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Major Depression and its Association to Lower Brain Volume and Fetal Alcohol Syndrome

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Major Depression and its Association to Lower Brain Volume and Fetal Alcohol Syndrome

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Bachelors of Science
Georgia Institute of Technology
2007

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An abstract of
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Abstract

Major Depression and its Association to Lower Brain Volume and Fetal Alcohol Syndrome
By Giorgina F. Donati

Fetal alcohol spectrum disorders (FASD) are different kinds of disorders that result from maternal alcohol consumption during pregnancy. Studies have shown that individuals who have the most severe form of the disorder, Fetal Alcohol Syndrome (FAS) have microcephaly (lower brain volume). However, few studies have shown the association between microcephaly as a result of FAS and its association to psychological disorders, in particular, major depression. The purpose of this research was to use an already existing set of data on individuals who have been diagnosed with FAS, and study whether there is an association between lower brain volume and the onset of major depression. In order to assess this relationship, a secondary data analysis was performed on 94 African-American young adults identified in the prenatal period. 3 groups (Control, n=27; Alcohol-exposed Neurodevelopmental Disorder, n=37 and Dysmorphic, n=30) have been imaged using structural magnetic resonance imaging (MRI). Depression was measured using the Composite International Diagnostic Interview (CIDI). The data was analyzed using bivariate and multivariate analyses. The results of this research indicate sex differences in amygdala volume, as well as intracranial volume differences within the groups. However, the results of this study did not find an association between lower brain volume as a result of FAS and developing psychological disorders.

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I. INTRODUCTION

Fetal alcohol spectrum disorders (FASD) is an umbrella term used to describe the range of teratogenic effects of alcohol on a developing fetus (Ipsiroglu, McKellin, & Loock, 2013 & Spohr, Willms, & Steinhausen, 2007). It is a serious public health, social and economic issue that affects not only children, but also adults across the world (Popova, Stade, Beckmuradov, Lange, & Rehm, 2011). Its effects have been recognized for centuries, as seen in the texts of Aristotle and Biblical writings (Manning & Hoyme, 2007). In 1899, Sullivan noted that alcoholic women, who were imprisoned in England and had access to alcohol, had higher rates of miscarriage and their children displayed unique patterns of birth defects (Manning & Hoyme, 2007). It was also noted that infants tended to be healthier if the pregnancy occurred while the mother was in prison with no exposure to alcohol (Manning & Hoyme, 2007). However, in modern times, the link between mothers who drank heavily throughout their pregnancy and abnormal fetal development was not made until 1968 (Lemoine et al., 1968).

Lemoine et al. (1968) were the first to link the two when they published a report in which common problems in children of women who drank during pregnancy were described (Manning & Hoyme, 2007). However, they did not specify diagnostic criteria for affected children (Manning & Hoyme, 2007). Jones and Smith, however, described in detail consistent patterns of malformations and consequences in children of mothers whom consumed alcohol during pregnancy (Jones & Smith, 1973). They coined the term *fetal alcohol syndrome* (FAS) and presented its diagnostic criteria as craniofacial abnormalities, growth retardation,

delayed psychomotor maturation, and impaired intellectual development (Goodlett, 2010**;** Manning & Hoyme, 2007**;** Spohr et al., 2007). FAS was also identified by French authors and became known for its major part in the development of intellectual disability (Spohr et al., 2007). Animal research has confirmed all of these observations and has been a crucial tool for advancing the understanding of alcohol-induced developmental disorders (Goodlett, 2010).

FASD disabilities fall along a spectrum that may vary from microcellular and neurochemical aberrations to gross structural anomalies (Astley et al., 2009 & Popova et al., 2011). Prenatal alcohol exposure is also a leading cause of developmental delay (Spohr et al., 2007). The neuropsychological effects vary, but may include problems with verbal and nonverbal learning, speech and language delays, attention deficits, and problems with executive functioning (Manning & Hoyme, 2007). Furthermore, individuals affected by a FASD also have birth defects, growth problems, and speech and language difficulties (Popova et al., 2011). It has also been shown that individuals with FAS are more susceptible to impaired vision, cardiac anomalies such as septal defects and hypoplastic pulmonary arteries, urogenital defects, skeletal abnormalities, and hearing problems (Manning & Hoyme, 2007**;** Popova et al., 2011, & Pruett, Waterman, & Caughey, 2013).

According to the Institute of Medicine, when a child is suspected of having a FAS diagnosis, three major areas of clinical features must be evaluated:

1) A characteristic pattern of minor facial anomalies that include:

a. Short palpebral fissures (the space between the margin of the eyelids) at or below the 10th percentile when compared to and plotted against racially appropriate norms (if available).
b. Smooth or flattened philtrum (midline groove in the upper lip that extends from the upper lip to the nose) with a score of 4 or 5 on the 5-point scale of the lip-philtrum guide, a 5-point pictorial ruler that is used by medical personnel to accurately measure philtrum smoothness and upper lip thinness (FAS Diagnostic & Prevention Network, 2014).
c. Thin vermilion border of the upper lip (demarcation between lip and adjacent normal skin) with a score of either 4 or 5 on the 5-point scale of the lip-philtrum guide.

2) Evidence of pre- and/or postnatal growth deficiency in length and weight of less than or equal to 10% in the affected fetus/child when compared to and plotted against racially appropriate norms (if available).
3) Evidence of central nervous system abnormalities that represent structural or functional brain damage and may include: microcephaly (reduced brain volume), structural brain anomalies, motor deficits, abnormal muscle tone, tremors, neurosensory hearing loss, and visual anomalies (Manning & Hoyme, 2007).

It is imperative that a thorough examination be conducted in the evaluation of a child or individual suspected of it (Manning & Hoyme, 2007). In addition to a sound physical examination, an evaluation must include a comprehensive

neurocognitive and behavioral assessment (Manning & Hoyme, 2007). In the last decade, it has become possible to directly study the effects of alcohol on human brain structure and functioning (Ma et al., 2005). Abnormalities in brain size and shape, agenesis of the corpus callosum, decreased cerebellar and ventricular size and small basal ganglia have been confirmed on both autopsy and imaging studies using computed tomography (CT) and magnetic resonance imaging (MRI) (Manning & Hoyme, 2007 & Pruett et al., 2013). These findings have been shown to persist throughout adolescence and young adulthood (Pruett et al., 2013).

The Fetal Alcohol Study Group of the Research Society on Alcoholism proposed the term *fetal alcohol effects* (FAE) to refer to children who demonstrated some, but not all of the features of FAS (Manning & Hoyme, 2007 & Spohr et al., 2007). However, it was later discontinued because of its lack of specificity (Manning & Hoyme, 2007). Different classification systems have been suggested to standardize and clarify the FASD continuum (Burd, Martsolf, & Kerbeshian 2003). In the past 10 years, diagnostic guidelines for FASD have been published including: the Institute of Medicine (IOM) FASD guidelines in 1996, the FASD 4-Digit Diagnostic Code in 1997, 1999, and 2004, the Centers for Disease Control and Prevention (CDC) FAS guidelines in 2004, the Canadian FASD guidelines in 2005, and the Hoyme FASD guidelines in 2005 (Astley et al., 2009). The Canadian guidelines are the most similar to the 4-Digit Code (Astley et al., 2009). On the other hand, the CDC guidelines only address FAS, and have a more relaxed facial and central nervous system (CNS) criteria (Astley et al., 2009). The Hoyme guidelines diverge

considerably from the 4-Digit Code, the CDC guidelines, and the Canadian guidelines, though they still address the full spectrum of outcomes (Astley et al., 2009).

In 2002, the CDC, acting through the National Center on Birth Defects and Developmental Disabilities (NCBDDD) FAS Prevention Team and in coordination with the National Task Force on Fetal Alcohol Syndrome and Fetal Alcohol Effect put together a series of federally funded programs to, among other things, incorporate diagnosis guidelines into curricula for medical and allied health students and practitioners (CDC, 2011). In 2013, the American Psychiatric Association included FAS as a condition under the newly-created Neurodevelopmental Disorders in the updated Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5), (Recent Updates to Proposed Revisions for DSM-5 | APA DSM-5, 2014).

Children who get diagnosed after the age of 12 have a significantly increased lifetime risk of legal problems, and use of drugs and alcohol relative to those children who are diagnosed earlier (Pruett et al., 2013). Early interventions provide the child with an adequate environment that is conductive to positive outcomes (Pruett et al., 2013). Neurobehavioral intervention plans should be long-term and customized to fit the needs of each child (Pruett et al., 2013). Even though the number of successful evidence-based interventions is slow, they include: recurring individualized sessions, small group activities and virtual-reality games (Pruett et al., 2013). The range of outcomes includes: improved social skills, mathematics and reading abilities, and knowledge of fire safety (Pruett et al., 2013).

Despite warnings emphasizing the dangers of alcohol consumption during pregnancy in the United States (US), out of the four million annual pregnancies that

occur each year, about 40% of women report drinking some amount of alcohol (Klug & Burd, 2003; Itthagarun, Nair, Epstein, King, 2007, & Pruett et al., 2013). Moreover, 3-5% of these women report drinking heavily throughout pregnancy (Burd, Martsolf, & Kerbeshian 2003). A study sponsored by the CDC has shown that, although drinking reported by pregnant women has decreased from 1995 to 1999, binge drinking (defined as at least five drinks per occasion) has remained stable at 2.9% and 2.7% in 1995 and 1999, respectively; chronic heavy drinking has remained unchanged at 3.5% and 3.3% in 1995 and 1999, respectively (Jones, 2003).

The prevalence of FASD ranges from a rate of 0.30 (FAS only) to 9.1 cases per 1,000 live births (FASD) and is highest in African American, American Indian, and Alaskan-native populations (Klug & Burd, 2003, & Itthagarun et al., 2007). This would suggest that the annual number of affected pregnancies in the United States ranges from 1,200 to 36, 400 (4.0 million pregnancies x rate of 0.30 per 1,000 live births to 4.0 million pregnancies x rate of 9.1 per 1,000 live births) (Burd, Martsolf, & Kerbeshian 2003). Moreover, cause-specific mortality for FASD is 6%, or about 2100 to 2300 deaths annually; this establishes FASD as an important cause of morbidity and mortality in the U.S. (Klug & Burd, 2003).

A cumulative risk model provides information regarding the number of risk factors a child is said to “tolerate” before deterioration in psychosocial adjustment is seen (Yumoto, Jacobson & Jacobson, 2008). African Americans have been underrepresented in studies examining cumulative risk; understanding the vulnerability to socio-environmental risk in this population is important because

they are disproportionately exposed to environments with high levels of psychosocial risk (Yumoto, Jacobson & Jacobson, 2008). Additionally, studies have demonstrated that lower socioeconomic status is associated with a wide range of poorer outcomes in children, including socio-emotional functioning and neuro-cognitive abilities (Yumoto, Jacobson & Jacobson, 2008). A study conducted by Levy-Shiff, Einat, Mogilner, Lerman, & Krikler (1994) examined the role of biological and psychosocial factors and their influence in long-term outcome in adolescents born prematurely at very low birth weight and compared them to adolescents born at full term with normal birth weight (Levy-Shiff, Einat, Mogilner, Lerman, & Krikler, 1994 & Yumoto, Jacobson, & Jacobson, 2008). The results suggest that socioeconomic status predicted visual-motor coordination and hyperactive behavior in the very low birth weight group but not in the control group, thus suggesting an interaction between biological vulnerability and environmental risk (Levy-Shiff et al., 1994 & Yumoto et al., 2008).

The financial impact of FASD in the US is troublesome. Individuals require lifelong care and commonly face continuity of care management problems (Ipsiroglu et al., 2013). The annual cost of FASD ranges from $74.6 to $9.7 billion per year (Klug & Burd, 2003). This difference is over 116-fold and very likely underestimates the true cost of care from all impacted service systems (Klug & Burd, 2003). Costs such as prevalence are strongly influenced by diagnostic thresholds. Therefore, using a FASD prevalence rate of 0.33 cases per 1000 live births would yield an annual cost of $74.6 million (Klug & Burd, 2003). Additionally, two cost studies have determined lifetime cost estimates (per case) of caring for someone with a FASD in

excess of $1.4 million (Burd, Martsolf, & Kerbeshian 2003, & Klug & Burd, 2003). Even though these numbers are already significant, they are likely to be minimal estimates since the data available does not include all affected people and/or costs (Klug & Burd, 2003**,** & Popova et al., 2011).

Many individuals with a FASD face cognitive difficulties and significant maladaptation that prevents them from leading productive, independent lives (Astley et al., 2009). One area of behavioral functioning that is difficult for children with FASD is the development of positive peer relationships (Frankel, Paley, Marquardt, & O'Connor, 2006). Clinical reports describe children with a FASD as having poor social judgment as well as failing to consider the consequences of their actions (Mooney & Varlinskaya, 2010). There have also been reports of children not understanding social cues, and having difficulty communicating in a social context (Frankel et al., 2006). These behaviors are seen as more challenging to treat because children with a FASD may respond only partially to pharmacological treatment (Ipsiroglu et al., 2013). In addition, studies of adolescents and adults with a FASD have shown that social skill deficits such as difficulty interacting with peers and deficits in responding to social cues continue well into adulthood (Frankel, 2006, & Mooney & Varlinskaya, 2010).

Sleep problems are also under-diagnosed in children with a FASD (Ipsiroglu et al., 2013). It's been estimated that there is a 75-80% prevalence rate of sleeping problems in the sleep habits of children with neuro-developmental disorders/disabilities (Ipsiroglu et al., 2013). The most common manifestations include insomnia, difficulties falling asleep and maintaining sleep; as a consequence,

sleep deprivation presents itself as daytime inattention, hyperactivity, and mood disturbances (Ipsiroglu et al., 2013). Another effect of FASD is the stigma it places on an individual's family. According to the Institute of Health and Economics (2009), "FASD also affects all other members of the immediate family, including siblings and the extended family. Emotional, financial, and social burdens can be considerable." (Ipsiroglu et al., 2013).

Current research suggests that prenatal alcohol exposure causes changes in the brain that can predispose an individual to have an increased risk of mental health disorders (Conry & Fast, 2010). It has been shown that children with a FASD are more prone to have secondary disabilities such as depression and anxiety disorders (Yumoto et al., 2008, & Hellemans, Sliwowska, Verna, & Weinberg, 2009). Major Depressive Disorder is defined in the DSM-IV-TR as

> "Depressed mood and/or loss of interest or pleasure in life activities for at least 2 weeks…[as well as] symptoms that cause clinically significant impairment in social, work, or other important areas of functioning almost every day" (DSM-IV-TR, APA, 2000).

Severe forms of depression affect between 2-5% of the population in the U.S., with up to 20% being affected by a milder form (Hellemans et al., 2009). In addition, the World Health Organization rates depression as one of the top 10 causes of morbidity and mortality worldwide (Hellemans et al., 2009).

Depression is one of the most commonly reported problems in children and adults with FASD (Hellemans et al., 2009). It is connected with the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis, which is reflected as an increase in

HPA tone or activity (Hellemans et al., 2009). Moreover, being prenatally exposed to alcohol increases HPA tone, which in turn results in HPA dysregulation throughout life; this parallels many of the HPA changes seen in depression (Hellemans et al., 2009).

The theoretical framework that will be used for this research study is the Diathesis-stress model. Central to this framework is the view that some individuals, because of a "vulnerability" in their make-up, whether behavioral/temperamental in character, physiological or endophenotypic in nature, or genetic in origin, are disproportionately likely to be affected adversely by some kind of environmental stressor (Belsky & Pluess, 2009). One common theme of research in this area is that these "vulnerabilities" inhibit successful adaptation when an individual is faced with adversity (Roisman et al., 2012). Research suggests that this model provides a powerful approach for elucidating mechanisms underlying the vulnerability to mental conditions among individuals with FASD (Hellemans et al., 2009).

Environmental stressor can be anything from child maltreatment, insensitive parenting, negative life events, etc (Belsky & Pluess, 2009 & Roisman et al., 2012). The idea is that the individuals who experience a negative event, or the ones who carry certain "vulnerability genes" which are latent diatheses, result in maladaptation when "triggered" by poor experience (social/environmental factors); as a result, there is manifestation of a psychopathological condition (for example, depression) when exposed to a stressor of interest (See Figure 1)(Belsky & Pluess, 2009 & Roisman et al., 2012). The Diathesis-stress model provides a solid

foundation as to why individuals with FASD are more likely to be diagnosed with mental health disorders.

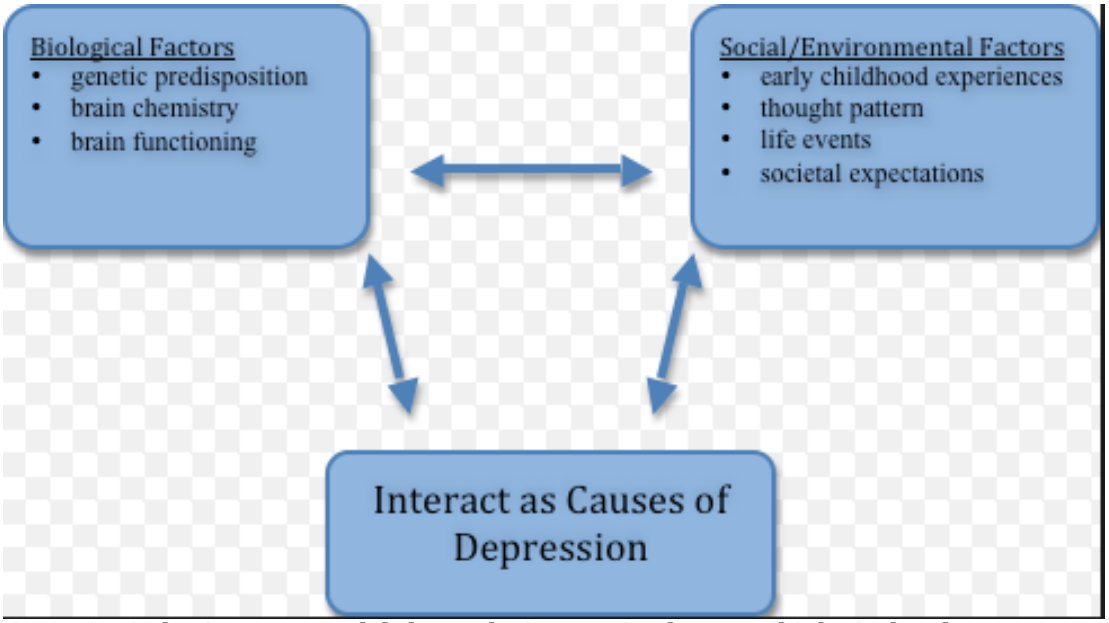

Figure 1. Diathesis-stress model shows the interaction between biological and social/environmental factors and how they may predispose an individual to depression, for example. http://psychproject.wordpress.com/theory/

It is important to study the association between having a FASD, low brain volume, and depression. Current literature supports the link between FASD and low brain volume, as well as FASD and depression. However, to our knowledge, no studies have looked at the association between all three. This study is being conducted in order to study the relationship between being diagnosed with FAS and developing major depressive disorder in adulthood. The findings from this research study could help develop prevention strategies for individuals who may be at risk of developing mental disorders, in particular, major depressive disorder. It can also help clinicians have a better understanding of the complete symptomatology of FASD and provide more resources and tools to those who may be most vulnerable. This research builds upon the findings obtained from a prior longitudinal study that

showed an association between the physical effects of prenatal alcohol exposure and deficits in memory. Therefore, based on previous research, we hypothesize that individuals with lower brain volumes as a result of FAS have a higher incidence of psychological disorders, in particular, major depressive disorder.

II. LITERATURE REVIEW

In order to better understand FASD, one must be able to understand the association between the diagnosis and its relationship to low brain volume. The literature suggests marked volume reductions in the cranial vault and as well as overall brain volume reductions in individuals with a FASD when compared to healthy controls (Coles et al., 2011;Nardelli, Lebel, Rasmussen, Andrew, & Beaulieu, 2011). It has also been suggested that alcohol may exert its teratogenic effects on the brain as a whole, rather than having specific pattern of effects (Chen, Coles, Lynch, & Hu, 2012). The literature also shows that the teratogenic effects of alcohol are associated with smaller head circumference; as head size decreases, the severity of FASD diagnosis increases (Coles et al., 2011 & Roussotte et al., 2012). In fact, microcephaly is one of the hallmarks of FAS diagnosis (Jones, 2003, & Roussotte et al., 2012).

Current research shows that individuals who are heavily exposed to alcohol prenatally not only experience significant deficits in cognitive and psychosocial functioning, but also alterations in brain structure that persist into adulthood (Coles et al., 2011 & Roussotte et al., 2012). A study by Roussotte et al., (2012) found significant correlations between general intellectual functioning and regional brain volumes in the FASD group, but not in the control group (Roussotte et al., 2012). Furthermore, they found the putamen to be one of the regions that most differed between the exposed and non-exposed group, which could play an important role in numerous cognitive and behavioral impairments that affect children prenatally exposed to alcohol (Roussotte et al., 2012). An MRI case report of two adolescents

with FAS demonstrated: disproportionately volume reductions of the basal ganglia by 46% and the thalamus by 61% relative to the 28% reduction of the cerebral vault (Nardelli et al., 2011). Subsequent studies on less affected children and adolescents with a FASD, however, showed basal ganglia and caudate reduction (but not the thalamus) to a greater extent than the cerebral vault; further studies with improved imaging quality have confirmed these findings (Nardelli et al., 2011). Furthermore, structural imaging studies have consistently showed abnormalities and reduced volume of multiple brain systems, including frontal, parietal, and temporal regions, cerebellum, corpus callosum, cerebral cortex, basal ganglia, and in the white matter that connects these brain regions (Astley et al., 2009, Fryer et al., 2012, Mohapel et al., 2011, & Roussotte et al., 2012). Studies have also found an association between these anatomical differences and cognitive function, thus suggesting clinical significance to the structural brain abnormalities (Roussotte et al., 2012).

In the Roussotte et al., (2012) study, seven subcortical brain regions-thalamus, caudate, putamen, pallidum, hippocampus, amygdala, and ventral diencephalon were measured in addition to hemispheric measures of total brain, total cortical gray matter, and total white matter volumes in 99 adolescents (Astley et al., 2009 & Roussotte et al., 2012). The results showed that, not only did the FASD group have smaller brain volumes overall, but they also showed highly significant volume reductions in all the brain regions that were evaluated (Roussotte et al., 2012). The literature suggests that the more alcohol a mother drinks while pregnant (as measured by maternal report of number of drinks consumed per week during

the first trimester) the greater the brain volume reductions later in life (Roussotte et al., 2012).

Additionally, Cortese et al., (2006) found in their study of children diagnosed with FAS, an overall 13% smaller brain size compared to the brains of the control group; a 12% brain size reduction was also seen in the alcohol exposed group (Cortese et al., 2006). These findings are supported by laboratory animal studies and human autopsy studies (Cortese et al., 2006). When cortical and deep grey matter was differentiated, the latter was disproportionally affected in the FASD group (Nardelli et al., 2011).

A study conducted by Chen et al., (2012) found a disproportionate prenatal alcohol exposure effect in several occipital and temporal regions in both brain hemispheres, none of which had been identified before (Chen, Coles, Lynch, & Hu, 2012). Additionally, they wanted to determine whether prenatal alcohol exposure effects on the brain differ within gender, an area that has not been previously investigated in human samples, although animal studies have shown brain structure differences in animals prenatally exposed to alcohol (Chen, Coles, Lynch, & Hu, 2012). As it was hypothesized, gender differences were identified; more specifically, a difference in prenatal alcohol exposure effect was shown in several cortical regions of interest (ROIs), suggesting that males may be more vulnerable to prenatal alcohol exposure than females (Chen, Coles, Lynch, & Hu, 2012).

In addition to the studies mentioned above, 21 adolescents (with a mean age of 13) with a history of heavy prenatal alcohol exposure were compared to seven healthy controls who underwent an MRI procedure and neurobehavioral testing

(Fryer et al., 2012). The results indicated moderate to large cognitive performance, as well as brain volume reductions in the alcohol-exposed cohort when compared to the healthy controls (Fryer et al., 2012). Additionally, within the alcohol-exposed group, caudate volume was found to be the most reliable predictor of neuropsychological performance (Fryer et al., 2012). These findings are supported by previous work in which disproportionate reduction of caudate volume has been observed in children prenatally exposed to alcohol (Fryer et al., 2012 & Roussotte et al., 2012).

Current research suggests that prenatal alcohol exposure causes changes in the brain that can predispose an individual to be at an increased risk of mental health disorders (Conry & Fast, 2010). Children and adolescents with FAS experience serious psychiatric and developmental disorders (Famy, Streissguth, & Unis, 1998). Additionally, children with a FASD are more prone to have secondary disabilities such as depression and anxiety disorders (Hellemans et al., 2009).

Although mental health conditions are not a criterion for a FASD diagnosis, they have been recognized in 87% and over 90% of subjects in two independent FASD studies (Barr et al., 2006 & O'Connor et al., 2002). In addition, Individuals with a FASD have a higher risk of developing mental illness (Fryer et al., 2012). Neuropsychological deficits contribute to negative life outcomes such as academic, social, and emotional problems (Kodituwakku, 2009). Additionally, Famy, Streissguth, & Unis, (1998) found a high risk of psychopathological conditions in their study cohort, manifested as alcohol and drug dependency.

Depression is one of the most commonly reported problems in children and adults with a FASD, and it is connected with the dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis (Hellemans et al., 2009). This is reflected as an increase in HPA tone or activity (Hellemans et al., 2009). The animal literature shows that fetal programming of the HPA axis by prenatal alcohol exposure alters neuroadaptive mechanisms that mediate stress response and sensitize the organism to stressors occurring later in life (Hellemans et al., 2009). This mechanism can mediate, in part, the increased vulnerability to depression (Hellemans et al., 2009). Changes in HPA activity, as well as regulation of prenatal alcohol exposure in animals have shown similarities to what is observed in patients with major depression; this is suggestive of increased HPA tone (Hellemans et al., 2009). There's also evidence that demonstrates sex-specific alterations in hormonal and behavioral responses to tasks that measure depressive behaviors in individuals prenatally exposed to alcohol (Hellemans et al., 2009). However, in the Famy, Streissguth, & Unis, (1998) study, the rate of major depression was not only surprisingly high, but it also did not differ between men and women (Famy, Streissguth, & Unis, 1998).

In a 30-year follow-up study, Lemoine et al., (2003) concluded that mental health problems are one of the most severe manifestations of a FASD in adulthood (Hellemans et al., 2009). Additionally, 3 16-year old adolescents who were prenatally exposed to alcohol showed higher rates of depressive symptoms when compared to a control group (Hellemans et al., 2009). It is important to point out that the increased risk in depression is not connected to mental retardation; the link

between being prenatally exposed to alcohol and depression also has been found in children and adults with normal intelligence (Hellemans et al., 2009). Psychiatric symptoms begin to develop at an early age in individuals with FASD (Conry & Fast, 2010). In a study of 25 subjects prenatally exposed to alcohol, the results revealed significant mental illness as the subjects matured; most also used some form of counseling or psychiatric treatment (Famy, Streissguth, & Unis, 1998). Moreover, in a patient sample, it was found that 63% had at least one psychiatric abnormality, exceeding findings from epidemiological studies in the general population (Conry & Fast, 2010 & Hellemans et al., 2009).

It has been suggested that environmental factors such as early maternal death, living with an alcoholic parent, maternal mood, child abuse and neglect, removal from the home by authorities, repetitive periods of foster care and other transient home placements, and being raised by adoptive or foster families could play a role in the increased incidence of depression that is observed in individuals who are prenatally exposed to alcohol (Conry & Fast, 2010 & Hellemans et al., 2009). When it comes to maternal mood, maternal depression was associated with high levels of negative affect; this constituted the highest scores on a child measure of depressive symptoms in 4-6-year old girls who present with high levels of prenatal alcohol exposure (Hellemans et al., 2009).

Negative affect, as well as a direct link between prenatal alcohol exposure and depressive symptoms is also seen in children who had lower levels of maternal connectedness with their mother; as a result, these children showed higher levels of depressive symptomatology (Hellemans et al., 2009). The findings indicate that

mental conditions are not only significant among adults and children with a FASD, but they also have the ability to impact health and well being (Hellemans et al., 2009). In some cases, these could be primary, rather than secondary disabilities (Hellemans et al., 2009).

In a 25- year study conducted by Barr et al. (2006) mental health conditions were assessed in a group of participants with a FASD and a group of healthy controls. The results identified a high frequency of psychiatric problems among participants with FASD (Barr et al., 2006). Additionally, the odds of having psychiatric disorders such as depression, anxiety, paranoid personality disorder, etc, were more than doubled in the FASD group (Barr et al., 2006). Another study found that 92% of individuals with a FASD in their study group had some sort of psychiatric diagnosis, which included mood disorders/depression, dysthymia, bipolar disorder, anxiety, and psychosis (Conry & Fast, 2010).

The research clearly shows that having FAS is associated with lower brain volume and increased vulnerability to mental conditions. Reduced volumes can be seen in the hippocampus, corpus callosum, thalamus, caudate, amygdala, among others. Similarly, prenatal exposure to alcohol causes changes in the brain that can predispose an individual to be at an increased risk of mental health disorders. The objective of this thesis is to study the association between having lower brain volume and the incidence of major depressive disorder. We hypothesize that there is a relationship between the observed changes in brain volume and the increased diagnosis of psychological problems.

III. METHODS

Participants

This secondary data analysis consists of a study sample of 94 young adults who participated in a longitudinal study measuring the effects of prenatal alcohol exposure on development. Mothers of participants were recruited from an urban hospital serving a predominantly African-American, low-income population between 1980 and 1986 in Atlanta, Georgia. Women were screened for the quantity and frequency of alcohol use when they applied for prenatal care. Mothers who reported consuming at least two drinks per week, or the equivalent of at least one ounce of absolute alcohol per week (the equivalent of two drinks) and those who reported consuming no alcohol while they were pregnant were invited to participate in the study. Women who reported drug use other than alcohol, cigarettes, and/or marijuana in pregnancy were excluded from the study. The exception to this exclusion criteria, however, was occasional cocaine use (not crack) by a few of the mothers identified between 1980 and 1983. There was no financial incentive offered at the time of recruitment.

The criteria for inclusion for the women who were considered drinkers ranged from 1 to 75 oz of absolute alcohol per week (oz/AA/wk). This is, on average, more than 20 drinks per week (10.3 oz/AA/wk). Alcohol consumption was determined by self-report since biological measures used to confirm alcohol use are unreliable in pregnancy. Women who drank during their pregnancy were advised of the dangers and negative consequences that alcohol could have for the baby and

that they should stop. Drinking women who decided to participate were provided with referrals to various treatment programs.

Infants who met inclusion criteria were enrolled at birth and have been evaluated on an ongoing basis for several follow up studies since then. Inclusion criteria included being born alive and without any major birth defects such as down syndrome. At the postnatal examination, infants were assessed for growth patterns, as well as presence of dysmorphic physical features that would correspond with being prenatally exposed to alcohol. Evaluations were completed at seven years of age, and at mid-adolescence (14 ½ years). As part of the protocol for the young adult follow-up (average age 23 years old), participants were evaluated for physical features using the Dysmorphia Checklist, already developed for use in the original infancy study. The test was administered by either a pediatric geneticist or a nurse (trained by the geneticist) and neither had prior knowledge of the participants' alcohol exposure status. It included a weighted list of 30 physical characteristics associated with prenatal alcohol exposure and yielded a summary score.

Participants considered to have typical features of fetal alcohol syndrome (absent/indistinct philtrium; short palpebral fissures) were weighted as "3". Other characteristics that are observed in fetal alcohol spectrum disorders were weighed as either "2" (ptosis, hypoplastic mandible) or "1" (clinodactyly). The scores were then summed to yield a total "dysmorphia" score. Validity was measured via correlation with alcohol consumption reported by mothers, and reliability was measured via test-retest assessments in a clinical setting. This was used consistently

throughout the study. Furthermore, at each follow-up, participants completed tests of intellectual ability.

For the young adult follow-up, 108 participants were selected for neuroimaging. Out of this cohort, 94 had useable data. There are 3 groups of participants: the control group (n=27) includes participants whose mothers did not consume alcohol during pregnancy; the dysmorphic group (n=30), which includes participants who were exposed to alcohol prenatally and received a checklist score of at least one standard deviation above the mean of the sample of all participants; and the alcohol exposed group (n=37), those participants who were exposed to alcohol prenatally, but whose dysmorphia scores were less than one standard deviation above the mean of the sample (designated as "alcohol related neurodevelopment disorder- ARND). Out of the 108 participants who were imaged, sixteen were excluded: two participants were left-handed (excluded from control and ARND groups), and 14 had poor quality images (three from the control group, eight from the dysmorphic group, and three from the ARND group).

Procedure

Participants who were eligible from the longitudinal cohort were contacted by mail or phone in regards to the young adult wave of the follow-up study. The ones who were interested and decided to participate in the study completed a consent form, in which the study goals and procedures were explained. Additionally, they were allowed to ask questions and voice any concerns. All the consent forms (approved by the Emory University School of Medicine Institutional Review Board)

were signed, and during this process, the confidentiality of participants' mothers was protected; no information about the mother's alcohol consumption or any other substance use during the pregnancy of the now-adult child was revealed. For the evaluation visit, project outreach workers transported the participants to the laboratory for a daylong evaluation that included an assessment of memory and ability, a medical evaluation, and an interview session. In addition to transportation, participants also received lunch and compensation ($100 per session) for their time and effort.

Participants who were eligible to go through the imaging component of the study (based on group assignment and intelligence scores) were screened for factors such as metal in the body (pins, screws, braces on teeth, bullet fragments), pregnancy, extreme obesity, and claustrophobia. If they had any of these, they were excluded from going through the imaging procedure. Additionally, women were asked to complete a pregnancy test on the day of the appointment. For the imaging session, participants were transported to the Emory University campus where they completed a training session for the task used in the functional portion of the imaging session. Once this was completed, the participant was walked over to the Emory University Hospital where the imaging session took place.

Measures

A number of variables designed to measure demographic characteristics were collected in the study. These variables include age at imaging, gender, ethnicity, monthly income (within the past 30 days), and education level completed.

Assessment of Depression

To assess depression, participants were given the Composite International Diagnostic Interview (CIDI), which was developed by the World Health Organization (WHO) in 1990 (World Health Organization, 2013). The CIDI is a fully structured diagnostic interview, designed to be administered by interviewers who are not clinicians (World Health Organization, 2013). The interview assesses mental disorders according to the definitions and criteria of the International Statistical Classification of Diseases and Related Health Problems (ICD-10), and the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (World Health Organization, 2013). The CIDI allows investigators to measure the prevalence and severity of mental disorders, determine the burden of these disorders, assess service use, assess the use of medications in treating mental disorders, and assess who is treated, who remains untreated, and what the barriers to treatment are (World Health Organization, 2004). The WHO, through field trials, has found the CIDI to have good inter-rater reliability, test-retest reliability, and validity of almost all diagnoses (Kessler et al., 1994).

The diagnoses that can be assessed using the CIDI include: depression, mania, separation anxiety, agoraphobia, panic disorder, generalized anxiety disorder, social and specific phobias, obsessive compulsive disorder, post-traumatic stress disorder, alcohol use, illegal substance use, tobacco, conduct disorder, attention deficit hyperactivity disorder, eating disorders, gambling, oppositional defiant disorder, and premenstrual dysphoric disorder (World Health Organization, 2004). The CIDI was administered by the research interviewer working on the study

at the time, and was obtained when the participants came to Emory University for their medical exam and laboratory visit.

Head Circumference

Head circumference was assessed at birth and obtained through medical records. Subsequently, a nurse involved with the study also measured head circumference in the laboratory.

Alcohol and Drug Exposure During Pregnancy

The amount of alcohol and drug exposure during pregnancy were assessed through maternal self-report, as well as through the use of a questionnaire administered to the expectant mothers during pregnancy.

Alcohol Use

Adult participants were asked a series of questions (from the Addiction Severity Index and the Drug Checklist) in regards to their own current alcohol and other drug use. The alcohol consumption information also included a quantity/frequency measure that allowed calculation of ounces of absolute alcohol used each week (oz/AA/wk) as well as information about alcohol use history. Furthermore, urine samples were collected to screen for drug use, and blood samples were collected to evaluate the effects of alcohol on liver function. To confirm self-reports, laboratory tests were performed.

Medical Evaluation

A nursing evaluation was completed for each of the participants. The evaluation included a hearing and vision screen, a medical history, and a completion of the Dysmorphia Checklist for the adult visit. Nurses who carried out the

evaluation were trained by a geneticist familiar with the physical signs related with prenatal alcohol exposure.

Archival records

Information obtained from archival records included maternal drug and alcohol use. It also included results of previous measurements of participants' ability and physical effects of alcohol (dysmorphia checklist scores). These measures were used initially to categorize the various groups for recruitment.

Brain Volume

Different volumes of regions of interest (ROIs) were obtained through an automated segmentation of T1-weighted images and multivariate analysis of variance was used to examine the impact of prenatal exposure on brain volume. Because women have smaller brain volumes than men, gender was used as a co-variate.

Structural Imaging

For each participant, T_1-weighted images were obtained using a 3.0 Tesla Siemens Magnetom TRIO scanner (Siemens Medical Solutions, Malvern, PA) with an MPRAGE sequence (TR= 2600 ms, TE= 3.02 ms, Flip Angle= 8°, voxel size= 1 x 1 x 1 mm^3). FreeSurfer (http://surfer.nmr.mgh.harvard.edu/fswiki, version 4.0.1 was used on the images to automatically segment sub-cortical structures and cortical regions through FreeSurfer's troubleshooting reconstruction work flow. During the procedure, the optical nerve was removed through manual edits, as well as part of the dura, which was incorrectly segmented as grey matter. Additionally, after the

reconstruction, volumetric data for the segmented cortical and sub-cortical regions were also automatically calculated using FreeSurfer.

Analysis

Descriptive statistics for the participants were performed using SPSS software. An independent sample t- test was performed using SPSS to compare intracranial volume within groups. In addition, an independent t-test was performed using SPSS to compare amygdala volume to gender, and amygdala volume within groups. To evaluate amygdala volume as a function of alcohol group status, a one-way ANOVA test was performed using SPSS. A chi square of independence was also performed using SPSS to assess participants' drinking habits.

In order to assess whether a participant scored high enough on the CIDI probability scale (and thus determine the probability of being a case vs. a non-case for major depression (MD)) a chi square of independence was performed using SPSS. To assess the relationship between weekly alcohol consumption and MD CIDI probability classification, a chi-square of independence was performed using SPSS. An independent sample t-test was also performed using SPSS to compare MD CIDI probability classification within groups. The level of significance was set at $p<0.05$ to determine associations in the bivariate analysis. A full multivariate logistic regression model was used to determine the relationship between MD CIDI probability classification, gender, amygdala volume, intracranial volume, and weekly alcohol consumption. An alpha of $p<0.05$ was used for this model.

IV. RESULTS

Demographics for the sample are shown in Table 1. Out of the 94 participants, 27 (28.7%) were part of the control group, 30 (31.9%) were part of the dysmorphic group, and 37 (39.4%) were part of the alcohol exposed group. 93 participants were African American (98.9%), and 1 was Native American (1.1%). 58 (61.7%) participants were females, while 36 (38.3%) were males. The mean age of the sample was 22.98 (sd= 1.86), while the mean monthly income was $1,008.65 (sd= 1,419.29). The mean number of years of attending school was 11.85 (sd=1.49). In addition, out of the 94 participants, 35(37.2%) reported not currently drinking alcohol, 22 (23.4%) reported drinking alcohol less than once per month, and 37 (39.4%) reported drinking alcohol more than once per month. The mean absolute ounce of alcohol consumed per week was 1. 02 oz/AA/wk (sd= 1.77). Out of the 94 participants' mothers, 83 (92.2%) reported not using cocaine during pregnancy, while 7 (7.8%) reported cocaine use during pregnancy. 67 (71.3%) of the participants' mothers reported not using marijuana during pregnancy, while 27 (28.7%) reported using the drug. The mean absolute ounces of alcohol consumed per week by the participants' mother was 7.03 (sd= 12.27).

Table 1. Demographics for Study Sample

Variable	N (%)
Race	
African American	93 (98.9%)
Native American	1 (1.1%)
Gender	

Females	58 (61.7%)
Males	36 (38.3%)
Age	22.98 (sd= 1.86)
Time spent in school	11.85 (sd=1.49)
Alcohol consumption	
Not currently drinking	35 (37.2%)
Drinking less than one drink per month	22 (23.4%)
Drinking more than one drink per month	37(39.4%)
Participants' mothers' drug consumption	
Reported not using cocaine during pregnancy	83 (92.2%)
Reported consuming cocaine during pregnancy	7 (7.8%)
Reported not using marijuana during pregnancy	67 (71.3%)
Reported using marijuana	27 (28.7%)

Table 2. shows data on brain characteristics and psychological disorders for the study population. The mean head circumference for the control group was 58.24

cm (sd= 3.43) while the mean head circumference for the dysmorphic and alcohol-exposed group was 56.03 cm (sd=3.48) and 57.53 cm (sd= 2.60) respectively. The mean intracranial brain volume for the control group was 1400904.20 cc (sd= 205205.37). The mean intracranial volume for the dysmorphic group was 1261151.80 cc (sd= 207893.57), while the mean intracranial volume for the alcohol-exposed group was 1328211.65 cc (sd= 154929.74). For brain areas associated with depression, the mean total volume for the amygdala in the control group was 3678.11 cc (sd= 675.61). In addition, the mean total amygdala volume for the dysmorphic group was 3234.03 cc (sd= 567.74), and the mean total amygdala volume for the alcohol-exposed group was 3516.97 cc (sd= 451.87).

The mean total volume for the hippocampus in the control group was 7287.15 cc (sd= 904.93), while the mean total hippocampal volume for the dysmorphic group and alcohol-exposed group was 6658.40 cc (sd=972.91) and 7076.70 cc (sd= 645.78) respectively. The mean total volume for the thalamus in the control group was 3678.11 cc (sd= 1813.53). Additionally, the mean total thalamic volume for the dysmorphic group and alcohol-exposed group was 11278.20 cc (sd= 1914.58) and 12103.62 cc (sd= 1268.00) respectively. The mean total volume for the right cerebral cortex in the control group was 209615.07 cc (sd= 29408.16), while the mean total volume for the right cerebral cortex in the dysmorphic group was 190436.43 cc (sd= 29241.54), and the mean total volume for the right cerebral cortex in the alcohol-exposed group was 199015.97 cc (sd= 21340.60). Furthermore, the mean total volume for the left cerebral cortex in the control group was 213264.93 cc (sd= 27656.73), while the mean total volume for the left cerebral

cortex in the dysmorphic group was 189091.23 cc (sd= 28797.64), and the mean total volume for the left cerebral cortex in the alcohol-exposed group was 203422.62 cc (sd= 22259.17).

The mean qualifying score for MD for the control group was 0.33 (sd=0.73), while the mean qualifying score for the dysmorphic and alcohol-exposed group was 0.37 (sd=0.77) and 0.32 (sd=0.75) respectively. For Generalized Anxiety Disorder (GAD), the mean qualifying score for the control group was 0.04 (sd=0.19), while the mean qualifying score for the dysmorphic and alcohol-exposed group was 0.03(sd=0.18) and 0.00 (sd=0.00) respectively. For Agoraphobia (AGO), the mean qualifying score for the control group was 0.07 (sd=0.38). The mean qualifying score for the dysmorphic and alcohol-exposed group was 0.03(sd=0.18) and 0.14 (sd=0.48) respectively.

Table 2. Brain Volume and Psychological Disorders among Controls, Alcohol-exposed, and Dysmorphic Groups

Variable	Control (n= 27)	Dysmorphic (n=37)	Alcohol-exposed (n= 30)
Head circumference (cm)	mean= 58.24 sd= 3.43	mean= 56.03 sd= 3.48	mean= 57.53 sd= 2.60
Intracranial volume (cc)	mean=1400904.20 sd= 205205.37	mean=1261151.80 sd= 207893.573	mean=1328211.65 sd= 154929.74
Volumes of brain areas associated with depression			
Amygdala (cc)	mean= 3678.11 sd= 675.61	mean=3234.03 sd=567.74	mean=3516.97 sd=451.87
Hippocampus (cc)	mean= 7287.15	mean= 6658.40	mean=7076.70

	sd= 904.93	sd=972.91	sd=645.78
Thalamus (cc)	mean= 3678.11 sd= 1813.53	mean= 11278.20 sd= 1914.58	mean=12103.62 sd=1268.00
Cerebral Cortex (cc)			
Right	mean= 209615.07 sd= 29408.16	mean= 190436.43 sd= 29241.54	mean=199015.97 sd=21340.60
Left	mean= 213264.93 sd= 27656.73	mean= 189091.23 sd= 28797.64	mean=203422.62 sd=22259.17
Psychological Disorders			
Major Depression (MD)	mean= 0.33 sd=0.73	mean= 0.37 sd=0.77	mean= 0.32 sd=0.75
Generalized Anxiety Disorder (GAD)	mean= 0.04 sd=0.19	mean= 0.03 sd=0.18	mean= 0.00 sd=0.00
Agoraphobia (AGO)	mean= 0.07 sd=0.38	mean= 0.03 sd=0.18	mean= 0.14 sd=0.48

Table 3 shows MD breakdown among the participants. Out of the study sample, 77 (81.9%) were a non-probable non-case for MD, meaning that they did not score high enough on the CIDI probability scale to be considered a case, and thus, had no probability of having the condition. 2 (2.1%) participants were a probable non-case, meaning that they qualified for CIDI scoring, but, did not score high enough to have a probability of caseness greater than 50%. 15 (16.0%) participants were a probable case, meaning that they qualified for CIDI scoring and

scored higher than 50% on caseness, and thus were considered to have the condition. For GAD, 92 (97.9%) of the participants were a non-probable non-case, and 2 (2.1%) participants were a probable case. For AGO, 89 (94.7%) of the participants were a non-probable non-case, 2 (2.1%) were non-probable case, and 3 (3.2%) participants were a probable case.

Table 3. MD Classification among the Study Sample

MD classification	N (%)
Non-probable non-case	77 (81.9%)
Probable non-case	2 (2.1%)
Probable case	15 (16%)

Bivariate Associations

The results of the independent t-test show that there is a statistically significant difference in total intracranial volume between the control and dysmorphic groups (t=2.55 df=55 p=0.014) where the participants in the control group have higher intracranial volume (mean=1400904.20 sd=205205.37) compared to the dysmorphic group (mean=1261151.80 sd=207893.57). However, the results of the independent t-test show that there is not a statistically significant in intracranial volume between the control and alcohol-exposed groups (t=1.62 df=62 p=0.111). Additionally, the results of the independent t-test show that there is not a statistically significant association in intracranial volume between the participants in the alcohol-exposed group and the participants in the dysmorphic group (t=-1.51 df=65 p=0.135).

Even though the hippocampus, thalamus and cerebral cortex have been associated with depression, this study focused on looking at amygdala volume only. Thus, the results of the independent t-test show that there is a statistically significant difference between amygdala volume and gender (t=3.77 df=55.46 p<0.001) with females having a smaller amygdala (mean= 3293.66, sd=449.73) than males (mean=3761.83, sd= 656.60) (the Levene test was significant, F= 5.87 p=0.017, equal variances were not assumed). Moreover, the results of the independent t-test show that there is a statistically significant difference in amygdala volume between the control and dysmorphic groups (t=2.70 df=55 p=0.009) where the participants in the control group have a bigger amygdala (mean=3678.11 sd=675.61) compared to the dysmorphic group (mean=3234.03 sd=567.74). The independent t-test also shows that there is a statistically significant association in amygdala volume between the dysmorphic and alcohol-exposed groups (t=-2.27 df=65 p=0.026) where the alcohol-exposed group has a bigger amygdala (mean=3516.97 sd=451.87) compared to the dysmorphic group (mean=3234.03 sd=567.74). On the other hand, the results of the independent t-test show that there is not a statistically significant association in amygdala volume between the participants in the control group and the participants in the alcohol-exposed group (t=1.08 df=42.48 p=0.29) (the Levene test was significant, F= 11.50 p=0.001, equal variances were not assumed).

This study also looked at the relationship between amygdala volume and the probability of being either a case or a non-case for MD. As such, the results of the independent t-test show that there is not a statistically significant association

between amygdala volume and whether a participant becomes a case or non-case for MD (t= 1.02 df= 92 p=0.311). When it comes to amygdala volume and weekly alcohol consumption (measured in oz/AA/wk), the results of a one-way ANOVA show that there is not a statistically significant difference in mean amygdala volume and how often the participants consumed alcohol (F=0.93 df=2 p=0.400). In addition, when it comes to drinking habits by the participants, the results of the chi square of independence indicate that females were significantly more likely to not be consuming alcohol at the time of the study (n= 25, 43.1%) compared to men, who most frequently reported consuming alcohol more than once a month (n=20, 55.6%) (chi square= 6.42 df= 2 p=0.040).

When it comes to CIDI probability scoring for MD in the cohort of participants, the chi square of independence indicated that there is no association between gender and probability of being a non-probable non-case, non-probable case or probable case (chi square=3.39 df=2 p=0.183). This means that, in this study, gender does not play a role in the probability of scoring greater than 50% in order for a participant to be considered to meet diagnosis for MD. Furthermore, the results of the chi-square of independence indicated that there is no statistically significant relationship between current alcohol use (i.e, currently drinking, drinking less than once per month, and drinking more than once per month) and probability of being a non-probable non-case, non-probable case and probable case (chi square=4.17 df=4 p=0.384).

Table 4 shows the results of the chi-square of independence between MD CIDI classification and the groups in the sample (control, dysmorphic, and alcohol-

exposed). The results of the chi square of independence show that 23 (85.2%) participants in the control group do not meet MD CIDI classification while 4 (14.8%) participants do meet MD classification. In addition, 25 (83.3%) participants in the dysmorphic group do not meet MD CIDI classification, but 5 (16.7%) participants do. In the alcohol-exposed group, 31 (83.8%) participants meet MD CIDI classification, while 6 (16.2%) do not meet MD CIDI classification.

Table 4. MD CIDI Classification between Control, Dysmorphic, and Alcohol-exposed Groups

Group	MD Classification	
	Non-probable non-case N (%)	Probable case N (%)
Control	23 (85.2%)	4 (14.8%)
Dysmorphic	25 (83.3%)	5 (16.7%)
Alcohol-exposed	31 (83.8%)	6 (16.2%)
Total	**79 (84.0%)**	**15 (16.0%)**

The results of CIDI probability scoring among the three groups are as follow: The results of the independent t-test show that there is not a statistically significant difference in CIDI probability scoring between the control and the dysmorphic group (t=-0.167 df=55 p=0.868). Furthermore, the results of the independent t-test show that there is not a statistically significant difference in CIDI probability scoring between the dysmorphic group and the alcohol-exposed group (t=0.23 df=65 p=0.820). Lastly, when it comes to CIDI probability scoring between the control and the alcohol-exposed group, the results of the independent t-test show that there is

not a statistically significant difference between the two groups (t=0.048 df=62 p=0.962).

Multivariate Analysis

Results for the logistic regression model and the full logistic regression model are shown in Table 5 and Table 6, respectively. In order to run this analysis, the CIDI probability scoring variable was dichotomized into two categories: variable "1" consisted of the non-probable non-cases and the non-probable cases, since both of these groups do not meet the probability to have MD. On the other hand, variable "3" consisted of the probable cases, meaning those cases who would be considered to meet the condition for MD. The results of the logistic regression indicate that the odds of scoring higher on the CIDI probability scale are independent of gender (df=1 p=0.664).

Table 5. Logistic Regression Model Using Gender as a co-variate for Predicting MD

Variable	B	S.E	Sig.	95% C.I	
				Lower	Upper
Gender	0.256	0.594	0.667	0.403	4.139

Moreover, when the full logistic regression model was performed using intracranial volume, amygdala volume, and weekly alcohol consumption as covariates, the results indicate that these variables do not account for the probability of getting a qualifying score for MD on the CIDI probability scale (df=3 p=0.651). However, the results do show a slight positive relationship (B=0.118) between meeting MD qualifying score and amount of alcohol consumed per week.

Table 6. Full Logistic Regression Model using Intracranial volume, Amygdala, and Alcohol consumption per week as co-variates for predicting MD

Variable	B	S.E	Sig.	95% C.I Lower	Upper
Intracranial Volume	0.000	0.000	0.954	1.000	1.000
Amygdala Size	-0.001	0.001	0.489	0.998	1.001
Alcohol Consumption per Week	0.118	0.153	0.439	0.834	1.520

V. Discussion

The results of this research indicate that there is a statistically significant difference in intracranial volume between the control group and the dysmorphic group. This is consistent with literature that has shown that individuals with FAS have lower brain volume (Coles et al., 2011, Ma et al., 2005 & Roussotte et al., 2012). Moreover, a study by Leigland, Ford, Lerch, & Kroenke, 2013 showed that abnormal MRI measurements of the brain and cerebral cortex are not only seen in the early stages of development, but also persist throughout adulthood (Leigland, Ford, Lerch, & Kroenke, 2013). However, this difference in brain volume was not seen between the control group and the alcohol-exposed group. Even though the participants in the alcohol-exposed group were prenatally exposed to alcohol, they did not meet clinical diagnosis for FAS. Therefore, their brains might not be as severely affected as those in the dysmorphic group, and hence, would be more structurally similar to those in the control group. These are all pieces to the puzzle that could help better understand why individuals with FAS experience lower brain volumes.

The amygdala was the brain area of focus for this study since it is a structure that is involved in MD. As such, when it comes to the relationship between its volume and gender, a significant association between the two was found, with females in the study having a smaller amygdala than men, regardless of what group they were in. Morris, Jordan, & Breedlove, 2008, note that in rodents, differences in brain size are due to circulating androgens that have been shown to cause sex differences in brain volume (Morris, Jordan, & Breedlove, 2008). However, even though there are sex-specific differences seen in brain development, the results of

this research showed a significant relationship in amygdala volume between the control group and the dysmorphic group, regardless of gender. This is an important finding as it shows that sex differences are not the only contributing factor to the differences in brain volume.

The results of this research also found no significant association between gender and classifying for MD depression diagnosis. This contradicts the literature that has shown that more women get diagnosed with major depression than men (National Institute of Mental Health, 2009). In today's social context, it is more socially acceptable for women to talk about their feelings and struggles than it is for men. For instance, Wang, Fick, Adair, & Laid D, 2007, found in their study that Canadian men considered depression to be a weakness of character (Wang, Fick, Adair, & Laid D, 2007). If this is the case, depression prevalence rates among men are most likely underrepresented, since they would be expected to have misconceptions about the condition (Wang, Fick, Adair, & Laid D, 2007). This can result in higher levels of stigma, which can then result in lower levels of diagnosis.

In regard to MD, the results showed that 16% of the participants met the CIDI classification criteria for MD. This is well above the national average of 4.1% that currently meet criteria for MD (CDC, 2012). The high percentage of depression found in this sample could be, in part, due to social and environmental factors, since the sample consisted of African Americans of low socioeconomic status. Moreover, the results are consistent with literature that has shown that African Americans are more likely to be depressed (CDC, 2012).

Additionally, even though the results of the chi square of independence did not show a statistically significant difference between MD CIDI classification between the groups studied in this research, it is still important to point out that there were more participants who met MD CIDI classification in both the dysmorphic and alcohol-exposed group. This is supported by literature that has shown that MD is more likely to occur in individuals that have been prenatally exposed to alcohol (Hellemans et al., 2010).

Conversely, the results also showed that there was no significant association between amygdala size and whether a participant became either a case or a non-case for MD. It could be that amygdala size is not so much the issue when it comes to MD diagnosis, but more so the brain region where it is found. Therefore, future studies could look at brain connectivity and functional activity to explore how they may play a role in the incidence of MD. In addition, the hypothalamic-pituitary-adrenal (HPA) axis has been shown to play a central role in the diagnosis of depression, as well as to be highly susceptible during fetal programming (Hellemans et al., 2010). Since the amygdala is more involved in reaction and stress, future studies should look at the HPA axis and its relationship to brain volume to see if there is a significant link. As mentioned elsewhere in this study, other brain structures are also involved in the onset of MD. Perhaps these structures (cerebral cortex, hippocampus, hypothalamus, thalamus) should also be studied, in conjunction with the amygdala, to examine their effect on receiving a MD diagnosis. The results also indicated that there was not a significant difference in MD CIDI

classification and gender. This means that, in this research, gender did not play a role or made the participants more likely to develop MD.

Lastly, when the full logistic regression model using intracranial volume, amygdala and alcohol consumption per week as co-variates was performed, there was no significant association between these variables and the probability of MD diagnosis. However, since a positive relationship between MD CIDI classification and the amount of alcohol consumption per week (by the participants) was noted, this could mean that, even though the effect wasn't statistically significant, there is something that could be playing a role in how much the participants are drinking and the likelihood of receiving MD diagnosis. Future studies should look into this relationship further and determine how much alcohol (i.e. how many drinks per week and/or month) a person would have to drink in order to meet criteria for MD.

Limitations

There are some limitations with this study. The study sample consisted of 94 participants. While some significant results were found, a bigger cohort would have to be studied in order to increase statistical power. In addition, since all participants in this study were African American and from a low-income background, the results cannot be generalized to other populations. Perhaps conducting the same research with a more heterogeneous sample would increase the study's external validity, and thus, shed more light on the true association between MD and low brain volume.

This study was also conducted using an already existing dataset that was originally collected for a different study. Therefore, the data was analyzed using already existing variables that might not have been the most appropriate to use for

the question that this research intended to answer. For example, most of the data collected for the original was study was gathered to study the relationship between FAS, low brain volume and memory. Having specific mental health related questions could have helped strengthen the findings of this study.

Strengths

A major strength of this study is the fact that participants have been followed and observed since birth. Therefore, they were not enrolled in the study because of MD diagnosis or because they were looking to get help for being depressed. This is an advantage as it provides a better estimate of the population as a whole more so than having a clinical sample would. As a result, the true incidence of MD in the population can be more easily detected.

As mentioned above, this is an ongoing observational study, which makes it ideal to study individuals in their natural environment and processes (Observational Research, 2014). There is no manipulation of variables, so it has high ecological validity, or resemblance to real-life events (Observational Research, 2014). Additionally, not only has the data has been collected longitudinally, but the participants involved in the study did not have to alter their behaviors in order to participate in the research. Thus their behaviors have remained more or less natural throughout the course of the study.

Conclusions

In conclusion, this research study examined the association between lower brain volume (in the form of amygdala volume) as a result of prenatal alcohol exposure and the probability of developing MD. The results indicate no association

between FAS and MD despite previous reports that depression is more common in clinical samples of individuals diagnosed with FAS (Hellemans et al., 2009). As such, future studies should look at different populations to assess whether this pattern is seen across different groups of individuals. Future studies should also look at psychological disorders that occur concomitantly with MD to study whether those are more prevalent than MD alone.

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