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The association between prenatal maternal stress, infant brain volumes, and temperament during the COVID-19 pandemic

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Abstract

Prenatal maternal stress (PNMS) is associated with altered trajectories of infant socio-emotional and brain development, including brain structures such as the amygdala and prefrontal cortex (PFC). During the COVID-19 pandemic, which was a major global stressor, PNMS was significantly elevated, yet the impact on infant neurodevelopment remains uncertain. The objective of the present study was to determine whether PNMS during the pandemic was associated with infant amygdala and PFC volumes as well as temperament. In addition, we examined whether social support and resilience during pregnancy were protective factors. Participants were enrolled in the Canadian 'Pregnancy during the COVID-19 Pandemic' cohort study. Pregnant individuals had their perceived stress, pandemic-related objective hardship, mental health, social support, and resilience measured via questionnaires. Infant magnetic resonance imaging (MRI) scans (n =100) were conducted at 3 months of age, and parents reported on infant temperament at 6 months of age. General linear models were used to examine the associations among PNMS, brain volumes, and developmental outcomes and to assess the role of protective factors. The results found that prenatal maternal anxiety negatively predicted 3-month left infant amygdala volumes. Smaller left amygdala volumes were also associated with greater infant 6-month negative emotionality. Maternal stress was associated with smaller infant PFC volumes, and this relationship was moderated by social support and resilience. This study provides evidence for infant brain alterations related to prenatal maternal perceived stress and anxiety, indicating that the impact of PNMS on infant development during the COVID-19 pandemic may have long-lasting implications for children's health. Our findings suggest that social support, resilience, and mental health may be key areas for screening and intervention during pregnancy to best support healthy infant development.

Key words

Amygdala; Prefrontal cortex; Prenatal maternal stress; COVID-19; Social support; Resilience

Summary for Lay Audience

Stress during pregnancy has been related to differences in children's brain, behavior, and emotions. Prenatal stress can increase a stress hormone called cortisol, which can negatively impact brain development in the fetus. Differences in brain development during pregnancy can impact children long-term. Given that perinatal anxiety and depression was at high levels during the COVID-19 pandemic, it is important to understand the impact of prenatal maternal stress on their children. Our study looked at the relationship between stress during pregnancy and two important brain regions for emotions: the amygdala and prefrontal cortex. We also looked at whether differences in brain volumes were related to infant temperament (i.e., innate emotional regulation style) at 6-months. Finally, we also studied whether partner support and resilience (i.e., ability to adapt/bounce back after a stressful event) lessened the link between prenatal stress and infant brain development. Our participants were a part of the Canadian 'Pregnancy during the COVID-19 Pandemic' (PdP) study. Questionnaires were used to assess individuals on their mental health, social support from their partner, resilience, and infant temperament at 6-months. Magnetic resonance imaging (MRI) was used to scan 100 3-month-old infants. Our findings showed that higher levels of anxiety during pregnancy was related to smaller amygdala volumes when infants were 3-months old. More negative infant temperament was also linked to smaller amygdala volumes. Social support and resilience lessened the relationship between maternal perceived stress and infant prefrontal cortex volumes. Our results suggest that prenatal stress during the pandemic could have long-lasting implications for children's health and brain development, and that partner support and resilience could have a protective effect.

Co-Authorship Statement

Chapter 2 includes my manuscript titled "Maternal stress and mental health in pregnancy during the COVID-19 pandemic and its associations with infant brain volumes and temperament". Drs. Emily S. Nichols, Lianne Tomfohr-Madsen, Gerald F. Giesbrecht, Kathryn Y. Manning, Catherine A. Lebel, Emma G. Duerden are all co-authors on this manuscript. Catherine Lebel, Lianne Tomfohr-Madsen, and Gerald Giesbrecht all conceived, designed, and developed the protocol for the larger PdP study. I wrote the manuscript, segmented the prefrontal cortex, and conducted the statistical analyses/data interpretation, under the supervision of Emma Duerden. All co-authors reviewed and edited the final manuscript.

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Chapter 1

1.1 Introduction

On March 11th 2020, the World Health Organization (WHO) declared a global pandemic as a result of the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In order to combat the spread of the virus, Canadians were required to wear masks in public, physically distance from one another, and self-isolate at times. Canada closed its borders, travel was restricted, schools and non-essential businesses were closed, and many people started working from home (Urrutia et al., 2021). These measures greatly impacted the daily lives of all Canadians.

This is particularly true for pregnant individuals as COVID-19 restrictions led to changes to prenatal care. Many individuals had their prenatal care appointments canceled or done online, had their birth plans changed, and were barred from bringing a support person to their prenatal appointments or birthing room (Groulx et al., 2021; Public Health Agency of Canada, 2020). The constant and rapid changes to prenatal care greatly impacted the mental health of these individuals (Groulx et al., 2021). In general, perinatal anxiety and depression levels were higher during the pandemic compared to pre-pandemic levels (Chmielewska et al., 2021; Lebel et al., 2020). Increases in prenatal maternal stress (PNMS) during the pandemic may also have a negative impact on infant development (Gunnar & Doyle, 2020; Lautarescu et al., 2020). However, there is little research studying PNMS during the pandemic on infant brain development in Canada at this time. In order to contribute to the current literature, the current study will examine the association between PNMS, infant amygdala and prefrontal cortex (PFC) volumes at 3-months, and 6-month temperament.

1.1.1 The Brain & Socio-emotional Development

Amygdala

The amygdala and PFC, including the white matter connecting them together, are important for emotional processing (Fuster, 2002; Seymour & Dolan, 2008; Tottenham & Gabard-Durnam, 2017). The amygdala is an almond-shaped mass of gray matter found in the superomedial part of the temporal lobe and forms part of the limbic system (Pruessner et al., 2000). The basic cytoarchitecture of the amygdala is already present at birth, with peak development occurring in the first trimester (Humphrey, 1968; Ulfig et al., 2003). The amygdala is connected to many brain areas, including the hippocampus, prefrontal cortex, and sensory cortices (Phelps, 2006). It is implicated in emotional & reward processing, affective recognition (particularly from facial expressions), fear conditioning, threat detection, memory, social cognition, and in determining the emotional valence of a stimulus, both positive and negative (Bauman & Amaral, 2008; Hariri et al., 2003; Sergerie et al., 2008; Tottenham et al., 2009; Tottenham & Sheridan, 2010). The amygdala helps us learn about threat and safety, which is particularly important in infancy when less is known about the environment (Tottenham & Sheridan, 2010). Various psychiatric disorders are linked to differences in the structure of the amygdala, particularly those related to social-emotional problems. Smaller amygdala volumes are linked to higher levels of internalizing symptoms in childhood (Rosso et al., 2005; Warnell et al., 2018). However, some studies found this association with larger volumes (Albaugh et al., 2017; De Bellis et al., 2000), while another did not find any (Koolschijn et al., 2013).

Prefrontal Cortex

The PFC is part of the cerebral cortex anterior to the primary motor and premotor cortex (Teffer & Semendeferi, 2012; Zelazo & Müller, 2002). It shares extensive connections with many brain areas, including the amygdala, hippocampus, basal ganglia, and motor cortex (Uytun, 2018; Wood & Grafman, 2003). Emerging in early infancy, the PFC plays a key role in cognitive and social-emotional processing (Grossmann, 2013a; Hodel, 2018). The medial prefrontal cortex (mPFC) is mainly involved in processing social and affective information, while the lateral PFC (lPFC) is involved in cognitive processes (memory and attention) and language (Grossmann, 2013a). In infancy, the mPFC plays a role in joint engagement; in the detection of self-relevant information, positively toned speech and infant-directed speech (particularly their mother's voice); as well as in the perception of faces, smiles, affective cues and eye gaze (Grossmann, 2013a, 2013b, 2015). The mPFC has an important part in the development of social cognition across the childhood (Grossmann, 2013b). Damage to the mPFC can cause severe impairment to a person's social behavior. Adults with mPFC legions obtained in infancy display an "insensitivity to future consequences of decisions" and deficits in social-moral reasoning, including violent and antisocial behaviors (Anderson et al., 1999; Grossmann, 2013b). Volumetric abnormalities in the PFC are also found in individuals with neurodevelopmental disorders, such as autism (Teffer & Semendeferi, 2012).

1.1.2 Prenatal Maternal Stress

Prenatal Stress & Social-Emotional Development

Pregnancy is a time of many physical, cognitive, and emotional changes. Pregnant individuals, partially due to these changes, are particularly vulnerable to stress. Prenatal maternal stress (PNMS) caused by an event has two components: objective hardship (i.e., level of exposure to an external stressor) and subjective perceived stress. Stressful events occurring during pregnancy have been linked to negative health outcomes for both the pregnant individual themselves as well as their future children. Greater PNMS due to a natural disaster, for example, is associated with greater symptoms of postnatal depression, anxiety, and post-traumatic distress (Brock et al., 2015; Paquin et al., 2021; Verstraeten et al., 2020). This kind of high stress level in pregnancy can also negatively affect the developing fetus (Gunnar & Doyle, 2020). Broadly, PNMS has been associated with poorer offspring neurodevelopment, temperament, behavior, cognitive development, motor skills, and birth outcomes (Van den Bergh et al., 2017). In terms of birth outcomes, for example, PNMS has been associated with a reduction in birth weight, birth length, and head circumference (Gilles et al., 2018). Fetal development is impacted differently depending on the particular point of gestation in which the event occurred and the developmental stage of specific brain areas at that time; there does not seem to be one specific vulnerable period of fetal development to PNMS (Van den Bergh et al., 2017).

A multitude of studies have looked at how PNMS impacts various aspects of social-emotional development in both infants and children. In one study of the 1998 Quebec Ice storm, greater subjective distress and maternal illness during pregnancy were related to negative infant temperament (e.g., fussy/difficult) at 6-months of age (Laplante et al., 2016). Other studies have similarly found that stressful life events and anxiety are associated with more fearfulness and difficult temperament in infancy (Austin et al., 2005; Bergman et al., 2007).

In 2011, a flood hit Queensland Australia. It destroyed thousands of homes and led to the evacuation of thousands of people, including pregnant individuals. Subsequently, researchers dedicated their time to studying the impact of PNMS on the social-emotional development of infants and children born to mothers who experienced the flood. In these first two studies, greater flood-related objective hardship predicted more difficult temperament, worse problem solving skills, and worse personal-social skills (e.g., solitary social play, interactions with others) in 6-month infants (Simcock, Elgbeili, et al., 2017; Simcock, Laplante, et al., 2017). In addition, higher levels of maternal subjective stress were associated with lower social-emotional competence (e.g., empathy, compliance, and prosocial behavior) in infants at 16 months (Lequertier et al., 2019) and worse performance on a theory of mind task at 30 months (Simcock, Kildea, et al., 2017). Finally, at 4-years old, higher level of objective hardship due to the flood (e.g., material loss and damage, changing homes) predicted higher child anxiety symptoms (McLean et al., 2018). Other studies have similarly found that higher levels of prenatal stress, anxiety, and depression have been linked to more externalizing and internalizing symptoms as well as other psychiatric problems in children, mostly independent of postpartum mental health (King et al., 2012; O'Connor et al., 2002; Van den Bergh et al., 2017).

PNMS & Brain Development

Maternal experiences during pregnancy can change the intrauterine environment and subsequently impact the central nervous system of the developing fetus, potentially influencing future brain and behavior development in infancy and childhood (Gunnar & Doyle, 2020). To further understand the effects of PNMS on brain development, a multitude of structural and functional MRI studies have been conducted. These studies found an association between PNMS and differences in amygdala as well as PFC volumes in children (Lautarescu et al., 2020). For example, higher levels of prenatal psychological distress was associated with smaller left amygdala volumes only in newborn males (Lehtola et al., 2020). Conversely, greater depression and maternal cortisol levels during pregnancy have been linked to larger right amygdala volumes in young girls, but not boys (Buss et al., 2012; Wen et al., 2017). In addition, higher levels of cortisol were associated with affective problems in girls, which was partially mediated by larger right amygdala volume (Buss et al., 2012). Jones et al., (2019) studied the effect of PNMS during the 1998 Quebec ice storm on amygdala volumes and child behaviors. The examination showed that bigger normalized amygdala volumes in 11-year-old girls mediated the association between higher levels of objective hardship and greater externalizing symptoms. At the same time, Rifkin-Graboi et al. (2013) did not find an association between prenatal depression and newborn amygdala volumes.

Reductions in gray matter volume of the frontal lobes in children have also been related to PNMS (Lautarescu et al., 2020). Higher pregnancy-anxiety in mid-pregnancy has been associated with smaller PFC volumes in young children, independent of postnatal stress (Buss et al., 2010). Prenatal depression has also been linked to thinner frontal lobes, including the frontal pole in childhood. The association between depression during pregnancy and externalizing behavior was then mediated by prefrontal cortical thinning (Sandman et al., 2015). Increased prenatal stress has also been associated with decreased functional connectivity and increased structural connectivity between the amygdala and medial-PFC in young infants (Humphreys et al., 2020). In terms of the rest of the brain, PNMS has been found to affect the development of the temporal lobe and other regions of the limbic system, such as the hippocampus, with decreases in volumes found in these areas. PNMS is also associated with white matter changes in limbic and frontal brain regions in childhood (Lautarescu et al., 2020).

Underlying mechanisms

Maternal inflammation, altered placental functioning, and greater fetal cortisol exposure may all contribute to the associations between PNMS and childhood development. (Glover et al., 2009; Gunnar & Doyle, 2020). According to the fetal programming hypothesis, maternal factors during pregnancy may affect fetal development in a permanent way. One important factor in this effect is the maternal endocrine system. PNMS is hypothesized to alter the fetal brain and subsequent behavioral development through the action of glucocorticoids (Gunnar & Doyle, 2020; Lautarescu et al., 2020). In response to stress, the body will increase its secretion of glucocorticoid hormones (e.g., cortisol) as a result of hypothalamic-pituitary-adrenal (HPA) axis activation. Abnormal or inappropriate levels of cortisol can have a neurotoxic effect on the fetus' developing brain. To counteract this effect, the placental enzyme 11β-hydroxysteroid dehydrogenase-2 (11β-HSD-2) will convert some cortisol into its inactive form. However, PNMS has been found to downregulate 11β-HSD-2 activity, thus allowing higher levels of cortisol to cross the placental barrier (Gunnar & Doyle, 2020; Lautarescu et al., 2020). The amygdala, for example, is vulnerable to maternal activation of the HPA axis as it is rich with cortisol receptors (Tottenham & Sheridan, 2010). Other factors such as the release of cytokines (immune signaling proteins) by the maternal immune system and reduced placental blood flow and fetal oxygen can also negatively impact the brain of the developing fetus (Gunnar & Doyle, 2020). The effect of PNMS may also depend on a variety of other factors including the type of stress, the time in gestation in which the event occurred, and fetal sex (Lautarescu et al., 2020). Fetal programming is hypothesized to have an evolutionary value. Maternal biological changes signal to the fetus that the external world is one of high stress/threat and will require a good amount of vigilance (Glover et al., 2010). Unfortunately, PNMS does not often accurately reflect the world the child will be born into once the stressful event has passed. Thankfully, research has shown that a positive environment in childhood may counteract the neurodevelopmental changes often linked to PNMS (Lautarescu et al., 2020).

1.1.3 Protective Psychosocial Factors: Resilience & Social Support

While pregnant individuals are a vulnerable population group, there is a subset of individuals that will experience less health problems as a result of personal protective factors, such as resilience and social support (Khoury et al., 2021; Kinser et al., 2021). Resilience is a muti-faceted personality factor. Individuals with greater resilience tend to display more healthy and adaptive functioning over time after experiencing a stressful event (Southwick et al., 2014). Greater resilience during the pandemic has been linked to lower anxiety and depression symptoms in the general population (Barzilay et al., 2020; Havnen et al., 2020) and in pregnant people (Kinser et al., 2021). There are very few studies looking specifically at the relationship between resilience, PNMS, and infant outcomes. Lower resilience has been associated with worse pregnancy (e.g., small for gestational age at birth) and neurodevelopmental outcomes (Bellido-González et al., 2019; Deutsch et al., 2022; Ramiro-Cortijo et al., 2021).

Due to pandemic lockdowns, pregnant individuals lost regular contact with their social network. Lower levels of social support during the pandemic has been associated with greater levels of anxiety and depression symptoms (Khoury et al., 2021; Suwalska et al., 2021). Higher levels of social support could support individuals' mental health through a reduction in loneliness and repetitive negative thinking. Greater social support allows people to talk about their thoughts, feelings, and problems, while less support may lead to "unproductive negative thought spirals" (Harrison et al., 2022). Social support from friends and family during the pandemic has been found to be particularly helpful (Corno et al., 2022). In general, social support can buffer the effect of PNMS on mental health problems by promoting positive health behaviors, positive emotions, and emotional regulation, especially during pregnancy when individuals are taking on new roles and responsibilities (Cohen & Wills, 1985; G. F. Giesbrecht et al., 2013). Social support during pregnancy has also been linked to infant outcomes, such as alterations in brain morphology (Spann et al., 2020), birth outcomes (e.g., Apgar scores, birth weight, fetal growth), and lower emotional distress in response to novelty (Stapleton et al., 2012). Although the findings here are inconsistent, with some studies showing direct effects of social support (Collins et al., 1993; Feldman et al., 2000), moderation effects (Nylen et al., 2013) or no effect at all (Dole et al., 2003).

1.1.4 The COVID-19 Pandemic

Pregnant Individuals during the Pandemic

The COVID-19 pandemic was a chronic global stressor. During this time, there were uncertainties regarding the effects of COVID-19 on pregnant individuals and their unborn children, changes to policies, and length of quarantine. In the midst of all of these worries, it's unsurprising that the prevalence of clinically significant depression, anxiety, and co-morbid symptoms in pregnant individuals were higher compared to pre-pandemic levels (Mateus et al., 2022). Both greater objective hardship, such as pandemic-related financial strain (Cameron et al., 2020) and having family members infected with COVID-19 (Zeng et al., 2020), as well as more subjective levels of stress, such as feelings of isolation and worries about the negative impact of COVID-19 on their unborn child (Lebel et al., 2020), have been associated with higher perinatal anxiety. In one study, those that felt burdened by COVID-19 restrictions, including social distancing and lower access to leisure activities, had significantly higher prenatal depression scores (Kajdy et al., 2023). During the pandemic, many women felt a sense of self-blame, guilt, regret, and lack of control regarding their experiences during pregnancy (Rice & Williams, 2022). They felt a sense of loss when their loves ones could not attend important moments and found virtual prenatal care appointments insufficient. On a positive note, extra time spent at home gave parents more opportunities for parent-infant boding (Adesanya et al., 2022).

Infants Born during the Pandemic

Emerging studies have also looked at infant development in the context of the pandemic. Duguay et al., (2022) found that higher levels of PNMS during the pandemic was related to delayed social-emotional development in 2-months old infants, where postnatal distress mediated this association. One study looked at infant behavior in response to an auditory stimulus. Infants whose mothers reported greater prenatal pandemic-related stress had a higher likelihood of displaying no communication or pointing when the sound was played. Higher prenatal stress was also associated with lower infant socio-cognitive scores in this study (Nazzari et al., 2023). More recent studies have also looked at infant temperament. They found that more severe pandemic-related stress was associated with greater infant negative affect (Buthmann et al., 2022). Infants born during the pandemic seem to have higher levels of negative affectivity compared to infants born pre-pandemic (Morris & Saxbe, 2023). The results of a complex model suggested that both higher levels of pandemic-related distress and low social support increased postnatal anxiety, which was intern associated with maternal parenting stress and less maternal bonding, which then both predicted lower infant regulatory capacity at 3-months (Provenzi et al., 2023). The association between pandemic-related maternal stress and temperament may be due to epigenetic changes occurring during pregnancy in relation to infant SLC6A4 methylation (i.e., potential biomarker of early adverse experiences) (Provenzi et al., 2021). Finally, neurodevelopment across infancy was studied. One meta-analysis compared levels of neurodevelopmental impairment (NDI) to before and during the pandemic. There were no differences between overall NDI among infants during vs. before the pandemic. However, in their subgroup analysis according to infantile age, infants at 12 months born during the pandemic had a higher risk of communication and personal-social impairment (Hessami et al., 2022). In terms of brain development, prenatal distress was associated with reduced infant amygdala-prefrontal functional connectivity during the pandemic, possibly indicating a disruption in the development of the connection of these two brain areas important for emotional regulation (Manning et al., 2022).

1.2 The Current Study

- **Aim 1:** Investigate the relationship between PNMS (prenatal objective hardship, and perceived stress) and mental health (prenatal depression, and anxiety) and infant amygdala/PFC volumes.
- **Aim 2:** Determine the extent to which psychosocial factors, including social support and resilience, moderate the association between maternal objective hardship and infant amygdala/PFC volumes, as well as moderate the association between perceived stress and amygdala/PFC volumes.
- **Aim 3**: Examine whether amygdala and PFC volumes are associated with temperament in infants.

1.3 Hypotheses

1. We hypothesized that greater prenatal stress (objective hardship and perceived stress) and worse maternal mental health (depression and anxiety) would predict larger amygdala volumes and smaller PFC volumes.
2. We predicted that the association between prenatal stress and brain volumes will be stronger given lower levels of prenatal social support, and self-reported resilience.
3. We hypothesized that larger amygdala volumes and smaller PFC volumes will be associated with more difficult temperament in infants.

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Chapter 2

2 Maternal stress and mental health in pregnancy during the COVID-19 pandemic and its associations with infant brain volumes and temperament

At the beginning of March 2020, a multitude of public health measures were implemented in Canada to combat the spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), including changes to prenatal care (Groulx et al., 2021; Public Health Agency of Canada, 2020; Urrutia et al., 2021). Pregnant individuals were faced with uncertainties and challenges, leading to higher perinatal anxiety and depression symptoms during the pandemic compared to pre-pandemic levels (Chmielewska et al., 2021; Lebel et al., 2020; Mateus et al., 2022; Papadopoulos et al., 2021). This is concerning given that prenatal maternal stress (PNMS) is associated with negative health outcomes for both pregnant individuals and their future children (Gunnar & Doyle, 2020; Lautarescu et al., 2020). PNMS is linked to poorer neurodevelopment, cognitive development, temperament, and behavioral problems in childhood as well as and negative birth outcomes (Papadopoulos et al., 2022; Van den Bergh et al., 2017).

PNMS due to an adverse event can be broken down into two components: objective hardship (i.e., level of exposure to an external stressor) and a more subjective psychological component of perceived stress (e.g., worries regarding infection and its impact on the fetus). Both forms of PNMS can impact different aspects of social-emotional development in infants and children. Prenatal anxiety, depression and stressful life events have been associated with both higher negative affectivity/emotionality (i.e., sadness, fearfulness, distress) and difficult temperament (i.e., excessive crying, irritability, slow adaptability) in infants and toddlers (Austin et al., 2005; Bergman et al., 2007; Van den Bergh et al., 2020). In the 1998 Quebec Ice storm study, higher prenatal subjective distress and maternal illness were associated with negative aspects of temperament (e.g., fussy/difficult, dullness, needs attention) in 6-month infants

(Laplante et al., 2016). Similarly, higher prenatal maternal objective hardship due to the 2011 Queensland floods was associated with lower problem solving skills, more difficult temperament (moderated by infant sex and gestational age at the time of the flood), and marginally associated with lower personal-social skills in infants at 6-months of age (Simcock, Elgbeili, et al., 2017; Simcock, Laplante, et al., 2017). Additionally, greater levels of both forms of PNMS have been associated with higher levels of internalizing, externalizing, and other psychiatric problems in childhood, mostly independent of postnatal mood (King et al., 2012; Van den Bergh et al., 2017).

Maternal experiences during pregnancy influence the uterine environment and alter the development of the fetal central nervous system, which can then “set probabilistic parameters for future brain and behavior development” in infancy and childhood (Gunnar & Doyle, 2020, pp. 275). Particularly, PNMS has been associated with differences in amygdala as well as prefrontal cortex (PFC) volumes in children (Lautarescu et al., 2020). Both the amygdala and PFC, as well as the white matter fibers connecting the two brain regions, play a key role in emotional regulation (Fuster, 2002; Seymour & Dolan, 2008; Tottenham & Gabard-Durnam, 2017). The amygdala is an almond-shaped bilateral structure of the limbic system. Psychological distress in mid-pregnancy was negatively related to left amygdala volumes in newborn males (Lehtola et al., 2020). At the same time, higher levels of depression and maternal cortisol (a biomarker of physiological stress) in the second trimester have been associated larger right amygdala volumes in girls during childhood, where amygdala volumes partially mediated the effect of high cortisol levels on affective problems in girls (Buss et al., 2012; Wen et al., 2017). Furthermore, Jones et al., (2019) found that larger amygdala volumes mediated the association between greater objective hardship due to the 1998 Quebec ice storm and externalizing symptoms in 11-year-old girls. One study, however, found no association between PNMS and amygdala volumes in neonates (Rifkin-Graboi et al., 2013). Smaller amygdala volumes have been associated with greater levels of internalizing problems in children (Rosso et al., 2005; Warnell et al., 2018), although other studies reported the opposite association (Albaugh et al., 2017; De Bellis et al., 2000).

The PFC is a region of the cerebral cortex that is heavily involved in social-emotional and cognitive processes, which emerge in early infancy (Grossmann, 2013a; Teffer & Semendeferi, 2012). PNMS has also been associated with reductions in gray matter volume of the frontal lobes in children (Lautarescu et al., 2020). For example, Buss et al. (2010) found that higher pregnancy anxiety at 19 weeks of gestation was associated with gray matter volume reductions in the prefrontal cortex of 6-9 year old children, independent of postnatal stress. Maternal depression at 25 gestational weeks was associated with cortical thinning of the entire cortex, and particularly the frontal lobes in children. Cortical thinning of the PFC mediated the association between prenatal depression and child externalizing behaviors (Sandman et al., 2015).

A variety of mechanisms have been proposed to explain the associations of PNMS with brain development and behavior, including maternal inflammation, altered placental functioning, and greater fetal cortisol exposure (Glover et al., 2009; Gunnar & Doyle, 2020). Abnormal or inappropriate levels of maternal cortisol due to hypothalamic-pituitary-adrenal (HPA) axis activation caused by high stress can have a neurotoxic effect on the fetus' developing brain (Gunnar & Doyle, 2020; Lautarescu et al., 2020). The amygdala in the fetus is rich with cortisol receptors and may be vulnerable to maternal activation of the HPA axis (Tottenham & Sheridan, 2010). PNMS mid-pregnancy may have the strongest impact on infant neuroanatomy (Lehtola et al., 2020). However, a positive postnatal environment, such as a sensitive mother-infant attachment, may alter neurodevelopmental changes associated with PNMS (Lautarescu et al., 2020).

Recent studies have examined infant neurodevelopment during the COVID-19 pandemic. More severe pandemic-related maternal stress has been linked to greater negative affect and changes to amygdala-prefrontal functional connectivity in infancy (Buthmann et al., 2022; Manning et al., 2022). Greater prenatal maternal distress during the pandemic was associated with delayed social-emotional development at 2-months in newborns (Duguay et al., 2022). Further, infants born during the pandemic have higher levels of negative affectivity and have a higher risk of communication and personal-social impairment compared to pre-pandemic. (Hessami et al., 2022; Morris & Saxbe, 2023).

Pregnant individuals are a vulnerable population and are at risk for poor mental and physical health, yet some pregnant individuals will experience less stress as a result of personal protective factors. Two such factors are resilience and social support (Khoury et al., 2021; Kinser et al., 2021). During the pandemic, particularly during periods of quarantine, pregnant individuals were less able to gather and connect with their social network, which could have had detrimental effects to their mental health. Lack of social support has been found to be a risk factor for anxiety and depression symptoms (Khoury et al., 2021; Suwalska et al., 2021). In terms of infant outcomes, prenatal social support has been associated with differences in brain morphology (Spann et al., 2020) and birth outcomes (e.g., birth weight, fetal growth, and Apgar scores) (Collins et al., 1993; Orr, 2004). Prenatal partner support has also been associated with lower infant emotional distress in response to novelty (Stapleton et al., 2012). Resilience is a muti-faceted personality factor, where the individual displays healthy, positive, and adaptive functioning over time after experiencing a stressful event (Southwick et al., 2014). A greater sense of resilience during the pandemic has been associated with lower symptoms of anxiety and depression both in the general population (Barzilay et al., 2020; Havnen et al., 2020) and in pregnant individuals (Kinser et al., 2021; Nichols et al., 2022). Higher resilience has been related to better pregnancy outcomes (e.g., lower likelihood of being born small for gestational age) and neurodevelopmental outcomes (Bellido-González et al., 2019; Deutsch et al., 2022; Ramiro-Cortijo et al., 2021). Resiliency in pregnancy may reduce the impact of prenatal stress on fetal development (Ungar et al., 2019), however less is known concerning the association between maternal resilience and infant brain volumes.

It is of utmost importance to study the impact of PNMS on infant development. However, there is a dearth of studies examining the effect of pandemic-related PNMS on infant brain development and factors that may protect against those effects. To fill this gap, we investigated the association between PNMS, infant temperament, and brain development, with a particular focus on the amygdala and prefrontal cortex. Our study had three main objectives; first, to investigate the relationship between PNMS (prenatal objective hardship and perceived stress), mental health (prenatal depression and anxiety), and infant amygdala/PFC volumes. The second aim was to determine the extent to which psychosocial factors, including social support and resilience, moderate the association between maternal objective hardship and infant amygdala/PFC volumes, and between perceived stress and amygdala/PFC volumes. The third aim was to determine whether amygdala and PFC volumes are associated with temperament in infants. We hypothesized that greater prenatal stress (objective hardship and perceived stress) and worse maternal mental health (depression and anxiety) would predict larger amygdala volumes and smaller PFC volumes. Secondly, we predicted that the association between prenatal stress and brain volumes would be stronger given lower levels of prenatal social support and self-reported resilience. Finally, we hypothesized that larger amygdala volumes and smaller PFC volumes will be associated with more difficult temperament in infants.

2.1 Methods

2.1.1 Procedure & Participants

Data were collected as part of the pan-Canadian Pregnancy During the COVID-19 Pandemic (PdP) Study. The PdP study was a prospective longitudinal cohort study that included multiple follow-up surveys completed during the prenatal and postpartum period. Recruitment was conducted between April 5th 2020 and April 30th 2021. The initial online survey was advertised on social media platforms. To be eligible for the study, individuals must have been pregnant, ≥17 years of age, living in Canada, able to answer questions in English or French, and ≤35 weeks of gestation at recruitment.

The initial survey was completed by participants during pregnancy using REDCap (Research Electronic Data Capture; Harris et al., 2009). It collected their demographic, socioeconomic, and obstetric characteristics (e.g., age, ethnicity, household income, health before and during pregnancy), in addition to their mental health, pandemic-related hardships, psychosocial protective factors, and other measures. Once a participant gave birth, they reported on their pregnancy outcomes, such as their mode of delivery as well as their infant's birthweight, length and gestational age. During the postpartum period, participants were sent further follow-up surveys when their child reached 3, 6, and 12 months of age.

The PdP study also included neuroimaging in the Calgary area. Infants were scanned at Alberta Children's Hospital using magnetic resonance imaging (MRI) at 3 months of age. Only infants born at full-term (≥37 weeks) were eligible for neuroimaging. Infants were excluded if they had a major birth complication or were diagnosed with any severe genetic or neurologic conditions.

All pregnant individuals who participated in the study signed an electronic informed consent form before starting the first questionnaire; parents provided consent for infants to undergo MRI. Participants who completed the prenatal surveys were entered in a monthly draw. Individuals who also participated in the follow-up surveys and imaging part of study received a small stipend. The data were manually checked for bots and invalid responses. This project received ethical approval from the University of Calgary Conjoint Health Research Ethics Board (REB20-0500).

2.1.2 Measures

Objective Hardship: The PdP study team developed the Pandemic Objective Hardship Index (POHI) to measure participants' level of objective hardship due to the pandemic within the past month (Giesbrecht et al., 2023). This measure has four subscales: Scope, Loss, Threat, and Change, each with a maximum score of 50 points. Scope refers to the duration and intensity of the hardship. Loss (i.e., financial, social or physical loss), Threat (i.e., physical and health-related consequences of the pandemic), and Change (i.e., changes to daily routines, prenatal care, work, and social interactions) were also measured. The sum of all four subscales creates the total score, with a maximum of 200 points.

Perceived Stress: The Perceived Stress Scale (PSS-10) was used to measure participants' subjective level of psychological stress during the previous month. Participants are asked 10 questions regarding how often they appraised their life as "unpredictable, uncontrollable, and overloaded" (Cohen et al., 1983). Each item is scored from 0 (*never*) to 4 (*often*), with total scores ranging from 0 to 40. Higher scores indicate a greater level of perceived stress. The PSS-

10 has high internal consistency (coefficient alpha reliability = .84 - .86) and validity. This scale is strongly correlated with other mental health measures, such as Beck Depression (r = 0.67) and Anxiety Inventory (r = 0.58) (Cohen et al., 1983; Lee, 2012).

Depression: At recruitment, the Edinburgh Postpartum Depression Scale (EPDS) measured prenatal depression symptoms over the past week (Murray & Cox, 1990). The EPDS contains 10 items, each scored on a scale from 0 to 3. Total scores range from 0 to 30, where a higher score indicates a greater level of depressive symptoms. Individuals who score above the clinical cut-off score of ≥13 are at risk for depressive disorder. The EPDS has good reliability, with a split-half reliability of .88 and a standardized alpha coefficient of .87 (Cox et al., 1987, 1996).

Anxiety: The Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety–Adult Short Form measured participants' general anxiety symptoms within the past week through a 7-item questionnaire (Pilkonis et al., 2011). Raw scores were converted to T-scores using the US general population norms. Possible T-score values ranged from 36.3 to 82.7 with a mean of 50 (SD = 10). T-scores between 60-69.9 indicate moderate anxiety levels, while scores ≥70 indicate severely elevated anxiety levels (Cella et al., 2010).

Social Support: At recruitment, quality of perceived social support from their romantic partner was measured through the 35-item Social Support Effectiveness Questionnaire (SSEQ) (Rini et al., 2006). The quality of three functional types of support (i.e., emotional, informational, and task support) are assessed over the past three months on a 5-point scale (Rini et al., 2006). A participant can receive a score from 0 to 80, where higher scores indicate greater levels of perceived support. The SSEQ has good internal consistency (Cronbach alpha = 0.87) (Rini et al., 2006).

<u>Resilience:</u> At recruitment, we assessed participants' perceived ability to adapt to change and bounce back after a stressful situation using the 2-item Connor-Davidson Resilience Scale (CD-RISC 2). Both items ranged from 0 (*not true at all*) to 4 (*true all the time*), with a combined total score ranging from 0 to 8. Higher scores indicate greater coping abilities (Vaishnavi et al., 2007).

<u>Infant Temperament:</u> Infant temperament was measured using the Infant Behavior Questionnaire–Revised Very Short Form (IBQ-R) at 6-months of age (Gartstein & Rothbart, 2003; Putnam et al., 2014). There are 37 items total, each asking parents to report on specific infant behaviors over the past week. The IBQ-R assesses three dimensions of temperament: negative emotionality, positive affectivity/surgency, and regulatory capacity/orienting. Parents score each item on a 7-point Likert scale ranging from 0 (*never*) to 7 (*always*), where higher scores indicate higher levels of each dimension of temperament. This scale has strong psychometric properties, with good overall test-retest reliability ($r = .54 - .93$), interparent agreement averaging $r = .41$, and high internal consistency (Cronbach alpha > 0.70), with specific scale internal consistencies of 0.81 (negative emotionality), 0.80 (positive affectivity), and 0.74 (Orienting/Regulatory Capacity) (Putnam et al., 2014).

<u>Image Acquisition & Analysis:</u> 100 infants were scanned at 3 months of age using a GE 3T MR750w MRI with a 32-channel head coil at the Alberta Children's Hospital to acquire brain imaging data. All infants were scanned while asleep atop an inflatable MedVac infant scanning bed. T1-weighted images were obtained (repetition time = 5200 ms, echo time = 2200 ms, inversion time = 540 ms, field of view = 1900 mm, matrix = 512 X 512, bandwidth = 41.67, voxel 1 X 1 X 1 mm^3, flip angle = 12°, 136 slices, total time = 3:32). The brain images were rotated according to the standard atlas and subsequently segmented using infant Freesurfer

(https://surfer.nmr.mgh.harvard.edu/). This program uses the intensity of each voxel to estimate the probability of whether it belongs to a particular brain structure (Fischl et al., 2002). The amygdala segmentations were visually inspected for segmentation quality by a trained expert (Sarah Al Saoud). The PFC volumes were manually segmented using ITK-SNAP. Only certain brain regions were selected to be visible (e.g., Frontal Pole, Caudal Middle Frontal, Lateral/Medial Orbitofrontal, Pars Opercularis/ Triangularis/ Orbitalis…). The cross-hairs were aligned by the corresponding section that, in a brain aligned in Talairach space, would be y=26, as described by Rajkowska & Goldman-Rakic (1995). The region anterior to this landmark was segmented. Three MRI files could not be processed by FreeSurfer. One amygdala and three PFC segmentations were removed from the study due to poor quality.

Covariates: Covariates included maternal education (i.e., highest education obtained) as well as infant variables (i.e., sex, gestational age at birth, total cerebral volumes [TCV]).

2.1.3 Data Analysis

Statistical analyses were conducted using IBM SPSS Statistics v26. General linear models were used to determine the magnitude of any association between perceived stress or objective hardship during pregnancy and left and right amygdala and total PFC volumes at 3 months of age, and the extent to which resilience and social support could moderate the association. Both moderation analyses were performed using the PROCESS Macro (Hayes, 2017). In addition, general linear models were used to determine the magnitude of the association between infant brain volumes (i.e., amygdala and PFC) at 3 months and temperament at 6 months of age. Sex, maternal education, gestational age at birth, maternal ethnicity, and total cerebral volume (TCV) were controlled for in most of our models.

2.2 Results

2.2.1 Participants

A total of 100 mother-infant dyads (mean age = 33.3 years old, SD = 4.33) were recruited from the Calgary area during the COVID-19 pandemic. Participants completed the recruitment questionnaires at an average of 18.3 weeks (SD = 16.38) after the initial Canadian country-wide shut down period on March 11, 2020. Approximately one third (28.6% [n = 28]) of individuals were enrolled in the study in the first trimester of pregnancy, 45.9% (n = 45) were in the second trimester, and 25.5% (n = 25) were in the third trimester. The majority of our participants were white (Caucasian), married or living with their partner, had a university education, and had an annual household income of above $70,000 CAD. Approximately half of participants (53.5% [n = 53]) did not have any other children. At intake, 18.8% (n = 19) of individuals exhibited clinically elevated prenatal depression symptoms above the EPDS cut-off score, while 30.1% (n = 28) exhibited clinically elevated prenatal anxiety levels compared to a general US population reference sample. Descriptive maternal characteristics are reported in Table 1. Participants gave birth at an average of 39.6 weeks gestation (SD = 1.28). Infants were 57% (n = 57) male and 43% (n = 43) female. Infant sample characteristics are presented in Table 2.

Table 1

Maternal Sample Characteristics.

Variable	**n**	**M (SD)**	**Range**
Maternal Age	100	33.3 (4.33)	[23 - 44]
Gestational Age at Birth (in weeks)	100	39.60 (1.28)	[36 - 42]
Objective Hardship (POHI)	94	54.2 (14.42)	[23 - 102]
Perceived Stress	96	16.04 (6.38)	[1 - 31]
Partner Support (SSEQ)	94	57.02 (13.12)	[14 - 80]
General Support (ISEL)	94	39.97 (5.94)	[26-48]
Resilience	99	6.16 (1.17)	[4 - 8]
Prenatal Anxiety at time 1 (PROMIS)	93	16.94 (5.45)	[7 – 28]
Prenatal Depression at time 1 (EPDS)	93	8.45 (4.95)	[0 – 22]

	n	**Valid %**
Marital Status		
Married	83	83.0
Common-Law/living with partner	15	15.0
Other	2	2.0
Education		
High school Diploma/Less Than HS Diploma	3	3.0
College/trade school	20	20.0
Undergraduate Degree	52	52.0
Master's Degree	15	15.0
Doctoral Degree	10	10.0
Household Income		
< $20,000- $69,000 CAD	12	12.0
$70,000-$149,999 CAD	46	46.0
$150,000-$200,000+ CAD	42	42.0
Ethnicity		
White (Caucasian)	83	83.0
Ethnic Minority	17	17.0
How many children do you have?		
0	53	53.5
1	32	32.3
2	10	10.1
3	4	4.0
Data not reported	1	1.0

Table 2

Infant Sample Characteristics.

Variable	n	M (SD)	Range
Birth Length (cm)	99	51.02 (2.72)	[43.0 – 56.0]
Birth Weight (grams)	100	3460.58 (457.65)	[2411.88 – 5164.25]
Negative emotionality (6m)	85	3.68 (0.92)	[1.44 – 5.83]
Positive Affectivity/Surgency (6m)	85	4.65 (0.71)	[2.80 – 6.20]
Orienting/Regulatory Capacity (6m)	85	5.42 (0.67)	[3.82 – 6.75]
Left Amygdala Volume (mm^3)	96	752.43 (104.31)	[544 – 974]
Right Amygdala Volume (mm^3)	96	832.02 (83.372)	[635 – 998]
PFC Volume (mm^3)	94	35210.09 (4116.31)	[28388-49560]
TCV (mm^3)	96	404314.21 (40745.77)	[277051.48 – 518105.65]

	n	Valid %
Infant Sex		
Female	43	43.0
Male	57	57.0

Note: Valid percent refers to the percentage of participants in each category when missing data are excluded.

2.2.2 Maternal stress, mental health, and infant brain volumes

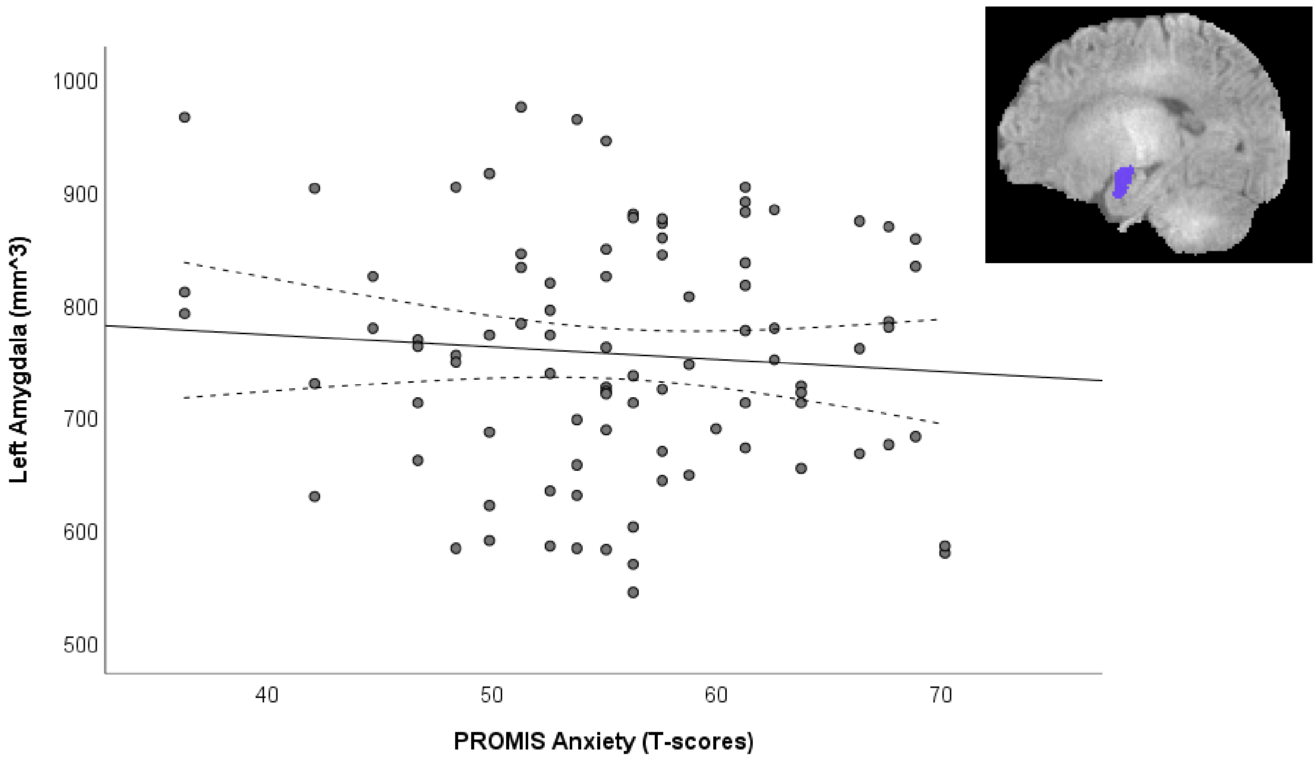
Our first aim was to examine the relationship between prenatal objective hardship, perceived stress, and infant brain volumes at 3 months of age. None of the regions of interest studied (i.e., left amygdala, right amygdala, total PFC volumes) were significantly associated with either maternal stress variables (all, $p > 0.05$). However, when maternal mental health (i.e., prenatal depression and anxiety) measures were included in the objective hardship and perceived stress model with infant brain volumes, greater prenatal anxiety was significantly negatively associated with smaller left amygdala volumes ($B = -5.919$, $p = 0.016$, Fig. 1). Neither prenatal depression ($B = -3.455$, $p = 0.813$) nor the interaction between anxiety and depression ($B = 0.174$, $p = 0.451$) were significant in the model (Table 3).

Table 3. General linear model of prenatal anxiety predicting infant amygdala volumes at 3 months.

Parameter	**B**	**Std. Error**	**95% Lower CI**	**95% Higher CI**	**P value**
Prenatal Anxiety	-5.919	2.4640	-10.748	-1.089	**0.016**
Prenatal Depression	-3.455	14.6026	-32.075	25.166	0.813
Prenatal Anxiety * Depression	0.174	0.2303	-0.278	0.625	0.451
Perceived Stress (highest gestation)	0.171	1.7475	-3.254	3.596	0.922
Objective Hardship	-0.835	0.7204	-2.247	0.577	0.247
Female sex	13.045	22.3163	-30.694	56.784	0.559
Parent education	14.617	10.5437	-6.049	35.282	0.166
Gestational age at birth	0.135	8.2609	-16.056	16.326	0.987
TCV	0.001	0.0003	0.001	0.002	**< 0.001**

CI: confidence interval, Education: highest education obtained, TCV: total cerebral volumes, Prenatal Anxiety * Depression: Interaction between prenatal anxiety and depression

Figure 1. Left amygdala volumes by prenatal anxiety T-scores



Note: Dashed lines indicate the confidence intervals

2.2.3 Moderating Effects of Social Support

The second aim was to determine the extent to which psychosocial factors, including social support and resilience, moderated the association between infant brain volumes and prenatal maternal stress variables. No significant interactions between social support and objective hardship were evident ($p > 0.05$). Social support did not interact with prenatal perceived stress to predict left amygdala volumes ($B = -0.150$, $p = 0.184$) nor right amygdala volumes ($B = -0.058$, $p = 0.554$) at 3 months.

When similar models were implemented to examine partner support and perceived stress in relation to PFC volumes, we found a significant interaction ($B= 4.939$, $p = 0.042$, Table 4). For participants with low partner support (i.e., <16th percentile [scores $\leq$ 42], lower level of the confidence interval), greater perceived stress was associated with smaller PFC volumes at 3-months (B = − 121.56; SE = 59.82; p = 0.046). However, the relationship between prenatal stress and PFC volumes was not significant for participants with high partner support (scores ≥ 71; top 84th percentile; B = 20.45; SE = 44.88; p = 0.65).

Table 4. General linear model of perceived stress predicting PFC volumes at 3-months with partner support as a moderator.

Parameter	B	Std. Error	95% Lower CI	95% Higher CI	P value
Perceived Stress Scale	-329.798	151.07	-625.90	-33.70	**0.029**
Partner support	-115.392	44.28	-202.17	-28.61	**0.009**
Perceived Stress * Partner support	4.939	2.42	0.190	9.69	**0.042**
Objective Hardship	-3.925	15.60	-34.51	26.66	0.801
Female sex	-761.66	494.84	-1731.53	208.21	0.124
Parent Education	-123.47	226.40	-567.20	320.25	0.585
Gestational age at birth	-106.45	194.48	-487.62	274.72	0.584
TCV	0.090	0.0062	0.078	0.103	**< 0.001**

CI, confidence interval, Education, highest education obtained, TCV, total cerebral volumes, Perceived Stress * Partner support: Interaction between perceived stress and partner support

2.2.4 Moderating Effects of Resilience

Resilience was a significant moderator of the association between perceived stress and PFC volumes (B = 60.240, p = 0.045, Table 5, Figure 2). Resilience did not interact with either objective hardship or perceived stress to predict any of the other brain volumes studied.

Table 5. General linear model of perceived stress predicting PFC volumes at 3-months with resilience as a moderator.

Parameter	B	Std. Error	95% Lower CI	95% Higher CI	P value
Perceived Stress Scale	-404.33	200.41	-797.13	-11.53	**0.044**
Resilience	-936.02	538.41	-1991.284	119.24	**0.082**
Perceived Stress * Resilience	60.24	30.09	1.268	119.21	**0.045**
Objective Hardship	-5.96	15.94	-37.206	25.28	0.708
Female sex	-725.55	491.08	-1688.05	236.96	0.140
Parent Education	-24.33	236.58	-488.03	439.37	0.918
gestational age at birth	-216.38	190.46	-589.69	156.92	0.256
TCV	0.090	0.0063	0.078	0.10	< **0.001**

CI, confidence interval, Education, highest education obtained, TCV, total cerebral volumes, Perceived Stress * Resilience: Interaction between perceived stress and resilience

Figure 2. Prenatal Perceived Stress Predicted 3-month PFC volumes as moderated by Resilience

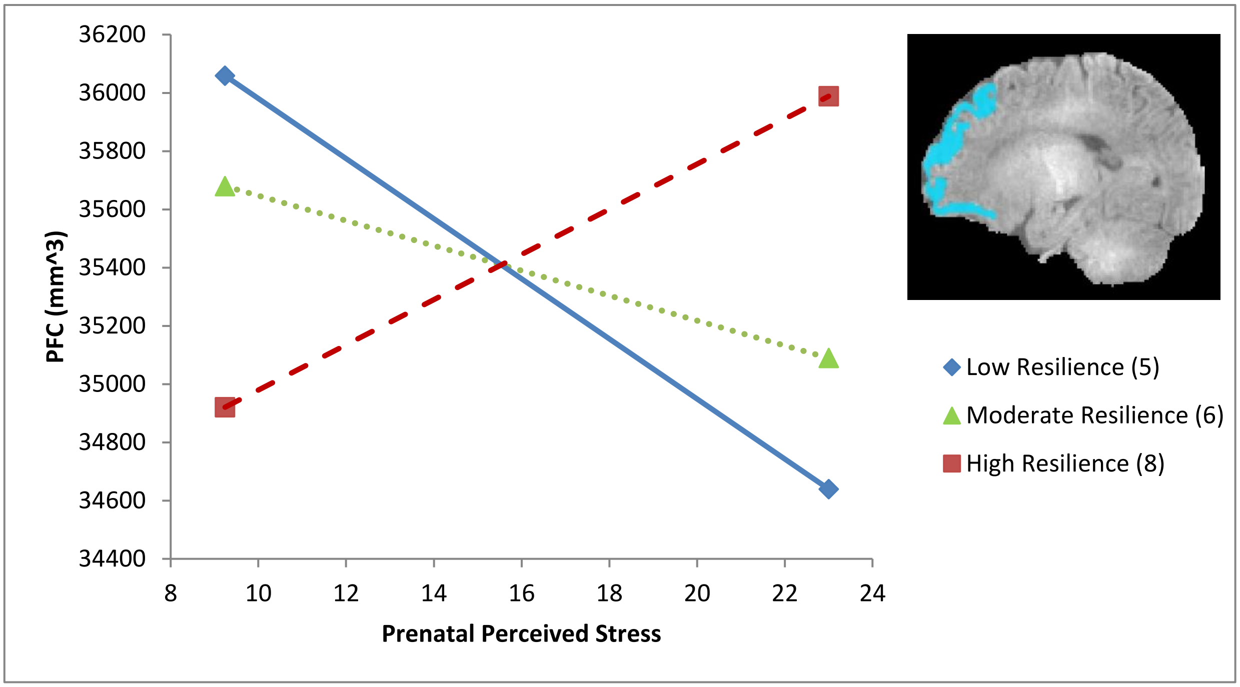


Figure 2. For participants with low resilience, greater perceived stress was associated with a decrease in PFC volumes. However, for participants with high resilience, higher levels of perceived stress predicted greater PFC volumes.

2.2.5 PFC & amygdala volumes and emotional regulation

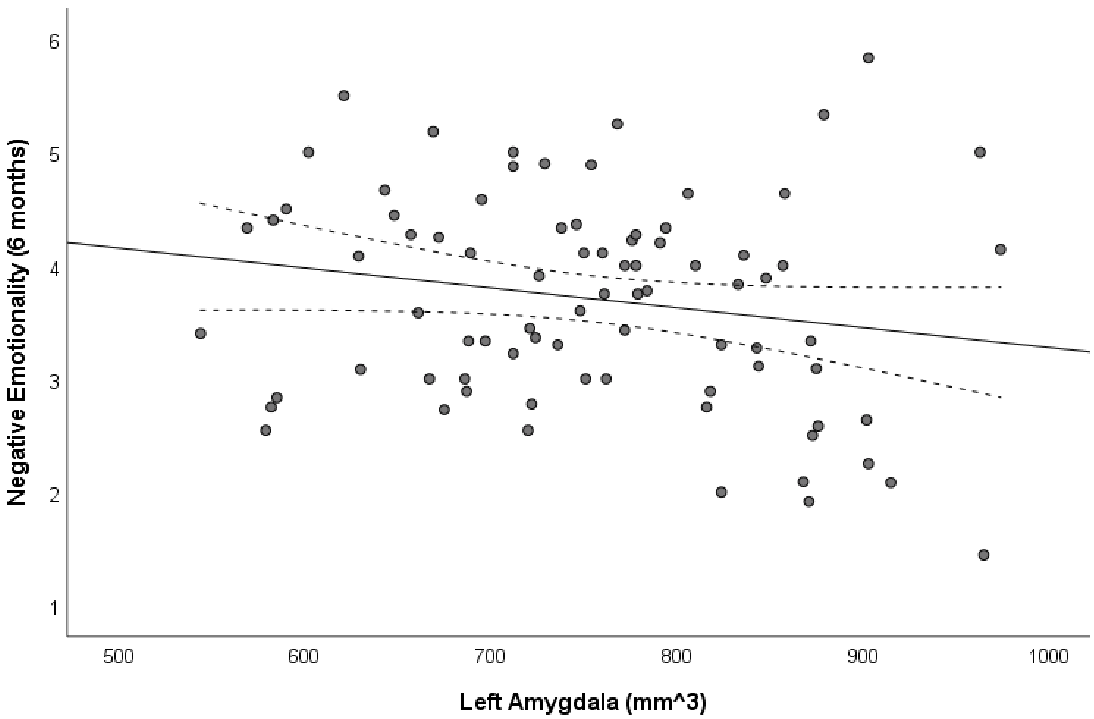
Our third aim was to examine the relationship between infant brain volumes at 3 months and temperament at 6 months of age. Using a general linear model, left amygdala volumes negatively predicted infant negative emotionality (B = -0.002, p = 0.035, Figure 3, Table 6); right amygdala volumes were not associated with temperament.

Table 6. General linear model of left amygdala volumes predicting infant negative emotionality at 6-months.

Parameter	B	Std. Error	95% Lower CI	95% Higher CI	P values
Left Amygdala	-0.003	0.0011	-0.005	-0.001	**0.016**
Right Amygdala	0.001	0.0012	-0.002	0.003	0.509
PFC	-0.00008	0.00005	-0.0002	0.00001	0.090
Female sex	0.006	0.2165	-0.419	0.430	0.979
Education	-0.069	0.1131	-0.290	0.153	0.543
Ethnicity	0.084	0.0317	0.022	0.147	**0.008**
TCV	0.000008	0.000005	-0.000002	0.00002	0.127

PFC, prefrontal cortex

Figure 3. Infant Negative Emotionality at 6 months by 3-month Left Amygdala Volumes



Note: Infants with greater left amygdala volumes were more likely to have lower levels of negative emotionality.

2.3 Discussion

As part of a larger longitudinal pan-Canadian study of pregnant individuals during the pandemic, we examined the association of prenatal maternal stress, anxiety, and depression with 3-month amygdala and PFC volumes in a subset of participants who returned for infant imaging scanning. First, we showed that greater prenatal anxiety was associated with smaller left amygdala volumes. Second, we examined how psychosocial factors, including social support and resilience, could moderate the association between PNMS and infant brain volumes. Both partner support and resilience moderated the association between prenatal perceived stress and PFC volumes. Finally, we also determined the extent to which infant brain volumes were associated with 6-month infant temperament. Our findings showed that smaller left amygdala volumes were associated with higher negative emotionality (e.g., more sadness, fear, crying, irritability).

The negative relationship between maternal anxiety and infant amygdala volumes adds to the growing body of literature describing the vulnerability of the amygdala to early stress. Our finding is supported by previous research that found altered amygdala volumes and functional changes in association with maternal stress during the intrauterine period of life (Lautarescu et al., 2020). Higher prenatal depression (Wen et al., 2017) and pregnancy-related anxiety (Acosta et al., 2019) symptoms have been associated with larger amygdala volumes in young girls (Acosta et al., 2019; Wen et al., 2017). Conversely, Lehtola et al. (2020) found that prenatal psychological distress, a combination of anxiety and depression symptoms, predicted smaller amygdala volumes in newborn males. Importantly, the direction of the effect of PNMS on amygdala volumes may vary based on the age of the children studied. The growth of the amygdala varies with age, with "rapid increases in volumes at early ages [that] decline as youth enter adolescence" (Russell et al., 2021, pp.117). PNMS could potentially affect the developmental trajectory of amygdala growth throughout time. In animal models, prenatal stress has resulted in reduced amygdala volumes (including decreases in amygdala neurons and glial cells) in offspring early postnatally (Charil et al., 2010). However, in later developmental stages, prenatal stress was related to greater amygdala volumes compared to controls (Charil et al., 2010). Previous studies have also used different measures of PNMS, including perceived stress, objective hardship, depression, and anxiety. The amygdala could be affected by different aspects of maternal stress in alternative ways. PNMS severity, timepoint in gestation, HPA-axis activation, and genetic influences could all affect the resulting offspring amygdala volumes (Gunnar & Doyle, 2020).

The second aim was to study the extent to which psychological factors, including partner support and resilience, moderated the associations between PNMS and infant brain volumes. This is one of first studies to show how partner support and resilience had a protective effect against the impact of prenatal perceived stress on PFC volumes. Higher perceived stress predicted reduced PFC volumes, but only for those with lower partner support. In the larger PdP sample, higher social support was associated with lower symptoms of maternal anxiety and depression during the pandemic (Lebel et al., 2020). Previous research has also found lower levels of perinatal depression and anxiety in mothers with better social support (Akiki et al., 2016; Friedman et al., 2020; Khoury et al., 2021). Positive social relationships can support the mental health of pregnant individuals by providing them with psychological and material resources, buffering their stress response, and improving their emotional regulation, coping skills, and positive affect (Cohen & Wills, 1985; G. F. Giesbrecht et al., 2013). Social support can be particularly important during pregnancy, as it is a period filled with many uncertainties, challenges, and changes. Partner support was especially important during the pandemic where lockdowns limited opportunities for social interactions. Not only can social support benefit the pregnant individual, but our study provides evidence that partner support can potentially lessen the intergenerational transmission of PNMS to the developing infant brain. Other studies have found that higher levels of social support are linked to better pregnancy outcomes (e.g., better labor progress, higher newborn APGAR scores, less preterm birth) (Collins et al., 1993; Orr, 2004; Ungar et al., 2019) and lower levels of infant negative temperament (Luecken et al., 2015). Social support can buffer the effects of maternal early life stress on the infant stress response (Thomas et al., 2018). Manning et al. (2022), also using PdP study data, showed that social support moderated the association between PNMS and infant amygdala-prefrontal functional connectivity during the pandemic, where high social support seemed to remove the effects of prenatal distress on children's brain function. The direction of this result is similar to the current study. One potential mechanism of these relationships are placental DNA methylation changes involved in fetal brain development, as well as lower inflammation, which are associated with maternal social support during pregnancy (Tesfaye et al., 2023; Uchino, 2006).

In addition, greater perceived stress was related to smaller PFC volumes only for participants with low resilience. Resilience could have buffered maternal stress levels during pregnancy, reducing fetal stress exposure and protected their unborn child from the deleterious effects of prenatal stress (Howland & Cicchetti, 2021). Di Paolo et al. (2022) found that resilience buffered the impact of prenatal objective hardship during the COVID-19 pandemic on postpartum anxiety. Resiliency in pregnancy has been associated with lower levels of maternal depression and anxiety symptoms, perceived stress, hair cortisol concentrations, and pregnancy concerns as well as improved psychological well-being (García-León et al., 2019; Kinser et al., 2021; Ramiro-Cortijo et al., 2021). Higher prenatal resilience levels have been related to better pregnancy outcomes (e.g., less preterm birth, larger birth weight) (Alves et al., 2021; Bhatia et al., 2015; Ramiro-Cortijo et al., 2021), lower odds of newborn neurological impairment (Deutsch et al., 2022), and better mother-infant bonding (Kokkinaki & Hatzidaki, 2022). Maternal resilience can also impact newborns at the cellular level; greater resilience have been associated with longer/healthier newborn telomere length (Verner et al., 2021). In childhood, greater prenatal resilience has been found to lower externalizing and internalizing behaviors (Tung et al., 2024) and reduced the impact of pregnancy-specific pandemic worries on child social-emotional development (White et al., 2023). Resilience can improve maternal and child health through various neurobiological, genetic, physiological, psychological, environmental, and social mechanisms (Alves et al., 2021; Ozbay et al., 2008; Ungar et al., 2019). For example, individuals with greater resilience tend to use more positive cognitive attributions, active coping styles, and engage in stress-buffering behaviors (e.g., better sleep patterns, exercise) (Nichols et al., 2022; Ungar et al., 2019; Yu et al., 2020).

In our third aim, we examined the relationship between infant temperament and infant amygdala as well as PFC volumes. We found that smaller left amygdala volumes were related to higher infant negative emotionality. Overall, in our study, higher prenatal anxiety predicted smaller left amygdala volumes, which in turn predicted greater negative emotionality. Infants with higher levels of negative emotionality tend to exhibit stronger negative emotional responses, such as sadness, crying, and irritability. Previous research has shown that PNMS is related to greater difficult/negative temperament, with more irritability and crying (for review see: Van den Bergh et al., 2020). Pandemic-related stress during pregnancy has also been linked to greater negative affect in infants (Buthmann et al., 2022). However, the association between amygdala volumes and temperament is mixed. Previous research found that smaller amygdala volumes were related to higher levels of infant negative affectivity, excessive crying and irritability (Demers et al., 2022; Sammallahti et al., 2023). Filippi et al. (2020) showed that infants with more negative temperament had slower growth in left amygdala volumes in childhood. In children, smaller amygdalae were related to pediatric depression and anxiety (Burrows et al., 2024; Milham et al., 2005; Rosso et al., 2005). Smaller amygdala volumes are also linked to higher aggression in school-aged children (Thijssen et al., 2015). In animal studies, mice with smaller basolateral amygdala nucleus volumes had a stronger fear response (Yang et al., 2008). The reduction of amygdalae volumes could be due to an excitotoxic process caused by PNMS (i.e., exposure to cortisol, inflammation) (Gunnar & Doyle, 2020). At the same time, some studies reported larger amygdalae volumes predict worse internalizing problems in children (Buss et al., 2012; De Bellis et al., 2000) and greater infant fear (Bezanson et al., 2023). The current study also provides some evidence towards lateralization of amygdala structure and function. Left and right amygdalae may have different functions, where the left amygdala is more involved in negative emotions and local processing (Baas et al., 2004). The left hemisphere also grows more quickly in early gestation (Andescavage et al., 2017), potentially making it more vulnerable to PNMS, similar to our results.

Possible limitations should be considered when interpreting our findings. While the original pan-Canadian sample included over 11,000 participants, only 100 infants in the Calgary area were scanned due to the pandemic, and infant movements during scanning affected the quality of some scans. The scans were performed at 3 months of age and temperament was measured at 6 months postpartum, thus postnatal factors, such as infant feeding, sleep, and infection, could have also influenced infant brain development and its relationship to PNMS. Almost all the maternal data were collected using self-report questionnaires, which could have introduced reporting biases. This measure could have varied by participant based on their recruitment date as there were rapid changes in government policies and COVID-19 cases during this time. Participants were recruited primarily from social media advertising, which could have contributed to selection biases. Participants were mostly white, financially stable, highly educated, and living in a country with a relatively contained outbreak and universal healthcare, both limiting the generalizability of our results and potentially underestimating the true effect of PNMS on infant brain development in populations with greater vulnerabilities. Finally, our cohort design limits the possibility for causal interpretation.

This study also had several major strengths. Its prospective longitudinal design allowed us to examine the associations between maternal stress variables (measured at different time points), infant brain volumes at 3 months, and infant temperament at 6 months of age. We had a relatively large sample size of 100 mother-infant dyads, resulting in a very rare and well-characterized cohort. Participant recruitment and data collection started at the early phases of the pandemic. Thus, our study was able to capture maternal stress levels related to the initial government mandated restrictions and rise of COVID-19 cases. The PdP study team developed a novel measure of Objective Hardship that captured participants level of loss, threat, and change due to the pandemic, as well as the duration and intensity of their hardship. Members of the research team had extensive experience in creating objective hardship measures due to population-level disasters for pregnant individuals. Thus, we were able to disentangle the relative effects of objective hardship, perceived stress, and maternal mental health on infant development while they were exposed to a relatively independent stressor (the pandemic). In addition, the study collected information on many potential confounding variables, and used measures that had strong psychometric properties, such as the EPDS and PROMIS.

Our findings have implications for perinatal policy and health care. The results suggest that screening for social support, resilience, stress, and anxiety could help us identify at-risk individuals during pregnancy. Those with greater vulnerabilities (e.g., low social support, high stress) could benefit from psychological interventions, such as cognitive behavioral therapy. Both social support and resilience could also be targets for prenatal interventions. The Care project, Perinatal Child–Parent Psychotherapy and MotherWise are all evidence-based interventions that were developed to reduce maternal psychopathology and improve resilience during pregnancy (Davis & Narayan, 2020). Resilience training can include emotional regulation training and positive reframing training through cognitive and behavioral approaches (Davis & Narayan, 2020). Stress reduction could also mitigate the impact of pandemic-related stress on infant brain development (Graham et al., 2022). The brain remains quite plastic throughout infancy and childhood. Thus, offspring of at-risk individuals may also benefit from early evidence-based interventions, such as those targeting emotional regulation. Future research should use longitudinal scanning to help us determine the effect of prenatal stress on the trajectory of brain development throughout childhood. Long-term follow-ups with these children will allow us to examine the link between pandemic-related prenatal stress, brain volumes, and many measures of child development, such as motor, behavioral, and social-emotional development. Future studies should also investigate other potential personal and environmental factors that could protect infant brain development from the negative effects of pandemic-related stress.

In conclusion, the present study described the relationship between prenatal stress during the COVID-19 pandemic, infant brain volumes, and temperament. We observed a negative association between prenatal anxiety and left amygdala volumes. Left amygdala volumes also predicted negative emotionality. Infant temperament, for example, may be partially programmed *in utero* and influenced by the development of the amygdala. In addition, partner support and resilience had moderating effects on the PFC. Overall, the current study supports the hypothesis that exposure to stress, such as the COVID-19 pandemic, influences infant development.

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Chapter 3

3 Study outcomes

In this study, higher levels of prenatal maternal anxiety were related to reduced left amygdala volumes in infancy. Greater anxiety symptomatology in pregnancy could have impacted fetal brain development through changes in the placenta as well as cortisol and inflammation levels (Gunnar & Doyle, 2020). Smaller left amygdala volumes at 3 months of age predicted greater negative emotionality at 6 months. Previous research has also found that PNMS was associated with negative emotionality and internalizing symptoms in childhood (Van den Bergh et al., 2017). Changes in amygdala volumes, a brain area important for emotional regulation, could explain the association between PNMS and temperament. Finally, prenatal perceived stress was associated with reduced PFC volumes. Both social support and resilience were found to be protective factors.

3.1 Implications

Our findings suggest that lower social support and resilience as well as higher levels of perceived stress and anxiety in pregnant individuals could have a negative impact on infant brain development. These measures can be screened for during pregnancy to identify individuals who are at a higher risk of poor infant outcomes. Individuals with greater vulnerabilities would benefit most from interventions designed to improve resilience and reduce PNMS. Van Haeken et al. (2023) developed a resilience-enhancing intervention for peripartum women. Women found that the program’s emphases on emotional regulation (e.g., awareness and recognition of one owns emotions, mindfulness, positive reframing, coping skills), self-care (e.g., relaxing, hobbies), and self-efficacy were important skills in developing resilience. While barriers included accessibility, affordability of resources, and stigma.

Universal prenatal mental health preventive interventions have a moderate effect on PNMS (d = 0.52) (Missler et al., 2021). Some of the most common interventions in pregnancy include cognitive behavioral therapy (CBT; focus on thoughts, emotions, and behaviors, positive activities, parenting strategies), mindfulness-based cognitive therapy (MBCT; tolerate uncomfortable emotions, body awareness, yoga, gratitude diary, meditation), and interpersonal psychotherapy (ITP; focus on social relationships), which have been shown to reduce prenatal depression and anxiety symptoms, as well as improve emotional regulation, and psychological well-being in pregnancy (Wazana et al., 2021; Zemestani & Fazeli Nikoo, 2020). Prenatal CBT programs can reduce cortisol levels in the pregnant individual themselves (Richter et al., 2012) as well as their infants (Urizar Jr & Muñoz, 2011). There are a variety of nonpharmacologic approaches for reduction in psychological stress in pregnancy including meditation, yoga, music, muscle relaxation, physical exercise, and expressive writing (Abera et al., 2024; Traylor et al., 2020). In the pandemic, many therapy programs switched to online services, which can still be effective at reducing prenatal psychological distress (Neo et al., 2022).

There are a variety of different evidence-based intervention programs designed to improve maternal psychopathology during pregnancy. For example, the MOMCare Project uses brief ITP to improve depression. Perinatal Child–Parent Psychotherapy (CPP) attempts to reduce the intergenerational transmission of stress in pregnant individuals by processing their unresolved trauma before birth. MotherWise is a relationship-based program that helps pregnant individuals learn to improve their communication and conflict resolution skills with their partners (Davis & Narayan, 2020). This program is particularly important in the context of this current study, as higher levels of positive partner support was found to be a protective factor in infant brain development. By improving the relationship between partners, we can simultaneously improve healthy infant development. Similarly, the Family Foundations program is a couples-focused psychoeducational program that helps first time parents improve their coparenting relationship before and after birth. The program is also associated with reductions in PNMS, higher newborn birthweight, and improved parenting quality (Feinberg et al., 2016).

Overall, women attending psychotherapeutic interventions during pregnancy were satisfied with their program. In group programs, pregnant individuals would discuss their difficult thoughts and feelings with others in a similar situation, reducing feelings of isolation, which was particularly important during the pandemic. In interviews, women said that they benefited from their program, especially when learning breathing, emotional regulation techniques (e.g. how to reflect on their own emotions, how to be kinder to themselves), and about the causes of stress (Evans et al., 2020).

Improvement of PNMS by psychological interventions in pregnancy has also been associated with infant health. One meta-analysis found that both preventive and treatment interventions for depression (e.g. CBT, psychoeducation), conducted during pregnancy were associated with better child neurobehavioral functioning, particularly reductions in infant dysregulation (Goodman et al., 2018). These interventions may also have a positive impact on obstetric (e.g., reduced caesarean deliveries, shorter delivery, fewer obstetric complications), fetal (e.g., altered neurobehavior), and newborn outcomes (e.g., lower preterm birth, improved Apgar score) (Abera et al., 2024; Bittner et al., 2014; Fink et al., 2012). This shows how prenatal interventions can possibly reduce the negative associations between PNMS and infant health shown in this current study.

While this paper focuses on partner support, support from ones own social network (e.g., friends, family, others within the community) can also improve maternal psychological wellbeing during pregnancy. There are different types of support, including emotional support (e.g., expressing feelings and reassurance), informational support (e.g., advice and guidance), instrumental support (e.g., material/monetary aid, tangible assistance), and social companionship (e.g., spending time with others, particularly those who are in similar situations) (Bedaso et al., 2021; De Sousa Machado et al., 2020). Emotional and tangible support in particular have been shown to be preventative against perinatal depression and anxiety (Milgrom et al., 2019). Adequate social support allows pregnant individuals to talk in-depth about their more difficult feelings to a nonjudgmental person who can be reassuring and accepting (De Sousa Machado et al., 2020). Inadequate social networks, however, can be a source of conflict and strain, thus negatively impacting mental health (Balaji et al., 2007).

Different sources of support can have complementary but distinct impacts on the wellbeing of pregnant individuals. Partners were rated as the most important source of support for pregnant individuals during the pandemic (Corno et al., 2022; Harrison et al., 2022). At the same time, friendships were found to particularly impact individual's life satisfaction and overall wellbeing. Perceived social support from friends and family were also associated with reduced prenatal anxiety and depression levels. (Corno et al., 2022). Greater support from friends and family could reduce repetitive negative thinking (i.e., rumination) and loneliness, thus improving mental health (Harrison et al., 2022). The internet was an important resource for individuals to keep in contact with their social network during the pandemic. While individuals had their in-person social network broken (e.g., less involved in prenatal classes, no conversations with other pregnant mothers), women could speak with family and friends using the phone, video calls and texts (Harrison et al., 2022). Social support during pregnancy has been associated with better pregnancy, birth, and infant outcomes (Collins et al., 1993; Luecken et al., 2015; Spann et al., 2020; Stapleton et al., 2012; Orr, 2004; Ungar et al., 2019).

Prenatal interventions should encourage pregnant individuals to keep in contact with their social network or even increase their number of social relationships. Larger and more supportive networks can reduce stress and improve wellbeing (Balaji et al., 2007). Perinatal support groups can also improve mental health. At the end of one intervention, 20-min weekly peer support groups and interpersonal psychotherapy groups both had lower anxiety, depression, and cortisol levels (Field et al., 2013). In addition, the 'Promoting Social Networks and Support' intervention developed for the general population can be used to improve social support and reduce depression levels in pregnant individuals. In a group, individuals learn about developing social support networks, the function of social support, social skills, communication, cognitive distortions and more (Martin et al., 2011).

In childhood, the brain is very plastic and can benefit from positive environmental stimulation. Despite the negative association between PNMS, brain development, and temperament found in this current study, school-based and parenting-based emotional regulation interventions during infancy and childhood may partially reverse the negative impact of PNMS during the COVID-19 pandemic. While temperament is a fairly stable trait, there have been some interventions developed to reduce negative emotionality in infancy. These are parent-based interventions that focus on the parent's response to their child's negative emotions. Parents learn specific, actionable parenting strategies and responsiveness so that they can better respond to their infant in a predictable, sensitive, and warm manner (Morawska et al., 2019). For example, the Attachment and Biobehavioral Catch-up (ABC) intervention helps parents learn about responsive caregiving and gives parents the tools to provide their children with a nurturing environment that supports the development of regulatory capabilities in infancy. The intervention targets three sensitive parenting strategies: "providing nurturance, following the child's lead with delight, and avoiding intrusive and frightening behaviors" (Hepworth et al., 2020, pp 713). Infants in this intervention used more mother-oriented emotion regulation strategies, had better attachment security, and lower cortisol levels compared to controls (Hepworth et al., 2020; Morawska et al., 2019). Psychoeducation for parents in prenatal care, developmental milestones in infancy, positive home environments, and stimulating toys can also reduce difficult temperament (Shipra & Shubhangna, 2009).

Interventions have also been designed for parents of toddlers and preschool age children. Children learn about appropriate self-soothing behavior through praise and parental acknowledgment as well as parental modeling of self-regulatory skills. Use of positive control (e.g., limit setting with positive guidance and scaffolding, validate child's emotions) instead of negative control (e.g., hostile, critical and controlling parenting styles, dismissing child's emotions) can result in higher levels of self-regulation in children (England-Mason & Gonzalez, 2020; Morawska et al., 2019). The Holding Hands program is a behavioural parenting intervention designed for parents of toddlers. The program teaches parents how to model behavioral and emotional skills to their children as well as how to reinforce desirable behavior. Toddlers in this program had significant improvement in emotional and behavioural functioning, and parents had reductions in stress, anxiety, depression (McAloon & Lazarou, 2019). In terms of preschool interventions, Tuning in to Kids (TIK), Parent-Child Interaction Therapy-Emotion Development (PCIT-ED), and Emotion Enhanced Triple P (EETP) are three interventions designed to improve children's emotional self-regulation skills (Rothenberg et al., 2019). In these interventions, parents learn to help their child label their emotions, emotional behaviors, and emotional causes. Parents learn to regulate their own emotions and praise their child when they exhibit positive self-regulation (e.g., “I love how you are being so calm even after the tower fell”) (Rothenberg et al., 2019, pp. 721). Studies found improvements in emotional regulation, emotional competence, and internalizing/externalizing symptoms after participating in these interventions (England-Mason & Gonzalez, 2020; Rothenberg et al., 2019).

Finally, there are interventions for school-aged children. Similar to the prenatal interventions presented earlier, CBT and mindfulness-based interventions can help children reduce negative emotionality and improve emotional regulation (Pandey et al., 2018; Pickerell et al., 2023). These are often curriculum-based interventions where classroom teachers are the main interventionist. Exercise-based, family-based, and social skills training are other methods used to teach children self-regulation skills. Interventions targeted to very young children often include storytelling, book reading, and self-talk while interventions for older children include “role play, cognitive modeling, and psychoeducational group therapeutic lessons” (Pandey et al., 2018, pp. 569). Mindfulness-based and cognitive behavioral interventions have been shown to improve positive affect, emotional self-awareness, and reduce depression, anxiety, and negative expressive behaviors in children (Pickerell et al., 2023). For example, the CBT-based transdiagnostic prevention program EMOTION has been found to decreases emotional dysregulation. The intervention targets internalizing symptoms and emotional regulation through “psychoeducation, behavioral activation, cognitive restructuring, building of a problem hierarchy, and gradual exposure to feared or avoided situations” (Loevaas et al., 2019, pp. 813). As another example, the school-based universal cognitive behavior intervention, FRIENDS, has been found to reduce anxiety, depression, and perfectionism in elementary aged students. Children learn strategies to manage anxiety and stressful events, including challenging anxious thoughts, coping skills, communication/problem-solving skills, and self-reward (Essau et al., 2012). On another note, middle school children who received mindfulness training had lower stress levels associated with lower amygdala activation and stronger functional connectivity between the amygdala and PFC (Bauer et al., 2019).

As shown by this current study and other research, PNMS can alter amygdala and PFC development and is associated with more difficult temperament. However, the brain in infancy and childhood is plastic and is sensitive to positive environments. The interventions described above may possibly reverse the negative impact of PNMS on temperament and emotional regulation in infancy and childhood. The current research suggests that infants born to mothers with greater vulnerabilities (e.g., high PNMS, low social support/resilience) may benefit from the interventions described. Through participating in these interventions, children can have the best chance at a healthy emotional regulation style. In addition, emotional regulation interventions may possibly impact amygdala volume and activation (Bauer et al., 2019; Joss et al., 2021).

3.2 Limitations and Future work

This work is not without limitations. First, compared to the initial 11,000 PdP sample, we only scanned 100 infants in the Calgary area. This reduced our sample size, power, and generalizability of our findings compared to other areas in Canada. As the scans were conducted at 3 months of age, there could have been many other postnatal factors that could have affected our results (e.g., infant feeding, sleep, and infection). The quality of some scans was also reduced due to infant movements. Recruitment using social media and the use of self-report questionnaires could have introduced reporting and selection biases. In addition, the objective hardship measure was only collected at one time point, while there were rapid changes in government policies and COVID-19 cases during this time, which could have impacted this measure. In general, our participants were highly educated and financially stable. Thus, our results may not be generalizable to people with lower socioeconomic status. Finally, as our study was conducted in Canada, which was a country with a relatively contained outbreak and universal healthcare, our study cannot be generalized to many other countries and potentially underestimating the true effect of PNMS on infant brain development in populations with greater vulnerabilities.

The PdP study will continue to scan our infant participants in the future, which will help us determine the effect of prenatal stress on the trajectory of brain development throughout childhood. Long-term follow-ups with these children will allow us to determine the association between PNMS, various brain regions, and measures of child development, such as motor, behavioral, and social-emotional development. In my PhD, I plan to assess whether varying aspects of PNMS (i.e., objective hardship and perceived stress) during the COVID-19 pandemic are associated with hippocampal growth measured from ages 3 months to 24 months. In addition, I would like to test whether hippocampal growth mediates the association between PNMS and measures of neurodevelopment (including problem solving, communication, and personal social skills) in 2-year-old children. The hippocampus is a brain structure important for memory formation, learning, spatial navigation, and emotional regulation (Andersen, 2007). Prenatal maternal stress (PNMS) has been shown to alter its development. Greater PNMS and anxiety are associated with smaller infant left hippocampal volumes (Moog et al., 2021), as well as slower bilateral hippocampal growth during a child's first 6 months of life (Qiu et al., 2013). The results of my PhD study will help us better understand infant development during the pandemic and the mechanisms through which maternal stress exposure may affect child development. Our findings may have vital implications for policy, prenatal care, and the development of interventions created to reduce the effect of PNMS on fetal development.

3.3 Final conclusions

In conclusion, PNMS was associated with alterations in infant brain volumes during the pandemic. Prenatal maternal anxiety was associated with smaller 3-month amygdala volumes, where smaller amygdala volumes also predicted negative emotionality at 6 months. Prenatal perceived stress was associated with reduced PFC volumes, which was moderated by partner support and resilience. Our findings suggest that partner support and resilience could be protective factors against PNMS during the pandemic. This current study adds to the literature on the developmental origins of health and disease. Prenatal and childhood interventions may reduce the impact of PNMS on pregnant individuals and their children. This current study may have important implications for universal prenatal mental health care and policy, including preventative interventions to protect fetal development from PNMS.

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A | D

AMBER-LEE DI PAOLO

MA CANDIDATE | SCHOOL AND APPLIED CHILD PSYCHOLOGY | WESTERN UNIVERSITY

Education

Master of Arts: School and Applied Child Psychology
University of Western Ontario | 2022 - 2024
Awards & Distinctions:
- Ontario Graduate Scholarship – $15,000 2023-2024
- Canada Graduate Scholarships – Master's (CIHR) – $17,500 2022-2023
- Faculty of Education Entrace Scholarship – $6,800 2022-2024

Bachelor of Science: Psychology Major
McGill University | CGPA: 3.99 out of 4.0 | 2015 - 2020
Awards & Distinctions:
- Dean's Honor List 2020
- Wallace B. Chung Scholarships – $2500 2019
- The Marion McCall Daly Award – $500 2018
- Dr. Dale Elaine Zilbert Memorial Prize – $440 2018
- Faculty of Science Scholarship – $100 2018
- DECLINED: H. Laurie Seybold Memorial Fund - $500 2017

Collegial Studies: Honours Health Science
Marianopolis College | 2013 - 2015
Awards & Distinctions:
- Marianopolis Scholar 2015
- Millennium Foundation Academic Award – $500 2013

Work Experience

Research Supervisor
Language and Working Memory Lab | Jan - June 2024
Supervisors: Dr. Lisa Archibald & Dr. Katrina Kelso
- I've been supervising a reading intervention study for 3rd to 8th grade students. Both phonics and reading comprehension is emphasized.
- My tasks include reviewing lesson plans, supervising intervention sessions, guiding interventionists through the program, and scheduling participants. I also ran a few intervention sessions

Youth Mental Health Coordinator
The Greene Avenue Community Centre | Feb - Aug 2022
- As coordinator of the Healthy Steps project, I ran interactive mental health workshops and organized events for youth ages 15-25 on resilience, emotions, mindfulness, healthy relationships, stigma and more. I developed activities, facilitated discussions, recruited participants, balanced the budget, and promoted events on social media

- I collaborated with local non-profit organizations and invited their members as guest speakers to promote mental health literacy within our community
- This project also empowered 'youth ambassadors' to develop their own mental health and wellness initiative at our centre. I worked together with our youth to organize their own mental health day, which included leading brainstorming sessions, developing schedules/action plans, and managing the group/assigning tasks

Research Assistant

The Canadian Institute for Obsessive Compulsive Disorders (CIOCD) | Nov 2020 – Nov 2021

Supervisor: Dr. Debbie Sookman

- I worked on a national survey project studying clinical services and training for OCD across Canada
- My main responsibilities were to coordinate a team of volunteers, disseminate surveys, manage data collection using Survey Monkey, summarize survey data, and call psychologists requesting information
- I also worked on a paper titled “Knowledge and competency standards for specialized cognitive behavior therapy for adult obsessive-compulsive disorder”. My tasks included conducting literature searches, reviewing proofs, formatting, requesting corrections from journal editors, and correcting in-text citations as well as the reference list
- I trained the new research assistant and seven volunteers through 3 one-hour training sessions on survey dissemination and literature searches

Research Experience

Summer Studentship

Centre for Research & Education on Violence Against Women & Children | May – August 2023

Supervisor: Dr. Katreena Scott

- I studied students’ beliefs on sexual violence & consent as well as their satisfaction of Western's Undressing Consent Program
- Tasks included summarizing student satisfaction surveys bi-weekly and developing common themes regarding the students' brainstorming sessions. Themes revolved around sexual desire, rejection, alcohol & consent

Master's Student

University of Western Ontario – Developing Brain Lab | Sep 2022 – Present

Supervisor: Dr. Emma Duerden

- I am working on a research project focusing three primary objectives:
  - To determine the association between prenatal maternal stress (objective hardship & perceived stress) during the COVID-19 pandemic and amygdala/PFC volumes in infants
  - To understand the extent to which psychosocial factors, including social support and resilience, moderate the association above
  - To determine whether larger amygdala and smaller PFC volumes are associated with more difficult temperament in infants
- Data has been collected as part of the Canadian Pregnancy During the COVID-19 Pandemic (PdP) study

Research Trainee

The Douglas Research Centre – King Lab | Sep 2020 – Present

Supervisor: Dr. Suzanne King

Paper title: Prenatal stress from the COVID-19 pandemic predicts maternal postpartum anxiety as moderated by psychological factors: The Australian BITTOC Study

- I wrote a research paper studying prenatal stress from the COVID-19 pandemic. The goal of my study was to determine the extent to which psychological factors, including resilience, tolerance of uncertainty, and a positive cognitive appraisal, moderate the association between prenatal objective hardship or subjective distress from the pandemic and 2-month postpartum anxiety
- My tasks included conducting literature searches, scientific writing, running statistical analyses using SPSS, and attending workshops and weekly meetings.
- I am currently writing a brief report on the extent to which objective hardship interacts with subjective distress to predict postpartum anxiety
- I presented my work at the Perinatal Society of Australia and New Zealand 2022 Congress, the Canadian National Perinatal Research Meeting, the DOHaD World Congress 2022, and the Douglas Undergraduate Research Expo

Volunteer

McGill University – Lydon Lab | June – Sep 2020

- I was involved in data cleaning, compiling participant information, quality testing psychological studies and questionnaires, and online focus groups

Volunteer

The Canadian Institute for Obsessive Compulsive Disorders | Sep 2019 – Nov 2020

Supervisor: Dr. Debbie Sookman

- My duties included calling hospitals to gather participant information, e-mailing surveys, summarizing data, conducting literature searches, and attending weekly meetings

Undergraduate Honours-Equivalent Thesis

Lady Davis Institute for Medical Research – Zelkowitz Lab | Sep 2019 – Apr 2020

Supervisor: Dr. Phyllis Zelkowitz

Thesis: The Relationship between Mental Health and Medical Leave among Pregnant Women Seeking Psychiatric Services

- I studied the relationship between psychological symptomatology (anxiety, depression, and pregnancy-related worry) and medical leave in a sample of pregnant women seeking psychiatric services at four mental health clinics across Quebec
- I used bivariate analyses in order to determine whether pregnant women who took medical leave and pregnant women who remained at work differed in their socio-demographic characteristics, prenatal anxiety, depression, and worry, and improvement in their mental health symptoms at six-weeks postpartum

Publications

- Di Paolo, A.-L., King, S., McLean, M. A., Lequertier, B., Elgbeili, G., Kildea, S., & Dahlen, H. G. (2022). Prenatal stress from the COVID-19 pandemic predicts maternal postpartum anxiety as moderated by psychological factors: The Australian BITTOC Study. *Journal of Affective Disorders*, *314*, 68–77. https://doi.org/10.1016/j.jad.2022.06.055

Conference Presentations

- Di Paolo, A.-L., King, S., McLean, M. A., Lequertier, B., Elgbeili, G., Kildea, S., & Dahlen, H. G. (2022, August 27-31). *Psychological Factors Moderate the Effect of Prenatal Stress from the COVID-19 Pandemic on 2-month Maternal Postpartum Anxiety: The BITTOC Birth in the Time of COVID Study* [Poster Presentation]. International Society for Developmental Origins of Health and Disease (DOHaD) World Congress 2022, Vancouver, Canada.

- Di Paolo, A.-L., King, S., McLean, M. A., Lequertier, B., Elgbeili, G., Kildea, S., & Dahlen, H. G. (2022, May 30 – June 3). *Prenatal Stress From the COVID-19 Pandemic Predicts Maternal Postpartum Anxiety as Moderated by Psychological Factors: The BITTOC Birth in the Time of COVID Study* [Virtual Poster Presentation]. 9th Annual Canadian National Perinatal Research Meeting (CNPRM).

- Di Paolo, A.-L., McLean, M.A., Lequertier, B., Elgbeili, G., Kildea, S., King, S., & Dahlen, H. G. (2022, May 15-18). *Prenatal Stress From the COVID-19 Pandemic Predicts Maternal Postpartum Anxiety as Moderated by Psychological Factors: The BITTOC Birth in the Time of COVID Study* [Oral Presentation]. Perinatal Society of Australia and New Zealand (PSANZ) 2022 Congress, Adelaide, Austraila.

Non-Research Related Volunteering History

FACES - Foster A Child to Excel

Tutor & Blog Writer | Oct 2020 - Aug 2022

- I tutored two students (1st and 9th grade) weekly in mathematics
- I wrote monthly blog posts focusing on personal stories, identity, nature, cooking, and more.

The Friendship Circle

Mar 2020 - Aug 2022

- The Friendship circle is a non-profit organization that gives children and young adults with special needs a safe space to make new friends and develop a variety of skills
- I volunteered at the Spring Break Camp, where I accompanied a young girl through various fun activities and field trips
- I participated in educational activities and friendly conversations during weekly Zoom meetings. I was involved in the Friendship Circle lounge (led by a professional therapist) and one-on-one hangouts with teens and young adults.

ELIMU Pamoja Online Tutoring Program

Sep 2019 – Nov 2019

- This program pairs McGill students with elementary school students from Raimu Primary School in Kianyaga, Kenya
- I tutored a 5th grade student in math once a week through Skype

Westmount Science Camp

June 2014 – Jul 2014

- I oversaw children ages 5 – 12 years old as they worked through different science experiments
- It was my responsibility to explain the overall premise of the experiment, help the children get into groups, watch as they did the experiment itself, and guide them through any problems they might have encountered

Languages & Skills

- Native English. Intermediate French. Basic Italian.
- Knowledge of SPSS, Endnote, Zotero, ITK-SNAP, and Microsoft Office
- Knowledge of survey databases including REDCap, Survey Monkey, and Qualtrics
- Knowledge of programming languages such as MATLAB, Lisp, and C

Intervention Certification

I've received training in the following interventions:

- Healthy Relationships Plus Program (HRPP)
- Supporting Transition Resilience of Newcomer Groups (STRONG)