariën, P. (2015). Social cognition and the cerebellum: A meta-analytic connectivity analysis. *Human Brain Mapping, 36*, 5137-5154. https://doi.org/10.1002/hbm.23002

Van Overwalle, F., DeConinck, S., Heleven, E., Perrotta, G., Oulad Ben Taib, N., Manto, M., & Mariën, P. (2019). The role of the cerebellum in reconstructing social action sequences: A pilot study. *Social Cognitive and Affective Neuroscience, 14*(5), 549-558. https://doi.org/10.1093/scan/nsz032

Vaurio, L., Riley, E. P., & Mattson, S. N. (2011). Neuropsychological comparison of children with heavy prenatal alcohol exposure and an IQ-matched comparison group. *Journal of the International Neuropsychological Society, 17*(3), 463-473. https://doi.org/10.1017/S1355617711000063

Vestal-Laborde, A. A., Eschenroeder, A. C., Bigbee, J. W., Robinson, S. E., & Sato-Bigbee, C. (2014). The opioid system and brain development: Effects of methadone on the oligodendrocyte lineage and the early stages of myelination. *Developmental Neuroscience, 36*, 409-421. https://doi.org/10.1159/000365074

Vishnubhotla, R. V., Zhao, Y., Wen, Q., Dietrich, J., Sokol, G. M., Sadhasivam, S., & Radhakrishnan, R. (2022). Brain structural connections in neonates with prenatal opioid exposure. *Frontiers in Neuroscience*, 1-14. https://doi.org/10.3389/fnins.2022.952322

Walhovd, K. B., Bjornebekk, A., Haabrekke, K., Siqveland, T., Slinning, K., Nygaard, E., Fjell, A. M., Due-Tonnessen, P., & Bjornerud, A. (2015). Child neuroanatomical, neurocognitive, and visual acuity outcomes with maternal opioid and polysubstance detoxification. *Pediatric Neurology, 52*(3), 326-332. https://doi.org/10.1016/j.pediatrneurol.2014.11.008

Walhovd, K. B., Westlye, L. T., Moe, V., Slinning, K., Due-Tonnessen, P., Bjornerud, A., van der Kouwe, A., Dale, A. M., & Fjell, A. M. (2010). White matter characteristics and cognition in prenatally opiate- and polysubstance-exposed children: A diffusion tensor imaging study. *American Journal of Neuroradiology, 31*, 894-900. https://doi.org/10.3174/ajnr.A1957

Ware, A. L., Crocker, N., O'Brien, J. W., Deweese, B. N., Roesch, S. C., Coles, C. D., Kable, J. A., May, P. A., Kalberg, W. O., Sowell, E. R., Jones, K. L., Riley, E. P., & Mattson, S. N. (2012). Executive function predicts adaptive behavior in children with histories of heavy prenatal alcohol exposure and attention deficit/hyperactivity disorder. *Alcoholism: Clinical and Experimental Research, 36*(8), 1431-1441. https://doi.org/10.1111/j.1530-0277.2011.01718.x

Weiner, K. S., & Zilles, K. (2016). The anatomical and functional specialization of the fusiform gyrus. *Neuropsychologia, 83*, 48-62. https://doi.org/10.1016/j.neuropsychologia.2015.06.033

Welle-Strand, G. K., Skurtveit, S., Jansson, L. M., Bakstad, B., Bjarko, L., & Ravndal, E. (2013). Breastfeeding reduces the need for withdrawal treatment in opioid-exposed infants. *ACTA Pediatrica, 102*, 1060-1066. https://doi.org/10.1111/apa.12378

Wechsler, D. (1974). *Handbook for Wechsler Intelligence Scale for Children—Revised (WISC-R)*. The Psychological Corporation.

Wechsler, D. (1989). *Manual for the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R)*. The Psychological Corporation.

Wechsler, D. (1991). *Wechsler Intelligence Scale for Children, Third Edition* (WISC-III). The Psychological Corporation.

Wechsler, D. (1997). *Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Manual*. The Psychological Corporation.

Wechsler, D. (2003). *WISC-IV Technical and Interpretive Manual*. The Psychological Association.

Wechsler, D. (2008). *Wechsler Adult Intelligence Scale, 4th edition* (WASI-IV) *Manual*. Pearson.

Wechsler, D. (2008). *Wechsler Preschool and Primary Scale Intelligence, Third Edition (WPPSI-III), Norsk version*. Harcourt Assessment.

Wechsler, D. (2012). *The Wechsler Preschool and Primary Scale of Intelligence, Fourth Edition (WPPSI-IV).* The Psychological Corporation.

Wechsler, D. (2014). *Wechsler Intelligence Scale for Children, Fifth Edition (WISC-V).* Pearson.

Whaley, S. E., O'Connor, M. J., & Gunderson, B. (2001). Comparison of the adaptive functioning of children prenatally exposed to alcohol to a nonexposed clinical sample. *Alcoholism: Clinical and Experimental Research, 25*(7), 1018-1024.

Whiteman, V. E., Salemi, J. L., Mogos, M. F., Cain, M. A., Aliyu, M. H., & Salihu, H. M. (2014). Maternal opioid drug use during pregnancy and its impact on perinatal morbidity, mortality, and the costs of medical care in the United States. *Journal of Pregnancy, 2014*, 1-8. https://doi.org/10.1155/2014/906723

Wiegand, S. L., Stringer, E. M., Stuebe, A. M., Jones, H., Seashore, C., & Thorp, J. (2016) Buprenorphine and naloxone compared with methadone treatment in pregnancy. *Obstetrics and Gynecology, 125*(2), 363-368. https://doi.org/10.1097/AOG.0000000000000640

Wilkinson, G. S. (1993). *Wide Range Achievement Test, Third Edition* (WRAT-3) *Administrative Manual*. The Psychological Corporation.

Williams, J. (2008). Basic opioid pharmacology. *British Journal of Pain, 1*(2), 2-5.

Winkelman, T. N., Villapiano, N., Kozhimannil, K. B., Davis, M. M., & Patrick, S. W. (2018). Incidence and costs of neonatal abstinence syndrome among infants with Medicaid: 2004-2014. *Pediatrics, 141*(4), 1-8. https://doi.org/10.1542.peds.2017-3520

World Health Organization. (2019). *International statistical classification of diseases and related health problems* (11th ed.). https://icd.who.int/

Wouldes, T. A., & Woodward, L. J. (2010). Maternal methadone dose during pregnancy and infant clinical outcome. *Neurotoxicology and Teratology, 32*, 406-413. https://doi.org/10.1016/j.ntt.2010.01.007

Wu, L., Zhu, H., & Swartz, M. S. (2016). Treatment utilization among person with opioid use disorder in the United States. *Drug and Alcohol Dependence, 169*, 117-127. https://doi.org/10.1016/j.drugalcdep.2016.10.015

Yeoh, S. L., Eastwood, J., Wright, I. M., Morton, R., Melhuish, E., Ward, M., & Oei, J. L. (2019). Cognitive and motor outcomes of children with prenatal opioid exposure: A systematic review and meta-analysis. *JAMA Pediatrics, 2*(7), 1-14. https://doi.org/10.1001/jamanetworkopen.2019.7025

Young, C. B., Reddy, V., & Sonne, J. (2022). *Neuroanatomy, basal ganglia*. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK537141/

Yuan, Q., Rubic, M., Seah, J., Rae, C., Wright, IMR, Kaltenbach, K., Feller, J. M., Abdel-Latif, M. E., Chu, C., & Oei, J. L. (2014). Do maternal opioids reduce neonatal regional brain volumes? A pilot study. *Journal of Perinatology, 34*, 909-913. https://doi.org/10.1038/jp.2014.111

Zedler, B.K., Mann, A. L., Kim, M. M., Amick, H. R., Joyce, A. R., Murrelle, E. L., & Jones, H. E. (2016). Buprenorphine compared with methadone to treat pregnant women with opioid use disorder: A systematic review and meta-analysis of safety in the mother, fetus and child. *Addiction, 111*, 2115-2128. https://doi.org/10.1111/add.13462

Zeitlin, S., Williamson, G. G., & Szczepanski, M. (1988). *Early Coping Inventory Manual*. Scholastic Testing Service.

Zhu, J. (1999). *Wechsler Abbreviated Scale of Intelligence (WASI): Manual*. Pearson.