Memory Profiles of Children and Youth with Prenatal Alcohol Exposure: The Potential Role of Postnatal Risks

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master thesis

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Memory Profiles of Children and Youth with Prenatal Alcohol Exposure: The Potential Role of Postnatal Risks

by

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Abstract

Fetal alcohol spectrum disorder (FASD) is a neurodevelopmental condition that results from prenatal alcohol exposure (PAE). PAE is commonly associated with potential congenital disabilities and developmental delays. Cognitive domains, including those integral for memory and learning, can also be compromised following PAE. In addition to PAE, individuals with FASD tend to experience other prenatal (i.e., exposure to other substances before birth) and postnatal adversities (i.e., maltreatment following birth) that can negatively impact mental health, adaptive functioning, and neurodevelopmental outcomes. To our knowledge, no study has investigated the immediate free and cued recall abilities of children and youth with PAE compared to those without PAE. The potential influence of additional postnatal adversities on memory deficits in individuals with PAE is another research area that has been relatively overlooked. The current study first explored the short-term verbal memory profiles of children and youth with PAE (n = 26) compared to those without PAE (n = 26) and examined if distinctions in memory abilities between these groups may be better accounted for by differences in cognitive functioning (IQ). Second, this study exclusively analyzed children and youth with PAE (n = 29) to investigate if elevated exposure to postnatal adversities would be associated with more profound memory deficits. Two separate samples of exposed and unexposed children and youth between the ages of 7 and 15 were analyzed. Overall, participants with and without PAE differed significantly in their free and cued memory recall abilities, with exposed children and youth recalling significantly fewer details on a story task. However, after controlling for intellectual functioning, these group differences were no longer statistically significant. Lastly, we found that children and youth with PAE who experienced moderate-high levels of postnatal exposures had similar memory abilities as children and youth with PAE who had absent-low
levels. Findings from the current study are consistent with the literature that documents verbal memory deficits within PAE populations; however, additional research on the potential associations between postnatal exposures and developmental outcomes within this population is needed. Areas for future research directions are discussed as well as study clinical implications and limitations.
Preface

This thesis is original, unpublished, independent work by the author, T. Wasylyshyn. The data reported in this study were covered by Review Ethics Board (REB) Certificate numbers REB17-0663 and REB13-1346, obtained by the University of Calgary Conjoint Health Ethics Board for the project “Mental health and brain alterations in children with multiple early risks” on May 28, 2021, and the project “Brain development in childhood and adolescence” on April 12, 2021.
Dedication

This work is dedicated to the neurodiverse children and youth I have had the pleasure of supporting and learning from over the years.
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It is with immense appreciation that I acknowledge the many individuals who have supported me throughout my graduate experience:

First and foremost, I would like to express my deepest gratitude to my supervisor, Dr. Carly McMorris, for her ongoing guidance, encouragement, and mentorship. I am continuously in awe of your ambitions and inspired by your motivation to make a difference in the lives of so many children and families. Thank you for your willingness to involve and support me in such meaningful work.

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Chapter 1: Introduction

Overview and Aims of Thesis

Fetal alcohol spectrum disorder (FASD) is a term used to describe a variety of conditions caused by PAE. Variances in timing, frequency, and amount of alcohol consumed during pregnancy contribute to the heterogeneous presentation of FASD (Glass & Mattson, 2017). While children and youth with PAE may slightly differ in their profile of abilities, in general, the brain abnormalities and neurodevelopmental deficits associated with PAE are considered to be widespread and complex (Cook et al., 2016; Lebel et al., 2011). Deficits in areas of verbal memory have been documented for children and youth with PAE (Crocker et al., 2011; Mattson et al., 1996; Mattson & Roebuck, 2002; Richardson et al., 2002; Willoughby et al., 2008); however, certain areas remain unexplored. While deficits in immediate free recall have been observed, cued recall ability has only been assessed, to our knowledge, following a delay. As such, the potential differences between exposed and unexposed children and youth on measures of both free and cued immediate recall are not well understood. In addition, as cognitive functioning is often compromised by PAE (De L. Ferreira & Cruz, 2017), investigating if memory differences between exposed and unexposed groups remain after controlling for FSIQ may provide further insight.

Children and youth with PAE commonly endure various adverse postnatal experiences, which can negatively impact several domains of functioning (Price et al., 2017). However, only one study appears to have investigated and determined the influence of such adverse experiences on memory abilities (Henry et al., 2007). Specifically, Henry and colleagues (2007) found that memory deficits were more common in children with both PAE and trauma exposures compared to trauma-exposed children who did not have PAE. However, all the participants in this study
had similar experiences of trauma, and the specific memory domains that were impaired remain unclear. To our knowledge, no study has compared children and youth with PAE and differing levels of adverse experience. This would suggest that the potential associations between postnatal exposures and memory deficits in children and youth with PAE is an area that has largely been overlooked, despite most individuals with PAE experiencing some sort of adverse exposure postnatally.

Using the characterization tool developed by Lebel and colleagues (2019), this study investigated the potential associations between postnatal adversities (i.e., abuse, neglect, care transitions, food/housing/income insecurity) and memory ability in children and youth with PAE. More specifically, the two main aims of this thesis were to: 1) observe differences in free and cued immediate memory recall between children and youth with and without PAE (when controlling and not controlling for IQ); and 2) explore if elevated levels of exposure to postnatal adversities would be associated with more significant memory deficits in children and youth with PAE.
Chapter 2: Literature Review

Fetal alcohol spectrum disorder (FASD) is a neurodevelopmental disorder caused by prenatal alcohol exposure (PAE). Alcohol is a teratogen, and when consumed during pregnancy, it can harm the developing fetus by causing irreversible damage to the brain and other organs (Popova et al., 2018). Currently, there is no known safe amount of alcohol to consume while pregnant (Centers for Disease Control and Prevention, 2021); however, PAE continues to be a substantial public health concern (O’Connor, 2014). Specifically, Tough and colleagues (2006) found that 50% of women in Alberta reported consuming alcohol before discovering they were pregnant, and 18% continued to consume alcohol after their pregnancy was confirmed (Tough et al., 2006). Worldwide, it is projected that approximately 10% of women in the general population consume alcohol during pregnancy, contributing to approximately 119,000 children born with fetal alcohol syndrome (FAS) each year (Popova et al., 2017). Despite being considered the leading preventable cause of congenital disabilities (Williams et al., 2015) and developmental delay among Canadians (Popova et al., 2018), in North America, it is estimated that FASD affects 2-5% of all births (May et al., 2018; Popova et al., 2018). Fetal alcohol spectrum disorder has considerable financial implications as children with PAE often require long-term assistance from various services, such as specialized healthcare and education (Popova et al., 2013, 2015). In 2013, the costs associated with productivity loss, corrections, and health care were the most prominent factors contributing to the $1.8B costs associated with FASD in Canada (Popova et al., 2015). On an individual level, the estimated lifetime costs of FASD in Canada are greater than $1M per person (Stade et al., 2007; Thanh & Jonsson, 2009).
Fetal Alcohol Spectrum Disorder (FASD)

Prior to 2016, FASD was a non-diagnostic term encompassing several alcohol-related diagnoses that differed in severity and physical presentation. These diagnoses included fetal alcohol syndrome (FAS), partial fetal alcohol syndrome (pFAS), alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD; Chudley et al., 2005). In 2005, the Canadian Guidelines outlined by Chudley et al. (2005) integrated the 4-Digit Diagnostic Code (Astley & Clarren, 2000) with the classifications outlined by the Institute of Medicine (IOM; Stratton et al., 1996). The IOM initially described the four key features of PAE as growth deficiency, brain dysfunction, facial features, and alcohol level recognition (Stratton et al., 1996). Shortly following, Astley and Clarren (2000) developed the 4-Digit Diagnostic Coding System which allowed for a more measurable approach to these four features. As such, these features were rated on a 4-point Likert scale as either having a (1) normal, (2) unknown/mild, (3) moderate, or (4) severe presentation (Astley, 2004). An objective in harmonizing these two diagnostic systems was that the IOM criteria could be used to describe the diagnosis, whereas the 4-Digit Code could be used to assess and objectively measure the features (Chudley et al., 2005).

The need for a multidisciplinary approach in assessing for FASD was also outlined by the 2005 Canadian guidelines (Chudley et al., 2005). These guidelines, endorsed by the Public Health Agency of Canada, recommended the screening of all pregnant and post-partum women for alcohol use, and that appropriate referrals for assessment be made when PAE was identified. Consistent with these guidelines, it was recommended that the diagnostic process also include a physical examination, neurobehavioral assessment(s), differential diagnosis, and confirmation of PAE (with the exception of a FAS diagnosis; Chudley et al., 2005).
In 2013, the Diagnostic and Statistical Manual of Mental Disorders – Fifth Edition (DSM-5; American Psychiatric Association, 2013) included “neurobehavioral disorder associated with prenatal alcohol exposure” (ND-PAE) as a recognized condition. This term has since been used to encompass the various disabilities that are associated with PAE (i.e., FAS, ARND, etc.; Olson, 2015). The inclusion of ND-PAE in the DSM-5 was recognized as a significant step in allowing for a wider identification of individuals with PAE (Olson, 2015).

Recently, Cook et al. (2016) revised the 2005 guidelines (Chudley et al., 2005) for diagnosing FASD across the lifespan. This revision was deemed essential as the field had evolved and additional research on FASD had emerged (Cook et al., 2016). As a result, several recommendations geared towards multidisciplinary diagnostic teams in Canada were put forth. The revised guidelines outlined that after screening individuals who may have FASD and making the appropriate referrals, a medical assessment (including family history, maternal alcohol history, a physical examination, and differential diagnosis) should be conducted (Cook et al., 2016). Consistent with previous guidelines, the University of Washington Lip-Philtrum Guide is to be used to objectively evaluate two of the three facial features required for a diagnosis (Chudley et al., 2005; Cook et al., 2016). To diagnose FASD, three sentinel facial features must be present: a palpebral fissure length ≥ 2 standard deviations (SDs) below the mean, and both the philtrum and upper lip rated 4 or 5 on the 5-point scale outlined by the University of Washington Lip–Philtrum Guide (Astley & Clarren, 2001). As the presence of all three features is highly specific to PAE in utero, confirmation of exposure is not necessary for a diagnosis of FASD if these three features are all present (Astley, 2013; Cook et al., 2016). If these features are not present, FASD can still be diagnosed with a confirmation of PAE and evidence of impairment in ≥ 3 central nervous system (CNS) domains (Cook et al., 2016). Of
importance, the estimated dose of PAE must be at a level known to be associated with neurodevelopmental effects (Cook et al., 2016).

The neurodevelopmental deficits associated with FASD are intricate (Cook et al., 2016). Therefore, no single neuropsychological profile is representative of all individuals that would meet the criteria for a diagnosis of FASD (Kodituwakku, 2007; Manning & Eugene, 2007; Nash et al., 2008; Paintner et al., 2012a; Riley et al., 2011). Consistent with the 2005 guidelines (Chudley et al., 2005), a diagnosis of FASD continues to require significant deficits as defined by scores that are $\geq 2$ SDs below the mean in at least three CNS domains: motor skills, neuroanatomy/neurophysiology, cognition, language, academic achievement, memory, attention, executive function, affect regulation, and adaptive behaviour or social skills/communication (Cook et al., 2016). Impairments in neuroanatomy or neurophysiology are considered present if: orbitofrontal head circumference is below the clinical cut-off ($\geq 2$ SDs below the mean), the individual has been diagnosed with a seizure disorder, not due to known postnatal influences, or brain imaging shows convincing evidence of structural brain abnormalities known to be associated with PAE and other etiologies have been ruled out (Cook et al., 2016; Glass et al., 2014; Mattson et al., 2001). After consideration of the requirements and careful evaluation, FASD is diagnosable if the individual meets either of the two criteria: FASD with sentinel facial features (previously FAS) or FASD without sentinel facial features (replacing pFAS and ARND). Alternatively, at-risk for neurodevelopmental disorder and FASD, associated with PAE, is a designation used to describe individuals who have confirmed PAE and neurodevelopmental concerns but fail to meet criteria for either of the two FASD diagnoses (Cook et al., 2016).

Throughout this thesis, the term FASD is used to describe children and youth with confirmed PAE. Individuals with PAE have varying ability levels, and their diagnoses fall along
the FASD spectrum based on presentation and severity. Of note, within the literature described in this thesis, researchers use different terminologies to describe participants depending on the nature of their sample. More specific terms (i.e., FAS) will be used throughout the document that are consistent with the language used by researchers in their studies.

**Challenges in Diagnosing FASD**

A diagnosis of FASD is an important step in improving outcomes for the affected individual (Cook et al., 2016); however, the process is not without its challenges. Obtaining an accurate history of alcohol consumption during pregnancy can be challenging, especially in situations where the child no longer has contact with their birth mother, as this necessitates reliance on indirect reports of maternal alcohol use (Astley, 2006). Even if a history of alcohol consumption during pregnancy can be obtained, maternal self-report can sometimes be unreliable and under-estimated (Benz et al., 2009). Alcohol consumption may be under-reported due to forgetfulness (Astley, 2006), or under-reporting may be a product of the stigma associated with women’s drinking behaviours during pregnancy (Pei et al., 2017). In Canada, pregnant women who use substances are often scrutinized, judged, and met with unsympathetic attitudes (Greaves et al., 2002; Poole and Dell, 2005; Rutman et al., 2000). As a result of the stigma associated with maternal substance use, estimating the prevalence of FASD involves various methodological challenges (Pei et al., 2017).

Accurately assessing for and diagnosing FASD is often challenging due to the complex clinical presentations of children and youth with FASD. Variances in timing, frequency, and amount of alcohol consumed during pregnancy all contribute to the heterogeneous presentation of FASD, and consequently, individuals with PAE vary significantly in their cognitive and behavioural profiles (Glass & Mattson, 2017). The substantial heterogeneity exhibited by
children and youth makes accurately identifying FASD more challenging for clinicians. The significant overlap in the presentation of FASD and other neurodevelopmental disorders, such as attention-deficit/hyperactivity disorder (ADHD), can also have implications in accurately diagnosing alcohol-affected individuals (Rasmussen et al., 2010). For these reasons, differentiation of FASD from other disorders can also pose challenges.

Lastly, FASD is not widely recognized by health care practitioners (Tough et al., 2003). In a Canadian survey, only 60% of health care workers were able to identify the three fundamental diagnostic features of FASD (Clarke et al., 2005). As such, clinicians may underdiagnose or misdiagnose in situations where a diagnosis of FASD would be appropriate. Lastly, there are multiple barriers to widely implementing FASD screening processes, including accessibility, financial cost, expertise, and cultural appropriateness (Benz et al., 2009). Without relevant screening, a diagnosis is unlikely, and as a result, children and youth may be further restricted in their access to essential services and interventions. Taken together, the absence of widespread recognition, lack of diagnostic consensus, and various barriers to screening likely create challenges for both families and clinicians and may ultimately prevent a diagnosis of FASD altogether.

**Prognosis**

While research on the developmental trajectory of FASD is relatively limited, there is some evidence that PAE contributes to a variety of lifelong consequences. The brain abnormalities associated with PAE are widespread (Lebel et al., 2011) and permanent (Canada FASD Research Network, 2021), and many of the physical and neurobehavioral features observed in alcohol-affected children are present in adulthood (Moore & Riley, 2015). Compared to the general population, the life expectancy of individuals with FASD is substantially lower
(~34 years) than that of the general population (~79 years for males, ~83 years for females; Statistics Canada, 2011), with the leading causes of death being suicide and accidents (Thanh & Jonsson, 2016).

Although little is known about the impact of PAE on adults (Moore & Riley, 2015), studies using animal models suggest that individuals with FASD may become more susceptible to disease as they age (Murugan et al., 2013; Polanco et al., 2010). Additionally, individuals with FASD are at an increased risk for later adversity (i.e., mental health problems, trouble with the law) if there is a lack of early diagnosis and intervention (Streissguth et al., 2004). The risk for developing co-occurring or secondary conditions, such as ADHD or school disruptions, is heightened when FASD is misdiagnosed or the diagnosis is delayed (Williams et al., 2015). Despite the high rates of adverse life outcomes observed in this population, receiving a diagnosis at an early age and having a stable home environment may potentially act as protective factors against adverse outcomes (Streissguth, 2004).

**Associated Physical Features**

When diagnosing FASD, the primary objective of the physical assessment is to distinguish between the specific physical features that are unique to PAE and those that may be present as a result of other causes (Chudley et al., 2005; Cook et al., 2016). While the Canadian diagnostic criteria (Cook et al., 2016) outlines three sentinel facial features associated with a diagnosis of FASD, there are several additional physical features that are characteristic of PAE. Additional congenital disabilities associated with PAE involve structural changes to the ears, eyes, palmar creases, fingers, and joints, and individuals with FASD are also at a higher risk for congenital heart defects and facial clefts (DeRoo et al., 2008; Jones et al., 2010; O'Leary et al., 2013a). The effects of PAE may also contribute to growth impairments in height and weight.
(Popova et al., 2013). In addition, individuals with FASD may present with visual and auditory deficits, heart irregularities, urogenital defects (i.e., of the urinary and/or genital organs) and skeletal abnormalities (Popova et al., 2016). Notably, the presence and severity of congenital disabilities depend on multiple factors, including the pattern and quantity of alcohol consumed as well as the developmental stage of the embryo when exposure occurred (Jacobson & Jacobson, 1994, 1999; O’Leary-Moore et al., 2011; Sood et al., 2001; Sulik, 2014). Another important consideration is that the common physical abnormalities are not always present, and consequently, FASD is often referred to as the ‘invisible disability’ (Rasmussen et al., 2008).

**Comorbidities**

With age, certain physical anomalies in children and youth with FAS may become less pronounced (Rasmussen et al., 2008); however, mental health symptoms are more incessant and may worsen (Spohr & Steinhausen, 1987; Spohr et al., 1993; Steinhausen & Spohr, 1998). Compared to individuals without FASD, those with FASD have a greater incidence of comorbid mental health issues (Mattson et al., 2011; O’Connor, 2014; Pei et al., 2011a). Specifically, mental health disorders are seen in over 90% of individuals with FASD (Kodituwakku, 2007; May et al., 2014; Pei et al., 2011a), compared to 20% in the general population (Smetanin et al., 2011). Fryer et al. (2007) compared the prevalence of mental health disorders in children with heavy PAE to unexposed controls. Using diagnostic interviews based on DSM-IV diagnostic criteria, Fryer and colleagues (2007) found that 97% of the children with heavy PAE met criteria for at least one Axis I disorder compared to 40% of age, sex, and socioeconomic status matched unexposed controls. Significant group differences were seen in the following categories: ADHD, depressive disorders, oppositional defiant disorders, conduct disorders, and specific phobias. Of note, the largest group differences were observed in ADHD, such that 94% of children with PAE
met the criteria for ADHD. Similarly, in a scoping review, Pei and colleagues (2011a) reported that both externalizing (e.g., ADHD) and internalizing (e.g., depression) disorders are frequently experienced in individuals with FASD.

**Secondary Disabilities**

Secondary disabilities, including disrupted school experiences, are not present at birth but instead may result from the presence of FASD, likely in interaction with environmental factors (Rasmussen et al., 2008; Streissguth, 1997). For individuals with FASD, secondary disabilities are generally common (Moore and Riley, 2015). Sexually deviant behaviours, involvement with the law, problems with employment, and dependent living are all examples of potential secondary disabilities that may occur because of the primary disabilities (i.e., inconsistent cognitive processing) associated with FASD (Centre for Addiction and Mental Health, n.d.). The elevated rates of secondary disabilities and mental health challenges seen in individuals with PAE (Streissguth et al., 2004) likely impact their ability to live independently in the future (Clark et al., 2004). Streissguth and colleagues (2004) measured common secondary disabilities in a referred clinical sample of individuals with FAS or fetal alcohol effects (FAE). These researchers reported increases in inappropriate sexual behaviours (from 39% in children to 48% in adolescents), disrupted school experiences for 14% of children and 61% of adolescents and adults (with the most frequent behavioural problems being disruptiveness and difficulty getting along with peers), trouble with the law for 14% of children and 60% of adolescents and adults, inpatient hospitalization for 8% of children and 50% of adolescents and adults (detention, jail, prison, or a psychiatric or alcohol/drug inpatient setting), and alcohol or drug problems for 35% of the participants 12 years of age and older (Streissguth et al., 2004). Taken together, it is
evident that children with PAE are at a heightened risk for experiencing secondary disabilities, which likely have negative implications for school and daily functioning.

**School and Adaptive Functioning**

Prenatal alcohol exposure can contribute to a variety of cognitive and behavioural deficits that may influence a child’s ability to learn and succeed in a classroom environment; thus, students with FASD often require extra support (Pei et al., 2017). While the severity of impairment varies among alcohol-exposed children, cognitive deficits in memory, executive functioning, visuospatial processing, attention, and language are relatively common in individuals with FASD (Coles, 2011; Davis et al., 2011; Flak et al., 2013; Kodituwakku, 2009; Mattson et al., 2011, 2013; Rasmussen, 2005; Streissguth et al., 1996). Academic challenges, especially in mathematics, have been observed for children with PAE between 6 and 14 years of age (Goldschmidt et al., 1996, 2004; O’Leary et al., 2013b; Streissguth et al., 1994). There is also evidence to suggest that PAE contributes to deficiencies in early reading ability and sequential memory (Coles et al., 1991). Various studies have also established that children with PAE experience deficits in the verbal encoding of information (Coles et al., 2010; Crocker et al., 2011; Kully-Martins et al., 2012; Rasmussen et al., 2009; Roebuck-Spencer & Mattson, 2004), which may underlie certain academic challenges.

Difficulties in planning, organizing (Coggins et al., 1998), analyzing social situations (McGee et al., 2008), understanding different perspectives (Stevens et al., 2015), paying attention (Streissguth et al., 1996, 2004), and following directions (Streissguth et al., 2004) are also seen in children affected by PAE. In addition to the deficits that appear to be a consequence of PAE, Pei et al. (2021) found that when compared to children with other neurodevelopmental disabilities (NDDs), a greater percentage of children with FASD had challenges in their home
environment that interfered with their classroom functioning. The constellation of effects resulting from, and in conjunction with PAE, can have a detrimental impact on a child’s ability to learn, consequently putting them at risk for academic problems (Coles, 2011; Hussong et al., 2010; Koponen et al., 2009). Thus, children with FASD generally require additional educational supports to ensure academic success (Millians, 2015).

Adaptive functioning, otherwise defined as the skills necessary for independent living, continues to be one of the most substantial deficits in children and youth with FASD (Kaemingk & Paquette, 1999; Streissguth et al., 2004), which likely contributes to the high rates of secondary disabilities (Rasmussen, 2008). In a sample of adolescents and adults with FAS/FAE, Streissguth and colleagues (1991) determined that these individuals had an average level of adaptive functioning of approximately seven years of age. Of note, while daily living skills appeared to be a relative strength, the most significant deficits were observed in the socialization domain (Streissguth et al., 1991). These findings are in line with additional studies that have deemed socialization to be the most affected domain of adaptive functioning in PAE populations (Crocker et al., 2009; McGee et al., 2008, 2009; Thomas et al., 1998; Whaley et al., 2001). Further, when compared to unexposed children, researchers have found that adaptive functioning appears to worsen with age in those with PAE (Crocker et al., 2009; Thomas et al., 1998; Whaley et al., 2001). This worsening trend may explain why individuals with FASD commonly experience great difficulty with employment and independent living later on in life (Spohr et al., 2007).

**Intellectual Functioning**

Overall, intellectual functioning in individuals with FASD is highly heterogeneous. For example, De L. Ferreira and Cruz (2017) recently reviewed 23 studies that assessed the overall
intellectual functioning of individuals with PAE and found that in most of the studies (60.9%), those prenatally exposed to alcohol had an IQ below 90 (or scores that fall below the average range). Ten of the studies in the review by De L. Ferreira and Cruz (2017) compared intellectual functioning between PAE and unexposed groups, and in 90% of these studies, significant differences pertaining to global IQ were observed. Consistent with previous literature (Kodituwakku, 2009; May et al., 2013), De L. Ferreira and Cruz (2017) found that those with the most severe presentation (i.e., FAS) had greater deficits in general, verbal, and non-verbal IQ (Dalen et al., 2009; Foroud et al., 2012; Molteno et al., 2010; Woods et al., 2015), when compared to other individuals with PAE. These findings would suggest that challenges in intellectual functioning appear to follow the spectrum of FASD, as the extent of impairment tends to present differently relative to the severity of the FASD diagnosis (De L. Ferreira & Cruz, 2017). Lastly, an important consideration when interpreting FSIQ (Full-Scale IQ) within this population is that many individuals with FASD have an uneven profile of abilities (Streissguth & O’Malley, 2000), which potentially renders their FSIQ unrepresentative of their true cognitive functioning (Mukherjee et al., 2006).

**Neurological Features**

The CNS is the system with the largest developmental window as the fetal brain develops throughout pregnancy; thus, the CNS has the greatest potential for developmental anomalies if alcohol is consumed during pregnancy (Paintner et al., 2012b). Exposure to alcohol prenatally can cause brain malformations by interrupting the normal development of brain cells and structures (Popova et al., 2018). Although it has been challenging to outline critical periods in human populations (Popova et al., 2018), research using animal models has demonstrated that the brain continues to be vulnerable to the effects of alcohol throughout all stages of
development (Sulik, 2014). Furthermore, susceptibility to damage due to alcohol exposure does not appear to be limited to a specific brain region (Sulik, 2014); instead, the teratogenic effects appear to affect most areas of the brain (Lebel et al., 2011).

In a review on structural magnetic resonance imaging (MRI), studies of brain abnormalities in individuals with PAE, Lebel and colleagues (2011) have reported a consistent pattern of abnormalities within the literature. Reductions in brain volume and malformations of the corpus callosum were among the most commonly observed anomalies (Lebel et al., 2011), as well as reductions in cerebral and cerebellar volumes and volumes of white and gray matter (Lebel et al., 2011). Interestingly, these researchers note that the only area of the brain that remains relatively spared from the adverse effects of PAE is the occipital lobe, a critical region for vision (Lebel et al., 2011). These findings were replicated in a more recent review that synthesized the existing MRI literature on the effects of PAE on the brain (Donald et al., 2015). Consistent with Lebel et al. (2011), Donald and colleagues (2015) found that most studies reported smaller total brain volume as well as white and gray matter in specific regions. Most uniformly reported were changes in the shape and volume of the corpus callosum and smaller volumes of the basal ganglia and hippocampus (Donald et al., 2015).

The hippocampus, a region of the brain that is critical for learning and memory, is especially vulnerable to the teratogenic effects of prenatal alcohol exposure (Autti-Rämö et al., 2007; Coles & Li, 2011; Fontaine et al., 2016; Willoughby et al., 2008). Researchers have established that in unexposed populations, hippocampal volume increases throughout late childhood and adolescence (Benes et al., 1994; Giedd et al., 1996; Suzuki et al., 2005). However, in a study comparing children with PAE to unexposed children, Willoughby et al. (2008) found preliminary evidence to suggest that PAE may have an association with long-term abnormalities
in the development of the hippocampus, as hippocampal volume only increased significantly with age in unexposed participants. In addition, Archibald et al. (2001) found greater reductions in hippocampal volume (proportional to overall brain size reduction) in children with FAS when compared to those with PAE and no facial dysmorphology, suggesting associations between the quantity of alcohol consumption and brain volume in this region. Reduced hippocampal volumes were also endorsed by Riikonen et al. (2005, 2007), as well as hippocampal asymmetry (smaller left volume), in children with PAE in comparison to unexposed children. Autti-Rämö et al. (2007) also found that the left hippocampus is especially prone to thinning in children with PAE. To this end, hippocampal development appears to remain adversely impacted long after the PAE occurs (Willoughby et al., 2008).

**Memory**

In their seminal work, Atkinson and Shiffrin (1968) proposed that memory involves three specific stages: sensory, short-term, and long-term. Once sensory input is received from the environment, it enters sensory memory, where it is briefly stored (Stangor & Walinga, 2014). After entering sensory memory, unless the information is attended to, it is forgotten; however, if attention is given to the information, it may pass onto short-term memory (Stangor & Walinga, 2014). Short-term memory refers to the place where small amounts of information may be temporarily stored, usually for less than a minute (Baddeley, 1990). Once information enters short-term memory, it becomes available to be processed (Stangor & Walinga, 2014). Information can then be maintained in short-term memory by using working memory to rehearse the information (Stangor & Walinga, 2014).

The terms short-term memory and working memory are often used interchangeably, and although they are not the same, it is suggested that they are not entirely distinct (Cowan, 2008). It
is understood that, unlike short-term memory, working memory is not a temporary store of memory but instead a set of memory procedures (Stangor & Walinga, 2014). Thus, working memory can be understood as the process by which an individual makes sense of and manipulates information in their short-term memory. Memories in short-term storage may be transformed into long-term memories through the process of consolidation (Squire et al., 2015). Long-term memory has a very large capacity, and once information enters, it can be held for years; however, some information can be lost over time (Stangor & Walinga, 2014; Wang et al., 2003).

In addition to these different memory stores, memory also involves three distinct processes: encoding, storing, and retrieval (Melton, 1963). Encoding refers to the initial input of information, storage refers to the retention of encoded information over time, and retrieval is the ability to access the stored information (McDermott & Roediger, 2021). It is understood that all three stages of the memory process must be intact to remember and recall specific information successfully (McDermott & Roediger, 2021). However, when retrieving information, forgetting or misremembering are two common errors that may occur (McDermott & Roediger, 2021). As all three memory processes are highly dependent on each other, when an individual forgets or misremembers information, determining the stage in which the error occurred is often difficult (McDermott & Roediger, 2021).

To summarize, the memory process is multifaceted and involves a variety of mechanisms. While there are many intricate areas of memory, for the purposes of the current study, emphasis will be placed on the domains of short-term and working memory to observe how these areas may be impacted by PAE and postnatal risks. Specifically, within the short-term
memory domain, this study investigates verbal memory, or memory for information that is provided orally.

**Memory Deficits in Children with PAE**

Structural brain malformations and irregularities often contribute to negative neurobehavioral outcomes. Commonly endorsed among these adverse outcomes are impairments in areas of learning and memory (Mattson et al., 1996; Pei et al., 2008; Roebuck-Spencer & Mattson, 2004). Children with FASD display a relatively complex configuration of memory challenges (Wheeler et al., 2011), and these individuals often exhibit weaker memory function in comparison to unexposed children (Manji et al., 2009; Mattson et al., 1996; Mattson & Riley, 1999; Pei et al., 2011b; Rasmussen et al., 2008; Willford et al., 2004). Areas such as visual and verbal memory (Girard et al., 2000; Mattson et al., 1996; Mattson & Riley, 1999; Rasmussen et al., 2004, 2013; Streissguth et al., 1989) and working memory (Glass et al., 2013; Green, 2007; Hemington & Reynolds, 2014; Kodituwakku, 2009; Pei et al., 2011b; Rasmussen, 2005) are specifically impacted in individuals with FASD.

**Verbal Recall.** Researchers have found that children and youth with PAE between 5 and 16 years of age have difficulties in verbal memory; that is, when provided with verbal information, they often have difficulty later recalling this information (Mattson et al., 1996; Mattson & Roebuck, 2002). Verbal memory tasks may include two types of recall: free recall and cued recall. *Free recall* tasks require individuals to remember and reproduce previously provided information in no specific order (i.e., crayons, marbles, blocks), whereas *cued recall* tasks provide additional cues (i.e., verbalizing “things to play with”) to help facilitate recall. As such, cued recall tasks are generally understood to be less challenging when compared to free recall tasks. In children with PAE, the California Verbal Learning Test – Children’s Version
CVLT-C), a measure of verbal learning and memory, has commonly been used to observe the influence of alcohol exposure on memory recall. A consistent finding is that when compared to unexposed children, those with PAE (5-16 years of age) have difficulty with free recall when verbally presented with a list of words (Crocker et al., 2011; Mattson et al., 1996). In addition, children in this age range with PAE tend to make more intrusion (i.e., recall of an item that is not presented) and perseverative (i.e., repetition of a previous response) errors than those without PAE (Mattson et al., 1996).

Interestingly, some evidence suggests that there may be differences in the verbal recall abilities of children with PAE based on the format in which the verbal information is provided. That is, Pei et al. (2008) found that children (9-16 years of age) with FASD exhibited greater difficulties in their recall ability for word-pair information compared to story information. However, while children with FASD exhibited stronger recall ability on the story task, they also recalled more incorrect information with a tendency to “add-in” information that made sense to them (Pei et al., 2008). While additional inaccurate information was not penalized on the story task, perseverative errors were penalized on the word-pair task; thus, scoring differences for these types of errors may have impacted performance (Pei et al., 2008). A plausible explanation for the differences observed in these two formats may also be partly due to the nature of the task (Willford et al., 2004). While stories provide a context in which the information can be remembered, word tasks require the individual to generate their own context for the verbal information they receive (Willford et al., 2004).

Furthermore, in studies that contrast performance among children (9-15 years of age) with and without FASD, significantly lower scores on both story and word-pair recall tasks have been observed in children with FASD (Willoughby et al., 2008). When investigating the
influence of PAE on story recall, PAE was associated with lower scores on a story memory task in children 10 years of age (Richardson et al., 2002); however, within the same cohort of participants, light to moderate PAE was not associated with deficits in story memory in 14-year-old youth (Willford et al., 2004). Ultimately, these relative age differences observed in light to moderate PAE populations may suggest that story recall ability has the potential to improve as a child gets older (Mattson et al., 2011); however, further research is needed to further understand this association.

Several studies have compared children with and without PAE on their recall ability; however, there are limitations to the previous research that impact generalizability. One limitation is whether IQ (intellectual functioning) is considered when comparing exposed and unexposed children’s memory performance. For example, Crocker and colleagues (2011) found group differences on the CVLT-C learning trials amongst unexposed children, unexposed children with ADHD, and children with both heavy PAE and ADHD (7-14 years of age), such that children with heavy PAE and ADHD exhibited the most difficulty in their ability to recall words. However, despite identifying group differences in intellectual functioning, IQ was not included as a covariate in the study. This is a potential limitation of the study, as it is difficult to determine if the differences observed would have been better explained by differences in intellectual functioning. Similarly, despite identifying significant differences in IQ and deficits in recall when comparing exposed to unexposed children (8-16 years of age), intellectual functioning was also not controlled for in the work of Mattson and Roebuck (2002). In studies where IQ was not controlled for, group differences in recall ability are apparent. However, in studies that control for IQ when analyzing group differences in recall ability, the results tend to vary. Two similar studies explored CVLT-C performance in alcohol-exposed and unexposed
children (between 5 and 16 years of age) after matching participants on IQ (Mattson et al., 1996; Vaurio et al., 2011). While free recall ability was not significantly different between the two groups in the study by Mattson et al. (1996), in the second study, differences in the total number of words recalled remained significant (Vaurio et al., 2011).

As a general trend, studies have either controlled or not accounted for IQ differences when investigating recall ability amongst exposed and unexposed populations. One exception is the study by Mattson et al. (1996), where significant differences in recall ability were observed prior to matching participants on mental age. However, most studies have not analyzed these potential differences. As such, comparisons on findings can only be made between most studies and not within. For this reason, investigating group differences in both circumstances (i.e., controlling and not controlling for IQ) within the same sample may provide further insight.

Another limitation of the existing literature is that most studies have primarily used the CVLT-C as a measure of verbal learning and memory. This is problematic as the CVLT-C does not include a trial that measures cued recall ability before a delay. For this reason, an area that has been largely overlooked is the potential differences between exposed and unexposed children on measures of both free and cued immediate recall. In addition, it is suggested that tasks such as those on the CVLT-C may favour verbal information retention, thereby increasing performance, as these tasks involve the implicit learning strategy of semantic categorization (Mattson & Roebuck, 2002; Roebuck-Spencer & Mattson, 2004). Of note, retention was not spared for children with FASD (9-16 years of age) on a word-list learning task that lacked an implicit learning strategy (Roebuck-Spencer & Mattson, 2004). For these reasons, it would be beneficial for future research to explore performance on both immediate free and cued recall ability within this population using a measure that does not provide as much retention support.
Verbal Learning. Compared to children without PAE, children between 5-16 years of age with PAE learn fewer words on the learning trials of the CVLT-C (Crocker et al., 2011; Mattson et al., 1996); however, there is evidence to suggest that children in this age range with and without PAE exhibit similar recall abilities when the number of words initially learned is controlled for (Mattson et al., 1996, 1998; Mattson & Roebuck, 2002). As such, some researchers have proposed that memory deficits seen in the PAE population may be largely rooted in the process of verbal encoding, or the first step in the memory process, which likely indicates that alcohol-exposed children have difficulty acquiring new information when it is presented in a verbal format (Crocker et al., 2011; Mattson et al., 1996; Mattson & Roebuck, 2002; Pei et al., 2008; Willoughby et al., 2008). Thus, the memory deficit in individuals with PAE may occur in the initial learning stage versus later processing stages.

Working Memory. Across age groups, children and youth with PAE commonly exhibit deficits in working memory, whereby they struggle to hold and manipulate information as required by a specific task (Burden et al., 2005; Green et al., 2009; Jacobson et al., 1998; Kodituwakku et al., 1995; Olson et al., 1998; O’Malley & Nanson, 2002; Rasmussen, 2005; Rasmussen et al., 2011; Streissguth et al., 1990). Streissguth et al. (1990) found that out of all subtests on the Wechsler Intelligence Scale for Children – Revised (WISC-R), the two subtests most highly associated with PAE were Arithmetic and Digit Span. These subtests, which require the manipulation of information, were negatively correlated with PAE in a sample of 6–8-year-olds (Streissguth et al., 1990), suggesting an inverse association. More recently, Aragón and colleagues (2008) found significant differences on the Digit Span subtest of the WISC-IV (Wechsler Intelligence Scale for Children – IV) when comparing children with FASD to those without FASD (aged 7-17 years), whereby non-FASD participants were able to correctly recall
more digits in both the forward and backward conditions. Working memory deficits in children with PAE have also been documented using caregiver-report questionnaires, such as The Behaviour Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000). That is, across various studies involving the BRIEF caregiver-report (for individuals ranging from 5-16 years of age), researchers commonly find that one of the most pronounced areas of difficulty for children with FASD is working memory (Gross et al., 2015; Rai et al., 2017; Rasmussen et al., 2006, 2007).

Taken together, these findings further support the notion that children with FASD exhibit executive dysfunction, especially in their ability to temporarily store and manipulate information. While it is evident that PAE adversely impacts certain memory abilities, there may be other exposures that contribute to or worsen these deficits as well. Given that most children and youth with PAE experience several additional prenatal exposures (i.e., prenatal exposure to other substances, maternal mental health problems, lack of prenatal care) and postnatal exposures (i.e., maltreatment, neglect, abuse), it is important to understand how these factors may influence memory, above and beyond the impacts of PAE.

**The Ecobiodevelopmental Framework**

Shonkoff and colleagues (2009) suggest that the cumulative burden of stress (i.e., due to chronic maltreatment) and environmental threats during sensitive periods (i.e., PAE) can cause changes in brain structure and function, consequently leading to later illnesses. This is in line with an aim of the current study to investigate the effect of stress (i.e., postnatal exposures) and PAE on memory function. According to the Ecobiodevelopmental (EBD) framework (Shonkoff et al., 2012), brain architecture is greatly impacted by both a child’s early experiences and other environmental influences as well. As such, the EBD framework can be applied to help
conceptualize the potential associations among childhood stressors, environmental factors, and memory deficits (resulting from altered brain development).

The EBD framework (Shonkoff et al., 2012) is an integrated theory that illustrates the impact of stress on child development. This theoretical model proposes that biological mechanisms may explain the associations between childhood adversities and their consequences on developmental outcomes (Branco & Linhares, 2018). According to the EBD framework, a child’s early experiences and environmental influences leave a lasting impression on the genetic predispositions that affect brain development and health (Shonkoff et al., 2012). This theory outlines three foundations of healthy development: 1) stable, responsive relationships that provide children with consistent, nurturing, and protective interactions; 2) safe, supportive environments that are free from toxins; and 3) appropriate nutrition. The biology of health and development is understood as the process by which these experiences and influences interact with genetic predispositions (Shonkoff et al., 2012). This interaction then results in various combinations of physiological adaptions or disruptions that impact outcomes in lifelong well-being (Shonkoff et al., 2012). This framework takes a developmental approach in understanding that toxic stress experienced in infancy can enhance the risk of developing cognitive deficits, including memory impairments, and future physical or mental diseases (Shonkoff, 2003; Shonkoff & Levitt, 2010).

**PAE and Additional Risk Exposures**

It is well-established that PAE rarely occurs in isolation, such that most children exposed to PAE also experience other prenatal exposures (e.g., other substances, food and housing insecurity, maternal mental health issues), as well as adverse experiences or postnatal exposures (e.g., neglect, maltreatment, unstable placements; Astley, 2010). More specifically, most
individuals with postnatal exposures have experienced more than just one, suggesting that these exposures commonly co-occur as well (Dong et al., 2004; Green et al., 2010; McLaughlin et al., 2012). The current study focuses solely on postnatal exposures versus other prenatal exposures (i.e., prenatal exposure to other substances). To this end, threat and deprivation are two dimensions in which postnatal exposures have been conceptualized and understood (McLaughlin et al., 2014; Sheridan & Mclaughlin, 2014). Threat can be broadly defined as the presence of experiences that threaten physical integrity, such as harm or threat of harm, including abuse and exposure to violence (McLaughlin et al., 2014). Whereas deprivation, or the absence of expected environmental inputs, involves forms of loss, including poverty and neglect (McLaughlin et al., 2014). As discussed in the following section, in addition to these two dimensions, more recent attempts to characterize risk within this population have also prioritized the consideration of exposure duration, frequency and timing (Lebel et al., 2019).

**Characterizing Risk and Exposures in Children and Youth with PAE**

Historically, research on child adversity and developmental outcomes has primarily focused on singular causes or risk factors (Felitti et al., 1998; Rutter, 1979, 1981). For instance, when predicting the likelihood that a child will experience a maladaptive outcome, cumulative risk models, including Rutter’s (1979) accumulation of risk model, posit that the quantity of risk factors is the most telling factor (Rutter, 1979, 1981). The emphasis placed on quantity suggests that the number of risk factors is the most influential determinant of a child’s developmental outcome. The adverse childhood experiences (ACEs) framework (Felitti et al., 1998) is a commonly used cumulative risk approach to projecting developmental outcomes through the lens of postnatal adversity. In the ACEs framework (Felitti et al., 1998), postnatal adverse exposures, such as experiences of abuse and neglect, are summed to provide a cumulative risk score. As the
number of adverse exposures increases, as does the likelihood of adult health problems, including risk behaviours (i.e., drug abuse) and diseases (i.e., cancer; Felitti et al., 1998). While cumulative risk models provide a framework in which risk factors can be characterized, they fail to consider the specific characteristics relative to an exposure that may contribute to their effects on developmental outcomes. As mentioned by Lebel et al. (2019), cumulative risk approaches, including the ACEs framework, do not consider the variances that may exist in frequency, duration, or amount of exposure. To better explain developmental outcomes, recent models have separated environmental experiences into two core dimensions, threat and deprivation (McLaughlin et al., 2014; McLaughlin & Sheridan, 2016). In comparison to cumulative risk models, research suggests that dimensional models (involving threat and deprivation) are better able to explain outcomes (Brumley et al., 2018; Dennison et al., 2019; Sheridan et al., 2017); however, both models lack the consideration of potential prenatal exposures. Threat involves various types of abuse, threats of harm, and exposures to violence, whereas deprivation includes multiple forms of neglect including an absence of met needs. Research on threat and deprivation suggests that these dimensions may impact the brain differently (McLaughlin & Sheridan, 2016). Specifically, threat and deprivation may influence emotional processing and cognitive domains, respectively (McLaughlin & Sheridan, 2016). These dimensions are described in more detail below.

Threats, including physical or emotional abuse, place individuals at a higher risk of developing depressive disorders (Norman et al., 2012). However, as a general trend, physical abuse is commonly associated with externalizing behaviours (Moylan et al., 2010), and emotional abuse is commonly associated with internalizing symptoms (Cecil et al., 2017; Maguire et al., 2015). Similar to that of physical abuse, exposure to violence has also been
associated with externalizing symptoms including aggression and problem behaviours (Evans et al., 2008; Fleckman et al., 2016). Sexual abuse is another form of maltreatment, and frequently reported long-term effects include self-destructive behaviours, depression, anxiety, poor self-esteem, sleep disturbances and suicidality (Browne & Finkelhor, 1986; Maniglio, 2009; Skinner et al., 2016).

In terms of deprivation, some researchers suggest that neglect during childhood may be just as harmful as forms of physical and emotional abuse (Norman et al., 2012). Children who experience neglect often exhibit amplified stress reactivity (Drury et al., 2012), disturbances in the child-parent attachment (McGoron et al., 2012; O’Connor & Rutter, 2000), limited peer interactions, cognitive and academic deficits, and social withdrawal (Hildyard & Wolfe, 2002). Multiple care transitions and insecurities in food, housing, or income may also put a child at risk for adverse developmental outcomes. With regards to care transitions, frequent moves can adversely impact social and emotional development (Stubenbort et al., 2010) and lead to increased levels of depression, anxiety, and feelings of loss (Berrick et al., 1998; Perry, 2006; Unrau et al., 2008). However, it is worth noting that adoption may mitigate some of the impacts of early neglect by acting as a protective factor, especially when the child is younger (Sheridan et al., 2012).

Despite the understanding that prenatal and postnatal exposures commonly co-occur (Astley, 2010; Astley et al., 2000; Gibbard, 2010), cumulative and dimensional models have generally only characterized postnatal and not prenatal risks (Lebel et al., 2019). As such, Lebel and colleagues (2019) developed a robust, hybrid cumulative risk/dimensional model that expands on the 4-digit diagnostic code for FASD (Astley, 2004) by taking into consideration not just the presence or absence of exposures, but exposure type, timing and frequency of both
prenatal and postnatal risks. As it pertains to children with PAE, this novel framework provides the opportunity to investigate if other prenatal and postnatal exposures may impact developmental outcomes beyond that of alcohol exposure (Lebel et al., 2019). Further, another advantage of this approach is that it can be used to consider various types of exposures and time periods (i.e., early and late) simultaneously (Lebel et al., 2019). Specifically, this framework ranks exposures in seven categories using a Likert-type scale from 1 to 4. To incorporate both prenatal and postnatal periods, the dimensions of risk in this model include: PAE, other prenatal substance exposure, other prenatal toxic stress, early postnatal threat (<age 24 months), early postnatal deprivation (<age 24 months), late postnatal threat (≥age 24 months), and late postnatal deprivation (≥age 24 months). To characterize the exposure or risk, each dimension is ranked based on the amount of exposure; 1 = no exposure (confirmed absence), 2 = unknown exposure (insufficient information), 3 = some exposure, and 4 = high exposure. This characterization process generates a seven-digit code that corresponds to each dimension, representing the individual’s level of risk (see Table 1).

Table 1

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>Description</th>
<th>Rank 3</th>
<th>Rank 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal alcohol exposure</td>
<td>Consumption of any form of alcohol during pregnancy</td>
<td>Exposure to prenatal alcohol not meeting criteria for a score of 4 or confirmed exposure of unknown amount</td>
<td>High exposure of ≥7 drinks/week or ≥ 2 binge episodes (≥4 drinks on one occasion) at some point in pregnancy</td>
</tr>
<tr>
<td>Other prenatal substance exposure</td>
<td>Exposure to harmful substances including marijuana, nicotine, cocaine, methamphetamines, and opioids during pregnancy</td>
<td>Exposure to nicotine or marijuana of any amount; low frequency use of other substances, or confirmed use of unknown amount</td>
<td>High frequency use (≥5 times in pregnancy) of an illicit substance (cocaine, methamphetamines, opioids, etc.)</td>
</tr>
<tr>
<td><strong>Other prenatal toxic stress</strong></td>
<td>Harm or threat of harm to the mother and fetus during pregnancy; lack of prenatal care, housing, food, or income to meet needs; maternal mental health problems</td>
<td>Symptoms of a mental health problem (undiagnosed), lack of prenatal care, housing/food/income insecurity ≤3 months, OR a single instance of domestic violence or sex trade work</td>
<td>DSM-5 diagnosis of mental health disorder, domestic violence or sex trade work at least twice during pregnancy, housing/food/income insecurity ≥3 months, or multiple exposures</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td><strong>Early postnatal deprivation (&lt;24 months)</strong></td>
<td>The basic needs of the child not being met or a risk of needs not being met, including attachment needs</td>
<td>One care transition (excluding from hospital), housing/food/income insecurity, or loss of caregiver (e.g., death, incarceration)</td>
<td>Multiple care transitions (≥2), neglect, or multiple exposures</td>
</tr>
<tr>
<td><strong>Late postnatal deprivation (≥24 months)</strong></td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
<tr>
<td><strong>Early postnatal threat (&lt;24 months)</strong></td>
<td>Harm or threat of harm, including physical, emotional, sexual abuse; or witnessing violence, substance abuse, or criminal activity in the home</td>
<td>Witnessing substance use or domestic violence, caregiver with mental illness</td>
<td>Abuse of any kind, or multiple exposures</td>
</tr>
<tr>
<td><strong>Late postnatal threat (≥24 months)</strong></td>
<td>Same as above</td>
<td>Same as above</td>
<td>Same as above</td>
</tr>
</tbody>
</table>

*Note. Adverse exposures were assessed on a Likert-type scale from 1 to 4. Specific criteria for Ranks 3 and 4 are shown above for each variable. Criteria for Ranks 1 and 2 are not shown, as they were the same for all variables. Scores of 1 represent a confirmed absence of any exposure, whereas 2 represents unknown exposure (generally due to insufficient information).*

Following the development of their novel risk characterization framework, Lebel and colleagues (2019) applied this approach to a cohort of 77 children with PAE to describe the various exposures and risk profiles within this population. Prenatal and postnatal exposure information was obtained from each participant’s child welfare file and through semi-structured interviews with foster/adoptive parents and birth families. Characterization of exposure was
completed through group consensus, which involved various experts in the field. Through this process, each child was scored (1-4) on the seven exposure variables mentioned previously. Overall, Lebel and colleagues (2019) found that children with PAE commonly have other co-occurring exposures; that is, almost all (99%) children had other co-occurring prenatal exposures and two-thirds of the sample presented with both prenatal and postnatal risks. Furthermore, participants identified as having “high” PAE (rank 4) were more likely to experience late (≥ age 24 months) postnatal risks. In addition, the presence of postnatal risks was significantly related to each other, whereby they were more likely to co-occur.

Consistent with Lebel and colleagues (2019) framework, there is evidence to suggest that negative exposures during the postnatal period are common for individuals with PAE to experience. For instance, in a study of 1,400 patients with PAE, 70% of individuals were no longer in the care of their birth parents and had experienced approximately three different out-of-home care placements (despite 90% of the population being under the age of 16; Astley, 2010). In addition, at least 34% of the patients had been physically abused, and 24% had been sexually abused (Astley, 2010). These findings are consistent with existing literature that highlights how many children with PAE also experience postnatal risks such as deprivation, abuse, neglect, and multiple care placements (Hussong et al., 2010; Koponen et al., 2009; Streissguth et al., 2004). Furthermore, children with FASD are vastly overrepresented in foster care and adoption settings (Knuiman et al., 2015; Lange et al., 2013; Miller et al., 2007), and these environments often pose additional risks. For instance, researchers comparing the outcomes of children with FASD living in child welfare care to those in other living situations (i.e., with biological or adoptive parents) found significantly higher rates of reported sexual and physical abuse among those in the child welfare system (Burns et al., 2020).
Kambeitz and colleagues (2019) compared the prevalence of ACEs and other neurodevelopmental disorders in individuals with and without FASD. The ACEs involved ten binary variables: verbal/emotional abuse, physical abuse, sexual abuse, unloving family/emotional neglect, parental mental illness, neglect, parents divorced/separated, mother abused, drinking or drugs in the house, and parent in prison. The researchers found that ACEs were more common in individuals with FASD compared to those without the diagnosis (Kambeitz et al., 2019). Specifically, 58% of non-FASD participants had low ACEs scores (0 or 1), compared to only 6% of individuals with FASD. Among participants with FASD, neglect (87%), parental substance abuse (85%), parental separation/divorce (50%), and physical abuse (50%) were the most prevalent ACEs scores. As such, it is quite evident that individuals with FASD are likely to experience postnatal risks above and beyond what would be typically observed in unexposed populations.

Developmental Outcomes of PAE and Postnatal Risks

Exposure to various postnatal risks may consequently place a child at risk for maladaptive developmental outcomes. While minimal research has explored the impact of PAE and postnatal risks on long-term outcomes, several researchers have suggested that most individuals with PAE have additional exposures that may influence their development (Astley, 2010; Astley et al., 2000; Gibbard, 2010; Hyter, 2012; Koponen et al., 2009). The extent to which postnatal risks impact development may vary relative to the severity, frequency, and duration of exposure; however, in the general population, postnatal risks in childhood are commonly associated with an increased risk of later substance use, suicide attempts, and mental health disorders (Heim et al., 2010). As mentioned, Astley (2010) established that in addition to PAE, the presence of other adverse exposures or events (i.e., prenatal drug exposure, multiple
home placements, physical/sexual abuse) was associated with more severe developmental outcomes. Furthermore, Kambeitz et al. (2019) reported that higher ACEs scores were associated with increased rates of other neurodevelopmental disorders (most commonly ADHD) for individuals with FASD. Children with both PAE and adverse childhood exposures are also more likely to experience deficits in areas of memory, attention, behaviour, and cognition (Price et al., 2017). Of note, these developmental outcomes appear to be influenced by the duration of exposure, whereby longer exposures to postnatal risks (i.e., violence) increase the likelihood of poorer outcomes for individuals with FASD (Streissguth et al., 2004).

**The Role of Postnatal Risks in Memory Abilities**

As previously outlined, the cumulative burden of stress and environmental threats (i.e., PAE) can cause changes in brain structure and function (Shonkoff et al., 2009). Given the high prevalence of postnatal exposures (i.e., stressors) commonly experienced by children and youth with PAE, it is worth investigating how these exposures potentially combine to impact cognitive domains, including those responsible for memory. It is understood that prolonged activation of a child’s stress response systems in the absence of supportive adult relationships and other protective factors can contribute to toxic stress (Shonkoff et al., 2012). Stressors such as child abuse and neglect can prolong the activation of the stress response system, thereby inducing a toxic stress response (Letourneau, 2020; Shonkoff et al., 2012). In young children, toxic stress can contribute to structural and functional changes in the brain (McEwen, 2005, 2006). These changes may be partly due to the plasticity of a developing brain, which makes it especially vulnerable to elevated stress hormones (National Scientific Council on the Developing Child, 2005, 2014). During stressful situations, cortisol is produced as a response to help the brain cope; however, if an individual is chronically stressed, it can have an adverse impact on memory
function (Sapolsky et al., 2000). Specifically, toxic stress contributes to elevated cortisol levels for extended periods, and as a result, regions of the brain that are integral for memory can be architecturally altered (Lupien et al., 1998, 2009). Cortisol is the brain chemical responsible for regulating the hypothalamic-pituitary-adrenocortical (HPA) system (National Scientific Council on the Developing Child, 2005, 2014), and sustained levels can adversely impact the hippocampus, which is a critical brain area for memory and learning (Brunson et al., 2002). In addition, neurogenesis is an important factor in memory encoding, and exposure to high cortisol levels can inhibit the formation of new neurons in the hippocampal region (Shonkoff et al., 2012).

Similar to that of toxic stress, the hippocampus is especially vulnerable to the effects of alcohol exposure (Autti-Rämö et al., 2007; Coles & Li, 2011; Fontaine et al., 2016; Willoughby et al., 2008). However, independent of toxic stress, memory deficits are commonly observed in individuals with PAE (Manji et al., 2009). Willoughby et al. (2008) compared the effects of PAE on hippocampal volume, verbal learning, and verbal recall between children with and without FASD. Children with FASD had poorer verbal learning and recall performance and reduced left hippocampal volumes (Willoughby et al., 2008). Relative to non-FASD participants, there was an association between hippocampal volume and verbal recall for the children with FASD (Willoughby et al., 2008). As such, the association between PAE and anomalies in hippocampal development may help explain the deficits observed in areas of verbal recall and learning. Working memory, which is highly dependent on the hippocampus, has also been found to be sensitive to the effects of PAE (Burden et al., 2005; Connor et al., 2000; Goldschmidt et al., 1996). In summary, when considered independently, both toxic stress and PAE appear to adversely impact areas of the brain that are important for memory function. However, the impact
of a combination of these effects on memory ability is an area of research that has been largely overlooked.

While the potential deficits resulting from a co-occurrence of PAE and postnatal risks have not been afforded much research attention, different findings have emerged. In a sample of individuals with FASD (aged 6-26 years), Mukherjee and colleagues (2019) determined that neglect did not have an additional impact on neurodevelopmental outcomes. Specifically, these researchers determined that PAE impacted neurodevelopmental outcomes (ADHD, autism spectrum disorder, etc.) independent of neglect, suggesting that postnatal neglect does not worsen developmental outcomes (Mukherjee et al., 2019). As such, Mukherjee and colleagues (2019) concluded that behavioural challenges within this population were likely a result of PAE versus environmental factors, including parenting. Alternatively, it is suggested that a compounding effect of PAE and childhood trauma on functioning may exist (Price et al., 2017).

In a systematic review of five articles, Price and colleagues (2017) found that children with both PAE and traumatic childhood experiences were more likely to present with deficits in areas of speech, language, intelligence, attention, memory, and exhibit more severe behavioural challenges when compared to children with just one of the two exposures. Of the five articles included in the review (Price et al., 2017), only Henry et al. (2007) assessed potential deficits in areas of memory. Specifically, Henry and colleagues (2007) compared neurodevelopmental outcomes between children (aged 6-16 years) with trauma and no PAE to children with both PAE and trauma. Ninety-seven percent of the children were deemed moderately to severely traumatized, based on the Traumagenic Impact of Maltreatment Rating (James, 1989), which was completed by senior clinicians who determined trauma level on a 1-10 scale (absent to severe). Memory deficits were more common in children with both trauma and PAE (87%) when
compared to trauma-exposed children without PAE (71%). To our knowledge, no study has examined if the same is true relative to children and youth with PAE who vary in their levels of exposure to traumatic events. Lastly, while memory deficits were reportedly more pronounced when both exposures were present, the specific memory domains or processes deemed impaired by Henry et al. (2007) remain unknown.

While the designs of each study included in the review by Price and colleagues (2017) did not allow for causal inferences to be made, these studies nonetheless provide preliminary evidence that a variety of deficits may exist to a more considerable extent in children with both exposures. These findings suggest that when PAE occurs alongside traumatic childhood experiences, these exposures compound and place a child at higher risk of experiencing challenges in other areas, including memory (Price et al., 2017).

Current Study

The current study aims to replicate and extend existing literature examining the verbal memory abilities, or the short-term verbal recall, learning, and working memory, of children and youth with and without PAE. Using the characterization tool developed by Lebel and colleagues (2019), this study will also investigate the potential influence of postnatal risks (i.e., abuse, neglect, care transitions, food/housing/income insecurity) on memory ability in children with PAE. In addition to standardized measures of verbal memory, this study will also incorporate caregiver-reported working memory ratings. Findings from this study will build on the existing literature documenting memory differences between children with and without PAE. Furthermore, this research will explore potential associations between postnatal exposures and memory deficits in children with PAE, as this is an area that has largely been overlooked in the literature.
Research Questions & Hypotheses

The current study aimed to address the following research questions:

1) Do children and youth with and without PAE differ in their short-term verbal memory abilities? Further, do these differences remain after controlling for IQ?

*Consistent with existing research, it was expected that children and youth with PAE would recall fewer items on a narrative memory task in both free and cued immediate recall conditions when compared to children and youth without PAE.*

2) How does the presence of additional postnatal exposures influence short-term memory abilities in children and youth with PAE?

*Children and youth with “moderate-high” levels of postnatal risk were expected to exhibit more pronounced memory deficits than children with “absent-low” levels of postnatal risk on measures of recall, learning, and working memory.*
Chapter 3: Methods

Secondary Data Sources

This study involved the secondary analysis of data collected from two independent studies. The first study, the Cumulative Risk Diagnostic Clinic (CRDC) pilot research project (REB #17-0663), examined the association between mental health and brain structure in children and youth exposed to alcohol prenatally. This study examined the relation between PAE, other prenatal (i.e., exposure to other substances, trauma to the fetus, maternal mental illness), and postnatal risks (i.e., multiple care transitions, neglect, abuse) and how these risks relate to developmental, behavioural, and neurological outcomes. This project was funded by a Addictions and Mental Health Strategic Clinical Health Network – Clinical Connections Grant (PIs: C. Lebel & C. McMorris) and data collection occurred between 2017-2019.

The second research project (Research Study 2) investigated healthy pediatric brain development using advanced brain imaging (REB #13-1346). This longitudinal study used magnetic resonance imaging (MRI) to provide a more comprehensive description of brain structure in healthy children and youth. More specifically, myelination was examined to describe typical brain maturation and associations between brain development and cognitive outcomes. This project was funded by the Natural Sciences and Engineering Research Council of Canada (NSERC) and the Alberta Children’s Hospital Foundation – Imaging Research Start-Up (PI: C. Lebel). Data was collected from 2014-2018, and participants completed three visits, each occurring two years following baseline. Given the longitudinal nature of this study, only data from the first visit (baseline) was included in the current study.
Participants

Research Study 2 Sample (Unexposed Participants) – Aim 1

To be eligible to participate in Research Study 2, participants were required to have: 1) an uncomplicated birth between 37- and 42-weeks gestation; 2) no history of a neurodevelopmental disorder (i.e., autism, Cerebral palsy, learning difficulties) or mental health disorder; 3) no history of neurosurgery; and 4) no contraindications to MRI (i.e., metal implants, dental devices, claustrophobia).

Twenty-six children and youth from Research Study 2 were included and age-matched within 12 months to the participants in the CRDC study to address Aim 1 (See Table 2). For the purposes of age-matching, only whole numbers were used (i.e., 9 years, 10 months = 9 years). Gender matching was prioritized when possible. The majority of the sample was male ($n = 15; 57.6\%$) and had a mean age of 9.84 ($SD = 1.78$). Since five unexposed participants could not be matched on both age and gender to the exposed participants (from the CRDC study), 10 participants out of 52 total (26 from each study) were matched on age only. To restrict potential bias, the matching process was completed based on the order in which participants had been assessed, starting with the participants who were tested first.

CRDC Study Sample (Exposed Participants) – Aim 1 and Aim 2

Forty children and youth between 7 and 16 years of age with PAE participated in the CRDC study. Participants were required to have a current diagnosis of FASD and/or confirmed and documented information about PAE. In line with current Canadian diagnostic guidelines (Cook et al., 2016), alcohol exposure was confirmed through the biological mother’s self-report, reliable observations by close family/friends, clinical observations, and/or medical, legal or child services records. Children and youth were deemed ineligible for the study if: 1) they lacked
documented and/or confirmed information regarding PAE; 2) they were currently in crisis (hospitalized in the last six months for mental health concerns) or actively suicidal; 3) their motivation to participate was solely to obtain an assessment to confirm an FASD diagnosis; and/or 4) consistent with the assessment protocol from the CRDC Clinic at Alberta Health Services, children and youth with a diagnosis of ADHD who were not taking appropriate medication were excluded. Further, exclusion criteria included birth before 34 weeks’ gestation, presence of major genetic or neurological disorders, autism, Cerebral palsy, or moderate to severe intellectual disability, and contraindications to MRI (i.e., orthodontic/dental implants with metal). Lastly, to ensure an accurate assessment of mental health, children and youth were required to be in a stable home placement for at least six months prior to study participation.

Data from 26 children and youth who participated in the CRDC study was included to address Aim 1 (see Table 2). The majority of the sample was male ($n = 16; 61.5\%$) and had a mean age of 9.89 ($SD = 1.78$). Of the original cohort from the CRDC study ($N = 40$), eight participants were excluded from the Aim 1 analysis due to missing information or incomplete assessments on variables of interest (i.e., free recall [as measured by the NEPSY-II] and cognitive functioning [as measured by the WASI-II]). Further, an additional six participants were excluded as they could not be age-matched within 12 months to any participants from Research Study 2.

Table 2

| Demographic Information for Exposed and Unexposed Children and Youth (Aim 1) |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
|                                  | Exposed ($n = 26$) | Range                        | Unexposed ($n = 26$) | Range                        |
| Age (years)                      | $9.89(1.78)$ | 7.90-13.78                   | $9.84(1.78)$ | 7.40-13.76                   |
| Sex (% male)                     | 61.5% ($n = 16$) |                             | 57.6% ($n = 15$) |                             |
Twenty-nine children and youth from the CRDC cohort were included in the data analysis for Aim 2 (see Table 3) and grouped based on their exposure to postnatal risks (described in more detail below). The majority of the sample was male \((n = 16; 55.2\%)\) and had a mean age of 10.53 \((SD = 2.40)\). As mentioned, eight participants were excluded from the initial 40 participants due to missing or incomplete information. An additional three participants were also excluded as they were missing data that was specifically relevant to the Aim 2 analysis (i.e., verbal [as measured by the CVLT-C] and working memory scores [as measured by the BRIEF]).

### Demographic Information for Exposed Children and Youth (Aim 2)

<table>
<thead>
<tr>
<th></th>
<th>Total ((n = 29))</th>
<th>Absent-Low ((n = 14))</th>
<th>Moderate-High ((n = 15))</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>(10.53(2.40))</td>
<td>(10.69(2.37))</td>
<td>(10.39(2.50))</td>
</tr>
<tr>
<td><strong>Sex (% male)</strong></td>
<td>55.2% ((n = 16))</td>
<td>50% ((n = 7))</td>
<td>60% ((n = 9))</td>
</tr>
</tbody>
</table>

*Note. Age is presented in decimal form (i.e., 9 years, 6 months = 9.5).*

### Measures

Both the CRDC Study and Research Study 2 involved various demographic, cognitive, behavioural, and neuropsychological measures. For the purposes of the present study, only the data from the following assessment measures were used in the analyses.

### Demographic Information

Demographic information for the CRDC study was obtained through a questionnaire asking parents/caregivers to provide the following information: date of birth, mental health and neurodevelopmental diagnoses, current medications, family members in the home, household
income, and services currently accessed. As information pertaining to the race/ethnicity of the child or youth was not obtained in the questionnaire, families were re-contacted over the phone.

For Research Study 2, basic demographic information was also obtained through a questionnaire that asked the participant’s parent/caregiver to provide information pertaining to the participant’s birthdate, previous diagnoses of neurodevelopmental disorders (for both the participant and their biological family), household information, and ethnicity.

**Prenatal and Postnatal Risk Determination and Characterization**

Within the CRDC cohort, information regarding early prenatal and postnatal exposure(s) was obtained from child welfare files (containing information from birth families, social workers, police records, and medical files) and through semi-structured interviews which were completed either in person (at the time of testing) or over the phone (when the Kiddie Schedule for Affective Disorders and Schizophrenia, Present and Lifetime Version [K-SADS-PL; Kaufman et al., 1997] was completed). Using the cumulative risk framework (Lebel et al., 2019), prenatal and postnatal exposure(s), including PAE, were characterized through group consensus involving a developmental paediatrician with expertise in FASD, a child welfare manager, a clinical child psychologist, and a neuroscientist. The exposure data that was collected includes: PAE, other prenatal substance exposures (i.e., marijuana), other prenatal toxic stress (i.e., harm to the mother), early postnatal threat (<24 months), early postnatal deprivation (<24 months), late postnatal threat (≥24 months), and late postnatal deprivation (≥24 months). Participants were ranked using the 1-4 criteria previously described (Lebel et al., 2019). For the purposes of the current study, only the postnatal exposure variables were analyzed.

All children and youth in the CRDC cohort were exposed to alcohol prenatally. The majority of the sample (55.2%; see Table 4) met criteria for “high risk” as characterized by
confirmed exposure of either 7+ drinks/week or 2+ episodes of binge drinking (4+ drinks and/or drinking to blacking out) at least twice during pregnancy or 3 sentinel facial features.

Table 4

*PAE Exposure Characterization (Aim 2)*

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>1 (absence of risk)</th>
<th>2 (unknown risk)</th>
<th>3 (some/moderate risk)</th>
<th>4 (high risk)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prenatal alcohol exposure</td>
<td>0(0%)</td>
<td>2(6.9%)</td>
<td>11(37.9%)</td>
<td>16(55.2%)</td>
</tr>
</tbody>
</table>

*Note. n = 29*

For the Aim 2 analyses, scores among the four postnatal categories (see Table 5) were summed for each participant (min: 4, max: 16). A median split (*Mdn* = 9) divided participants into two groups based on their level of exposure to postnatal risk(s); absent-low or moderate-high. Of the 29 participants, nearly half (*n* = 14) had postnatal risk scores of eight or below, while the remaining participants (*n* = 15) had postnatal risk scores of nine or above. Thus, the participants were separated into two groups: “absent-low” risk group (min: 4, max: 8; *M* = 5.86, *SD* = 1.56) or the “moderate-high” risk group (min: 9, max 16; *M* = 12.07, *SD* = 2.89).

Table 5

*Risk Characterization Based on Participant’s Postnatal Exposures (Aim 2)*

<table>
<thead>
<tr>
<th>Exposure Type</th>
<th>Absent-Low (n = 14)</th>
<th>Moderate-High (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M(SD)</td>
<td>Range</td>
</tr>
<tr>
<td>Early postnatal deprivation (&lt;24 months)</td>
<td>1.79(.98)</td>
<td>1.00 – 3.00</td>
</tr>
<tr>
<td>Late postnatal deprivation (≥24 months)</td>
<td>1.29(.73)</td>
<td>1.00 – 3.00</td>
</tr>
<tr>
<td>Early postnatal threat (&lt;24 months)</td>
<td>1.29(.47)</td>
<td>1.00 – 2.00</td>
</tr>
</tbody>
</table>
Late postnatal threat
(≥24 months)

1.50(1.02)  1.00 – 4.00
2.53(1.46)  1.00 – 4.00

Total risk score
5.86(1.56)  4.00 – 8.00
12.07(2.89)  9.00 – 16.00

Note. Total risk score based on summation of participant’s scores across each postnatal exposure type.

Cognitive Functioning

Wechsler Abbreviated Scale of Intelligence - Second Edition (WASI-II). The WASI-II (Wechsler, 2011) was used to assess cognitive functioning in both the CRDC and Research Study 2 samples. The WASI-II is an efficient, reliable measure of intellectual functioning that has strong psychometric properties. This abbreviated measure of cognitive intelligence is designed for use with individuals between the ages of six and 90 years. The WASI-II consists of four subtests: Vocabulary and Similarities, which form the Verbal Comprehension Index (VCI), and Block Design and Matrix Reasoning, which form the Perceptual Reasoning Index (PRI). Performance on the WASI-II can be compared to the normative sample by converting raw scores into standard scores ($M = 100, SD = 15$). Scores on Vocabulary and Matrix Reasoning combine to form the Full-Scale IQ-2 (FSIQ-2), while all four subtests combine to form the Full-Scale IQ-4 (FSIQ-4). Only the FSIQ-4 composite score was used in the current analysis. All index and composite variables are presented as standard scores ($M = 100, SD = 15$). Of note, IQ scores from psychological assessments completed within the last two years (i.e., from a participant’s FASD assessment or school psychoeducational report) were accepted in place of the WASI-II assessment.

Within the measure’s normative sample, interrater reliability coefficients range from .94 to .99 across the four subtests, with the highest interrater agreement for the more objective
subtests. Internal consistency was measured with reliability coefficients for the subtest scores ranging between .87 and .92. Additionally, reliability coefficients for the VCI, PRI, FSIQ-4, and FSIQ-2 composites range from .92 to .97. Based on normative studies, concurrent validity has been demonstrated between the WASI-II and other measures of intellectual functioning, including the original WASI, the Wechsler Intelligence Scale for Children, Fourth Edition (WISC-IV), and the Wechsler Adult Intelligence Scale, Fourth Edition (WAIS-IV). Correlations between scores on the WASI-II and those on the WASI, WISC-IV, and WAIS-IV are strong, ranging from .71 to .92 (McCrimmon & Smith, 2013).

**Verbal Memory**

**Developmental Neuropsychological Assessment - Second Edition (NEPSY-II; Narrative Memory subtest).** The NEPSY-II (Korkman et al., 2007) was utilized in both studies to assess verbal memory. The NEPSY-II is a tool used to assess neuropsychological functioning for children and youth between the ages of three and 16 years. The NEPSY-II assesses six cognitive domains: Attention and Executive Functioning, Language, Memory and Learning, Sensorimotor, Social Perception, and Visuospatial Processing. Included within the Memory and Learning domain are the subtests of List Memory, Memory for Designs, Memory for Faces, Memory for Names, Narrative Memory, Sentence Repetition, and Word List Interference.

Data from the Narrative Memory (NM) subtest, which assesses memory for organized verbal material under free recall, cued recall, and recognition conditions, was used in analyses for both study aims. For the free recall condition of this subtest, participants are required to listen to a story and are then asked to repeat the story. In the cued recall condition, the participant is asked questions to elicit missing details from his or her recall of the story. For the current study, both the free and cued recall raw scores from the NM subtest were used in the analyses. Scaled
scores ($M = 10$, $SD = 3$) for free and cued recall are presented in the form of descriptive information. Recognition scores were not included in the analyses as the recognition questions on the NEPSY-II are only administered to individuals between five and 10 years of age. Test-retest reliability for the Narrative Memory subtest ranges from .61 to .83 for individuals three to 16 years old (Brooks et al., 2009).

**California Verbal Learning Test – Children’s Version (CVLT-C).** The CVLT-C (Delis et al., 1994) was used to assess verbal memory in the CRDC study only and was used in the Aim 2 analyses. The CVLT-C is a measure designed to assess the strategies and processes that children and youth use when learning and recalling verbal material. The CVLT-C is administered to individuals between five and 16 years of age, and it adopts a process-oriented approach in assessing a variety of verbal learning and memory components. The process-oriented approach helps to parse apart various memory and learning components which aids in the observation of distinct memory profiles. The CVLT-C uses words presented as part of two shopping lists, and it measures recall and recognition of the words over several trials. For the first five recall trials, the participant is presented with a 15-word list (List A) which contains five words from each of the three semantic categories (i.e., fruits, clothing, and toys). After the participant is asked to recall the words for the fifth time, they are presented with a one-trial 15-word distractor list (List B) and instructed to recall the new words. List B is divided equally across three semantic categories (i.e., fruits, furniture, and dessert). This is followed by the short-delay free and cued recall of List A, and in the cued trial, the three semantic categories are provided. The long-delay free and cued recall trials are presented after a 20-minute delay in which nonverbal measures are administered. Lastly, a “yes/no” recognition trial is presented, which requires the participant to distinguish between List A and distractor items.
In the normative sample, reliability was assessed using measures of internal consistency and test-retest reliability (Delis et al., 1994). The CVLT-C has strong internal consistency; the coefficient for the five trials of List A ranges from .84 to .91, and the across-semantic-category consistency coefficient ranges from .64 to .80 (Fine & Delis, 2011). Test-retest reliability ranges from .17 to .90, with higher correlations for measures of overall performance (Fine & Delis, 2011). Further, alternate forms reliability was reported at .84 (Delis et al., 1994), indicating appropriate reliability for multiple administrations.

Based on the normative sample, raw scores for each variable are converted into standard scores ($z$-scores: $M = 0$, $SD = 1$). $Z$-score values can range from positive to negative numbers, with negative scores indicating poorer performance. Of note, the standard score for List A Total Trials 1-5 is presented in a $T$-score metric ($M = 50$, $SD = 10$).

**Working Memory**

**Behaviour Rating Inventory of Executive Functioning (BRIEF; Working Memory subtest).** The BRIEF (Gioia et al., 2000) was used to assess working memory in the CRDC study only and was used in the Aim 2 analyses. The BRIEF is used to measure executive functioning (EF) behaviours in children and youth (aged 5-18) in both home and school environments. The BRIEF assesses EF using eight clinical scales (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Monitor, and Organization of Materials) and two validity scales (Inconsistency and Negativity). The eight scales form two broader indexes, Behavioral Regulation (BRI) and Metacognition (MI), as well as an overall score, the Global Executive Composite (GEC). The BRI is made up of the Inhibit, Shift, and Emotional Control scales, whereas the MI is comprised of the Initiate, Working Memory, Plan/Organize, Monitor, and Organization of Materials scales. The Negativity scale measures the extent to which items were
selected in an unusually negative manner, and scores on the Inconsistency scale indicate the extent to which similar items were answered inconsistently.

The parent and teacher forms of the BRIEF each contain 86 items that measure various aspects of executive function. Respondents are required to answer a variety of questions using a three-point scale: N (Never), S (Sometimes), or O (Often). This scale reflects the frequency of a specified behaviour for the child or youth that is being evaluated. Only the parent form was administered.

The measure provides normative data based on the age and sex of the examinee; separate normative tables for each of the two forms provide T-scores ($M = 50$, $SD = 10$), percentiles, and 90% confidence intervals. Of importance, this sample included children and youth with developmental disorders or acquired neurological disorders. High internal consistency (.80 to .98) and test-retest reliability (.82 for parents and .88 for teachers) were found. For the current study, only the Working Memory raw scores were used in the analysis. The T-scores from the Working Memory scale were presented as descriptive information. Elevated T-scores on the BRIEF are categorized through ranges between 60-64 (mildly elevated), 65-69 (potentially clinically elevated), or ≥70 (clinically elevated).

**Procedure**

**Data Collection**

**CRDC Study.** Recruitment for the study occurred via advertisements in caregiver support groups and organizations throughout Alberta (i.e., Calgary Fetal Alcohol Network, Edmonton Fetal Alcohol Network, Calgary Urban Project Society, First 2000 Days Network). In addition, support from clinicians and social workers helped facilitate recruitment in both the Cumulative Risk Diagnostic Clinic (CRDC) and Child & Family Services, respectively.
Children and youth, along with their parents/caregivers, provided informed assent and consent, respectively. For participants that were 14 years of age or older, mature minor status was determined based on the participant's understanding of the risks and benefits of the study. For their first visit, participants completed a variety of assessment measures (taking approximately 30 to 90 minutes); however, as mentioned previously, the present study only utilized data from the WASI-II, NEPSY-II, CVLT-C, and the BRIEF. The following day, an MRI scan was also completed at the Alberta Children’s Hospital. Upon completion, all families were provided with a summary of their child’s performance on some of the measures, along with any necessary resources. Finally, all families received a $50 gift card for their participation.

Research Study 2. Unexposed participants were recruited from the local Calgary community via advertisements and posters (at local schools/community centres), a website submission, mailing lists, and word of mouth. Previous participants and researchers’ acquaintances were also recruited.

All subjects provided informed assent, and parents/caregivers provided written informed consent prior to participation. For participants that were 14 years of age or older, mature minor status was determined based on the participant's understanding of the risks and benefits of the study. A variety of cognitive, behavioural, and neuropsychological assessments were completed on the same day as the MRI scan (either before or after, depending on the MRI scheduling). For the purposes of the current study, only data from the NEPSY-II and the WASI-II were used. As an incentive, participants received $30 for their participation along with brain anatomical images.

Data Analysis

All statistical analyses were performed using IBM SPSS Statistics (Version 26). Of note, due to the nature of the exposed population, outliers were anticipated. Thus, outliers were
deemed meaningful and were not removed or treated in any of the following analyses. In both the Aim 1 and 2 analyses, all assumptions were checked, and it was confirmed that they met the required assumptions unless otherwise specified. Raw scores were used in all analyses as it was anticipated that scaled scores may minimize meaningful variance in the data. Alternatively, scaled scores were presented as descriptive statistics to permit visual comparisons between the groups.

As mentioned above, for Aim 1, participants from the exposed sample were individually age-matched (within 12 months) and gender-matched when possible to the unexposed participants. Independent-samples $t$-tests were conducted to ensure that participants were correctly age-matched, as well as to compare intellectual functioning (as measured by the FSIQ-4 composite score) between the exposed and unexposed participants. To determine if exposed and unexposed children and youth differ in their short-term verbal memory abilities (Aim 1), additional independent-samples $t$-tests were conducted on scores from the free and cued recall measure on the NEPSY-II. As it was anticipated that potential IQ differences between the groups may account for variance in memory ability, two separate analyses of covariance (ANCOVAs) were conducted to observe group differences on the free and cued NEPSY-II tasks while controlling for IQ. A Bonferroni correction was used to account for Type I Error ($0.05/2; \alpha = 0.025$).

To determine the role of postnatal risks in memory abilities of children and youth with PAE (Aim 2), participants from the CRDC study were split into two groups based on their level of exposure to postnatal risk(s) and performance across various memory measures were compared. A Mann-Whitney U test was used to ensure that the two groups were approximately equivalent on age after being separated on the basis of exposure to postnatal risks. An additional
Mann-Whitney U test and four independent-samples t-tests were conducted to determine potential group differences (absent-low versus moderate-high) across various memory measures (NEPSY-II: free recall and cued recall, BRIEF: working memory, CVLT-C: list A total trials and list A trial 1 free recall). The Bonferroni correction method was used to account for Type I Error (0.05/5; $\alpha = 0.01$).
Chapter 4: Results

Research Question #1

Do children and youth with and without PAE differ in their short-term verbal memory abilities? Further, do these differences remain after controlling for IQ?

Age-Matching

There was no statistically significant difference in age, \( t(50) = .001, p = 1.00 \), as the exposed sample \((M = 9.38, SD = 1.75)\) and the unexposed sample \((M = 9.38, SD = 1.75)\) were equivalent.

Full-Scale IQ

Full-Scale IQ scores for the exposed and unexposed samples are presented in Table 6. To observe potential differences in cognitive functioning (as approximated by the Full-Scale IQ) between exposed and unexposed participants, an independent-samples \( t \)-test was conducted. A significant difference was observed between participants based on the presence or absence of prenatal alcohol exposure, \( t(50) = -6.250, p < .001, d = 1.73 \). Specifically, unexposed participants had significantly higher intellectual functioning \((M = 110.12, SD = 15.75)\) than the exposed participants \((M = 86.19, SD = 11.53)\), such that children and youth with PAE have poorer cognitive abilities compared to unexposed children and youth.

Table 6

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exposed ((n = 26))</th>
<th>Unexposed ((n = 26))</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>( M(SD) )</td>
<td>Range</td>
</tr>
<tr>
<td>WASI-II</td>
<td>86.19(11.53)</td>
<td>63.00-106.00</td>
</tr>
</tbody>
</table>

*Note. FSIQ-4 is presented as a standard score \((M = 100, SD = 15)\).*
**NEPSY-II - Free & Cued Recall**

Free and cued recall scores on the NEPSY-II are presented in Table 7. Two separate independent-samples $t$-tests were conducted to determine if there were differences in free and cued (story) recall scores between exposed and unexposed participants. A significant difference in free recall ability was observed between the exposed and unexposed groups, $t(50) = -2.580, p = .013, d = .72$, such that unexposed participants had significantly higher free recall scores ($M = 11.58, SD = 4.19$) than exposed participants ($M = 8.23, SD = 5.12$). Similarly, a significant difference in cued recall ability was observed between participants based on the presence or absence of alcohol exposure, $t(50) = -2.786, p = .008, d = .77$. Given that unexposed participants also had significantly higher cued recall scores ($M = 26.81, SD = 7.43$) than exposed participants ($M = 20.27, SD = 9.38$), these findings suggest that PAE is associated with deficits in both free and cued memory recall abilities.

Table 7

<table>
<thead>
<tr>
<th>Measure</th>
<th>Exposed ($n = 26$)</th>
<th>Unexposed ($n = 26$)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$M(SD)$</td>
<td>Range</td>
</tr>
<tr>
<td>NEPSY- II Free Recall</td>
<td>8.62(3.34)</td>
<td>3.00-17.00</td>
</tr>
<tr>
<td>NEPSY- II Cued Recall</td>
<td>8.58(3.28)</td>
<td>2.00-16.00</td>
</tr>
</tbody>
</table>

*Note. Raw scores were used in the statistical analyses.*

As mentioned previously, the exposed and unexposed participants also had substantial differences in their intellectual functioning as observed by the Full-Scale IQ scores. As such, to determine if the variance in memory would be best accounted for by differences in intellectual functioning, ANCOVAs were conducted. Two separate ANCOVAs were used to determine the effect of PAE on free and cued (story) recall ability after accounting for FSIQ.
After controlling for FSIQ, there was no statistically significant difference in free recall ability between the exposed and unexposed participants, $F(2, 49) = .414, p = .664$, partial $\eta^2 = .017$. A second ANCOVA was used to determine if groups differed on cued recall after controlling for FSIQ. The assumption of homogeneity of variances was violated, as assessed by Levene’s test for equality of variances ($p = .025$). As such, this assumption was further investigated using a second, more robust test. The Brown-Forsythe’s test was used to check for equality of variances, and the assumption was met ($p = .097$). Similarly, after controlling for FSIQ, there was no statistically significant difference in cued recall ability between the exposed and unexposed participants, $F(1, 49) = .136, p = .714$, partial $\eta^2 = .003$, as such, post hoc analyses were not performed. Taken together, these findings would suggest that differences in free and cued memory recall ability between exposed and unexposed children and youth may be better explained by differences in intellectual functioning.

**Research Question #2**

**How does the presence of additional postnatal exposures influence short-term memory abilities in children and youth with PAE?**

As previously mentioned, due to the nature of the exposed population, outliers were anticipated. Thus, outliers were deemed meaningful and were not removed or treated in any of the following analyses. Of note, descriptive scaled scores for the four independent-samples $t$-tests are presented in Table 9.

**Age-Matching**

After dividing PAE participants based on their level of exposure to postnatal risks, an analysis was conducted to rule out potential variance due to age differences. This was done to ensure that the two groups were still relatively equivalent on age after separation on the basis of
postnatal risks. There was one outlier in the data as assessed by inspection of a boxplot. Age differences were not normally distributed, as assessed by Shapiro-Wilk’s test ($p = .017$). As a result, a Mann-Whitney U test was completed. Distributions of age for the two groups were similar, as assessed by visual inspection, thus medians were used instead of mean ranks. Age was not statistically significantly different between the absent-low risk group ($Median = 9.72$) and the moderate-high risk group ($Median = 9.43$), $U = 98$, $z = -.306$, $p = .760$, using an exact sampling distribution for $U$ (Dinneen & Blakesley, 1973). As such, variance in memory scores was not assumed to be due to any potential age differences between the two groups.

**NEPSY-II – Free Recall**

Free recall scores on the NEPSY-II are presented in Table 8. An analysis was conducted to determine if there were differences in free (story) recall scores between PAE participants based on their level of exposure to postnatal risk(s). There was one outlier in the data (absent-low exposure condition), as assessed by inspection of a boxplot. Free recall score differences were not normally distributed, as assessed by Shapiro-Wilk’s test ($p = .027$). As a result, a Mann-Whitney U test was used. Distributions of the free recall scores for the two groups were not similar, as assessed by visual inspection, thus mean ranks were used instead of medians. Free recall scores for the absent-low risk group (mean rank = 12.93) and the moderate-high risk group (mean rank = 16.93) were not statistically significantly different, $U = 134$, $z = 1.276$, $p = .202$, using an exact sampling distribution for $U$ (Dinneen & Blakesley, 1973). Despite the moderate-high risk group having a higher mean rank, statistically, both groups performed similarly. This would suggest that additional exposure to postnatal risks does not appear to worsen free recall ability in story contexts for children and youth with PAE.

Table 8
**NEPSY-II Free Recall Scaled Scores (Aim 2)**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Absent-Low (&lt;i&gt;n = 14&lt;/i&gt;)</th>
<th>Moderate-High (&lt;i&gt;n = 15&lt;/i&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median</td>
<td>Mean Rank</td>
</tr>
<tr>
<td>NEPSY- II Free Recall</td>
<td>7.00</td>
<td>12.68</td>
</tr>
</tbody>
</table>

*Note.* Raw scores were used in the statistical analysis.

**NEPSY-II – Cued Recall**

An independent-samples <i>t</i>-test was used to determine if there were differences in cued (story) recall scores between PAE participants based on their level of exposure to postnatal risk(s). There was no statistically significant difference between cued recall scores, <i>t</i>(27) = -1.867, <i>p</i> = .073, <i>d</i> = .70, for participants with absent-low risk exposures (<i>M</i> = 16.79, <i>SD</i> = 7.48) and moderate-high risk exposures (<i>M</i> = 22.87, <i>SD</i> = 9.81). This would suggest that additional exposure to postnatal risks does not appear to worsen cued recall ability in story contexts for children and youth with PAE.

**BRIEF – Working Memory**

An independent-samples <i>t</i>-test was used to determine if there were differences in working memory scores between PAE participants based on their level of exposure to postnatal risk(s). There was one outlier in the data (absent-low exposure condition), as assessed by inspection of a boxplot. There was no statistically significant difference between working memory scores, <i>t</i>(27) = .994, <i>p</i> = .329, <i>d</i> = .37, for participants with absent-low risk exposures (<i>M</i> = 24.64, <i>SD</i> = 5.08) and moderate-high risk exposures (<i>M</i> = 22.93, <i>SD</i> = 4.17). While the moderate-high risk group had a lower mean, indicating stronger working memory ability, statistically, both groups performed similarly according to the caregiver reports. This would suggest that additional exposure to postnatal risks does not appear to worsen working memory ability for children and youth with PAE.
Working Memory T-Scores from the BRIEF are reported in Table 9. On average, the participants with absent-low levels of exposure to postnatal risk \((n = 14)\) fell within the clinically elevated range, whereas participants with moderate-high risk exposure levels \((n = 15)\) fell within the potentially clinically elevated range.

**CVLT-C – List A Total Trials**

An independent-samples \(t\)-test was used to determine if there were differences in list learning ability between PAE participants based on their level of exposure to postnatal risk(s). There were two outliers in the data (moderate-high exposure condition), as assessed by inspection of a boxplot. There was no statistically significant difference in list learning ability, \(t(27) = -1.432, p = .164, d = .53\), for participants with absent-low risk exposures \((M = 37.57, SD = 13.55)\) and moderate-high risk exposures \((M = 44.40, SD = 12.13)\). This would suggest that additional exposure to postnatal risks does not appear to worsen list learning abilities for children and youth with PAE.

**CVLT-C – List A Trial 1 Free Recall**

An independent-samples \(t\)-test was used to determine if there were differences in free (list) recall scores between PAE participants based on their level of exposure to postnatal risk(s). There were two outliers in the data (moderate-high exposure condition), as assessed by inspection of a boxplot. There was no statistically significant difference in free recall ability, \(t(27) = -.355, p = .725, d = .13\), for participants with absent-low risk exposures \((M = 5.57, SD = 1.99)\) and moderate-high risk exposures \((M = 5.87, SD = 2.45)\). This would suggest that additional exposure to postnatal risks does not appear to worsen free recall ability for words provided in a list format for children and youth with PAE.
<table>
<thead>
<tr>
<th>Measure</th>
<th>Absent-Low</th>
<th>Moderate-High</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEPSY-II Cued Recall</td>
<td>M(SD)</td>
<td>Range</td>
</tr>
<tr>
<td>Cued Recall</td>
<td>7.64(2.93)</td>
<td>2.00-14.00</td>
</tr>
<tr>
<td>BRIEF Working Memory*</td>
<td>72.79(10.77)</td>
<td>50.00-89.00</td>
</tr>
<tr>
<td>CVLT-C List A Total Trials*</td>
<td>37.79(17.32)</td>
<td>0.00-61.00</td>
</tr>
<tr>
<td>CVLT-C List A Trial 1 FR</td>
<td>-.32(.93)</td>
<td>-1.50-1.50</td>
</tr>
</tbody>
</table>

Note. Raw scores were used in all the statistical analyses. *T*-scores are reported for the BRIEF and CVLT-C Total Trials.
Chapter 5: Discussion

This study compared the verbal short-term memory abilities of children and youth with and without PAE. Given that PAE rarely occurs in isolation (Astley, 2010; Flannigan et al., 2021; Lebel et al., 2019), this study also explored the potential association between postnatal exposures and memory deficits in children and youth with PAE. Lebel et al.’s (2019) characterization tool was used to categorize various prenatal and postnatal exposures. Our findings suggest that PAE is associated with verbal memory deficits in areas of recall. However, we did not observe any associations between exposure to postnatal risks and memory deficits within the PAE sample. It is clear that additional research is needed to explore the associations between postnatal risks and neurodevelopmental outcomes. However, the memory differences observed between exposed and unexposed groups in the current study may help outline areas in need of support for children and youth with PAE.

Consistent with existing literature (Crocker et al., 2011; Mattson et al., 1996; Mattson & Roebuck, 2002; Richardson et al., 2002; Willoughby et al., 2008), children and youth with PAE exhibited difficulties in their verbal memory abilities, such that, exposed participants recalled significantly less information within a story context than unexposed participants on both free and cued immediate memory recall tasks. These findings align with previous studies identifying differences in free recall ability in children with PAE when lists of words were verbally presented (Crocker et al., 2011; Mattson et al., 1996). Our findings are also consistent with studies that have used story contexts (i.e., Willoughby et al., 2008), where they found that children and youth with FASD had significantly lower free recall scores on both story and word-pair tasks compared to children and youth without FASD. While previous studies (Crocker et al., 2011; Mattson et al., 1996; Willoughby et al., 2008) have also measured cued recall
performance, this has occurred after a delay and only in word-list formats due to the nature of the tasks. There is no previous research, to our knowledge, that has investigated immediate free and cued recall abilities within story contexts between children and youth on the basis of PAE. For this reason, it is uncertain if immediate recall can be supported through the use of cues within this population. Therefore, our findings extend upon the current literature by providing insight on how exposed and unexposed groups differ on these forms of immediate recall, specifically within situations where information is verbally provided in a story format. We anticipated that group differences would be less substantial in the cued condition as cues may help facilitate recall. However, given that significant group differences were observed in both the free and cued conditions, these findings highlight that children and youth with PAE may require support above and beyond simple verbal memory cues when presented with information in story formats.

It is well known that there are differences in FSIQ between exposed and unexposed individuals (De L. Ferreira & Cruz, 2017). Consequently, we investigated potential differences in intellectual functioning between these two groups in this study, and as anticipated, there were significant differences in FSIQ between the two groups, such that children and youth with PAE had lower FSIQ scores than the unexposed group. As such, we examined if variances in intellectual functioning would better account for the differences observed on both memory recall tasks. After controlling for FSIQ, the exposed and unexposed children and youth did not significantly differ in their free and cued memory recall abilities; thus, it is likely that differences in intellectual functioning may explain the variance in memory profiles. These findings are consistent with Mattson and colleagues (1996) as they observed significant free recall differences on the basis of PAE before, yet not after, controlling for variance in intellectual functioning. Conversely, after controlling for FSIQ, Vaurio et al. (2011) found significant differences in that
children and youth with PAE recalled fewer words than children and youth without PAE. These findings are fascinating as the word task used in the study (Vaurio et al., 2011) involved an implicit learning strategy of semantic categorization. This learning strategy is thought to favour verbal information retention as participants are provided with the same list of words several times (Mattson & Roebuck, 2002; Roebuck-Spencer & Mattson, 2004). However, despite this implicit learning strategy, it is evident that even after accounting for differences in intellectual functioning, differences in list learning ability remained apparent (Vaurio et al., 2011). In the current study, although our free and cued immediate recall tasks did not involve a similar learning strategy, evidence suggests that children with FASD exhibit stronger recall abilities on story tasks than word formats (Pei et al., 2008). As a possible explanation, stories may provide a context in which information can be remembered (Willford et al., 2004). In contrast, word tasks require the individual to generate their own context for the verbal information they receive (Willford et al., 2004). As such, despite the lack of implicit learning strategies in our free and cued recall tasks, it is possible that story formats also favour recall abilities but in different ways.

Since the exposed and unexposed groups differed on FSIQ in the current study, we wanted to further investigate if the variance in intellectual functioning would better account for the observed memory differences. To account for these differences in IQ, researchers examining neurocognitive processes in individuals with FASD have statistically controlled for IQ in their data analyses or matched participants based on their cognitive abilities (Mattson et al., 1996; Vaurio et al., 2011; Willoughby et al., 2008). This approach is also quite common in neurocognitive research involving other NDDs, including ADHD (Ahmadi et al., 2014; Cockcroft, 2011; McLean et al., 2004) and autism (Funabiki & Shiwa, 2018; Macizo et al., 2016; Southwick et al., 2011). A plausible explanation for opting to use FSIQ as a covariate or
matching variable is that in doing so, researchers can rule out alternative explanations for statistical differences. For instance, if significant findings are observed after controlling for FSIQ, researchers can be more confident that performance differences are not due to potential differences in intellectual functioning.

The decision to match on, control, or not control for FSIQ within neurodiverse populations, however, is a highly controversial topic that has been met with scrutiny and uncertainty. When studying neurocognitive outcomes in individuals with neurodevelopmental disabilities (NDDs), it has been argued that using FSIQ as a covariate or a matching variable is generally a misguided approach (Dennis et al., 2009). There are a variety of reasons as to why controlling for or matching on FSIQ is problematic, potentially counterintuitive, and often inappropriate within NDD populations. First, Dennis and colleagues (2009) explain that NDDs lack a period of normal development by nature. As such, FSIQ scores for a child with an NDD are continuously confounded by the condition itself. Therefore, separating an FSIQ score from the effects of the disorder is ultimately not possible (Dennis et al., 2009). In addition, researchers have also suggested against using a variable for which populations differ as a covariate (Adams et al., 1985; Dennis et al., 2009). When considering the relation between FSIQ and memory, it is also thought that controlling for FSIQ may remove meaningful variance in the data (Crocker et al., 2011). Further, it is suggested that using FSIQ as a covariate or as a matching variable may overcorrect findings on neurocognitive functioning (Dennis et al., 2009). For these reasons, the appropriateness of using these methods when studying neurocognitive outcomes within NDD populations has been called into question.

As mentioned previously, many individuals with FASD have an uneven profile of abilities (Streissguth & O’Malley, 2000), suggesting that their FSIQ may not be entirely
representative of their actual cognitive functioning (Mukherjee et al., 2006). As such, when controlling for FSIQ in exposed populations, the findings may not be entirely informative. Further, attaching such values to the exposed and unexposed groups may be inappropriate as the FSIQ scores are likely more meaningful and accurate for the unexposed cohort. Considering this information, while differences in FSIQ may better explain memory deficits, this interpretation must be cautioned as FSIQ is not entirely representative of intellectual functioning in FASD populations. There are drawbacks and limitations to both methods (i.e., controlling or not controlling for FSIQ) when studying neurocognitive outcomes within NDD populations. Ultimately, as implied by Burack and colleagues (2004), there is no perfect matching strategy. Instead, methodologies must be guided and informed by research objectives, and findings should be interpreted within the context of the chosen methods (Burack et al., 2004). As mentioned, studies have generally either controlled or not accounted for IQ differences when observing recall ability amongst exposed and unexposed populations. For the reasons outlined by Dennis et al. (2009), and in line with the work of Mattson and colleagues (1996), the current study opted to present findings using both methods in hopes of providing a comprehensive, unbiased analysis. By implementing both methods of analysis on the same two groups (i.e., exposed and unexposed), we were able to make valid comparisons while limiting extraneous variables.

Intellectual functioning appears to be an influential mechanism in the memory abilities of children and youth with PAE. However, in addition to FSIQ, it is essential to recognize other underlying factors that may account for the observed memory challenges. As previously outlined, PAE appears to adversely affect most areas of the brain (Lebel et al., 2011; Sulik, 2014), especially the hippocampus, which is a critical region for memory and learning (Autti-Rämö et al., 2007; Coles & Li, 2011; Fontaine et al., 2016; Willoughby et al., 2008). As such,
the reductions in hippocampal volume commonly observed in PAE populations (Archibald et al., 2001; Riikonen et al., 2005, 2007; Willoughby et al., 2008) may help explain the observed deficits in areas of memory and recall. Further, as externalizing and internalizing disorders are commonly experienced by individuals with FASD (Fryer et al., 2007; Pei et al., 2011a), there is potential for memory challenges to be further exacerbated by other comorbidities (i.e., attentional challenges due to ADHD). For instance, as memory tasks require sufficient attention (Chun & Turk-Browne, 2007), children and youth who meet the criteria for both diagnoses are likely at a more substantial memory disadvantage. Given the high rates of comorbidity, it may be the case that working to improve attention may also indirectly improve memory performance within this population.

The second research question aimed to investigate if the presence of postnatal risks was associated with more pronounced memory deficits for children and youth with PAE. Specifically, the memory domains of interest included free and cued (story) recall, working memory, list learning, and free (list) recall. Among the children and youth with PAE, we anticipated that participants with moderate-high levels of exposure to postnatal risks would experience memory deficits above and beyond that of individuals with absent-low levels of exposure to postnatal risks. This hypothesis was in line with the EBD framework (Shonkoff et al., 2012), positing that a combination of stressors and environmental threats can lead to brain structure and function changes. After dividing the PAE participants according to their level of exposure to postnatal risks, the groups did not significantly differ concerning their memory abilities across any of the five assessment measures of interest; however, a slight pattern was observed. The Aim 2 findings did not approach significance; however, a slight pattern in the moderate-high exposure group was observed such that they had slightly higher memory scores.
than the absent-low exposure group, but these differences were small. Interestingly, the pattern was not in line with what was hypothesized; however, an overinterpretation is cautioned as each analysis lacked statistical significance. We might anticipate that with a larger sample size, group differences may have been identified, with children and youth in the absent-low exposure group potentially outperforming the moderate-high group on all memory tasks.

While the pattern of the findings was unexpected, a similar theme has emerged in previous literature. As discussed, Mukherjee and colleagues (2019) determined that neglect did not have an additional impact on the neurodevelopmental outcomes of individuals with FASD (aged 6-26 years). However, the inclusion of multiple postnatal risks in a recent risk characterization framework (Lebel et al., 2019) demonstrates the importance of considering several other potential risk factors in addition to neglect. Adverse outcomes arise due to the interplay among various risk factors (Astley, 2010), and as such, focusing solely on neglect may limit the generalizability of these findings.

In a study that utilized a more comprehensive postnatal risk approach, Andre and colleagues (2020) found that children and youth with PAE who had no adverse postnatal exposures (PAE-) exhibited more structural brain differences than those with both exposures (PAE+) when compared to controls. As such, these researchers suggest that prenatal and postnatal risks may interact differently with brain development, whereby adverse postnatal exposures may ultimately accelerate brain development (Andre et al., 2020). As it pertains to the current study, the findings by Andre et al. (2020) may help explain why the moderate-high group demonstrated slightly stronger performance than the absent-low exposure group across all of the memory measures. However, as mentioned, each of the analyses lacked statistical significance; thus, this interpretation should be cautioned. Further, while an acceleration may explain the lack
of measurable brain differences between controls and PAE+ participants (aged 7-16 years), Andre and colleagues (2020) suggest that this acceleration likely coincides with an early developmental plateau. This is in line with other studies highlighting that premature brain development can consequently lead to underdevelopment later on as a result of the early plateau (Courchesne et al., 2007; Deoni et al., 2016; Shaw et al., 2006).

In summary, there is some evidence to suggest that PAE may account for more neurodevelopmental harm than postnatal risks (Mukherjee et al., 2019) and that children with both exposures (PAE and postnatal risks) may more closely reflect typical brain development than individuals with PAE only (Andre et al., 2020). However, there is also evidence that dual exposures pose more significant risks, above and beyond that of PAE, for neurodevelopmental deficits across various domains, including areas of memory (Henry et al., 2007; Price et al., 2017). In light of this conflicting evidence, additional research is required to understand and delineate the potential associations between postnatal exposures and neurodevelopment within PAE populations.

Implications

Taken together, the findings from the present study have various implications for children and youth with PAE. While deficits in FSIQ may help explain memory challenges in this population, it is equally important to appreciate that FSIQ may not be representative of true functioning for these children and youth (Mukherjee et al., 2006). There are also other potential mechanisms (e.g., presence of comorbid mental health issues) that may underlie memory difficulties seen in children and youth with PAE. Regardless of the mechanisms that best account for memory deficits within PAE populations, it remains apparent that these children and youth exhibit deficits in several domains, including memory. As such, this is an area in need of
continued support as challenges in memory recall may undermine academic achievement. In multiple environments, tasks that require the use of free and cued memory recall abilities may need to be adapted or accommodated for individuals with PAE. For instance, in classroom settings, children and youth with PAE will likely benefit from explicit step-by-step instruction, continuous repetition and reminders, limited distractions, and the use of multiple teaching modalities (i.e., pairing verbal information with additional visual or sensory cues). In addition, given the observed challenges, it will be important for educators to set reasonable expectations around tasks that require recall abilities.

Additionally, there are further implications when considering the nature and characteristics of the data collected. In line with expectations, PAE frequently occurred alongside other prenatal risks and additional postnatal adversities for children and youth in the current study. In conjunction with PAE, these additional exposures highlight the complexities within this population and the importance of considering other experiences when conducting research or working clinically within this area. While we were unable to establish memory differences based on postnatal exposures in the current study, the consideration of these exposures remains essential. As discussed by Lebel and colleagues (2019), other co-occurring exposures may be overlooked when deficits or negative outcomes are attributed to only one cause (i.e., PAE). By considering additional experiences or exposures, including the child’s environment, diagnostic accuracy may be improved (Lebel et al., 2019). Furthermore, when a child receives an accurate diagnosis, it helps to inform treatment and interventions that are appropriate and consistent with the child’s needs (Lebel et al., 2019). In summary, through considering other exposures that commonly accompany PAE/FASD, it is believed that the challenges and needs of individuals within this population will be best understood.
Limitations

While the present study has meaningful implications, limitations are important to consider. First and foremost, it is important to recognize that the children and youth who expressed personal interest in being included in the study may not be entirely representative of all individuals with FASD. As such, a generalization of these findings should be cautioned. In addition, as measured by the BRIEF, working memory ability was the product of caregiver evaluation. It is possible that caregivers may lack an accurate understanding of their child’s neurocognitive functioning. Additionally, for the second aim, children and youth with PAE were divided based on their level of exposure to all postnatal exposures (both threat and deprivation exposures). However, as mentioned, threat and deprivation are thought to influence emotional processing and cognitive domains, respectively (McLaughlin & Sheridan, 2016). As a result of small sample sizes, these two dimensions of postnatal risk (threat and deprivation) were not separated. Due to the nature of our research question and the emphasis on memory, there is potential that experiences of deprivation may have been more telling as they are suggested to influence cognitive domains (McLaughlin & Sheridan, 2016). Another limitation is that we created the two postnatal exposure groups using a median split. This split type is not entirely ideal because it assumes that every value above or below the median is equal (Grace-Martin, n.d.), and this was not the case for the current sample. Further, categorizing a continuous variable (i.e., postnatal risk score) reduces power (Aiken et al., 1991), meaning that the median split made it more challenging to identify any true potential associations between postnatal risks and memory ability.

Consistent with the literature (Astley, 2010; Flannigan et al., 2021; Lebel et al., 2019), PAE commonly occurred alongside additional risks and adverse experiences in the current study.
Specifically, children and youth with PAE in our sample were very heterogeneous in their prenatal exposures. For instance, maternal alcohol consumption ranged substantially from unknown amounts \((n = 2)\) or multiple occurrences throughout pregnancy to daily binges (4+ drinks and/or drinking to blacking out). However, despite these varying levels of PAE, all participants were considered to be equal in this respect, as PAE rankings (i.e., 2-4; Lebel et al., 2019) were not used in the analyses. Similar to PAE, prenatal exposure to other substances and maternal toxic stress was highly variable within the sample. Despite the importance of considering multiple exposures and experiences, the current study did not include other prenatal substance exposures (i.e., marijuana) or prenatal stressors (i.e., harm to the mother). This group of children and youth with PAE were also exceptionally diverse in their postnatal exposures. While the majority \((n = 23)\) of the participants had been adopted into stable environments, many children and youth had still been exposed to postnatal risks (i.e., physical abuse), depending on the age of stable placement. Unfortunately, instances of sexual and emotional abuse were also reported for several participants. In light of how heterogeneous the PAE sample was in both their prenatal and postnatal exposures, it is challenging to make conclusions about how postnatal risks may be associated with memory deficits.

Findings from the current study highlight the need for future research. First, as discussed, the analyses were largely underpowered due to small sample sizes, especially in the second aim. Post-hoc power analyses were conducted and indicated that a substantially larger sample size was needed in order to see a medium effect size \((0.5)\). For example, 128 participants were needed for the independent-samples \(t\)-tests (Aim 1 and 2), 269 for the ANCOVAs (Aim 1), and 134 for the Mann-Whitney U tests (Aim 2). As such, to make accurate conclusions about the memory profiles and potential role of postnatal risks for children and youth with PAE, future
studies would greatly benefit from larger and more homogeneous samples. Second, as threat and deprivation appear to influence different systems and areas of development, future analyses with larger samples may benefit from separating these risks when looking to understand specific associations with memory ability. Third, the literature outlining potential associations between PAE, postnatal risks, and impaired cognitive domains is conflicting and relatively sparse. As such, the field would likely benefit from a continued focus on understanding the mechanisms behind various prenatal and postnatal exposures and how these interactions may predict developmental outcomes for children and youth. Lastly, there appears to be a gap in the literature regarding research on interventions for memory deficits in individuals with PAE/FASD. Considering the free and cued memory recall differences observed between exposed and unexposed children and youth, it would be beneficial to explore potential interventions that aim to support these memory challenges in various environments and contexts.

**Conclusions**

Fetal alcohol spectrum disorder is an NDD attributable to PAE. Despite the well-documented teratogenic nature of alcohol when consumed during pregnancy, PAE remains a prevalent health concern that is known to impair various areas of functioning. In particular, verbal memory is a domain known to be implicated by exposure to alcohol in utero. While memory deficits have been well-documented within this population, specific gaps have remained. To expand upon the literature, the present study investigated group differences in short-term verbal memory ability between exposed and unexposed children and youth. As groups differed on the basis of exposure, our findings suggest that PAE is associated with deficits in areas of memory, namely free and cued immediate recall. While these difficulties may be better
explained by impairments in intellectual functioning, the identified challenges necessitate adequate support for children and youth with PAE, nonetheless.

Further, it is well-documented that PAE rarely occurs in isolation; most children and youth with PAE also experience other exposures and adversities, including postnatal threats and deprivations. While the current study confirms the heterogeneous nature of other exposures in children and youth with PAE, further research is needed to understand the unique associations between adverse prenatal and postnatal exposures and developmental outcomes within this population. Additional insights into the developmental trajectories of PAE in conjunction with postnatal risks may help inform interventions for exposed individuals and their families. As demonstrated by Lebel and colleagues (2019), there is a marked need for PAE research to involve consideration and recognition of the additional exposures that individuals within this population commonly experience and endure. The presence of postnatal risks may influence memory deficits; however, to permit valid conclusions, it is recommended that future researchers study larger samples of children and youth with homogeneous exposures and consider taking a longitudinal approach.
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