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Cannabis Exposure During Pregnancy and Neural Mechanisms of Parenting: Assessing Neural Responses to Infant Cues and Parenting Outcomes

Shannon Powers

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Abstract

As legalization of cannabis and cannabinoids spreads in the United States, access and use of cannabis during the prenatal period has increased. There is limited knowledge on the effects of prenatal cannabis use on the parental brain. One way to identify potential effects of cannabis on parenting is through studying parenting brain functions and behavior. Cannabis use disorder (CUD) has been shown to be associated with lower positive parenting and lower sensitivity to infants, but it is unclear by what mechanisms. The following two studies address this gap in knowledge by examining the association between cannabis use during the prenatal period and functional response to infant related stimuli. Study One examines the association between cannabis use during the prenatal period, functional response to infant cries, and explores behavioral interactions between gestation parent and child. This study found that cannabis use over the prenatal period was associated with increased neural response to infant cry sounds particularly within parenting neural networks for emotion regulation, theory of mind, and affective processing. Study Two examines the association between cannabis use during the prenatal period, functional response to infant picture, and explores behavioral interactions between gestation parent and child. This study found that cannabis use over the prenatal period was associated with increased neural response to other (unknown) infant pictures, particularly within parenting neural networks for reward and salience. These studies suggest that cannabis use during the prenatal period affects functional responses to infant important for parenting behavior.

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ABSTRACT

As legalization of cannabis and cannabinoids spreads in the United States, access and use of cannabis during the prenatal period has increased. There is limited knowledge on the effects of prenatal cannabis use on the parental brain. One way to identify potential effects of cannabis on parenting is through studying parenting brain functions and behavior. Cannabis use disorder (CUD) has been shown to be associated with lower positive parenting and lower sensitivity to infants, but it is unclear by what mechanisms. The following two studies address this gap in knowledge by examining the association between cannabis use during the prenatal period and functional response to infant related stimuli. Study One examines the association between cannabis use during the prenatal period, functional response to infant cries, and explores behavioral interactions between gestation parent and child. This study found that cannabis use over the prenatal period was associated with increased neural response to infant cry sounds particularly within parenting neural networks for emotion regulation, theory of mind, and affective processing. Study Two examines the association between cannabis use during the prenatal period, functional response to infant picture, and explores behavioral interactions between gestation parent and child. This study found that cannabis use over the prenatal period was associated with increased neural response to other (unknown) infant pictures, particularly within parenting neural networks for reward and salience. These studies

suggest that cannabis use during the prenatal period affects functional responses to infant important for parenting behavior.

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CHAPTER ONE: STUDY ONE INTRODUCTION

As legalization of cannabis and cannabinoids spreads throughout the United States, access and use of cannabis has increased, including rising rates among pregnant individuals (Arterberry et al., 2019; Gnofam et al., 2020; Odom et al., 2020; Skelton et al., 2020a, 2020b; Smart & Pacula, 2019; Volkow, Han, et al., 2019; Young-Wolff et al., 2021). Nationally, the prevalence of cannabis use during the first postpartum year has nearly doubled from 2004 to 2017, with percentages rising from 9.0% to 19.5% (Alshaarawy et al., 2021). Recent literature has attempted to quantify the reported percentage of cannabis use during pregnancy from the National Survey on Drug Use and Health, and reported ranges from 5.3%-7.0% of pregnant individuals in the United States reported cannabis use in the last 30 days (Odom et al., 2020; Volkow, Han, et al., 2019). While estimates vary from preconception to postpartum, the literature supports an increase in use during this period as legalization has spread.

Current research has focused primarily on effects of cannabis use during the prenatal period on infant development (Crume et al., 2018a, 2022; Grant et al., 2018, 2020; Grewen et al., 2015; Huizink, 2014; Jutras-Aswad et al., 2009; Metz & Borgelt, 2018). There has also been studies to understand reasons and perceptions of cannabis use during pregnancy with common reported reasons including: previous use, help with pregnancy related nausea, to alleviate symptoms of anxiety and depression, and perceptions of cannabis as a safer alternative to medications such as antidepressants

(Bayrampour & Asim, 2021; Chang et al., 2019; Corsi et al., 2019; Jaques et al., 2014; Jarlenski et al., 2016; Ko et al., 2015; Metz et al., 2022; Skelton et al., 2020b; Taylor et al., 2021; Weisbeck et al., 2021; Young-Wolff et al., 2017; Young-Wolff, Gali, et al., 2020; Young-Wolff, Sarovar, et al., 2020). However, limited evidence exists on the effects of cannabis exposure on the health and well-being of pregnant individuals, including the brain and behavioral transition to parenthood (Azenkot et al., 2022; Bayrampour & Asim, 2021; Crume et al., 2022; Metz & Borgelt, 2018; Odom et al., 2020; Volkow, Han, et al., 2019).

1.1. Gestational parent brain adaptations in the postpartum period

There are dynamic functional changes associated with pregnancy and child rearing that promote parent-infant relationships during the early postpartum period (Barba-Müller et al., 2019; Bornstein et al., 2017; Endendijk et al., 2020; Hoekzema et al., 2017; P. Kim, 2016; Witteman et al., 2019). Research has supported that the strength of neural activation in parental networks postpartum is associated positively with parent-child interactions and subsequent child development (Abraham et al., 2016, 2018; Atzil et al., 2011, 2017; Barrett et al., 2012; Feldman, 2017). This sensitivity to infant cues within parental reward and motivation networks is thought to be related to increases in oxytocin and dopamine networks during late pregnancy and the first months of the postpartum period associated with birthing parent behavior (Brunton & Russell, 2008, 2010; Numan, 2017, 2020; Russell et al., 2001). Functional Magnetic Resonance Imaging (fMRI) studies of the postpartum brain primarily focus on neural networks of parenting through neural responses to infant affective and relevance cues. Infant affective and relevance cues, through cries and facial expressions, are one of the main ways infants convey

important information to parents and elicit a parental response in the early postpartum period (Bornstein et al., 2017; Brosch et al., 2007; Caria et al., 2012; Liszkowski, 2014; K. Zhang et al., 2020). Investigating these infant cues has been shown to be important both mechanistically to understand the neurobiology of parenting behavior, and for future parenting interventions (Bornstein et al., 2017; Numan, 2020; Rigo, Kim, et al., 2019; Rutherford et al., 2020; Squire & Stein, 2003).

Within parenting neural networks of the brain, research has highlighted increased neural activation to regions of networks related to reward, parental motivation, social information processing, emotion regulation, and theory of mind (TOM) networks (P. Kim, 2016; Numan, 2020; Squire & Stein, 2003; Swain, 2008). While these networks exist before pregnancy, the postpartum period sees heightened sensitivity to these networks related to infant cues. Within these networks an increase in activation is related to positive parenting behaviors and saliency of infant cues (P. Kim, 2016; Numan, 2020). In reward and parental motivation networks heightened activation in regions of the nucleus accumbens and the amygdala is associated with increasing saliency related to their own infant (Atzil et al., 2011, 2017; P. Kim, 2016; Numan, 2020). Within social information processing and attention networks there is heightened activation in regions of the insula, precuneus, superior temporal gyrus, right frontoinsular cortex, inferior frontal gyrus, medial frontal gyrus, visual regions of the occipital lobe, presupplementary motor area, parietal cortex, and connectivity within the nucleus accumbens amygdala and medial prefrontal cortex (PFC) network important for both interpreting emotional and social cues from their infants and appropriately responding (Atzil et al., 2011, 2017; Hipwell et al., 2015; P. Kim, 2016; Numan, 2020). In regions of emotion regulation and

affective processing there is heightened activation in the anterior cingulate cortex, medial PFC, and lateral PFC thought to be important for regulating emotions with the high stress of life circumstance changes of parenting (Barrett et al., 2012; P. Kim et al., 2011; P. Kim, 2016; Numan, 2020; Rutherford et al., 2015). Finally, within regions of TOM there is heightened activation in regions of the medial PFC, anterior cingulate cortex, superior temporal sulcus and gyrus, precuneus, and temporoparietal junction important for considering thoughts and feelings of their infants (Atzil et al., 2017; Molenberghs et al., 2016; Numan, 2020). Different literature has explored timing of neuroimaging postpartum, and highlighted the importance and future correlation with parenting behaviors of neuroimaging responses to infant cues within the first three months postpartum (P. Kim, 2016; Numan, 2020; Swain et al., 2007; Swain, 2008).

1.2. Gestational parent brain response to infant crying

Research has supported salience of neural networks in response to infant crying that promote caregiving behaviors as infant cries are the only communication method for infants under three months (Bornstein et al., 2017; Liszkowski, 2014; Newman, 2007; Witteman et al., 2019). The innate nature of infant cries initiates a rapid and instinctive reaction from caregivers, prompting immediate efforts to console and provide care to the infant. This response is driven by the perception of the cry as an indicator of the infant's need for attention, comfort, or assistance. Within parents, there exists a strong motivation for parents to stop the crying, reflecting the desire to alleviate both the infant's distress and their own emotional discomfort. This urgency and distress of the cue is a powerful communicative tool that elicits swift and attentive caregiving behaviors in parents (Witteman et al., 2019). When comparing nulliparous individuals to birthing parents,

both groups show slight increase in activation in TOM regions of the medial PFC and posterior cingulate cortex in the context of self-orienting tasks, while birthing parents showed increased activation in goal-oriented tasks towards infants, highlighting a potential sensitivity to infant cries among birthing parents (Rigo, Esposito, et al., 2019). Another study found that administration of intranasal oxytocin when listening to infant cries in nulliparous individuals reduced neural activation in the amygdala, and increased activation in the insula and inferior frontal gyrus pars triangularis, suggesting oxytocin is an important moderator for increasing caregiving responses (Riem et al., 2011). Studies have documented neural network responses to infant cries in the postpartum period in emotion regulation regions, as well as salience regions of the auditory cortex, thalamocingulate pathways, midbrain-dopaminergic pathways, fronto-insular cortex, and dorsomedial PFC (Bornstein et al., 2017; Newman, 2007; Rilling, 2013; Swain, 2008, p. 201; Swain et al., 2014; Witteman et al., 2019). When comparing relevance of infant crying, own infant cry versus other, a greater response was seen in social information and motivation networks of the amygdala, inferior frontal gyrus, and the anterior insula cortex with breastfeeding heightening this response (P. Kim et al., 2011) and neural response to own (versus other cry) has been shown to be related to birthing parent attachment behavior (Laurent & Ablow, 2012b). These findings are significant for understanding caregiving behaviors.

While often there is an increase in activation towards infant cues in parenting neural networks associated with positive behavioral outcomes, contrarily heightened activation can be associated with dysregulated responses. The anterior insula has key regions within empathy networks, and heightened activation in the postpartum period to

their own infant cry was associated with more intrusive parenting behaviors (Li et al., 2018; Musser et al., 2012). In regions of the hippocampus, gestational parents with lower gestational parent care in childhood had heightened activation to infant cries generally (P. Kim et al., 2010). Another study found that emotional neglect during the gestational parent's childhood was also associated with increased insula and anterior cingulate cortex activation to their own infant's cries (Wright et al., 2017). This heightened response to infant crying can also lead to negative parenting outcomes through intensifying affective processing, impeding effective emotion regulation processes in parents. Increased activation in brain regions associated with affective processing, such as the amygdala and insula, may contribute to heightened emotional response to infant cries (Li et al., 2018). This heightened response, combined with greater effort required for emotion regulation, can lead to parental stress and frustration which could behaviorally show up in less sensitivity and responsive caregiving behaviors (Musser et al., 2012). Consequently, this could impact the parent-child relationship and the infant's socioemotional development. In a review on plasticity during pregnancy, it was found that stress exposure—in the form of childhood maltreatment, environmental stress, and parenting stress—can cause dysregulated levels of activation to infant cues in regions of gestational parent motivation, emotion regulation and empathy (P. Kim, 2021). Both heightened and dampened responses in parental networks from stress exposure impacted neural responses and behavioral outcomes, highlighting the complex nature of an attenuated response to infant cues.

1.3. Gestational parent substance use and brain adaptations in the postpartum period

Caregiving behavior is variable depending on a number of factors (Hrdy, 2016; Numan, 2017, 2020). Exposure to stress, mood disorders, and substance use has been associated with differential responses to infant affective and relevance cues, and subsequent parenting behaviors (A. Bjertrup et al., 2021; A. J. Bjertrup et al., 2019, 2021; P. Kim et al., 2020a, 2022; S. Kim et al., 2017; Landi et al., 2011; Laurent & Ablow, 2012b; Rutherford et al., 2016, 2020). Within the substance use literature, there is limited information on how substance use during pregnancy and the postpartum period might affect neural responses to affective cues, and subsequent parenting behavior. In adult populations with substance use disorder, neuroimaging has demonstrated increased responses related to drug processing, and blunted or impaired processing among non-drug related processing networks (Koob & Volkow, 2010, 2016; R. Zhang & Volkow, 2019; Zilverstand et al., 2018). With this dysregulated response, researchers hypothesized parenting networks overlap with reward and motivation, emotion regulation, affective processing, and social information processing networks as these regions are effected by substance exposure (Rutherford & Mayes, 2017; Zilverstand et al., 2018).

Current literature on the effects of prenatal substance use on infant cries has conflicting evidence. One study found overall reduced activation in auditory regions of the right superior and middle temporal gyri, and PFC to low distress cries suggesting less saliency of infant cues (Landi et al., 2011, 2013), while another found no differences in neural responses to short duration (2 seconds) infant cries when comparing birthing parents postpartum who used and did not use substances (Rutherford et al., 2020). Additionally, in an ERP study no latency was found among substance use in gestational parents postpartum to short (2 second) duration of cries in the P300 and N100 responsible

for attentional and perceptual processes (Wall et al., 2022). Potentially, longer duration of cries might mimic real world saliency of cries and thus shorter duration of cries demonstrated null results. Differences could also be due to both studies having inclusion criteria of poly-substance exposure measured dichotomously, and thus having different group exposures to substances. Overall, infant cries are a salient stimulus and could be altered in regions of affective processing of parents who use substances. Behavioral studies have hypothesized that this dysregulation of activation can lead to more hostile and intrusive parenting, and self-report data from birthing parents who use substances reports more stressful parenting increasing the risk of infant neglect (Rutherford & Mayes, 2017; Strathearn & Mayes, 2010). While some neuroimaging evidence exists, looking at substances in isolation is limited, and there is a limited understanding of cannabis use (Crume et al., 2022).

1.4. Gestational parent cannabis use and brain adaptations in the postpartum period

Cannabis is hypothesized to respond on similar reward neural circuitry as other substances such as tobacco, alcohol, and opioids that could affect parenting behaviors (Filbey et al., 2009; Gillespie et al., 2009; Moreno-Rius, 2019; Volkow, Michaelides, et al., 2019). As potency of cannabis increases, researchers have called for new studies to understand how this change in potency may effect reward neural circuitry (Filbey et al., 2009; Hutchison et al., 2019; National Academies of Sciences, 2017). In the parenting literature, research on effects of prenatal cannabis use is focused on infant outcomes and parenting behaviors in the first months postpartum. Cannabis use during pregnancy has been associated with decreased birth weight, reduced length of infant, and smaller head

circumference (Crume et al., 2018a; Gray et al., 2010). In animal models, cannabis use during pregnancy was associated with diminished pup rearing behaviors in open fields, but due to potency shifts this research could be outdated (Abel & Tan, 1987). Cannabis use disorder (CUD) is associated with lower positive parenting (decreased monitoring, support, and consistency) and lower sensitivity during infant interactions similarly to other substances of abuse (Eiden et al., 2018; Hill et al., 2018). Previous literature has also supported that frequency of use, rather than potency, is an important predictor of health problems and was related to higher cannabis use problems (Steeger et al., 2021). One study found that higher reported use during the postnatal period was associated with lower gestational parent sensitivity measured by the Ainsworth scale of attachment at 9 months postpartum during gestational parent-child free play interactions (Eiden et al., 2018). While this data points to cannabis acting on similar reward neural circuitry and having similar effects on parenting behaviors as other substances, there is limited evidence of how this will affect neural mechanisms of parenting.

Cannabis use during pregnancy has been difficult to characterize due to decrease in use as pregnancy progresses (Crume et al., 2022; Gray et al., 2010). The National Survey on Drug Use and Health reported the highest prevalence of use was during the first trimester, and this use pattern drops by half by the third trimester (Alshaarawy et al., 2021; Crume et al., 2022; Odom et al., 2020; Volkow, Han, et al., 2019). As use pattern varies, and neuroanatomic changes to attenuate pregnant individuals to infant cues begins early in pregnancy, it is important to highlight how quantity and duration could implicate parental networks (Martínez-García et al., 2021). A review on cannabis use in adult populations found mixed findings on the effects for quantity of use and cognitive/neural

effects, but had some evidence that amount of use compared to onset and duration might be associated with heightened activation in reward networks and decision making neural circuitry (Nader & Sanchez, 2018; Vaidya et al., 2012). In an exploratory study on cannabis use during pregnancy and neural response to infant cues, cannabis use was associated with heightened response to infant cries in the dorsal medial PFC in the second trimester (Powers et al., 2023). This heightened response seen as early as the second trimester, suggests potential dysregulation in affective processing to infant cries. Taken together, these findings suggest a complicated relationship between parental adaptations and the effect of stressors on the gestational parent brain. In summary, the complex relationship between cannabis use during pregnancy and parental adaptations, as well as its impact on the gestational parent brain, underscores the need for further research to understand the implications of quantity and duration of use on parental networks and emotion regulation.

1.5. Study rationale

In the present study, we compare neural response to infant cries and parenting behavior among individuals who used cannabis during pregnancy and those who did not, hypothesizing that reward and affective processing networks might show differences. This study aimed to address the following specific questions: 1) are there differences in neural response to infant cries related to prenatal cannabis use?; 2) are these differences related to parenting behaviors in the postpartum period?; and 3) are there differences in parenting behavior related to prenatal cannabis use? Based on previous studies, we hypothesized that cannabis exposure during the prenatal period will respond on similar neural circuitry as other substances of abuse in response to infant cries. While some

studies found dampened response to cries, we hypothesized heightened BOLD response in longer duration cries due to previous cannabis use literature in pregnancy. Additionally, we hypothesized that greater use would be associated with increased BOLD response to infant cries in reward and affective processing regions of the right superior and middle temporal gyri, and the PFC to infant cries but acknowledge that the lack of literature on this topic could demonstrate the null of this hypothesis. We also hypothesized that neural response to cannabis exposure during the prenatal period will be correlated with decreased birthing-parent child interactions as measured by the sensitivity and non-intrusiveness constructs of the Emotional Availability scale. In addition, this study explored parenting behaviors in isolation of neural results, hypothesizing that cannabis during the prenatal period will respond on similar reward circuitry as other substances of abuse, and will demonstrate lower sensitivity and lower non-intrusiveness scores in birthing-parent child interactions as measured by the Emotional Availability scale. Additional analysis on the quantity of prenatal use was examined.

Based on this literature, the current study firsts encompassed any individual exposed to cannabis at any period during their pregnancy to be more representative of cannabis use during this time. The main study assessed differences between groups in the first months of the postpartum period (cannabis use during the prenatal period and no cannabis use during the prenatal period) similar to other substance use literature during the pregnancy and postpartum period hypothesizing heightened BOLD response to cries (S. Kim et al., 2017; Landi et al., 2011, 2013; Rutherford et al., 2020; Rutherford & Mayes, 2017). To test the potential impact of duration of cannabis use, the second model assessed first trimester use compared to ongoing trimester use hypothesizing that ongoing

use would elicit heightened BOLD response to cries compared to first trimester and control groups (Metz et al., 2023). In addition, based on the literature suggesting cumulative use could impact neural outcomes, this study completed an analysis on cumulative prenatal use as there is individual variability in the amount of use during pregnancy, also hypothesizing that greater prenatal use would be related to heightened BOLD response to cries (Eiden et al., 2018; Metz et al., 2023; Steeger et al., 2021).

CHAPTER TWO: STUDY ONE MATERIALS AND METHODS

2.1. Participants

Eligibility criteria included: age 18-45 years, singleton pregnancy, and fluency in English. Exclusion criteria included: use of current psychotropic medications; lifetime diagnosis of other psychiatric/neurological illness other than depression, anxiety, or post-traumatic stress disorder; positive urine drug screen for non-cannabis illicit substances; or self-reported heavy nicotine or alcohol use. The present paper focused on data collected during pregnancy and at one month postpartum. A total of 125 individuals were scanned for the present study, and 11 of which were excluded. Participants were excluded for the following reasons: (1) did not finish the task due to claustrophobia, (1) technical error during data collection, (1) AQI (AFNI metric for artifact) was an outlier, (1) susceptibility distortion correction failed, (1) tested positive for morphine prenatally, and (1) tested positive for methamphetamines during their second postnatal visit. Additionally, we excluded the following participants from the analysis because they did not meet the criteria for either control or prenatal cannabis use group - (3) only used cannabis in the preconception period, (1) only used cannabis in the preconception and postnatal period, and (1) only used cannabis in the postnatal period. As a result, the cannabis group included 39 pregnant individuals that have cannabis use during pregnancy. The control group included 75 pregnant individuals that have not been exposed to cannabis during the pregnancy period.

2.2.1. Cannabis Exposure

As reported on, cannabis use during pregnancy varies, with the majority of cannabis being reported during the first trimester (Alshaarawy et al., 2021; Odom et al., 2020; Volkow, Han, et al., 2019). In the first model, the study chose to investigate prenatal cannabis use as a dichotomous variable (prenatal cannabis use or no prenatal use), to identify how use during this period may affect postpartum neural mechanisms of parenting in line with previous literature (S. Kim et al., 2017; Landi et al., 2011, 2013; Rutherford et al., 2020; Rutherford & Mayes, 2017). Since not all immunoassay can detect cannabis use, and cannabis use during the pregnancy period is variable, cannabis use during pregnancy will be defined by immunoassay, Timeline Followback (TLFB), and/or self-report (Metz & Borgelt, 2018; Robinson et al., 2014; Sobell et al., 1979).

To account for potential within group differences, a second model of cannabis that examines first trimester use only and continued use pass the first trimester similar to previous literature examining the effects of early and ongoing cannabis exposure during pregnancy was examined (Metz et al., 2023). This model also defined cannabis use by immunoassay, TLFB, and/or self-report. Finally, a third analysis of the prenatal cumulative use as a continuous variable was assessed, but lacks adequate power and should be interpreted preliminarily. Participants who had completed TLFB at all three prenatal visits were included in this third model. Their quantity of use was summed over their prenatal period, to create a cumulative score. The control group stayed the same for all the analyses.

2.2.2. Immunoassay for Cannabis

After consent, participants provided a urine sample for a Nic-Alert test to evaluate for nicotine metabolite and a CLIA-waived 5-panel drug immunoassay at their first study visit. If participants tested positive for any other substances besides cannabis, they were ineligible for the study. Participants who tested positive for nicotine or cannabis use were enrolled. Because urine drug testing at future visits were added later in the study, some immunoassays for cannabis are missing at second and third prenatal visits. For a full breakdown of how many immunoassays were conducted and results, see Tables 2, 5, and 7 for each model.

2.2.3. Timeline Followback (TLFB)

Since cannabis use can be infrequent, and urine can be negative despite recent use, participants also underwent a detailed interview by a trained researcher who asked about any cannabis use prior to the visit. This interview methodology has been shown to be an accurate reflection of self-reported cannabis use (Metz & Borgelt, 2018; Robinson et al., 2014; Sobell et al., 1979). Because TLFB testing at future visits were added later in the study, some data is missing (see Tables 2, 5, and 7). This measure was added to every visit and was filled out if participants self-reported, or tested positive on the immunoassay and were willing to give detailed information about their use. Additionally, this measure was utilized for the cumulative model. Participants who self-reported cannabis use, were asked about the number of times that cannabis had been used since the prior visit. This total number was reported through units of number of ingestible items were taken, or how many times in a day a cannabis product was inhaled. For the cumulative model, the total quantity of either how many times a product was inhaled or an ingestible was taken was added up to get a sum for that day. Data from the date of

conception to the date of birth was added up to create a cumulative prenatal use total variable.

2.2.4. Self-Report

During the initial interview portion of each visit, participants were asked if they had used cannabis since the prior visit. At the first visit, participants were asked if they had used cannabis since conception. Researchers recorded a dichotomous yes or no to this question.

2.3. Procedures

Participants were recruited from the Department of Obstetrics and Gynecology at Denver Health Medical Center, through the University of Colorado Anschutz Medical Campus, and through flyers and brochures. The University of Denver Institutional Review Board approved all procedures prior to recruitment. These participants were recruited as a part of a larger study investigating income during the prenatal and postpartum period. A subset of this study investigated cannabis use during pregnancy and the early postpartum period. As part of the parent study, birthing parents have visits during pregnancy (one at each trimester), and one visit and subsequent MRI at one month postpartum.

During the study participants were given an immunoassay drug screen to assess for cannabis exposure, demographic questionnaires, depression and anxiety surveys (through EPDS, CESD, and STAI), a brief psychological questionnaire (SCID) to assess for any mental health related diagnosis specifically depression and anxiety, and TLFB. In addition, due to a change in protocol, participants at the start of the study only had one

immunoassay at their first trimester visit, and did not have a TLFB, but have a yes/no self-report.

2.4. Measures

2.4.1. Demographics

Gestational parents self-reported their age, total years of education, yearly household income, race, and child date of birth (See Tables 1, 4, and 6). The average age of this sample was 29.18 (SD = 5.59). This data was collected through medical records when applicable or self-report at scan. The average total weeks of gestation for this sample was 39.06 (SD = 1.53).

2.4.2. Gestational parent depression and anxiety

Cannabis use during the prenatal period has been shown to be related to higher reported anxiety and depression symptomatology (Crume et al., 2022; Goodwin et al., 2020; Latuskie et al., 2019; Skelton et al., 2020b; Taylor et al., 2021; Weisbeck et al., 2021; Young-Wolff, Sarovar, et al., 2020). *Edinburg Postnatal Depression Scale (EPDS):* Participants completed the EPDS asking about their feelings in the past 7 days on a 4-point scale from 0 = yes, all the time to 3 = no, not at all (Cox et al., 1987). Questions consisted of items such as, “I have been able to laugh and see the funny side of things” and “I have felt scared or panicky for no very good reason.” This scale has been shown to reliably predict postpartum and prenatal depression outcomes among a diverse range of populations and is a valid measure of current depression status, including with cannabis use during pregnancy (Bunevicius et al., 2009; Mark et al., 2021; Shrestha et al., 2016; Young-Wolff, Sarovar, et al., 2020). *Center for Epidemiological Studies-Depression (CESD):* Participants completed the 20-item questionnaire asking them about

how often in the past week they experienced symptoms associated with depression. This questionnaire included items such as, “I was bothered by things that usually don’t bother me,” “I felt depressed,” “I was happy,” and “I talked less than usual.” These items were rated on a 3-point scale from 0 = rarely or none of the time (less than 1 day) to 3 = all the time (5-7 days). This scale has been shown to be highly reliable and valid for predicting current levels of depression, including with cannabis use during pregnancy (Lewinsohn et al., 1997; Pinquart & Sörensen, 2003; Radloff, Lenore, 1977; Young-Wolff, Sarovar, et al., 2020; Zuckerman et al., 1989). *State-Trait Anxiety Inventory (STAI)-state:* Participants completed the 20-item questionnaire about how they are feeling right now at this moment. This questionnaire included items such as, “I feel calm,” “I feel strained,” and “I feel satisfied.” These items were rated on a 3-point scale from 0 = not at all to 3 = very much so. This scale has been shown to be highly reliable and valid for predicting current levels of anxiety, including with substance use during pregnancy (Newham et al., 2012; Spielberger, 1989; Spielberger et al., 1983). Mood symptoms were collected at each trimester and once postnatally.

2.4.3. Birthing Parent-Child Interaction

At the first postnatal visit, trained research staff recorded a 10-minute naturalistic interaction between parent and child. This task was coded using the Emotional Availability (EA) coding scheme that has been validated to measure emotional availability, as well as sensitivity in the first month of postpartum and be predictive of child development outcomes later on (Biringen & Easterbrooks, 2012; Clark et al., 2021; Frigerio et al., 2019). The EA scale has 4 adult subscales that include sensitivity, structuring, non-intrusiveness, and non-hostility. Sensitivity broadly measures an adult’s

warm and emotional connection with the child with an emphasis on the adult's affect and appropriate responsiveness to the child. Structuring broadly measures how the adult structures the play and follows the child's lead with an emphasis on the number of successful attempts made to structure, and how proactive they are. Non-intrusiveness broadly measures the lack of intrusive behaviors, with a focus on following the child's lead and non-interruptive ports of entry into their interaction. Finally, non-hostility broadly measures the lack of covert or overt forms of hostility, with a focus on a lack of negativity in the face and voice, as well as words and actions. Together these subscales can be predictive of overall parent emotional availability and have been well validated among populations that use substances and important for clinical implications (Frigerio et al., 2019; Goldman Fraser et al., 2010; Porreca et al., 2018). Due to the age of infants at time of parent interaction, most infants were sleeping or did not have enough interaction to code, and thus infant scores were not used in this analysis. In the main sample only 100 participants completed the parent-child interactions. Of those 100, (4) did not have non-hostility coded due to the parent not speaking English in the interaction. This main sample group used for analysis (N = 114) had a mean sensitivity score of 5.54 (SD = 1.08), mean structuring score of 5.45 (SD = 1.25), mean non-intrusiveness score of 5.57 (SD = .99), and mean non-hostility score of 5.43 (SD = 1.25). On average, the cannabis group conducted their postnatal visit with the parent-child interaction later in the postpartum period, $t(111) = -2.189$, $p = 0.031$. Two independent trained coders rated the videos. Inter-rater reliability was calculated using Intraclass Correlation Coefficients on a randomly selected subsample of 20% of the cases, with values ranging from 0.73 to 0.87

(sensitivity scale = 0.83; structuring scale = 0.73; non-intrusiveness scale = 0.75; non-hostility scale = 0.78). Disagreements were resolved by conference.

2.5. fMRI Paradigm

The naturalistic infant cry paradigm has been evaluated in postpartum fMRI research (P. Kim et al., 2011, 2020b; Numan, 2020; Swain, 2008). In addition, this task has been tested in exposure to teratogenic substances (Landi et al., 2011, 2013; Rutherford et al., 2020). Participants were given 2 runs of the task were they listen to a control cry, their own baby cry, and matched white noise to the cries using sound editing software (*Cool Edit Pro*, 2002). The same control cry and generated white noise was used for all participants. Participants own baby cry was collected during a diaper change or during a hunger cry. The control cry was collected during a diaper change, see previous studies for information on cry collection (P. Kim et al., 2020b, 2022). The infant cry paradigm is organized by 4 blocks: own and control cry; and own and control matched white noise. Each stimulus lasts for 20 seconds with an 8-12 second jittered rest (with an average of 10 seconds) of silence between each sound. A cross hair is presented on the screen the entire time and participants are asked to stare at the screen. In each block there is 5 own cries, 5 control cries, 5 own matched white noise, and 5 control matched white noise stimuli randomly presented to the participants. There is a total of 20 trials lasting 13.3 minutes. Participants are asked to listen and pay attention to the sounds, while letting themselves experience the thoughts and feelings they are having naturally. After the scan participants rated cry and noise sounds in a post-scan rating task. Participants rated cries in regard to how urgent, arousing, piercing, healthy, comforting, aversive, distressing, and pleasurable the cries sounded. They also responded on how much they

would like to approach the sound. These items were rated on a 5-point scale from 0 = not at all to 5 = very. In the main sample (3) participants are missing data from the post scan task. When significant clusters were identified, neural activation was correlated with pleasantness, distress, and aversiveness response. Based on previous literature, stressful conditions, such as substance use disorder, can increase emotional distress and aversiveness to infant cries in gestational parents leading to differences in parental sensitivity response (Barr, 2012; P. Kim et al., 2020b; Laurent & Ablow, 2012a; Paris et al., 2015). In addition, cannabis dependence in non-pregnant adult populations has been associated with increased perception of pleasantness compared to healthy controls, suggesting potential social processing effects of heavy cannabis use (Zimmermann et al., 2019).

2.6. fMRI data acquisition and processing

2.6.1. fMRI Acquisition

Images were acquired on a Siemens Prisma (3.0 T) MRI scanner with 32-channel parallel imaging located at the Intermountain Neuroimaging Consortium (University of Colorado, Boulder). Functional imaging used a T2*-weighted gradient-echo, echo-planar imaging (repetition time [TR] = 460 ms, echo time [TE] = 27.20 ms, flip angle = 44°, 56 slices parallel to the orbitofrontal cortex, thickness = 3 mm, zero gap, 82x82 in-plane resolution, in-plane FOV = 24.8cm, multi-band acceleration factor = 8). A high-resolution T1-weighted anatomical scan was collected for each participant to localize functional activity. MRIQC (22.06) was used to visually inspect the data. AQI (from Anatomical Functional Analysis software) in MRIQC was used to identify outliers in the data. There was one subject that was an outlier, and thus excluded from data analysis.

2.6.2. fMRI Processing

All images were processed using the standardized fMRIPrep (22.0.02) pipeline. Overarching steps included tissue segmentation, normalization to MNI space, surface reconstruction, susceptibility distortion correction, and alignment of functional to anatomical data. In line with fMRIPrep guidelines, please see the full pipeline in the supplementary materials. No participant had more than 20% of the TRs removed. Anatomical Functional Analysis software (AFNI, 24.0.06) was used for statistical analysis of functional data. Images were smoothed and scaled. The first ten images of each run of the infant cry task were discarded to account for magnetic equilibrium. At the level of individual participants, a general linear model was done to estimate the hemodynamic response's configuration to each condition: own infant cry, control infant cry, own infant cry matched noise, and control infant cry matched noise. The design matrix encompassed four conditions, integrating a boxcar function convolved with the hemodynamic response function, along with third-order polynomials and six motion parameters. The resulting beta images captured the estimated activation levels corresponding to each condition for every participant, serving as the basis for subsequent group-level analyses.

2.7. Analysis

2.7.1. Covariate selection

Independent t-tests and chi-squared tests were conducted to assess differences between groups. The following sociodemographic variables were tested in SPSS to see if they were significantly ($p < .05$) different between groups: preterm birth, total gestational weeks of pregnancy, gestational parent age at time of the scan, total years of education,

total yearly income, parity (pregnancy past 20 weeks), postpartum days at time of scan, gestational parent depression and anxiety symptoms at the third trimester and first postnatal visit, and nicotine status. The following were selected to include in the whole brain analysis model: gestational parent age at time of the scan, postpartum days at the time of scan, and parity. Parity and postpartum days was added to the model as there is evidence that they significantly impact gestational parent neural response and recommend to be included in analysis (Hillerer et al., 2014). Parent age at time of scan was additionally selected as a covariate as it differed between groups, and there is evidence of the effect of age on neural response (Grady et al., 2006; Luo et al., 2020). Additional significant differences between groups were assessed in post-hoc analyses.

2.7.2. fMRI Analysis

A 3dLME, a linear mixed-effects model in AFNI, was conducted on a whole brain analysis. The beta values from this model were used as a representation of activation. The most encompassing repeated measures model tested group differences (cannabis use versus no cannabis use) of these beta values with sound (cry vs. noise) and identity (own vs. other) as withing-subject variables in Model 1. Main effect of sound by group were also tested for infant cry. In the second model (Model 2), first trimester vs beyond first trimester use was conducted with the main group and a group variable consisting of: control, first trimester and beyond use. In the final model (Model 3) an analysis was conducted in a smaller sample using cumulative prenatal use from TLFB data. The findings underwent correction for multiple comparisons across the entire brain using a cluster extent threshold of $k \geq 16$ alongside a height threshold of $p < 0.001$ for Models 1 and 2. For Model 3 due to a change in sample size, the findings underwent

correction for multiple comparisons across the entire brain using a cluster extent threshold of $k \geq 15.6$ alongside a height threshold of $p < 0.001$. This threshold combination ensures a whole brain corrected false positive probability of $p < 0.05$, as determined by employing the spatial autocorrelation function (ACF) option in AFNI's 3dClustSim. Significant interactions surviving this cluster threshold in AFNI were extracted and decomposed in SPSS version 28.0 (*IBM SPSS Statistics for Windows*, 2021). Post-hoc analyses of these significant interaction values to adjust for group differences were conducted in SPSS. Variables identified in previous covariate analyses that significantly differed between groups were tested with partial correlations and repeated measures ANCOVA. Associations between cannabis grouping, neural activation (data pulled from the significant interaction clusters from the whole brain analysis), parenting behaviors, and post-scan ratings were further examined using independent sample t-tests and correlations in SPSS. For findings were only the group by sound interaction was significant, and not group by sound by identity, sounds were averaged together (own cry and control cry; own matched noise and other matched noise).

2.7.3. Exploratory associations with parenting behavior

Subsequent independent sample t-tests to compare EA scores was conducted in SPSS between groups. Additional exploratory associations were examined with cumulative prenatal TLFB and EA gestational parent scales.

Once the significant brain clusters are identified from the whole-brain analysis, correlations were conducted to explore the relationships between brain activation patterns extracted from the clusters in SPSS and EA gestational parent subscales (sensitivity, structuring, non-intrusive, and non-hostility).

2.7.4. Exploratory post scan responses

Post scan responses were averaged across own and other for cry and white noise conditions as significant clusters were found in averaged conditions. Post scan responses were explored when significant clusters were identified in the whole brain analysis using independent sample t-tests. In addition, when significant clusters were identified, neural activation was correlated with post scan responses to pleasantness, aversiveness, and distress rating responses.

CHAPTER THREE: STUDY ONE RESULTS

3.1. Model 1: Dichotomous prenatal cannabis

3.1.1. Characteristics of the sample

Participant demographics for this model are presented in Table 1 and cannabis use breakdown is presented in Table 2. The scans were conducted at an average 37.97 (SD = 21.41) days postpartum. In the full sample, participants who used cannabis during the pregnancy were significantly more likely to be younger($t(112) = 2.43$, $p = 0.017$, $d = 0.479$), have lower total years of education ($t(103.09) = 3.72$, $p < .001$, $d = 0.656$), lower income at consent ($t(89.77) = 4.25$, $p < .001$, $d = 0.697$), more likely to be Black/African American ($X^2(5, N = 112) = 14.04$, $p = 0.015$, $V = 0.354$) and more likely to test positive on a nicotine immunoassay at consent ($X^2(1, N = 111) = 6.89$ $p = 0.009$, $V = 0.249$). Participants did not differ on the first, third trimester and postnatal mood symptoms. Mood scores in the main sample only differed in the second trimester on CESD, with the cannabis group having higher CESD scores, $t(95) = -2.202$, $p = 0.030$, $d = -0.469$. Despite previously reported higher rates of symptoms among substance use and anxiety, this study did not identify any additional differences (see Supplementary Table 16) (Young-Wolff, Sarovar, et al., 2020). In addition, despite previous research reporting higher rates of preterm birth among parents who used substances, this sample did not have significantly differing rates potentially due to sample size. At consent, participants who self-reported or tested positive were asked to report reasons for why they used

cannabis. The sample consisted of 25 participants who responded to supplying reasons for why they used. Regarding anxiety, participants reported this most commonly with 44% of the sample reporting use for anxiety. Next commonly, participants reported using to help with sleep (36% reported this was a reason), and to help with nausea (32% reported this was a reason).

3.1.2. fMRI analysis of the differences between groups and brain activation

In the first model, we investigated prenatal cannabis as a dichotomous variable to examine the three-way interaction of cannabis x sound (cry vs. noise) x identity (own vs. other) controlling for gestational parent age at scan, postpartum days at scan, and parity. There were no significant clusters in this model. Next, we investigated the two-way interaction cannabis x sound (averaged cry vs. averaged noise). In this model, there was one significant cluster in the left temporal pole (Table 3; Figure 1). We decomposed the interaction and found that the cannabis group had higher activation to averaged infant cry sounds compared to the control group, $t(112) = -2.995$, $p = 0.003$. Activation to average white noise did not significantly differ between groups.

Additional post-hoc analysis to account for group differences was conducted using extracted interaction clusters. A repeated measures-ANCOVA was conducted to examine the group on sound, controlling for the covariates. This cluster remained significant after controlling for total education years, yearly income at consent, and nicotine immunoassay, $ps<.001$.

3.1.3. Exploratory associations between brain activation and parenting behaviors

When testing group differences through independent means t-test, groups did not significantly differ on any EA parent scale. Associations between EA gestational parent

scales and neural activation in the significant functional cluster where the cannabis group had higher brain response to averaged infant cry were examined. Brain activation to averaged cry response in this cluster was not associated with any EA gestational parent scales.

3.1.4. Exploratory post scan associations between brain activation and group status

First, group differences in response to feelings about averaged (across own and other sounds) cry and noise sounds were assessed. Groups only differed on ratings of aversiveness to matched white noise with participants in the cannabis group rating the sound as less aversive than the control group, t(88.75) = 2.463, p = 0.016, d = 0.459. Next, the average cry sound in the left temporal pole was correlated with average pleasantness, distressing, and aversiveness of cry rating responses. Activation in the left temporal pole to cry sound was correlated with average post scan rating response to how distressing the cries sounded, with higher activation relating to higher distress response rating (r = 0.266, p = 0.004) (Figure 2). Activation was not correlated with pleasantness or aversiveness rating.

Table 1 (Infant Cry): Sample demographics for groups in Model 1

	Control (n= 75)		**Cannabis (n= 39)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*
Preterm Birth (less than 37 weeks)	3	4.0%	2	5.1%
Total Gestational Weeks	39.08+/-1.59	32.57-41.71	39.02+/-1.43	35.00-41.14
Parent Age at MRI*	30.08+/-5.47	19—42	27.46+/-5.46	19—38
Education at consent**	15.21+/-2.82	11—20	13.54+/-1.95	10—17
Yearly Income at consent**	88,528.85+/-80,419.90 *(9 missing)*	0—504,000	41,846.67+/-28,671.41 *(3 missing)*	38.00—130,000

Single Relationship Status at consent	8 *(1 missing)*	10.7%	8 *(1 missing)*	20.5%
Parity	50	66.7%	26	66.7%
Infant Age at MRI (weeks)	5.45+/-3.11	1.29—14.29	5.37+/-2.99	1.14--14.43
Infant Age at 1st postnatal visit (weeks)*	3.07+/-1.72	.86—8.71	3.88+/-2.12 *(1 missing postnatal visit)*	.71--8.57
Hispanic	21 *(1 missing)*	28.0%	13	33.3%
Race*	*(2 missing)*	2.7%		
American Indian/Alaska Native	2	2.7%	1	2.6%
Asian	2	2.7%	0	
Black or African American	7	9.3%	14	35.9%
Native Hawaiian or Other Pacific Islander	2	2.7%	0	
White/Caucasian	49	65.3%	17	43.6%
Other	1	14.7%	7	17.9%
CESD at third trimester visit	13.72 +/-8.05 *(1 missing)*	4.00—39.00	14.93+/-7.70 *(2 missing)*	3.00—35.00
EPDS at third trimester visit	6.13+/-4.80 *(1 missing)*	0—18.00	6.50+/-5.15 *(1 missing)*	0—16.00
STAI at third trimester visit	31.15+/-11.15 *(1 missing)*	20.00—68.00	33.30+/-10.54 *(1 missing)*	20.00—62.00
CESD at postnatal visit	12.14+/-8.50	1.00—35.00	15.32+/-9.98 *(2 missing)*	1.00—44.00
EPDS at postnatal visit	4.98+/-4.56	0—18.00	6.24+/-5.00 *(2 missing)*	0—18.00
STAI at postnatal visit	29.56+/-10.06	20.00—61.00	32.13+/-10.60 *(2 missing)*	20.00—57.00
NicAlert Positive at Consent*	7 *(2 missing)*	9.3%	11 *(1 missing)*	28.2%
EA Parent Scale				
Sensitivity	5.61+/-1.01 *(6 missing)*	3.50—7.00	5.37+/-1.23 *(8 missing)*	2.50—7.00
Structuring	5.60+/-1.14 *(6 missing)*	3.00—7.00	5.12+/-1.40 *(8 missing)*	3.00—7.00
Non-intrusiveness	5.60+/-.95 *(6 missing)*	3.00—7.00	5.50+/-1.09 *(8 missing)*	3.50—7.00
Non-hostility	5.54+/-1.23 *(8 missing)*	3.00—7.00	5.17+/-1.27 *(10 missing)*	3.00—7.00

Note: CESD is the Center for Epidemiological Studies-Depression; EPDS is the Edinburg Postnatal Depression Scale; STAI is the State-Trait Anxiety Inventory, State; EA is the Emotional Availability Scale. Significant difference between groups based on t-test or chi-squared, *$p<.05$; **$p<.001$

Table 2: (Infant Cry) Sample distribution of cannabis use across prenatal and postnatal visits for Model 1

Characteristic	Control (n= 75)		Cannabis (n= 39)	
	μ / n	*range / %*	*μ / n*	*range / %*
First Trimester Self-Report [a] [d]	0	-	32	88.9%
First Trimester TLFB [c]	0	-	101.73+/-157.295 *(6 missing, 3 no reported use)*	0--707
First Trimester Positive Immunoassay for Cannabis [a]	0 *(1 missing)*	-	16 *(1 missing)*	45.7%
Second Trimester Self-Report [a]	0	-	18 *(1 missing)*	51.4%
Second Trimester TLFB [c]	0	-	130.55+/-173.48 *(5 missing, 14 no reported use)*	0--710
Second Trimester Positive Immunoassay for Cannabis [a]	0 *(37 missing)*	-	12 *(11 missing)*	34.3%
Third Trimester Self-Report [b]	0	-	18 *(1 missing)*	46.2%
Third Trimester TLFB [c]	0	-	95.06+/-139.44 *(7 missing, 15 no reported use)*	1--462
Third Trimester Positive Immunoassay for Cannabis [b]	0 *(33 missing)*	-	12 *(10 missing)*	41.4%
1st Postnatal Visit Self-Report [b]	0	-	15 *(1 missing)*	38.5%
1st Postnatal Visit TLFB [c]	0	-	39.60+/-34.75 *(8 missing, 21 no reported use)*	1--90
1st Postnatal Visit Positive Immunoassay for Cannabis [b]	0 *(30 missing)*	-	11 *(14 missing)*	44.0%
1st MRI Visit Positive Immunoassay for Cannabis [b]	0 *(20 missing)*	-	16 *(7 missing)*	41.0%

Note: [a]:11 control subjects were recruited at the third trimester and 4 cannabis subjects were recruited at the third trimester. For the first and second trimester N=64 for the control group and N= 35 for the cannabis group. The table totals for first trimester and second trimester data show the results based on the totals at each visit with associated missing data. Immunoassay was added to all visits later on and thus there is a larger portion of missing data after the first trimester visit.

[b]:For the third trimester data, the additional 11 control subjects (N=75) and 4 cannabis (N=39) subjects where recruited and thus the totals are reflected with associated missing data for the third trimester and postnatal data.

[c]:For the TLFB data, third trimester starts were asked about retrospective use since conception. Total for the control is N=75, and total for cannabis is N=39

[d]:One third trimester start self-reported cannabis use up to 12 weeks in the first postpartum period, thus their data point is listed in first trimester self-report for first trimester use only (N=36), but they are missing TLFB data.

TLFB= Timeline follow back data. TLFB was only filed out when participants tested positive or self-reported cannabis use.

Table 3: Brain regions showing statistically significant Cannabis Group x Sound Condition interactions and post-hoc analyses with education, income, and nicotine assay.

Region	BA	Side	MNI Coordinates			Cluster size	F
			x	y	z		
Temporal Pole	38	L	-27	10	-31	18	23.98**

Note: BA = Brodmann Area, MNI = Montreal Neurological Institute; ** $p < .001$, ** $p < .05$

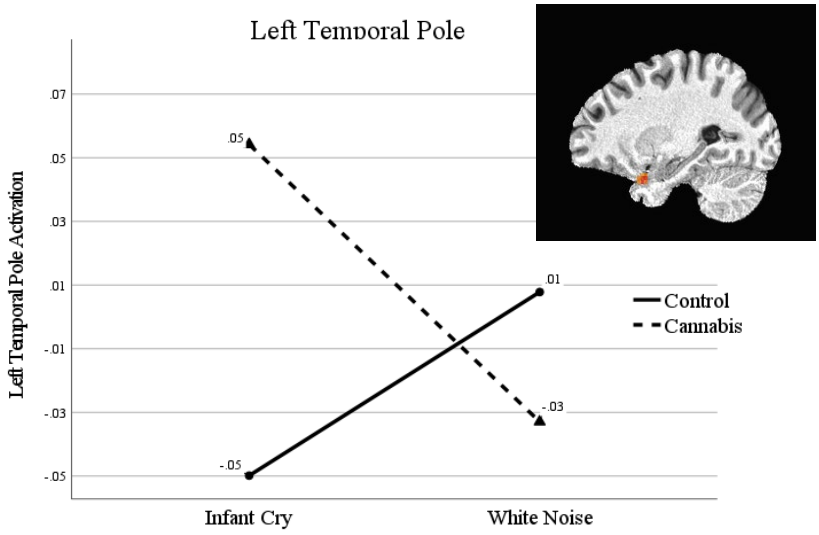

Figure 1: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry by White Noise contrast in prenatal cannabis use and control groups in the left temporal pole (BA38; x,y, z = -27, 10, -31; k = 18, $p = .001$, corrected)

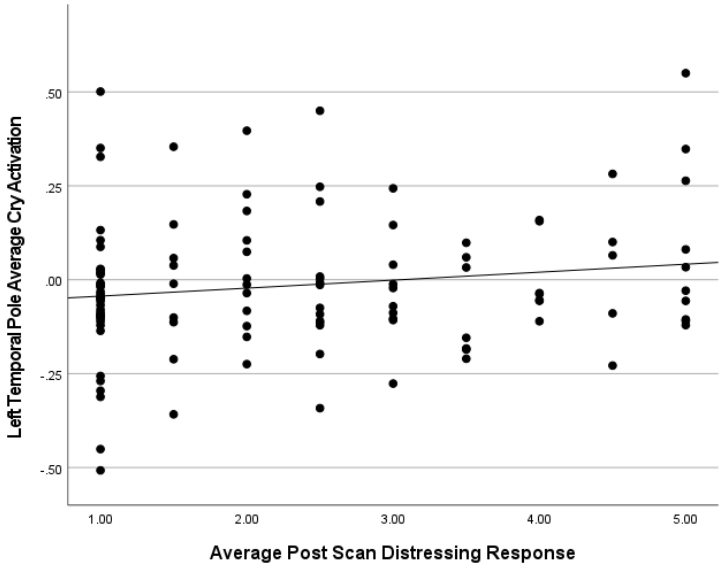

Figure 2: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry by White Noise contrast with average post scan distressing response ratings in the medial PFC to infant cry

3.2. Model 2: First trimester use compared to beyond the first trimester prenatal cannabis use

3.2.1 Characteristics of the sample

Participant demographics for this model are presented in Table 4 and descriptives for cannabis use are presented in Table 5. Group differences were assessed with chi-square and ANOVA. Groups differed on parent age at the MRI ($F(2,111) = 3.231$, $p = 0.043$, $\eta^2 = 0.055$), education at consent ($F(2,111) = 6.795$, $p = 0.002$, $\eta^2 = 0.109$), yearly income at consent ($F(2, 99) = 6.556$, $p = 0.002$, $\eta^2 = 0.117$), race ($X^2(10, N = 112) = 23.493$ $p = 0.009$,$V = 0.458$) and nicotine status (X^2 $(2,N = 111) = 11.386$, $p = 0.003$, $V = 0.320$). Groups did not differ on mood symptoms at the third trimester or postnatal visit.

3.2.2. fMRI analysis of the differences between groups and brain activation

In the second model, we investigated control, prenatal cannabis first trimester use only, and prenatal cannabis continued beyond the first trimester in the three-way interaction of cannabis x sound (cry vs. noise) x identity (own vs. other) controlling for gestational parent age at scan, postpartum days at scan, and parity. In this three-way interaction, there were no significant clusters. In the next two-way interaction of groups x sound (averaged cry vs. averaged noise) there were no significant clusters.

3.2.3. Exploratory associations between brain activation and parenting behaviors

Group differences were assessed through chi-square, groups did not significantly differ on any EA parent scale. Associations between EA gestational parent scales and neural activation were not examined as there were no significant clusters identified.

3.2.4. Exploratory post scan associations between brain activation and group status

Group differences were assessed through ANOVA in cry and white noise responses to pleasure, aversiveness, and distress. In averaged post scan responses to cry sounds, the first trimester use had higher ratings of aversiveness to cry sounds, $F(2, 110) = 3.122$, $p = 0.48$, $\eta^2 = 0.054$). Groups did not differ on white noise responses. Due to no significant brain regions, post scan associations were not examined.

Table 4: (Infant Cry): Sample demographics for groups in Model 2

	Control (n= 75)		**First Trimester Cannabis (n= 11)**		**Beyond First Trimester Cannabis (n=28)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*	*μ / n*	*range / %*
Preterm Birth (less	3	4.0%	1	9.1%	1	3.6%

than 37 weeks)						
Total Gestational Weeks	39.08 +/- 1.59	32.57-41.71	39.17+/- 1.67	35.00—41.14	38.96+/- 1.35	36.29—41.14
Parent Age at MRI*	30.08 +/- 5.47	19—42	28.55+/- 5.54	19--36	27.04+/- 5.47	19--38
Education at consent*	15.21 +/- 2.82	11—20	14.55+/- 1.97	12--17	13.14+/- 1.82	10--16
Yearly Income at consent*	88,528.85+/- 80,419.90 *(9 missing)*	0—504,000	65,432.00+/- 32,648.72 *(1 missing)*	28,000—130,000	32,775.39+/- 21,425.33 *(2 missing)*	38.00—82,000
Single Relationship Status at consent	8 *(1 missing)*	10.7%	2 *(1 missing)*	18.2%	6	21.4%
Parity	50	66.7%	6	54.5%	20	71.4%
Infant Age at MRI (weeks)	5.45+/- 3.11	1.29—14.29	4.91+/-2.28	1.14—8.71	5.55+/- 3.25	1.14—14.43
Infant Age at 1st postnatal visit (weeks)	3.07+/- 1.72	.86—8.71	3.58+/-1.92	1.43—7.71	4.00+/- 2.22 *(1 missing)*	.71—8.57
Hispanic	21 *(1 missing)*	28.0%	5	45.5%	8	28.6%
Race*	*(2 missing)*	2.7%				
American Indian/Alaska Native	2	2.7%	1	9.1%	0	
Asian	2	2.7%	0		0	
Black or African American	7	9.3%	1	9.1%	13	46.4%
Native Hawaiian or Other	2	2.7%	0		0	

Pacific Islander						
White/Caucasian	49	65.3%	6	54.5%	11	39.3%
Other	1	14.7%	3	27.3%	4	14.3%
CESD at third trimester visit	13.72 +/- 8.05 *(1 missing)*	4.00—39.00	15.73+/- 9.84	5.00—35.00	14.60+/- 6.79 *(2 missing)*	3.00—31.00
EPDS at third trimester visit	6.13+/-4.80 *(1 missing)*	0—18.00	6.91+/-5.70	0—16.00	6.33+/- 5.02 *(1 missing)*	0—16.00
STAI at third trimester visit	31.15 +/- 11.15 *(1 missing)*	20.00—68.00	36.09+/- 11.85	20.00—55.00	32.16+/- 9.97 *(1 missing)*	20.00—62.00
CESD at postnatal visit	12.14 +/- 8.50	1.00—35.00	19.00+/- 11.05	6.00—35.00	13.77+/- 9.27 *(2 missing)*	1.00—44.00
EPDS at postnatal visit	4.98+/-4.56	0—18.00	6.73+/-5.02	0—15.00	6.04+/- 5.08	0—18 *(2 missing)*
STAI at postnatal visit	29.56 +/- 10.06	20.00—61.00	35.46+/- 13.40	20.00—57.00	30.73+/- 9.12 *(2 missing)*	20.00—54.00
NicAlert Positive at Consent*	7 *(2 missing)*	9.3%	1	9.1%	10 *(1 missing)*	37.0%
EA Parent Scale						
Sensitivity	5.61+/-1.01 *(6 missing)*	3.50—7.00	5.81+/-1.23 *(2 missing)*	3.00—7.00	5.19+/- 1.21 *(6 missing)*	2.50—7.00
Structuring	5.60+/-1.14 *(6 missing)*	3.00—7.00	5.72+/-1.44 *(2 missing)*	3.00—7.00	4.88+/- 1.34 *(6 missing)*	3.00—7.00

Non-intrusiveness	5.60+/-.95 *(6 missing)*	3.00—7.00	6.00+/-.97 *(2 missing)*	4.50—7.00	5.30+/-1.09 *(6 missing)*	3.50—7.00
Non-hostility	5.54+/-1.23 *(8 missing)*	3.00—7.00	5.77+/-1.05 *(3 missing)*	4.00—7.00	4.94+/-1.30 *(7 missing)*	3.00—7.00

Note: CESD is the Center for Epidemiological Studies-Depression; EPDS is the Edinburg Postnatal Depression Scale; STAI is the State-Trait Anxiety Inventory, State; EA is the Emotional Availability Scale. Significant difference between groups based on t-test or chi-squared, **p<.05; **p<.001*

Table 5: (Infant Cry) Sample distribution of cannabis use across prenatal and postnatal visits for Model 2

Characteristic	Control (n= 75)		First Trimester Use (n= 11)		Beyond Trimester Use (n= 28)	
	μ / n	*range / %*	*μ / n*	*range / %*	*μ / n*	*range / %*
First Trimester Self-Report [a d]	0	-	11	100%	21	84.0%
First Trimester TLFB [c d]	0	-	6.30 +/- 16.10 *(1 missing)*	0—52.00	149.45+/-174.501 *(5 missing, 3 no reported use)*	0--707
First Trimester Positive Immunoassay for Cannabis [a]	0 *(1 missing)*	-	0	-	16 *(1 missing)*	64.0%
Second Trimester Self-Report [a]	0	-	0	-	18 *(1 missing)*	72.0%
Second Trimester TLFB [c]	0	-	0 *(11 no reported use)*	-	130.55+/-173.48 *(5 missing, 3 no reported use)*	
Second Trimester Positive Immunoassay for Cannabis [a]	0 *(37 missing)*	-	0 *(3 missing)*	-	12 *(8 missing)*	48.0%

Third Trimester Self-Report [b]	0	-	0	-	18 *(1 missing)*	64.3%
Third Trimester TLFB [c]	0	-	0 *(11 no reported use)*	-	95.06+/-139.44 *(7 missing, 4 no reported use)*	1--462
Third Trimester Positive Immunoassay for Cannabis [b]	0 *(33 missing)*	-	0 *(2 missing)*	-	12 *(8 missing)*	42.9%
1st Postnatal Visit Self-Report [b]	0	-	0	-	15 *(1 missing)*	53.6%
1st Postnatal Visit TLFB [c]	0	-	0 *(11 no reported use)*	-	39.60+/-34.75 *(8 missing, 10 no reported use)*	1--90
1st Postnatal Visit Positive Immunoassay for Cannabis [b]	0 *(30 missing)*	-	0 *(4 missing)*	-	11 *(10 missing)*	39.3%
1st MRI Visit Positive Immunoassay for Cannabis [b]	0 *(20 missing)*	-	0 *(2 missing)*	-	16 *(5 missing)*	57.1%

Note:[a]:11 control subjects were recruited at the third trimester and 4 cannabis subjects were recruited at the third trimester. For the first and second trimester N=64 for the control group and N= 10 for the first trimester cannabis group, and N=26 for the beyond first trimester group. The table totals for first trimester and second trimester data show the results based on the totals at each visit with associated missing data. Immunoassay was added to all visits later on and thus there is a larger portion of missing data after the first trimester visit.
[b]:For the third trimester data, the additional 11 control subjects (N=75) and 4 cannabis (N=11 for first trimester use and N=28 for beyond first trimester use) subjects where recruited and thus the totals are reflected with associated missing data for the third trimester and postnatal data.
[c]:For the TLFB data, third trimester starts were asked about retrospective use since conception. Total for the control is N=75, and total for first trimester use is N=11 and beyond first trimester use is N=28.
[d]:One third trimester start self-reported cannabis use up to 12 weeks in the first postpartum period, thus their data point is listed in first trimester self-report for first trimester use only (N=11), but they are missing TLFB data.
TLFB= Timeline follow back data. TLFB was only filed out when participants tested positive or self-reported cannabis use.

3.3. Model 3: Cumulative quantity of prenatal cannabis

3.3.1. Characteristics of the Sample

Participant demographics for this model are presented in Table 6 and descriptives of cumulative cannabis use are presented in Table 7. While groups differed on total education years at consent, yearly income at consent, CESD postnatally, positive nicotine immunoassay at consent, only positive nicotine immunoassay (r = 0.450, $p < 0.001$, 95% CI [-0.306, 0.086]) was related to cumulative prenatal use. Due to group differences, additional post-hoc was conducted with these variables.

Cumulative prenatal use was not correlated with CESD at the third trimester or postnatal visit. Cumulative prenatal use was positively correlated with EPDS at the third trimester and postnatal visit with higher cumulative use related to higher EPDS scores (r = 0.215, $p = 0.035$, 95% CI [0.016, 0.399]; r = 0.208, $p = 0.042$, 95% CI [0.008, 0.392]). Cumulative prenatal use was also positively correlated with STAI at the third trimester visit but not the postnatal visit, with higher cumulative use related to higher STAI scores (r = 0.301, $p = 0.003$, 95% CI [0.107, 0.473]).

3.3.2. fMRI analysis of the amount of use and brain activation

In the third model, we conducted an analysis looking at a subset of participants who used cannabis who had completed TLFBs at each prenatal visit. The summation of cannabis use over the prenatal period was assessed as a continuous variable by sound (cry vs. noise) x identity (own vs. other) controlling for gestational parent age at scan, postpartum days at scan, and parity. In this three-way interaction, there were no significant clusters. In the next two-way interaction of groups x sound (averaged cry vs. averaged noise) 32 clusters were identified (see Table 8; Figure 4 for all clusters across the brain, Figures 5-8 for example regions and plots of activation**)**. In all clusters except one (cluster 20), greater averaged response to cry sounds (such as the thalamus, putamen,

superior frontal gyrus, medial PFC, superior temporal gyrus, superior medial frontal gyrus, dorsolateral PFC, caudate, and precuneus) was associated with higher prenatal cumulative use score (see Table 8). In cluster 20, in the fusiform gyrus, heightened averaged response to white noise was associated with higher prenatal cumulative use (see Table 8).

Next, additional post-hoc analyses to account for group differences and correlations with cumulative prenatal use was conducted using extracted clusters. A partial correlation with BOLD response (averaged cry-averaged noise) was examined in each cluster controlling for potential covariates. All clusters remained significant after controlling for total education years at consent, yearly income at consent, CESD postnatal score, and positive nicotine immunoassay at consent, $ps < 0.05$, in all clusters except for positive nicotine immunoassay at consent in cluster 29 where $p = 0.05$. All clusters remained significant after controlling for CESD at the third trimester, EPDS at the third trimester and postnatal visits, and STAI at the third trimester.

3.3.3. Exploratory associations between brain activation and parenting behaviors

Cumulative prenatal use was correlated with gestational parent EA scales. Cumulative prenatal use was negatively associated with the non-hostility scale, meaning higher cumulative prenatal use was associated with lower non-hostility scores or more hostile parenting behavior (r = -0.268, $p = 0.013$, 95% CI [-0.455, -0.058]) (see Figure 3).

Associations between EA gestational parent scales and neural activation in the significant functional clusters of infant cries where the cannabis group had higher activation, and the cluster in the fusiform gyrus that had higher activation to white noise

were examined through correlations. No regions were significantly correlated with EA gestational parent scores.

3.3.4. Exploratory post scan associations between brain activation and group status

First, cumulative prenatal use was correlated with average post scan responses to cry (pleasure, aversive, and distressing) and matched white noise sounds (pleasure, aversive, and distressing). Cumulative prenatal use was negatively associated with average aversiveness rating to cry sounds, with the higher total use being associated with lower ratings of aversiveness ($r = -0.226$, $p = 0.03$, 95% CI [-0.407, -0.027]). Cumulative prenatal use was not correlated with matched white noise sound ratings.

Next, all significant cry clusters (except cluster 20), were correlated with average post scan responses to cry pleasantness, aversiveness, and distress ratings. Twelve clusters (2, 4, 8, 9, 11, 14, 17, 21, 22, 23, 26, and 32) were positively correlated with average distress rating to cry sounds with heightened activation in these regions associated with higher distress ratings (See Table 8). Seven clusters (4, 9, 12, 17, 21, 26, 27, and 32) were positively correlated with average aversiveness rating to cry sounds with heightened activation in these regions associated with higher aversiveness ratings (See Table 8 and Figures 9a-c).

Finally, in cluster 20 averaged white noise sound was correlated with average post scan pleasantness, aversiveness, and distress responses to white noise. Cluster 20, in the right fusiform gyrus, was associated with average distressing rating to white noise sounds, with greater activation in cluster 20 related to higher distressing ratings to white noise sounds ($r = 0.275$, $p = 0.007$). It was not associated with pleasantness or aversiveness rating.

Table 6: (Infant Cry): Sample demographics for groups in Model 3

	Control (n= 75)		**Cannabis (n= 23)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*
Preterm Birth (less than 37 weeks)	3	4.0%	2	8.7%
Total Gestational Weeks	39.08+/-1.59	32.57-41.71	38.94+/-1.60	35.00—41.14
Parent Age at MRI*	30.08+/-5.47	19—42	26.78+/-4.86	19--38
Education at consent*	15.21+/-2.82	11—20	13.26+/-2.03	10--17
Yearly Income at consent**	88,528.85+/-80,419.90 *(9 missing)*	0—504,000	39,390.67+/-24,646.06 *(2 missing)*	38—90,000
Single Relationship Status at consent	8 *(1 missing)*	10.7%	5 *(1 missing)*	21.7%
Parity	50	66.7%	15	65.2%
Infant Age at MRI (weeks)	5.45+/-3.11	1.29—14.29	5.21+/-2.57	1.14—11.71
Infant Age at 1st postnatal visit (weeks)	3.07+/-1.72	.86—8.71	4.12+/-2.42 *(1 missing)*	.71—8.57
Hispanic	21 *(1 missing)*	28.0%	6	26.1%
Race*	*(2 missing)*	2.7%		
American Indian/Alaska Native	2	2.7%	1	4.3%
Asian	2	2.7%	0	
Black or African American	7	9.3%	10	43.5%
Native Hawaiian or Other Pacific Islander	2	2.7%	0	
White/Caucasian	49	65.3%	11	47.8%
Other	1	14.7%	1	4.3%
CESD at third trimester visit	13.72 +/-8.05 *(1 missing)*	4.00—39.00	15.34+/-7.34 *(1 missing)*	3.00—31.00
EPDS at third trimester visit	6.13+/-4.80 *(1 missing)*	0—18.00	7.09+/-5.51 *(1 missing)*	0—16.00
STAI at third trimester visit	31.15+/-11.15 *(1 missing)*	20.00—68.00	34.15+/-10.96 *(1 missing)*	20.00—62.00
CESD at postnatal visit*	12.14+/-8.50	1.00—35.00	17.10+/-11.27 *(2 missing)*	4.00—44.00
EPDS at postnatal visit	4.98+/-4.56	0—18.00	7.29+/-5.85 *(2 missing)*	0—18.00
STAI at postnatal visit	29.56+/-10.06	20.00—61.00	32.76+/-11.35 *(2 missing)*	20.00—54.00

NicAlert Positive at Consent*	7 *(2 missing)*	9.3%	9 *(1 missing)*	39.1%
EA Parent Scale				
Sensitivity	5.61+/-1.01 *(6 missing)*	3.50—7.00	5.28+/-1.17 *(3 missing)*	3.00—7.00
Structuring*	5.60+/-1.14 *(6 missing)*	3.00—7.00	4.77+/- 1.34 *(3 missing)*	3.00—7.00
Non-intrusiveness	5.60+/-.95 *(6 missing)*	3.00—7.00	5.45+/-1.11 *(3 missing)*	3.50—7.00
Non-hostility*	5.54+/-1.23 *(8 missing)*	3.00—7.00	4.87+/-1.23 *(4 missing)*	4.00—7.00

Note: Demographics are split up by group to show group differences, but cumulative use was tested continuously in the model. CESD is the Center for Epidemiological Studies-Depression; EPDS is the Edinburg Postnatal Depression Scale; STAI is the State-Trait Anxiety Inventory, State; EA is the Emotional Availability Scale. Significant difference between groups based on t-test or chi-squared, **p<.05; **p<.001*

Table 7: (Infant Cry) Sample distribution of cannabis use across prenatal and postnatal visits for Model 3

Characteristic	Control (n= 75)		Cannabis (n= 23)	
	μ / n	*range / %*	*μ / n*	*range / %*
First Trimester Self-Report [a]	0	-	19	86.4%
First Trimester TLFB [c]	0	-	116.70+/-164.22	1--707
First Trimester Positive Immunoassay for Cannabis [a]	0 *(1 missing)*	-	11 *(1 missing)*	50.0%
Second Trimester Self-Report [a]	0	-	12 *(1 missing)*	54.6%
Second Trimester TLFB [c]	0	-	111.91+/-168.33	0--710
Second Trimester Positive Immunoassay for Cannabis [a]	0 *(37 missing)*	-	10 *(3 missing)*	45.5%
Third Trimester Self-Report [b]	0	-	13 *(1 missing)*	56.5%
Third Trimester TLFB [c]	0	-	68.91+/-126.99	0--462
Third Trimester Positive Immunoassay for Cannabis [b]	0 *(33 missing)*	-	9 *(4 missing)*	39.1%
1st Postnatal Visit Self-Report [b]	0	-	10 *(1 missing)*	43.5%
1st Postnatal Visit TLFB [c]	0	-	15.52+/-29.82	0--90
1st Postnatal Visit Positive Immunoassay for Cannabis [b]	0 *(30 missing)*	-	9 *(6 missing)*	39.1%
1st MRI Visit Positive Immunoassay for Cannabis [b]	0 *(20 missing)*	-	12 *(2 missing)*	52.2%

Note :[a]:11 control subjects were recruited at the third trimester and 1 cannabis subjects were recruited at the third trimester. For the first and second trimester N=64 for the control group and N= 22 for the cannabis group. The table

totals for first trimester and second trimester data show the results based on the totals at each visit with associated missing data. Immunoassay was added to all visits later on and thus there is a larger portion of missing data after the first trimester visit.

[b]:For the third trimester data, the additional 11 control subjects (N=75) and 1 cannabis (N=23) subjects were recruited and thus the totals are reflected with associated missing data for the third trimester and postnatal data.

[c]:For the TLFB data, third trimester starts were asked about retrospective use since conception. Total for the control is N=75, and total for cannabis is N=23

TLFB= Timeline follow back data. TLFB was only filed out when participants tested positive or self-reported cannabis use.

Table 8: Brain regions showing statistically significant Cannabis TLFB x Sound Condition interactions and post-hoc analyses with education, income, and nicotine assay.

	Region	BA	Side	MNI Coordinates			Cluster size	F	Cry Response and Cumulative Use Correlation	Noise Response and Cumulative Use Correlation	Distress Rating Response to Cry Sounds	Aversive Rating Response to Cry Sounds
				x	y	z						
1	Thalamus	-	R	6	-18	20	242	36.68***	.299**	-0.14	0.194	0.161
2	Lateral occipital cortex	17	L	-12	-93	-21	199	55.12***	.344**	-.203*	.256*	0.170
3	Cerebellum	-	L	-36	-75	-57	117	40.33***	.376**	-0.19	0.073	0.177
4	Supplementary motor area	6	R	10	3	56	114	23.02***	.294**	-0.04	.330**	.290**
5	Superior frontal gyrus	8	R	6	30	65	101	31.92***	.420**	-0.07	.211*	0.150
6	Cerebellum cortex	-	R	3	-66	-48	98	24.21***	.417**	-0.10	0.167	0.155
7	Cerebellum cortex	-	R	30	-78	-448	96	28.67***	.367**	-.214*	0.068	0.174
8	Middle frontal gyrus	10	R	46	58	12	81	39.68***	.391**	-0.04	.208*	0.158
9	Putamen	16	L	-30	-21	5	79	26.56***	.351**	-0.09	.218*	.208*
10	Superior frontal gyrus	8	L	-18	16	56	70	19.75***	.318**	-0.17	0.089	0.134
11	Cerebellum cortex	-	R	15	-42	-48	67	33.57***	.398**	-0.12	.205*	0.135

12	Medial prefrontal cortex	9	R	0	49	17	57	25.62***	.281**	-0.17	0.118	.214*
13	Middle frontal gyrus	9	L	-51	34	36	55	30.02***	.364**	-0.04	0.114	0.115
14	Precuneus	31	R	18	-45	32	49	27.16***	.231*	-.274**	.237*	0.156
15	Middle temporal gyrus	21	R	66	-6	-21	47	26.73***	.464**	0.18	0.067	0.130
16	Middle temporal gyrus	21	L	-60	-11	-19	46	33.50***	.336**	-0.17	0.169	0.154
17	Superior temporal gyrus	38	L	-39	28	-28	44	20.84***	.239*	-.245*	.366**	.321**
18	Superior medial frontal gyrus	10	R	0	70	17	38	20.01***	.407**	-0.05	0.092	0.092
19	Orbitofrontal cortex	10	R	6	67	-9	37	28.18***	.371**	-0.16	0.114	0.088
20	Fusiform gyrus	37	R	37	-48	-19	34	46.67***	-0.15	.354**	-	
21	Precentral gyrus	6	L	-33	-2	44	34	20.06***	.320**	-0.03	.239*	.229*
22	Fusiform gyrus	37	L	-51	-75	-16	33	29.14***	.285**	-.214*	.251*	0.195
23	Brainstem	-	L	-6	-51	-72	31	20.10***	.419**	-0.13	.290**	0.088
24	Cerebellum	-	L	-15	-87	-43	30	24.81***	.325**	-0.18	0.091	0.093

25	Superior frontal gyrus	8	R	15	28	39	28	16.24***	.256*	-0.15	0.145	0.111
26	Inferior temporal gyrus	20	R	46	-18	-19	26	26.90***	.356**	-.206*	.206*	.208*
27	Dorsal lateral prefrontal cortex	9	R	42	16	36	26	28.69***	.254*	-0.11	0.196	.230*
28	Cerebellum	-	L	-2	-54	-21	24	21.50***	.243*	-.211*	0.199	0.142
29	Precuneus	23	L	0	-51	17	22	15.07***	.286**	-0.01	0.199	0.151
30	Caudate	24	R	15	25	15	20	18.95***	.334**	-0.17	0.132	0.099
31	Posterior cingulate	31	R	6	-33	39	19	22.22***	.254*	-0.10	-0.019	0.189
32	Precentral gyrus	6	R	34	-9	56	16	14.66***	.343**	0.01	.295**	.232*

Note: BA = Brodmann Area; MNI = Montreal Neurological Institute; Distress rating response not conducted for cluster 20 due to significance in noise; distress rating to matched noise was correlated with cluster 20 with heightened activation related to higher distress rating to noise sounds *(r = 0.275, p = 0.007); *** p < .001, **, p<.01,*p < .05.*

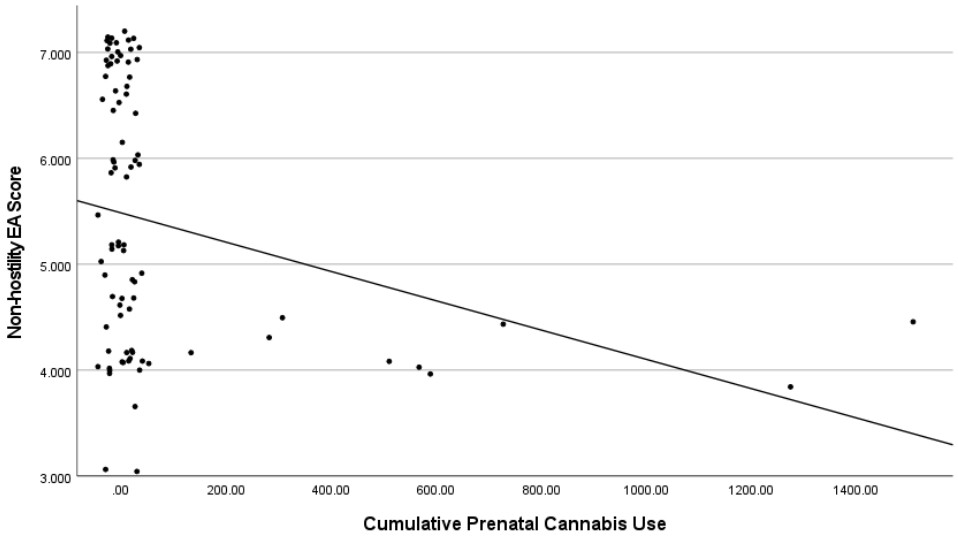

Figure 3: Correlation of the non-hostility scale with cumulative prenatal cannabis use

Note: EA = Emotional Availability Scale

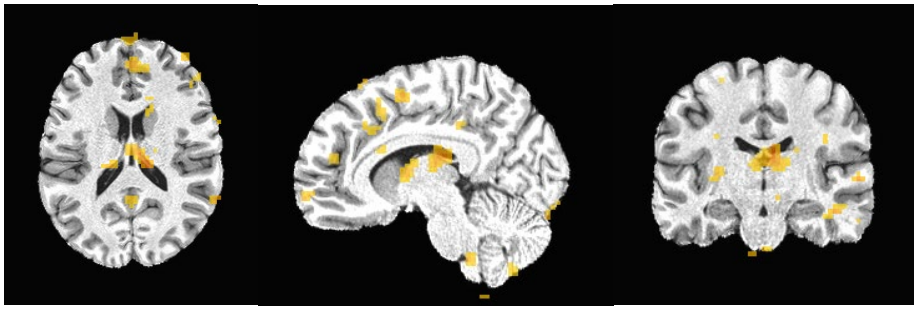

Figure 4: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry-White Noise contrast in cumulative cannabis use during the prenatal period

Note: due to over skull stripping some regions appear outside the brain; PFC = prefrontal cortex

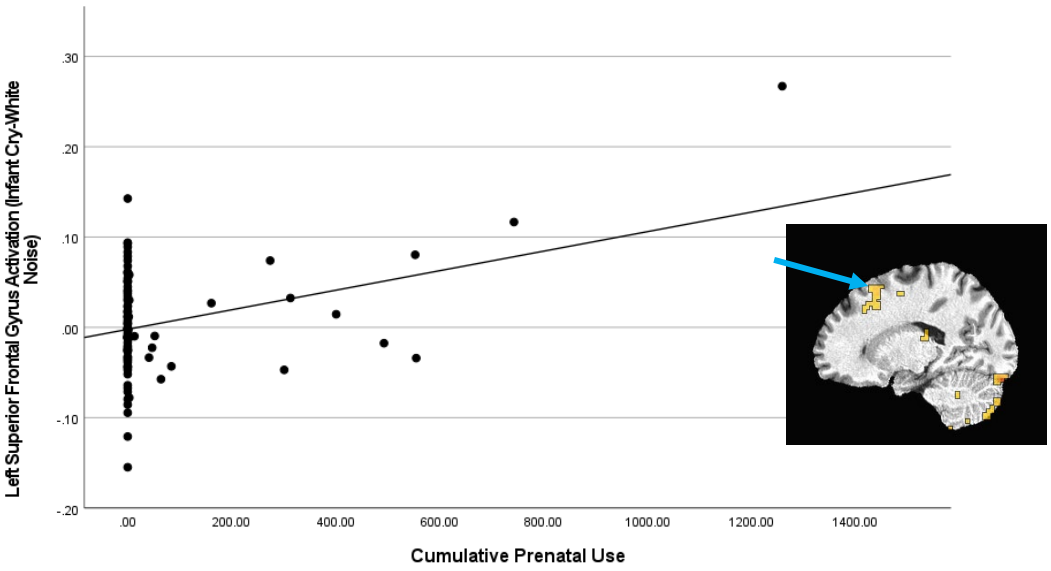

Figure 5: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry-White Noise contrast in cumulative cannabis use during the prenatal period with example correlation maps in superior frontal gyrus (BA8; x,y, z = -18, 16, 56; k = 70, p = .001, corrected)

Note: due to over skull stripping some regions appear outside the brain

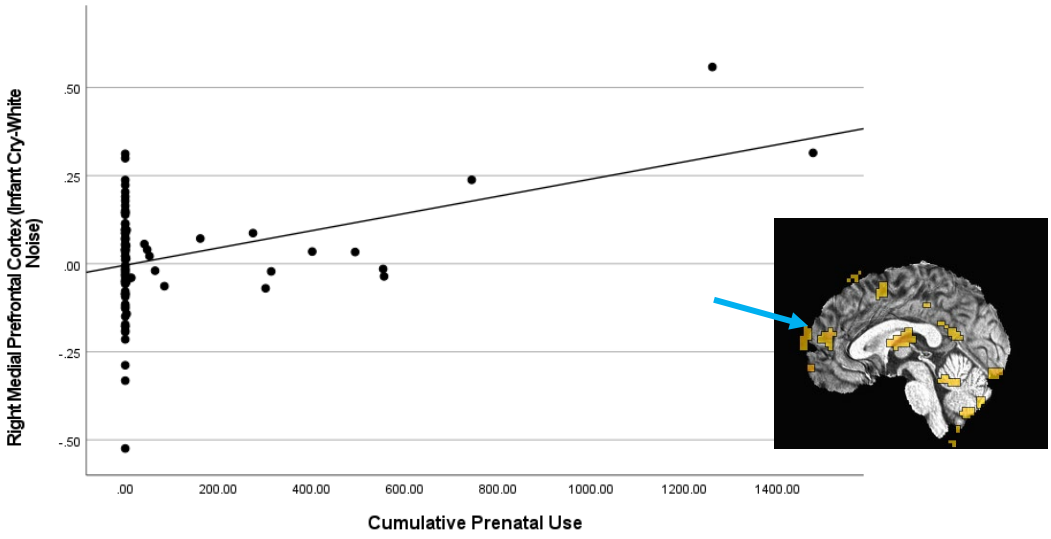

Figure 6: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry-White Noise contrast in cumulative cannabis use during the prenatal period with example correlation maps in the medial PFC (BA9; x,y, z = 0, 49, 17; k = 57, p = .001, corrected)

Note: due to over skull stripping some regions appear outside the brain; PFC = prefrontal cortex

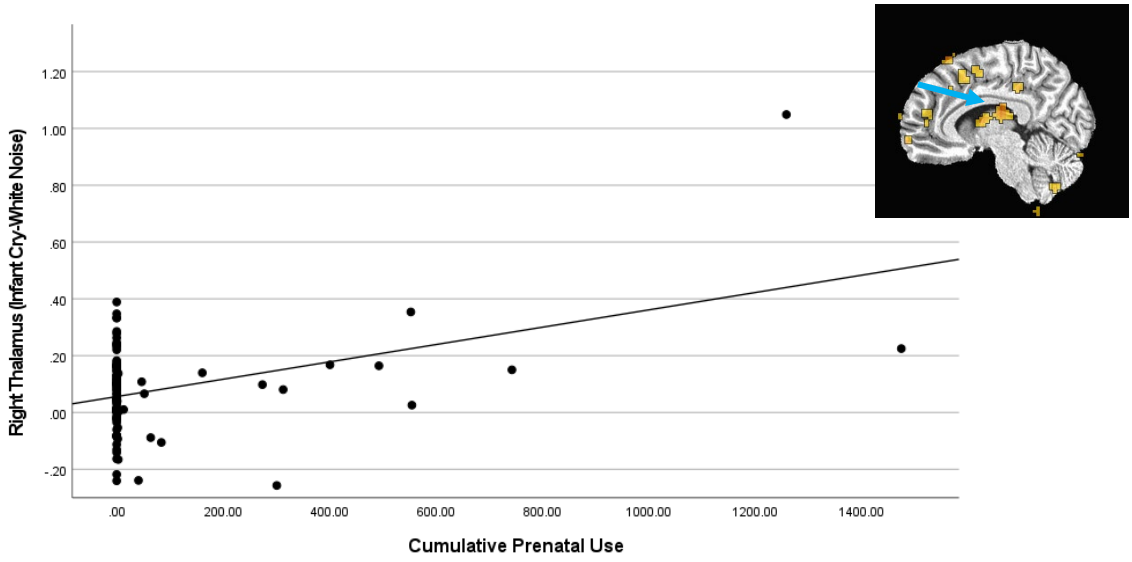

Figure 7: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry-White Noise contrast in cumulative cannabis use during the prenatal period with example correlation maps in the right thalamus and surrounding caudate (x,y, z = 6, -18, 20; k = 242, *p* = .001, corrected)

Note: due to over skull stripping some regions appear outside the brain

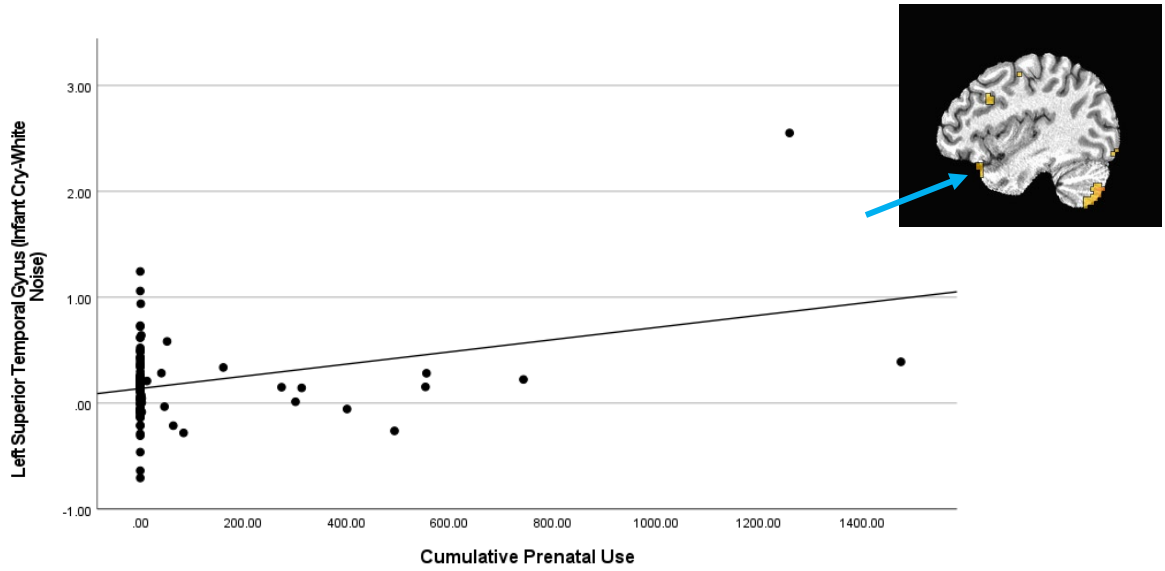

Figure 8: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry-White Noise contrast in cumulative cannabis use during the prenatal period with

example correlation maps in the left superior temporal gyrus (BA 38; x,y, z = -39, 28, -28; k = 44, p = .001, corrected)

Note: due to over skull stripping some regions appear outside the brain

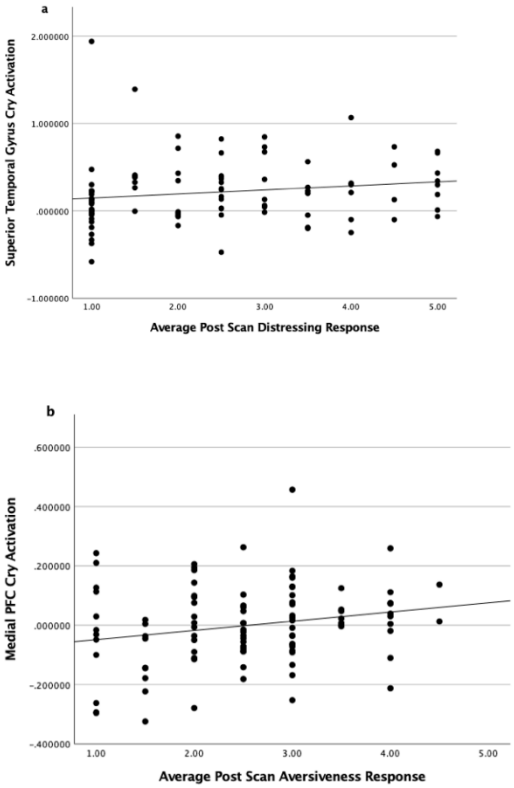

Figure 9a: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry contrast with average post scan distressing response to cry ratings in the superior temporal gyrus to infant cry

Figure 9b: Blood Oxygenation Level Dependent (BOLD) activation illustrating Infant Cry by White Noise contrast with average post scan aversiveness response to cry ratings in the medial PFC to infant cry

Note: PFC = prefrontal cortex

CHAPTER FOUR: STUDY ONE DISCUSSION

The current study sought to assess potential differences in neural activation to infant cries between gestational parents who used cannabis during the prenatal period and gestational parents who did not. In addition, this study assessed potential differences in parenting outcomes between groups, and their relation to neural activity. In line with previous literature, this study assessed prenatal cannabis use dichotomously, and between first trimester and beyond first trimester use. A third model was conducted with cumulative total cannabis use over the prenatal period.

This study found that higher total cumulative prenatal cannabis use was associated with heightened BOLD response to cry sounds in empathy and TOM networks, suggesting possible inefficiency in salience processing of infant cues. This study also found that cannabis use assessed dichotomously during pregnancy was associated with heightened BOLD response in the left temporal pole associated with higher distress cry ratings, suggesting potential inefficiency in semantic processing of infant cues. Finally, this study neural differences when assessing early trimester compared to ongoing prenatal cannabis use, but found no significant results. Taken together, these findings suggest the role of affective processing, theory of mind, emotion regulation, and semantic processing in saliency of infant cry cues.

4.1. Dichotomous model to neural and behavioral response

In the first dichotomous model, the study found increases in BOLD signal activation to infant cry sounds in the left temporal pole relative to matched white noise in the cannabis group contrary to our hypothesis that there would be neural differences to cries in reward regions. This region is involved in auditory processing of infant cries, and often heightened response here in non-substance use parent populations is associated with semantic processing of infant cries through the level of discomfort or type of cry (hunger vs. pain) (Witteman et al., 2019). There were no associations with parenting behavior or group differences in parenting behavior measured by the EA scale. Higher reports of how distressing the cries sound after the scan was associated with increases in BOLD signal. This heightened response could be interpreted as heightened salience processing of infant cues. The left temporal pole is one auditory region that is thought to be part of the neural circuitry response to infant cries. As cries are the only form of communication for infants, heightened salience to the semantics of cries is important to identify the appropriate parenting response, and the urgency of that response (Hickok & Poeppel, 2007; LaGasse et al., 2005; Newman, 2007; Soltis, 2004; Witteman et al., 2019). Additionally, the cannabis groups activation to cry sounds was correlated with higher ratings of the cries sounding distressing in the left temporal pole. This could be interpreted that cannabis has heightened sensitivity to this cry cues, but this heightened response could also be interpreted as a stressing signal. While infant cries should initiate an urgent response, potentially this heightened salience, combined with higher reports of how distressing the cries sound, could be a stress response and eventually lead to less sensitivity parenting later on (P. Kim, 2021). Additionally, the cannabis group reported the white noise sounding more aversive, potentially matching previous literature of heightened sensitivity

in cannabis use to potentially anxiety inducing or aversive stimuli (Wilcockson & Sanal, 2016).

4.2. Cumulative prenatal use to neural and behavioral response

This cumulative model found increases in BOLD signal activation to infant cry sounds in regions of reward networks (thalamus, caudate, posterior cingulate), motivation networks (cerebellum and putamen), emotion regulation networks (medial PFC, lateral PFC, and orbitofrontal PFC), social information processing networks (superior temporal gyrus, inferior frontal gyrus, occipital cortex, precentral gyrus, supplementary motor area, left fusiform gyrus), and theory of mind networks (superior frontal gyrus, precuneus, posterior cingulate) overlapping with the hypothesis that neural response in reward regions would differ in relation to amount of use (Bornstein et al., 2017; P. Kim et al., 2011, 2020a; Nader & Sanchez, 2018; Newman, 2007; Riem et al., 2011; Rigo, Esposito, et al., 2019; Vaidya et al., 2012; Witteman et al., 2019). Increased activation in these regions could be related to heightened salience processing. Infant cries are already a salient cue, and heightened activation in parental networks is important for increasing sensitive parenting in the early postpartum period (P. Kim, 2016; Witteman et al., 2019). While activation is important for saliency of infant cues, as cries are distressing, increased activation in these regions could also be a stress response (P. Kim, 2021). Previous exploratory research in cannabis use during the prenatal period, found heightened activation in the dorsal medial PFC to infant cry sounds, suggesting an increase in saliency to cries that could be related to deficits in emotion regulation (Powers et al., 2023). An additional study found heightened activation in regions of the PFC related to emotion regulation processing (Zimmermann et al., 2017, 2018). Heightened

activation in these regions could reflect unsuccessful attempts at emotion regulation. As cries are a strong stimulus, this heightened response could reflect distress and unsuccessful affective processing. This is demonstrated in the post scan responses, where increased activation in regions of motivational networks (putamen and cerebellum), theory of mind (superior frontal gyrus and precuneus), saliency and reward (inferior and superior temporal gyri), and social information processing (middle and medial frontal gyri and fusiform gyrus) were associated with higher distress and aversiveness ratings of cry sounds. A meta-analysis investigating the effects of cannabis on non-pregnant adult populations also found heightened response in the left superior temporal gyrus, middle temporal gyrus, and right inferior frontal gyrus during higher-order cognition tasks, suggesting alterations in cognitive function due to cannabis use (Duperrouzel et al., 2020). Combined with these studies findings, cannabis use could be disrupting these processes in parents.

Compared to the dichotomous model, this cumulative model had more significant regions. Previous research has identified that higher and more problematic cannabis use is associated with greater deficits in neurocognition (Scott et al., 2018). Additionally, heavier cannabis use (greater than 10 times a month) was associated structural and functional changes in cognitive and sensorimotor regions compared to less frequent use (less than 10 times a month) suggesting that heavier use may have more widespread implications for neural function (Hirjak et al., 2022). Cannabis has also been previously hypothesized to not respond as robustly as other substances, and potentially this cumulative model was able to capture the differences at higher levels of use (Zehra et al., 2018). Within the cumulative analysis, this study's results did suggest that potentially

heavier/chronic use of cannabis might be more associated with heightened activation in regions of reward, salience, and social information processing. In line with previous research, greater total cannabis use may be more predictive of neural functioning differences as demonstrated in our cumulative model. Future research should look specifically at differences in chronic cannabis use and parenting neural networks.

Moreover, in the exploratory analysis greater cumulative prenatal use was associated with lower non-hostility (meaning more negative parenting behaviors through facial expression and language). Infant cries are particularly salient during the early postpartum period before emotional valance of faces and language helps parents interpret child needs. Previous literature has shown that CUD is associated with lower positive parenting through less monitoring, support and consistency, and less sensitivity in infant interactions (Eiden et al., 2018; Hill et al., 2018). However, it should be noted that no neural activation was associated with parenting behavior measured by the EA Scale and these findings are exploratory.

The cannabis groups activation to cry sounds was also correlated with higher ratings of the cries sounding distressing and higher ratings of aversiveness to cry sounds. This dysregulation of heightened activation and distress, and aversiveness could suggest a dysregulated response. Potentially, the heightened saliency of the cue requires heightened affective processing leading to dysfunction in parental networks. These results were not shown in the main sample model and should be interpreted cautiously.

The study also found increases in BOLD signal activation to white noise in social information processing region of the right fusiform gyrus in the cumulative prenatal use model. Heightened activation in the right fusiform gyrus to white noise was correlated

with higher distress ratings of the white noise sound, suggesting heightened sensitivity to aversive cues. Previous exploratory research found heightened response to white noise in the dorsolateral PFC, suggesting heightened response to negative auditory cues (Powers et al., 2023). In the fusiform gyrus, previous research in non-pregnant populations who used cannabis showed heightened activation in this region related to cannabis cue stimuli (Sehl et al., 2021). Additional research in alcohol use disorder found that heightened activation in the fusiform to aversive face stimuli was associated with poorer stress response and increase relapses (Charlet et al., 2014). Potentially, increased activation in the fusiform gyrus in gestational parents who used cannabis could demonstrate inefficient social processing. Future studies should look at later time points to assess if differences in neural response and self-report ratings impact parenting behavior.

Parenting neural networks overlap in regions implicated by substance use disorder (Koob & Volkow, 2016; Rutherford & Mayes, 2017; Volkow, Michaelides, et al., 2019; Zilverstand et al., 2018). Cannabis use disorder has been theorized to have similar pattern of neural dysregulation as other substances, but less robust changes in neural reward circuitry compared to other substances of abuse (Volkow, Michaelides, et al., 2019; Zehra et al., 2018). These findings add to the limited research on the effects of cannabis use on the brain, and the even more limited knowledge on cannabis use in the prenatal period on parenting neural networks. Within reward regions of the putamen, caudate, PFC, and cingulate, there are high expression of cannabinoid-1 receptors (CB1). In animal models, chronic activation of the CB1 receptors in these reward regions is associated with decreased reward sensitivity (Parsons & Hurd, 2015; Zehra et al., 2018). In human studies, administration of THC led to an increase in the salience of non-salient

stimuli (Bhattacharyya et al., 2012). Within neural modals of substance use disorder in non-pregnant populations, drug related cues are associated with an increase in activation in regions of executive networks, reward networks, salience networks, and social-emotional processing, and non-drug related cues are associated with dampened responses in these networks (Volkow, Michaelides, et al., 2019; Zilverstand et al., 2018). In contrast, infant cry sounds have been tied to increases in reward and saliency networks in parent populations without substance use disorder (Bornstein et al., 2017; Witteman et al., 2019). In the current study, higher reported cannabis use was associated with heightened activation to infant cries within emotion regulation and theory of mind networks. As heightened chronic cannabis use has been demonstrated to show increased activation in these networks, this response could reflect poorer emotion regulation with the heightened saliency of the cries. Emotion regulation networks within parenting are important for facilitating approach and care behaviors.

4.3. Alternative explanations

Alternatively, increased activation in these regions in both the dichotomous and cumulative models could be a protective factor. Emotional and cognitive empathy are important domains of parenting. Emotional empathy is critical to help parents share feelings with their infants, and cognitive empathy is important for parents to understand what their infant feels (P. Kim, 2021; Shamay-Tsoory et al., 2009). Heightened activation in cognitive empathy regions of the medial PFC and precuneus are associated with response to infant cues (Abraham et al., 2018; Hipwell et al., 2015). Additionally, research in cannabis use and empathy networks in non-pregnant populations found that cannabis is related to heightened functional connectivity between the anterior cingulate

cortex and the pre-posterior central gyrus that behaviorally related to heightened cognitive empathy (Olalde-Mathieu et al., 2024). In this sample, heightened activation could be acting on cognitive empathy and theory of mind networks through decreasing anxiety. While emotion regulation networks are important for regulating their own emotions to response to their infants, engaging theory of mind networks is also important for parents to understand the mental states of their infant. Heightened response in theory of mind regions such as the superior frontal gyrus, seen in the present study and others could reflect heightened sensitivity to the mental state of others, but this heightened sensitivity could make it more difficult for parents to regulate their emotions resulting in heightened perceptions of how distressing the cries sound.

As many participants reported use for anxiety, nausea, and sleep, potentially cannabis helped support neural activation through decreasing negative symptoms during pregnancy. Cannabis in non-pregnant populations has also been associated with increase in prosocial behaviors, again suggesting that cannabis could be acting on parenting networks through increasing emotional and social information processing (Vigil et al., 2022). A review on the efficacy of cannabis for treating anxiety found that survey and participant report data showed cannabis was helpful in reducing anxiety (Van Ameringen et al., 2020). As cannabis has been found to alleviate anxiety symptoms in non-pregnant populations, use during pregnancy may have contributed to reduced negative pregnancy outcomes, potentially through enhanced brain activation. Research suggests heightened activation in regions associated with cognitive empathy could facilitate parental responsiveness to infant cues. Cannabis use might have supported neural activation by decreasing anxiety, thus promoting emotional and cognitive empathy crucial for effective

parenting during pregnancy. Future research should investigate cognitive empathy in gestational parents that use cannabis to better understand how these neural responses might impact behavior.

This study differs from previous literature that shows dampened responses and non-significant responses to cry sounds in gestational parents who used substances (Landi et al., 2011, 2013; McCurdy et al., 2024; Rutherford et al., 2020; Rutherford & Mayes, 2017). This could be due to the relatively higher rates of use compared to previous studies that had relatively mild substance use reporting during the prenatal period (McCurdy et al., 2024; Rutherford et al., 2020). Possibly, this increased saliency during the early postpartum period changes to a dampened response later as seen in previous parental substance use literature. Though it matches previous exploratory work that shows heightened activation in regions of the PFC to infant cries in gestational parents who used cannabis during the prenatal period (Powers et al., 2023).

4.4. First trimester and beyond first trimester use to neural and behavioral response

In the second model assessing first trimester, beyond first trimester, and no cannabis use there were no differing brain regions, contrary to the hypothesis that continued use would have differing responses. Research on first trimester and ongoing prenatal cannabis use found that ongoing exposure, not early first trimester exposure, was associated with higher pregnancy outcome risk (stillborn birth, preterm birth, decreased birth weight and length, and hypertensive disorders such as preeclampsia) (Metz et al., 2023). This study attempted to assess if continued use compared to early use was associated with differing neural responses but found no differences, potentially due to sample size in the first trimester only use group.

4.5. Associations with mood symptoms and cannabis use

Previous literature has documented differences in mood symptoms related to cannabis use status (Crume et al., 2022; Goodwin et al., 2020; Latuskie et al., 2019; Skelton et al., 2020b; Taylor et al., 2021; Weisbeck et al., 2021; Young-Wolff, Sarovar, et al., 2020). In this sample we did not find any differences in depression or anxiety symptoms at the third trimester or postnatal visit. This sample did report cannabis use for anxiety symptoms, and research supports that active use can mitigate perceived anxiety reporting (Pujol et al., 2014). Additionally, cumulative use was associated with depression and anxiety symptoms, though the regions stayed significant after accounting for mood scores. As previous research has documented cannabis use and higher rates of depression and anxiety, future studies should assess these findings in a sample with higher reported rates of depression and anxiety symptoms.

4.6. Strengths, limitations, and future directions

Few parental neuroimaging studies have tested the effects of cannabis use on parental neural networks and parenting behaviors. As cannabis is the most commonly used substance, understanding potential effects on parenting are imperative. Studying cannabis in isolation of other substances is also necessary, as pregnant populations are using cannabis in isolation of other substances besides tobacco (Crume et al., 2018b). While parenting neural mechanisms of substance use literature is limited, and neural circuity of substance use disorder overlaps across substances, it is important to match population level use and investigate substances within their own class. Additionally, using longitudinal designs to examine the role of prenatal cannabis use on the postpartum

brain in the first few weeks after a child's birth allows for a detailed understanding of the effects of prenatal compared to postpartum use.

A limitation of this study is the lack of immunoassay for all time points. While, immunoassay may not detect cannabis use in less consistent patterns of use, future studies should include immunoassay to understand more biological effects on neural networks. Another limitation is the lack of TLFB data for all participants. Due to the small sample size, cumulative use was assessed. This smaller sample size with quantity of use is a limitation. Future studies should investigate detailed TLFB data and the effects of quantity and timing on neural networks of parenting and parenting behavior. Participants could also self-report or test positive for cannabis in the postpartum period, including at the MRI visit. While concurrent use in parenting substance use literature is common, future studies should look at the effects of neural responses to infant stimuli and active THC intoxication. Heavy tobacco use was exclusionary for this study, but some tobacco use was accepted. While both groups in all models had participants who reported tobacco use, future studies should look at cannabis use without tobacco co use. Additionally, this study cannot rule out the effects of cannabis prior to pregnancy. Future research should investigate prior to pregnancy use and its effects on the postpartum outcomes to understand the effects on timing of use. Previous research has also documented differences in relationship status among prenatal cannabis use, while this study did not show group differences, future research should look at the effects of social support during pregnancy during this time (Crume et al., 2018a, 2022). In addition, parent-child interactions were conducted on average under one month postpartum. While literature supports coding of interactions at this time, future research should look at additional

timepoints such as 6 months and 1 year to include infant scales which are important for understanding parenting behavior (Biringen & Easterbrooks, 2012; Clark et al., 2021; Frigerio et al., 2019). Finally, this study cannot rule out additional factors that are associated with cannabis use, such as previous experience of childhood trauma, prior non cannabis substance use disorder, and neglect. Neural responses in the first three months of the postpartum period has shown to be influenced by stressors during a range of timing in the pregnancy period (Hoekzema et al., 2017; Martínez-García et al., 2021; Numan, 2020; Rutherford et al., 2016). Higher activations to own children in regions of parental motivation, such as the orbitofrontal cortex, ventral pallidum, periaqueductal gray, anterior insular cortex, and dorsal raphe nucleus was related to less self-reported parenting stress (Noriuchi et al., 2019). Severe stress, such as childhood neglect and abuse of the gestational parent, has been associated with a blunted neural response in emotional and social processing regions of the orbitofrontal gyrus, middle temporal gyrus, superior frontal gyrus, and fusiform gyrus to infant cries (P. Kim et al., 2010, 2020a). Whereas environmental stress, such as living conditions and socioeconomic status, have been associated with increased response to infant cries in the hippocampus, striatum, fusiform gyrus, and posterior insula which could be associated with increased salience in regions regulating stress response and emotion regulation (P. Kim et al., 2015, 2020a). Future research should disentangle these effects comparing cannabis use in populations with and without childhood trauma, prior substance use disorder, or childhood neglect.

4.7. Conclusion

In conclusion, this study contributes to the limited understanding of the effects of prenatal cannabis use on parental neural networks and parenting behaviors. Our findings revealed increased activation in reward, salience, affective, and social information processing regions in response to infant cry sounds among gestational prenatal cannabis use. This heightened neural response contrasts with previous literature showing dampened responses to infant cues in gestational parents with substance use. The study also identified exploratory differences in parenting behaviors, with the cumulative cannabis use group exhibiting lower non-hostility scores compared to controls. These results highlight the complex interplay between prenatal cannabis use, neural responses to infant cry sounds, and parenting behaviors. Moving forward, future research should further investigate the impact of chronic cannabis use on parenting neural networks, considering variations in timing, quantity, and patterns of cannabis use. Additionally, longitudinal studies with larger sample sizes and more comprehensive assessments of substance use, mood symptoms, and parenting behaviors are needed to understand the long-term effects of prenatal cannabis exposure on parental functioning and child development. These findings provide insight into the potential the role of empathy and salience to infant cues during the early postpartum period and provide potential therapeutic targets for intervention, such as targeting emotion regulation networks and stress reduction. While gestational parents who used cannabis did not report higher levels of subjective negative affect or distress, cannabis use may have implications on neural distress responses to infant cries and subsequent parenting behavior. In line with previous literature, cannabis use in adults seems to have a widespread effect in reducing subjective symptoms of negative affect and distress, but continued use may exacerbate depression

and anxiety symptoms over time, particularly during pregnancy (Cuttler et al., 2018; Mammen et al., 2018; National Academies of Sciences, 2017; Wilcockson & Sanal, 2016). Educating gestational parents about the risk of cannabis use during pregnancy while also increasing equitable access to safe alternatives is imperative to provide equitable care to pregnant populations.

CHAPTER FIVE: STUDY TWO INTRODUCTION

Cannabis legalization in the United States has expanded and with that there has been an increase in use in all adult populations, including pregnant individuals (Arterberry et al., 2019; Gnofam et al., 2020; Odom et al., 2020; Skelton et al., 2020a, 2020b; Smart & Pacula, 2019; Volkow, Han, et al., 2019; Young-Wolff et al., 2021). As cannabis use prevalence has doubled to 19.5% in adult populations, the National Survey on Drug Use and Health reported a range of 5.3%-7% prevalence of cannabis use in pregnant populations over the last 30 days (Alshaarawy et al., 2021; Odom et al., 2020; Volkow, Han, et al., 2019). This data has shown that there are increases in cannabis use among pregnant individuals, yet there is limited data on the effects in this population.

Literature on the perceptions of cannabis use during pregnancy has shown that many pregnant individuals are not comfortable disclosing to their provider, using cannabis to self-medicate for depression and anxiety disorders, and are viewing cannabis as a safer alternative to prescription medications (Bayrampour & Asim, 2021; Chang et al., 2019; Corsi et al., 2019; Jaques et al., 2014; Jarlenski et al., 2016; Ko et al., 2015; Metz et al., 2022; Skelton et al., 2020b; Taylor et al., 2021; Weisbeck et al., 2021; Young-Wolff et al., 2017; Young-Wolff, Gali, et al., 2020; Young-Wolff, Sarovar, et al., 2020). While providers are cautioning against use during this time-period, there are still rising rates of cannabis use in pregnant populations. With that, providers have limited knowledge on how cannabis use during pregnancy effects the gestational parent brain. To

date there is limited evidence on the effect of cannabis on neural responses to infant faces in the postpartum period, and limited evidence on how that may impact parenting behaviors.

1.1. Gestational parent brain adaptation in the postpartum period to infant picture

Throughout pregnancy, increases in hormones such as oxytocin and dopamine are thought to be related to functional and anatomical changes that occur during pregnancy and the early postpartum period, preparing gestational parents for their newborn (Bornstein et al., 2017; Brunton & Russell, 2010; Hoekzema et al., 2017; Numan, 2017, 2020; Russell et al., 2001). Functional changes in neural networks have been shown to be related to the strength of parent-child interactions, helping to promote child development. Functional Magnetic Resonance Imaging (fMRI) studies in the postpartum period have assessed neural responses to infant cues, particularly affective and relevance studied through infant faces and cries. Effects of these neural network responses have been predictive of parent-child interactions identifying five neural networks that are responsible for parenting behaviors: reward networks, parental motivation networks, social information processing networks, emotion regulation networks, and theory of mind (TOM) networks. Sensitivity in these networks to infant cues, including both infant faces and cries, in the postpartum period are related to more positive parenting behaviors and subsequent social-emotional child development.

When comparing nulliparous individuals and new birthing parents, infant faces elicits a larger blood oxygenated level dependent (BOLD) response in social information processing regions of the bilateral inferior and middle frontal gyri, right middle temporal gyrus, and biliteral middle and inferior occipital gyri (K. Zhang et al., 2020). In studies

assessing differences in neural responses during the postpartum period between own infant face stimuli and other face infant stimuli, birthing parents show increased activation in both reward and parental motivation network regions of the medial prefrontal cortex (PFC), dorsolateral PFC, anterior cingulate cortex, insula cortex, amygdala, and approach networks of primary motor areas when viewing their own infant compared to an unknown infant face (Barrett et al., 2012; Caria et al., 2012; Rigo, Kim, et al., 2019; Strathearn et al., 2008). Increases in amygdala activation to infant faces is associated with sensitive parenting, but heightened activation in this region is also associated with intrusive parenting and higher stress (Atzil et al., 2011; P. Kim et al., 2017). Other literature has attempted to assess differences of emotional valence of faces, and found variability in responses can be predictive of parenting behavior (Rutherford et al., 2020; Squire & Stein, 2003). Research studies have shown that own smiling, but not sad, compared to other smiling infant faces elicits social information and reward/motivation regions of cerebrum, midbrain, and orbitofrontal cortex tracks, including the substantia nigra and amygdala (Nitschke et al., 2004; Rigo, Kim, et al., 2019; Strathearn et al., 2008; Strathearn & Kim, 2013). Taken together, these findings suggest infant faces activate regions important for caregiving behaviors within parenting neural networks.

While infant cries elicit neural networks important for specific distress response to caregiving behavior to responds to cues, infant faces elicit activation in reward networks that are important for positive salience. Infant cries are more specific to infant distress and often require urgency in response, whereas infant faces are a positive salient stimulus and could be more predictive of daily gestational parent interactions with their

child. Research indicates that infant faces can evoke positive reactions, even sad expressions as they are often perceived as cute or endearing (Rigo, Kim, et al., 2019). Additionally, infant faces are particularly salient, with their own baby face being an especially salient stimulus. This suggests that infant faces carry inherent positive valence and possess unique characteristics that evoke strong emotional responses from caregivers. Particularly, investigating differences in brain responses to faces of own vs. other infants could help unpack underlying responses in gestational parents who use substances.

1.2. Gestational parent substance use and brain adaptation to infant faces

Literature has also investigated the effects of neural responses to infant faces in gestational parents who used substances. A few studies reported dampened neural responses in reward and motivation networks to own infant happy faces and distressed faces in birthing parents who used substances during pregnancy in regions of the ventral medial and lateral PFC, hypothalamus, and ventral striatum compared to birthing parents who were not exposed (S. Kim et al., 2017; Landi et al., 2011, 2013; Rutherford et al., 2020). When investigating the differences between own infant faces and other infant faces without emotional salience in birthing parents, substances use in the postpartum period increased activation to own infant faces in the superior medial frontal, inferior parietal, and middle temporal regions compared to those who were not exposed (Rutherford et al., 2020). This combination of dampened activation to emotional valence of faces, and heightened activation to own infant faces, could potentially demonstrate a dysregulation of reward and stress circuits leading to heightened anxiety when viewing own infant images. Potentially, this dysregulated response can be interpreted as stress inducing. Additional research showed that when responding to feelings about infant

faces, gestational parents who used substances had lower affective empathy brain responses related to lower inferior frontal gyrus, amygdala, and insula BOLD response to unknown infant stimuli (McCurdy et al., 2024). Within gestational parents who use substances, we would expect to see heightened activation to their own infant faces.

Within cannabis use, this potential heightened activation to own infant faces could be related to postpartum caregiving behaviors. While cannabis has been shown to response on similar reward networks as other substances of use, research has supported less robust effects that other illicit substances (Filbey et al., 2009; Gillespie et al., 2009; Moreno-Rius, 2019; R. Zhang & Volkow, 2019). The body of literature examining substance use and its impact on parenting is limited, with cannabis research being notably sparse. Research has shown that pregnancy outcomes related to cannabis use during pregnancy mirror tobacco with higher risk of preterm birth, lower birth weight and length, and increased risk of hypertensive disorders during pregnancy (Crume et al., 2018b; Gray et al., 2010; Metz et al., 2023). Cannabis use disorder (CUD) and higher postpartum use has been associated with less structuring and support, and less sensitivity in parent child interactions (Eiden et al., 2018; Hill et al., 2018). Within prenatal cannabis use and infant faces, an exploratory study looked at prenatal cannabis use in the second trimester and emotional valence of faces, finding that cannabis use in the prenatal period was associated with dampened response in the dorsal lateral PFC to infant sad faces, mirroring other substance use literature (Powers et al., 2023). To date there is no literature looking at prenatal cannabis use and neural saliency of non-emotional infant faces in the postpartum period.

1.3. Study Rationale

In the present study, we compare neural salience of neutral infant faces among individuals who used cannabis during pregnancy and those who did not, hypothesizing that reward and motivation networks might show differences. This study aimed to address the following specific questions: 1) are there differences in neural response to infant faces related to prenatal cannabis use?, and 2) are these differences related to parenting behaviors in the postpartum period? Based on previous studies, we hypothesized that cannabis use during the prenatal period will respond on similar reward neural circuitry as other substances of abuse in response to relevance of infant faces showing increased activation in the superior frontal gyrus, inferior frontal gyrus, inferior parietal, and middle temporal region to own versus other infant faces. We also hypothesized that neural response to cannabis exposure during the prenatal period will be correlated with decreased birthing-parent child interactions as measured by the sensitivity and structuring constructs of the Emotional Availability (EA) scale.

The first model assessed matches previous parenting substance use literature looking at cannabis dichotomously (any prenatal use compared to no use) hypothesizing that the cannabis group would have increased response to their own infant faces (S. Kim et al., 2017, 2017; Landi et al., 2011, 2013; McCurdy et al., 2024; Rutherford et al., 2020). As cannabis use varies, a second model was tested comparing first trimester cannabis use to ongoing cannabis use beyond the first trimester in line with new research showing that ongoing use was associated with higher risk of negative postpartum outcomes, hypothesizing that cannabis use in the beyond first trimester group would be associated with heighted response to own infant faces (Metz et al., 2023). A final model was conducted to look at cumulative cannabis use continuously, as some literature

suggests cumulative amount might be more predictive of neurocognitive responses, hypothesizing that greater cumulative use would mirror other substances of abuse and show heightened response to own infant faces (Hirjak et al., 2022; Scott et al., 2018). When significant brain regions were identified, they were related to parenting outcomes measured on the EA scale hypothesizing these neural responses would be associated with lower scores on sensitivity and structuring parenting behaviors.

CHAPTER SIX: STUDY TWO MATERIALS AND METHODS

2.1. Participants

The inclusion criteria for participants were: being between the ages of 18 and 45, having a singleton pregnancy, and proficiency in English. Exclusion criteria included current use of psychotropic medications; a lifetime diagnosis of psychiatric or neurological illnesses other than depression, anxiety, or post-traumatic stress disorder; a positive immunoassay for non-cannabis illicit substances; or self-reported heavy nicotine or alcohol use. This study specifically examines data collected during pregnancy and one month postpartum, and demographic information is detailed in Tables 9, 11, and 13.

A sample of 125 individuals were scanned for the study, 11 of which were excluded. Participants in this sample were excluded for the following reasons: (2) technical error during data collection, (1) did not complete the task due to time constraints (1) susceptibility distortion correction failed, (1) tested positive for morphine prenatally, and (1) tested positive for methamphetamines during their second postnatal visit. This study additionally excluded the following participants from the analysis because they did not meet the criteria for either the control or prenatal cannabis use group - (3) only used cannabis in the preconception period, (1) only used cannabis in the preconception and postnatal period, and (1) only used cannabis in the postnatal period. As a result, 73 individuals that had not used cannabis during pregnancy were included in

the control group. The cannabis group included 41 individuals with prenatal cannabis use during pregnancy.

2.2.1. Cannabis Exposure

Previous studies have indicated that while cannabis use varies, there is good justification that pregnant individuals will self-report starting in the first trimester (Alshaarawy et al., 2021; Odom et al., 2020; Volkow, Han, et al., 2019). In the initial model prenatal cannabis use was explored dichotomously for any prenatal use, in line with previous substance use neural parenting papers (S. Kim et al., 2017; Landi et al., 2011, 2013; Rutherford et al., 2020; Rutherford & Mayes, 2017). Given the variability in detection sensitivity among immunoassay methods and the dynamic nature of cannabis usage during pregnancy, exposure to cannabis during gestation was operationalized based on immunoassay results, Timeline Followback (TLFB) data, and/or self-reported usage at any point during pregnancy (Metz & Borgelt, 2018; Robinson et al., 2014; Sobell et al., 1979). This operationalization of cannabis was used for Model 1 and Model 2.

In Model 2, cannabis was divided between first trimester use only and beyond the first trimester use. In line with previous cannabis prenatal research, first trimester use was defined as the first trimester only, while beyond the first trimester use was any use beyond the first trimester during the prenatal period (Metz et al., 2023).

In Model 3, cannabis was operationalized as a continuous variable. This analysis calculated a sum score of self-reported prenatal use from the TLFB. This is a subsample of the main data set as only a portion of participants had TLFB data for all three prenatal timepoints.

In all three models, the control group stayed the same. The control group had no self-report, no positive immunoassay, and no self-report on the TLFB at any timepoint from preconception to the first postnatal visit or imaging visit, whichever was later.

2.2.2. Immunoassay for Cannabis

At the initial consent visit, an immunoassay was completed to evaluate current substance and tobacco status using the Nic-Alert and CLIA-waived 5-panel drug immunoassays. All other substances besides cannabis and tobacco were exclusionary at consent. Positive immunoassays for other substances besides cannabis and tobacco at later prenatal visits were excluded from this analysis. Due to a change in protocol and COVID-19, immunoassays are missing from some subjects. See Tables 10, 12, and 14 for this data.

2.2.3. Timeline Followback (TLFB)

Detailed interviews assessing cannabis use were conducted by trained research staff if participants self-reported cannabis use at any time during their visit, or tested positive for cannabis by immunoassay (Metz & Borgelt, 2018; Robinson et al., 2014; Sobell et al., 1979). See Tables 10, 12, and 14 for this data. This measure was also used to create a sum score for the cumulative model. Self-reported cannabis by participants allowed them to fill out information on the TLFB. They were asked about the number of times that cannabis had been used since the prior visit, particularly how many times they used it through numbers of ingestible items were taken, or how many times in a day a cannabis product was inhaled. In the final cumulative model, a total quantity of this data for each day was added up and then a summation variable from conception to child date of birth was calculated. The total sum of this variable was used for the cumulative model

as a total quantity for the prenatal period.

2.2.4. Self-Report

All participants were asked about cannabis use at each visit. Participants were asked to self-report if they had used cannabis at any timepoint between the last visit and the current visit. At their consent visit, participants were asked about any cannabis use since conception. This data was recorded by researchers with a dichotomous yes/no.

2.3. Procedures

This study had approval by the University of Denver Institutional Review Board. Recruitment for this study was done in collaboration with the Department of Obstetrics and Gynecology at Denver Health Medical Center, University of Colorado Anschutz Medical Campus, and through paper advertisements. The main study was exploring income during pregnancy and the postpartum period in gestational parents and their infants. The sample used for this paper was a subset within this larger study investigating cannabis use during pregnancy. This analysis uses data from the gestational parent sample of this study which includes three prenatal visits, one postnatal visit, and one neuroimaging visit.

For this analysis, data related to cannabis use, demographic questions, and mood surveys (EPDS, CESD, and STAI) for each timepoint was used. This study had a change in protocol that included additional immunoassays beyond consent, and thus earlier participants are missing later prenatal and postnatal immunoassays. As participation was voluntary, some TLFB data is missing. It should be noted that this is a limitation of data collection. Finally, some participants were recruited in their third trimester, and thus do

not have immunoassay or self-report data for earlier in their visits. Please see a detailed breakdown of the data in Tables 10, 12, and 14.

2.4. Measures

2.4.1. Demographics

Participants reported their total years of education, household income, race and ethnicity at their consent visit. Child date of birth was collected at the neuroimaging or postnatal visit, and when applicable cross checked with medical records. Parents self-reported age was collected at through medical records or at the time of the scan when medical records were not accessed. The average age of the main sample was 29.16 (SD = 5.59), and the average total gestation weeks for the sample was 39.07 (SD = 1.530).

2.4.2. Gestational parent depression and anxiety

Cannabis use previously has shown associations with higher mood symptoms, and thus this study reported measures of depression and anxiety at all visits (Crume et al., 2022; Goodwin et al., 2020; Latuskie et al., 2019; Skelton et al., 2020b; Taylor et al., 2021; Weisbeck et al., 2021; Young-Wolff, Sarovar, et al., 2020). *Edinburg Postnatal Depression Scale (EPDS):* Postpartum depression symptoms where asked through the EPDS about the past 7 days on a 4-point scale from 0 = yes, all the time to 3 = no, not at all (Cox et al., 1987). *Center for Epidemiological Studies-Depression (CESD):* An additional 20-item depression scale was conducted asking participants about their feelings over the past week (Lewinsohn et al., 1997; Pinquart & Sörensen, 2003; Radloff, Lenore, 1977; Young-Wolff, Sarovar, et al., 2020; Zuckerman et al., 1989). *State-Trait Anxiety Inventory (STAI)-state:* Anxiety symptoms were measured on this 20-item scale to assess anxiety symptoms concurrently (Newham et al., 2012; Spielberger, 1989;

Spielberger et al., 1983). All measures have been validated in substance use populations and pregnancy.

2.4.3. Birthing Parent-Child Interaction

During the postnatal visit research staff recorded a 10-minute free play interaction. Participants were asked to interact with their infant for 10 minutes as they normally would. Trained researchers coded the interaction using the Emotional Availability scale. This scale includes four parent domains: sensitivity (parental warmth and responsiveness), structuring (success of structure and guidance in the interaction), non-intrusiveness (lack of intrusive behaviors towards infant), and non-hostility (lack of hostility and negativity both overt and covert). Due to the age of infants at the time of this visit, the 2 child domains were not assessed in this study as infants had minimal interaction or were sleeping. This scale has been validated in the early prenatal period to be predictive of child development outcomes in substance use populations (Biringen & Easterbrooks, 2012; Clark et al., 2021; Frigerio et al., 2019; Goldman Fraser et al., 2010; Porreca et al., 2018). In the main group analysis (N = 100), the mean sensitivity score was 5.54 (SD = 1.07), the mean structuring score was 5.50 (SD = 1.23),the mean non-intrusiveness score was 5.57 (SD = 1.00), and the mean non-hostility score was 5.43 (SD = 1.26) (non-hostility N = 95, 5 were not to do parents not speaking English during the interaction). Two independent trained research staff coders scored the videos. Inter-rater reliability was calculated using Intraclass Correlation Coefficients on a randomly selected subsample of 20% of the cases. These values ranged from 0.73 to 0.87 (sensitivity scale = 0.83; structuring scale = 0.73; non-intrusiveness scale = 0.75; non-hostility scale = 0.78). All disagreements were resolved by conference.

2.5. fMRI Paradigm

The infant faces paradigm has been evaluated to show differences in postpartum samples in neuroimaging research, as well as in substance use parenting literature (Brosch et al., 2007; Endendijk et al., 2020; Landi et al., 2011, 2013; Numan, 2020; Rutherford et al., 2020; Swain, 2008). This task has not been conducted in cannabis parent populations. Participant infant pictures were collected at the home with infants making a neutral expression in a white onesie to match control images with a total of 10 images used. Control images were of neutral babies taken from the Yale Baby Face Dataset with an average age of 3 months to match timing of the MRI scan. Emotional expressions in infants due not consistently appear until 6-12 weeks postpartum, and thus when studying salience of infant cues postpartum it is recommended to use relevance of stimuli versus emotional valence as most infants cannot yet show valence (Numan, 2020; Swain, 2008; Wörmann et al., 2012). Faces were matched on White or Black infant stimuli based on participant reported infant race, and randomly presented to participants. Participants were shown each face for 2 seconds each with a jittered 0.5 - 6 second cross hair rest (average 2 seconds) in between each presentation. There were 30 presentations of own infant faces, and 30 presentations of other "control" infant faces for a total of 60 trials lasting 4 minutes. Participants were asked to pay attention to the images and let themselves experience the thoughts and feelings they are having naturally. After the neuroimaging scan, participants completed a post scan task where they were asked to rate on a scale of 1 to 9 how pleasant or unpleasant the picture made them feel, and how they thought the baby was feeling for the own and other baby images they saw in the scanner

(1 = being most negative, 9 = being most positive). In the main sample 28 participants are missing data from the post scan task.

2.6. fMRI data acquisition and processing

2.6.1. fMRI Acquisition

Images were collected on a 3.0T Siemens Prisma MRI scanner using a 32-channel parallel imaging coil at the Intermountain Neuroimaging Consortium, University of Colorado, Boulder. The functional images were collected with a T2*-weighted gradient-echo, echo-planar imaging (repetition time [TR] = 460 ms, echo time [TE] = 27.20 ms, flip angle = 44°, 56 slices parallel to the orbitofrontal cortex, thickness = 3 mm, zero gap, 82x82 in-plane resolution, in-plane FOV = 24.8cm, multi-band acceleration factor = 8). High-resolution T1-weighted anatomical scan was used to localize functional activity for each participant. Preprocessing steps included MRIQC (22.06) for a visual inspection of data and AQI within MRIQC from Anatomical Functional Analysis software extraction. All participants were included in this initial step.

2.6.2. fMRI Processing

All neuroimaging data underwent processing using the standardized fMRIPrep (version 22.0.02) pipeline, which encompassed several key steps including: tissue segmentation, normalization to the MNI space, surface reconstruction, susceptibility distortion correction, and alignment of functional to anatomical data. Detailed information on the pipeline can be found in the supplementary materials in accordance with fMRIPrep guidelines. No subjects had more than 20% of its TRs removed. Images were spatially smoothed and scaled. To address magnetic equilibrium, the first ten images

of the task were discarded. Statistical analysis of functional data was performed using Anatomical Functional Analysis software (AFNI, version 24.0.06).

At the individual participant level, a general linear model was employed to estimate the configuration of the hemodynamic response to each condition: own infant face and control infant face matched on race. The design matrix included two conditions integrating a boxcar function convolved with the hemodynamic response function, and with third-order polynomials and six motion parameters. The resulting beta images are the estimated activation levels that correspond to the conditions for each subject to be used in further group-level analysis.

2.7. Analysis

2.7.1. Covariate selection

Covariates for the whole brain analysis and post-hoc analysis were conducted to assess differences between groups. The variables were analyzed in SPSS to determine if there were significant differences ($p < 0.05$) between groups. These variables included preterm birth, total gestational weeks of pregnancy, gestational parent age at the time of the scan, total years of education, total yearly income, previous live birth, postpartum days at the time of scan, gestational parent depression and anxiety symptoms at the third trimester and first postnatal visit, and nicotine immunoassay status. For the whole brain analysis model, the following variables were selected: gestational parent age at the time of the scan, postpartum days at the time of the scan, and parity status (pregnancy beyond 20 weeks). Parity and postpartum days were added as covariates in the model based on previous literature that highlights neural changes due to number of pregnancy and postpartum days of parenting (Hillerer et al., 2014). Additionally, parent age at time of

scan was selected as a covariate due to group differences, and the effects of age and neural response (Grady et al., 2006; Luo et al., 2020). If significant clusters were extracted from the whole brain analysis, additional group differences were assessed in a post-hoc analysis.

2.7.2. fMRI Analysis

Using AFNI's 3dLME (linear mixed-effects modeling), a whole brain analysis was examined. Beta values in the 3dLME are used as representation of hemodynamic response. The most comprehensive repeated measures model assessed group differences (cannabis use vs. control) with identity (own vs. other) in the first model. In the second model testing early use and continued prenatal use, group differences (early cannabis use, continued cannabis, and control) with identity (own vs. other) was examined. Finally, in the third model, cumulative prenatal cannabis use and identity (own vs. other) was examined. Using AFNI's 3dClustSim, findings underwent correction for multiple comparisons on the whole brain level with a cluster threshold of $k \geq 15.4$ at $p < 0.001$. This was determined using AFNI's spatial autocorrelation function (ACF) with 3dClustSim ensuring a whole brain corrected false positive probability of $p < 0.05$. If significant interactions survived this cluster threshold, they were extracted from AFNI to decompose in SPSS version 28.0 (*IBM SPSS Statistics for Windows*, 2021) with post-hoc analysis. Any covariates from the initial covariate analysis that were not added to the 3dLME model, were tested in SPSS through partial correlations and ANCOVAs. The main effect of the interaction was also decomposed in SPSS with the data extracted from significant interaction clusters in AFNI using independent t-tests and correlations.

2.7.3. Exploratory associations with parenting behavior

Extracted significant clusters from the interaction results of the whole-brain analysis were further associated with parenting behavior at the first postpartum visit when applicable. In SPSS correlations with the clusters and EA parent scale of sensitivity, structuring, non-intrusiveness, and non-hostility were done to relate brain and parenting behavior. Additionally, group differences on EA scales was assessed through independent t-tests for models 1 and 2. For model 3, cumulative prenatal TLFB was correlated with EA parent scales.

2.7.4. Exploratory post scan responses

Group differences were explored using independent sample t-tests. When clusters were significant from the whole brain analysis, neural activation was correlated with average post scan responses.

CHAPTER SEVEN: STUDY TWO RESULTS

3.1. Model 1: Dichotomous prenatal cannabis

3.1.1. Participant characteristics

Expanded participant demographics are listed in Table 9 and cannabis use descriptives are listed in Table 10. Scans were conducted on an average of 38.00 (SD = 21.76) days postpartum. Between group differences in the main sample showed the prenatal cannabis use group were younger ($t(112) = 2.556$, $p = 0.012$, $d = 0.499$), had lower total years of education ($t(107.609) = 3.782$, $p < 0.001$, $d = 0.666$), had lower reported yearly income at consent ($t(87.559) = 4.4121$, $p < 0.001$, $d = 0.684$), a higher likelihood of being Black/African American ($X^2(5, N = 113) = 14.343$, $p = 0.014$, $V = 0.356$), and higher likelihood of testing positive for nicotine at their consent visit (X^2 (1, $N = 111) = 5.860$, $p = 0.015$, $V = 0.230$). In the main sample, participants did not differ on mood symptoms in the third trimester and the postpartum period, contrary to previous literature (Young-Wolff, Sarovar, et al., 2020). In the second trimester, mood scores differed on the CESD with the cannabis group having higher CESD scores, $t(94) = -2.159$, $p = 0.033$, $d = -0.458$. Mood descriptives are listed in Supplementary Table 2. Infants differed at average age at the first postnatal visit when parent-child interactions were conducted, $t(111) = -2.465$, $p = 0.015$, $d = -0.485$. During the consent visit, participants were asked to report reasons for why they used cannabis. In this sample (N =

25), 44% of participants said that one of the reasons for use was due to anxiety, 35% said one of the reasons for use was to help with sleep, and 32% reported to help with nausea.

3.1.2. fMRI analysis of the differences between groups and brain activation

In this first model with the whole sample, we investigated the two-way interaction of group status (control vs. any prenatal cannabis use) x identity (own vs. other) controlling for gestational parent age at scan, postpartum days at scan, and parity. There were no significant clusters in this model.

3.1.3. Exploratory associations between brain activation and parenting behaviors

Group differences were assessed through independent sample t-tests. EA parent scales did not significantly differ between groups. Correlations between EA gestational parent scales and neural activation were not examined as there were not significant clusters found in the interactions.

3.1.4. Exploratory associations with post scan responses

Group differences to think and feel ratings were assessed with how pleasant or unpleasant the other and own baby images made them feel, and how they thought the baby was feeling for own and other through independent means t-test. Groups did not significantly differ in responses to any conditions. Associations with neural activation were not conducted due to no significant clusters.

Table 9 (Infant Picture): Sample demographics for groups in Model 1

	Control (n= 73)		**Cannabis (n= 41)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*
Preterm Birth (less than 37 weeks)	3	4.1%	2	4.9%

Total Gestational Weeks	39.10+/-1.60	32.57—41.71	39.02+/-1.41	35.00—41.14
Parent Age at MRI*	30.14+/-5.53	19--42	27.41+/-5.32	19--38
Education at consent**	15.51+/-2.82	11—20	13.46+/-1.93	10—17
Yearly Income at consent**	87,583.14+/-80,675.04 *(8 missing)*	0—504,000.00	42,115.26+/-28,661.44 *(3 missing)*	38—130,000
Single Relationship Status at consent	8 *(1 missing)*	11.0%	9 *(1 missing)*	22.0%
Parity	49	67.1%	27	65.9%
Infant Age at MRI (weeks)	5.42+/-3.15	1.29—14.29	5.44+/-3.08	1.14—14.43
Infant Age at 1st postnatal visit (weeks)*	3.05+/-1.74	.86—8.71	3.96+/-2.11 *(1 missing postnatal visit)*	.71—8.57
Hispanic	20 *(1 missing)*	27.4%	14	34.1%
Race*	*(1 missing)*	1.4%		
American Indian/Alaska Native	2	2.7%	1	2.4%
Asian	2	2.7%	0	
Black or African American	7	9.6%	15	36.6%
Native Hawaiian or Other Pacific Islander	2	2.7%	0	
White/Caucasian	48	65.8%	18	43.9%
Other	11	15.1%	7	17.1%
CESD at third trimester visit	13.79+/-8.13 *(1 missing)*	4.00—39.00	15.22+/-7.74 *(2 missing)*	3.00—35.00
EPDS at third trimester visit	6.14+/-4.85 *(1 missing)*	0—18.00	6.58+/-5.03 *(1 missing)*	0—16.00
STAI at third trimester visit	31.38+/-11.21 *(1 missing)*	20.00—68.00	33.18+/-10.30 *(1 missing)*	20.00—62.00
CESD at postnatal visit	12.21+/-8.54	1.00—35.00	15.21+/-9.77 *(2 missing)*	1.00—44.00
EPDS at postnatal visit	5.04+/-4.59	0—18.00	6.05+/-4.95 *(2 missing)*	0—18.00

STAI at postnatal visit	29.67+/-10.16	20.00—61.00	32.35+/-10.37 *(2 missing)*	20.00—57.00
NicAlert Positive at Consent*	7 *(2 missing)*	9.6%	11 *(1 missing)*	26.8%
EA Parent Scale				
Sensitivity	5.61+/-1.00 *(6 missing)*	3.50—7.00	5.41+/-1.20 *(8 missing)*	2.5—7.00
Structuring	5.62+/-1.100 *(6 missing)*	3.00—7.00	5.24+/-1.43 *(8 missing)*	3.00—7.00
Non-intrusiveness	5.59+/-.97 *(6 missing)*	3.00—7.00	5.50+/-1.08*(8 missing)*	3.50—7.00
Non-hostility	5.51+/-1.24 *(9 missing)*	3.00—7.00	5.26+/-1.28 *(10 missing)*	3.00—7.00

Note: CESD is the Center for Epidemiological Studies-Depression; EPDS is the Edinburg Postnatal Depression Scale; STAI is the State-Trait Anxiety Inventory, State; EA is the Emotional Availability Scale. Significant difference between groups based on t-test or chi-squared, **p<.05; **p<.001*

Table 10: (Infant Picture) Sample distribution of cannabis use across prenatal and postnatal visits for Model 1

Characteristic	Control (n= 73)		Cannabis (n= 41)	
	μ / n	*range / %*	*μ / n*	*range / %*
First Trimester Self-Report [a] [d]	0	-	33	89.2%
First Trimester TLFB [c]	0	-	103.38+/-152.55 *(6 missing, 3 no reported use)*	0--707
First Trimester Positive Immunoassay for Cannabis [a]	0 *(1 missing)*	-	17 *(1 missing)*	47.2%
Second Trimester Self-Report [a]	0	-	19 *(1 missing)*	52.8%
Second Trimester TLFB [c]	0	-	125.09+/-166.06 *(5 missing, 14 no reported use)*	0--710
Second Trimester Positive Immunoassay for Cannabis [a]	0 *(36 missing)*	-	13 *(11 missing)*	36.1%
Third Trimester Self-Report [b]	0	-	20 *(1 missing)*	48.8%
Third Trimester TLFB [c]	0	-	86.84+/-133.75 *(7 missing, 15 no reported use)*	1--462
Third Trimester Positive Immunoassay for Cannabis [b]	0 *(32 missing)*	-	13 *(10 missing)*	31.7%

1st Postnatal Visit Self-Report [b]	0	-	17 *(1 missing)*	41.5%
1st Postnatal Visit TLFB [c]	0	-	37.55+/-33.66 *(9 missing, 21 no reported use)*	1--90
1st Postnatal Visit Positive Immunoassay for Cannabis [b]	0 *(29 missing)*	-	12 *(14 missing)*	29.3%
1st MRI Visit Positive Immunoassay for Cannabis [b]	0 *(20 missing)*	-	18 *(7 missing)*	43.9%

Note: [a]:11 control subjects were recruited at the third trimester and 5 cannabis subjects were recruited at the third trimester. For the first and second trimester N=62 for the control group and N= 36 for the cannabis group. The table totals for first trimester and second trimester data show the results based on the totals at each visit with associated missing data. Immunoassay was added to all visits later on and thus there is a larger portion of missing data after the first trimester visit.
[b]:For the third trimester data, the additional 11 control subjects (N=73) and 4 cannabis (N=41) subjects where recruited and thus the totals are reflected with associated missing data for the third trimester and postnatal data.
[c]:For the TLFB data, third trimester starts were asked about retrospective use since conception. Total for the control is N=73, and total for cannabis is N=41
[d]:One third trimester start self-reported cannabis use up to 12 weeks in the first postpartum period, thus their data point is listed in first trimester self-report for first trimester use only (N=37), but they are missing TLFB data.
TLFB= Timeline follow back data. TLFB was only filed out when participants tested positive or self-reported cannabis use.

3.2. Model 2: First trimester use compared to beyond the first trimester prenatal cannabis use

3.2.1. Participant characteristics

The participant demographics are listed in Table 11 and cannabis use descriptives between control, first trimester and ongoing use are listed in Table 12. Significant group differences were assessed with chi-square and ANOVA. In this model, groups differed on parent age at the MRI ($F(2,111) = 3.579$, $p = 0.031$, $\eta^2 = 0.061$), education at consent ($F(2,111) = 7.301$, $p = 0.001$, $\eta^2 = 0.116$), yearly income at consent ($F(2, 100) = 6.479$, $p = 0.002$, $\eta^2 = 0.115$), infant age at the first postnatal visit ($F(2,110) = 3.337$, $p = 0.039$, $\eta^2 = 0.057$), race ($X^2(10, N = 113) = 23.959$, $p = 0.008$, $V = 0.326$) and nicotine status ($X^2(2, N = 111) = 9.645$, $p = 0.008$, $V = 0.230$). Groups did not differ on mood symptoms at the third trimester or postnatal visit.

3.2.2. fMRI analysis of the differences between groups and brain activation

In the next model, the whole sample was investigated through a two-way interaction of

(control vs. first trimester use vs. beyond first trimester use) x identity (own vs. other) controlling for gestational parent age at scan, postpartum days at scan, and parity. There were no significant clusters in this second model.

3.2.3. Exploratory associations between brain activation and parenting behaviors

Group differences were assessed through chi-square. EA parent scales did not significantly differ between the three groups. Correlations between neural activation and EA scales were not examined as there were not significant clusters found in the model interactions.

3.2.4. Exploratory associations with post scan responses

Group differences using a chi-square to think and feel ratings were assessed with how pleasant or unpleasant the other and own baby images made them feel, and how they thought the baby was feeling for own and other. Groups did not significantly differ in responses to any conditions. Associations with neural activation were not conducted due to no significant clusters.

Table 11: (Infant Picture): Sample demographics for groups in Model 2

	Control (n= 73)		**First Trimester Cannabis (n=11)**		**Beyond First Trimester Cannabis (n=30)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*	*μ / n*	*range / %*
Preterm Birth (less than 37 weeks)	3	4.1%	1	9.1%	1	3.3%

Total Gestational Weeks	39.10+/-1.60	32.57—41.71	39.17+/-1.67	35.00—41.14	38.97+/-1.32	36.29—41.14
Parent Age at MRI*	30.14+/-5.53	19--42	28.55+/-5.54	19--36	27.00+/-5.28	19--38
Education at consent*	15.51+/-2.82	11—20	14.55+/-1.97	12--17	13.07+/-1.78	10--16
Yearly Income at consent*	87,583.14+/-80,675.04 *(8 missing)*	0—504,000.00	65,432.00+/-32,648.72 *(1 missing)*	28,000—130,000	33,787.86+/-22,296.70 *(2 missing)*	38.00—820,000
Single Relationship Status at consent	8 *(1 missing)*	11.0%	2 *(1 missing)*	18.2%	7	23.3%
Parity	49	67.1%	6	54.5%	21	70.0%
Infant Age at MRI (weeks)	5.42+/-3.15	1.29—14.29	4.91+/-2.28	1.14—8.71	5.63+/-3.34	1.14—14.43
Infant Age at 1st postnatal visit (weeks)*	3.05+/-1.74	.86—8.71	3.58+/-1.92	1.43—7.71	4.11+/-.20 *(1 missing)*	.71—8.57
Hispanic	20 *(1 missing)*	27.4%	5	45.5%	9	30.0%
Race*	*(1 missing)*	1.4%				
American Indian/Alaska Native	2	2.7%	1	9.1%	1	9.1%
Asian	2	2.7%	0		0	
Black or African American	7	9.6%	1	9.1%	1	9.1%
Native Hawaiian or Other Pacific Islander	2	2.7%	0		0	
White/Caucasian	48	65.8%	6	54.5%	6	54.5%
Other	11	15.1%	3	27.3%	3	27.3%

CESD at third trimester visit	13.79+/-8.13 *(1 missing)*	4.00—39.00	15.73+/-9.84	5.00—35.00	15.02+/-6.95 *(2 missing)*	3.00—31.00
EPDS at third trimester visit	6.14+/-4.85 *(1 missing)*	0—18.00	6.91+/-5.70	0—16.00	6.45+/-4.86 *(1 missing)*	0--16
STAI at third trimester visit	31.38+/-11.21 *(1 missing)*	20.00—68.00	36.09+/-11.85	20.00—55.00	32.08+/-9.64 *(1 missing)*	20.00—62.00
CESD at postnatal visit	12.21+/-8.54	1.00—35.00	19.00+/-11.05	6.00—35.00	13.71+/-8.99 *(2 missing)*	1.00—44.00
EPDS at postnatal visit	5.04+/-4.59	0—18.00	6.73+/-5.02	0—15.00	5.76+/-4.99 *(2 missing)*	0—18.00
STAI at postnatal visit	29.67+/-10.16	20.00—61.00	35.46+/-13.40	20.00—57.00	31.13+/-8.91 *(2 missing)*	20.00—54.00
NicAlert Positive at Consent*	7 *(2 missing)*	9.6%	1	9.1%	10 *(1 missing)*	33.3%
EA Parent Scale						
Sensitivity	5.61+/-1.00 *(6 missing)*	3.50—7.00	5.81+/-1.23 *(2 missing)*	3.00—7.00	5.26+/-1.18 *(6 missing)*	2.50—7.00
Structuring	5.62+/-1.100 *(6 missing)*	3.00—7.00	5.72+/-1.44 *(2 missing)*	3.00—7.00	5.06+/-1.42 *(6 missing)*	3.00—7.00
Non-intrusiveness	5.59+/-.97 *(6 missing)*	3.00—7.00	6.00+/-.97 *(2 missing)*	4.500—7.00	5.31+/-1.08 *(6 missing)*	3.50—7.00
Non-hostility	5.51+/-1.24 *(9 missing)*	3.00—7.00	5.77+/-1.05 *(3 missing)*	4.00—7.00	5.08+/-1.32 *(7 missing)*	3.00—7.0

Note: CESD is the Center for Epidemiological Studies-Depression; EPDS is the Edinburg Postnatal Depression Scale; STAI is the State-Trait Anxiety Inventory, State; EA is the Emotional Availability Scale. Significant difference between groups based on t-test or chi-squared, **p<.05; **p<.001*

Table 12: (Infant Pic) Sample distribution of cannabis use across prenatal and postnatal visits for Model 2

Characteristic	Control	First Trimester Use	Beyond Trimester Use

	(n= 73)		(n= 11)		(n= 30)	
	μ / n	*range / %*	*μ / n*	*range / %*	*μ / n*	*range / %*
First Trimester Self-Report [a d]	0	-	11	100%	22	84.6%
First Trimester TLFB [c d]	0	-	6.30 +/- 16.10 *(1 missing)*	0—52.00	147.50+/-166.48 *(5 missing, 3 no reported use)*	0--707
First Trimester Positive Immunoassay for Cannabis [a]	0 *(1 missing)*	-	0	-	17 *(1 missing)*	65.4%
Second Trimester Self-Report [a]	0	-	0	-	19 *(1 missing)*	73.1%
Second Trimester TLFB [c]	0	-	0 *(11 no reported use)*	-	125.09+/-166.06 *(5 missing, 3 no reported use)*	0--710
Second Trimester Positive Immunoassay for Cannabis [a]	0 *(36 missing)*	-	0 *(3 missing)*	-	13 *(8 missing)*	50%
Third Trimester Self-Report [b]	0	-	0	-	20 *(1 missing)*	66.7%
Third Trimester TLFB [c]	0	-	0 *(11 no reported use)*	-	86.84+/-133.75 *(7 missing, 4 no reported use)*	1--462
Third Trimester Positive Immunoassay for Cannabis [b]	0 *(32 missing)*	-	0 *(2 missing)*	-	13 *(8 missing)*	43.3%
1st Postnatal Visit Self-Report [b]	0	-	0	-	17 *(1 missing)*	56.7%
1st Postnatal Visit TLFB [c]	0	-	0 *(11 no reported use)*	-	37.55+/-33.66 *(9 missing, 10 no reported use)*	1--90
1st Postnatal Visit Positive	0 *(29 missing)*	-	0 *(4 missing)*	-	12 *(10 missing)*	40.0%

Immunoassay for Cannabis [b]						
1st MRI Visit Positive Immunoassay for Cannabis [b]	0 *(20 missing)*	-	0 *(2 missing)*	-	18 *(5 missing)*	60.0%

Note :[a]:11 control subjects were recruited at the third trimester and 5 cannabis subjects were recruited at the third trimester. For the first and second trimester N=62 for the control group and N= 10 for the first trimester cannabis group, and N=26 for the beyond first trimester group. The table totals for first trimester and second trimester data show the results based on the totals at each visit with associated missing data. Immunoassay was added to all visits later on and thus there is a larger portion of missing data after the first trimester visit.
[b]:For the third trimester data, the additional 11 control subjects (N=73) and 5 cannabis (N=11 for first trimester use and N=30 for beyond first trimester use) subjects where recruited and thus the totals are reflected with associated missing data for the third trimester and postnatal data.
[c]:For the TLFB data, third trimester starts were asked about retrospective use since conception. Total for the control is N=73, and total for first trimester use is N=11 and beyond first trimester use is N=30.
[d]:One third trimester start self-reported cannabis use up to 12 weeks in the first postpartum period, thus their data point is listed in first trimester self-report for first trimester use only (N=11), but they are missing TLFB data.
TLFB= Timeline follow back data. TLFB was only filed out when participants tested positive or self-reported cannabis use.

3.3. Model 3: Cumulative quantity of prenatal cannabis

3.3.1. Participant Characteristics

Demographics for this sample are split into groups for visualization purposes in Table 13, as well as cannabis use descriptives in Table 14. Cumulative prenatal use was not correlated with CESD at the third trimester or postnatal visit. Cumulative prenatal use was correlated with EPDS at the third trimester, but was not at the postnatal visit (r = 0.219, p = 0.032, 95% CI [0.019, 0.402]). STAI was correlated with cumulative prenatal use at the third trimester visit, but not the postnatal visit (r = 0.296, p = 0.003, 95% CI [0.102, 0.469]). Cumulative prenatal use was not associated with group differences with total education years at consent, yearly income at consent, CESD postnatal score. Cumulative use was associated with positive nicotine immunoassay at consent (r = 0.405, p < 0.001, 95% CI [0.261, 0.589]). All potential covariates through group differences were accounted for in post-hoc analysis.

3.3.2. fMRI analysis of the amount of use and brain activation

In the final model, the whole sample was investigated through a two-way interaction of cumulative cannabis over the prenatal period as reported on the TLFB as a continuous variable x identity (own vs. other) controlling for gestational parent age at scan, postpartum days at scan, and parity. There was one significant cluster in the inferior frontal gyrus (see Table 15 and Figure 10). In this region, greater activation to the control baby was associated with greater cumulative prenatal cannabis use as reported on the TLFB. Additional post-hoc analysis to account for potential group differences was conducted in this cluster. A partial correlation with BOLD response (averaged own baby-averaged other baby) was conducted. This cluster remained significant after controlling for total education years at consent, yearly income at consent, CESD postnatal score, positive nicotine immunoassay at consent, *ps* <.001. The cluster also remained significant after controlling for EPDS and STAI scores at the third trimester visit, *ps* < 0.001.

3.3.3. Exploratory associations between brain activation and parenting behaviors

Cumulative prenatal use was correlated with gestational parent EA scales within this sample. Cumulative prenatal use was negatively correlated with the non-hostility scale, with higher cumulative prenatal use associated with lower non-hostility scores or more hostile parenting behavior (r = -0.248, p = 0.022, 95% CI [-0.438, -0.037]). Correlations between EA gestational parent scales and neural activation in the inferior frontal gyrus where the cannabis group had greater activation to unknown (other) baby were investigated. There were no significant associations between any EA gestational parent scale and activation in the inferior frontal gyrus.

3.3.4. Exploratory post scan associations between brain activation and group status

Cumulative prenatal use was correlated with average post scan responses how pleasant or unpleasant the picture made them feel, and how they thought the baby was feeling for the own and other baby images. Total prenatal use was not correlated with any post scan responses. Next, the significant cluster in the inferior frontal gyrus was correlated to post scan responses. No post scan responses were correlated with activation in the inferior frontal gyrus.

Table 13: (Infant Picture): Sample demographics for groups in Model 3

	Control (n= 73)		**Cannabis (n= 25)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*
Preterm Birth (less than 37 weeks)	3	4.1%	2	8.0%
Total Gestational Weeks	39.10+/-1.60	32.57—41.71	38.94+/-1.56	35.00—41.14
Parent Age at MRI*	30.14+/-5.53	19--42	26.76+/-4.66	19--38
Education at consent**	15.51+/-2.82	11—20	13.16+/-1.97	10--17
Yearly Income at consent**	87,583.14+/-80,675.04 *(8 missing)*	0—504,000.00	40,048.00+/-25,069.47 *(2 missing)*	38—90,000
Relationship Status at consent	8 *(1 missing)*	11.0%	6 *(1 missing)*	24.0%
Parity	49	67.1%	16	64.0%
Infant Age at MRI (weeks)	5.42+/-3.15	1.29—14.29	5.33+/-2.79	1.14—11.71
Infant Age at 1st postnatal visit (weeks)*	3.05+/-1.74	.86—8.71	4.25+/-2.37 *(1 missing)*	.71—8.57
Hispanic	20 *(1 missing)*	27.4%	7	28.0%
Race*	*(1 missing)*	1.4%		
American Indian/Alaska Native	2	2.7%	1	4.0%
Asian	2	2.7%	0	
Black or African American	7	9.6%	11	44.0%

Native Hawaiian or Other Pacific Islander	2	2.7%	0	
White/Caucasian	48	65.8%	12	48.0%
Other	11	15.1%	1	4.0%
CESD at third trimester visit	13.79+/-8.13 *(1 missing)*	4.00—39.00	15.77+/-7.42 *(1 missing)*	3.00—31.00
EPDS at third trimester visit	6.14+/-4.85 *(1 missing)*	0—18.00	7.17+/-5.28 *(1 missing)*	0—16.00
STAI at third trimester visit	31.38+/-11.21 *(1 missing)*	20.00—68.00	33.89+/-10.55 *(1 missing)*	20.00—62.00
CESD at postnatal visit*	12.21+/-8.54	1.00—35.00	16.74+/-10.88 *(2 missing)*	4.00—44.00
EPDS at postnatal visit	5.04+/-4.59	0—18.00	6.87+/-5.76 (*2 missing)*	0—18.00
STAI at postnatal visit	29.67+/-10.16	20.00—61.00	33.07+/-10.88 *(2 missing)*	20.00—54.00
NicAlert Positive at Consent*	7 *(2 missing)*	9.6%	9 *(1 missing)*	36.0%
EA Parent Scale				
Sensitivity	5.61+/-1.00 *(6 missing)*	3.50—7.00	5.34+/-1.13 *(3 missing)*	3.00-7.00
Structuring	5.62+/-1.100 *(6 missing)*	3.00—7.00	4.97+/-1.44 *(3 missing)*	3.00—7.00
Non-intrusiveness	5.59+/-.97 *(6 missing)*	3.00—7.00	5.46+/-1.10 *(3 missing)*	3.50—7.00
Non-hostility	5.51+/-1.24 *(9 missing)*	3.00—7.00	5.02+/-1.27 *(3 missing)*	4.00—7.00

Note: Demographics are split up by group to show group differences, but cumulative use was tested continuously in the model. CESD is the Center for Epidemiological Studies-Depression; EPDS is the Edinburg Postnatal Depression Scale; STAI is the State-Trait Anxiety Inventory, State; EA is the Emotional Availability Scale. Significant difference between groups based on t-test or chi-squared, **p<.05; **p<.001*

Table 14 (Infant Picture) Sample distribution of cannabis use across prenatal and postnatal visits for Model 3

Characteristic	Control (n= 73)		Cannabis (n= 25)	
	μ / n	*range / %*	*μ / n*	*range / %*
First Trimester Self-Report [a]	0	-	20	87.0%
First Trimester TLFB [c]	0	-	117.60+/-157.60	1--707

First Trimester Positive Immunoassay for Cannabis [a]	0 *(1 missing)*	-	12 *(1 missing)*	52.2%
Second Trimester Self-Report [a]	0	-	13 *(1 missing)*	56.5%
Second Trimester TLFB [c]	0	-	108.60+/-161.67	0--710
Second Trimester Positive Immunoassay for Cannabis [a]	0 *(36 missing)*	-	11 *(3 missing)*	47.8%
Third Trimester Self-Report [b]	0	-	15 *(1 missing)*	60.0%
Third Trimester TLFB [c]	0	-	64.76+/-122.43	0--462
Third Trimester Positive Immunoassay for Cannabis [b]	0 *(32 missing)*	-	10 *(4 missing)*	40.0%
1st Postnatal Visit Self-Report [b]	0	-	12 *(1 missing)*	48.0%
1st Postnatal Visit TLFB [c]	0	-	14.96+/-28.72	0--90
1st Postnatal Visit Positive Immunoassay for Cannabis [b]	0 *(29 missing)*	-	10 *(6 missing)*	40.0%
1st MRI Visit Positive Immunoassay for Cannabis [b]	0 *(20 missing)*	-	14 *(2 missing)*	56.0%

Note :[a]:11 control subjects were recruited at the third trimester and 2 cannabis subjects were recruited at the third trimester. For the first and second trimester N=62 for the control group and N= 23 for the cannabis group. The table totals for first trimester and second trimester data show the results based on the totals at each visit with associated missing data. Immunoassay was added to all visits later on and thus there is a larger portion of missing data after the first trimester visit.

[b]:For the third trimester data, the additional 11 control subjects (N=73) and 1 cannabis (N=25) subjects where recruited and thus the totals are reflected with associated missing data for the third trimester and postnatal data.

[c]:For the TLFB data, third trimester starts were asked about retrospective use since conception. Total for the control is N=73, and total for cannabis is N=25

TLFB= Timeline follow back data. TLFB was only filed out when participants tested positive or self-reported cannabis use.

Table 15: Brain regions showing statistically significant Cannabis TLFB x Identity Condition interactions and post-hoc analyses with education, income, and nicotine assay.

Region	BA	Side	MNI Coordinates			Cluster size	F	Own Baby Response and Cumulative Use Correlation	Control Baby Response and Cumulative Use Correlation
			x	y	z				
Inferior Frontal Gyrus	47	L	-30	22	-24	20	32.08***	.065	.398**

Note*:* BA = Brodmann Area; MNI = Montreal Neurological Institute, **** p < .001, **, p<.01,*p < .05.*

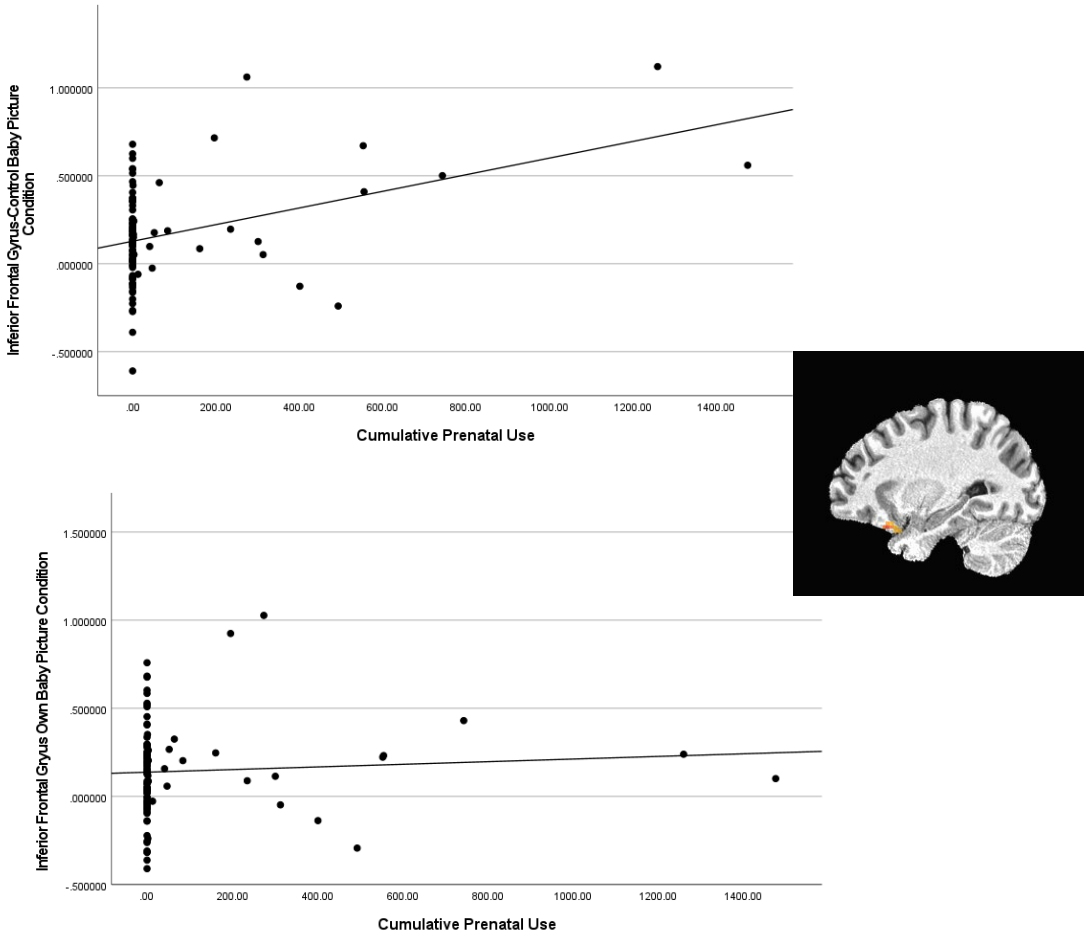

Figure 10: Blood Oxygenation Level Dependent (BOLD) activation illustrating Own and Control baby picture contrast in cumulative cannabis use during the prenatal period (BA47; x,y, z = --30, 22, -24; k = 20, *p* = .001, corrected)

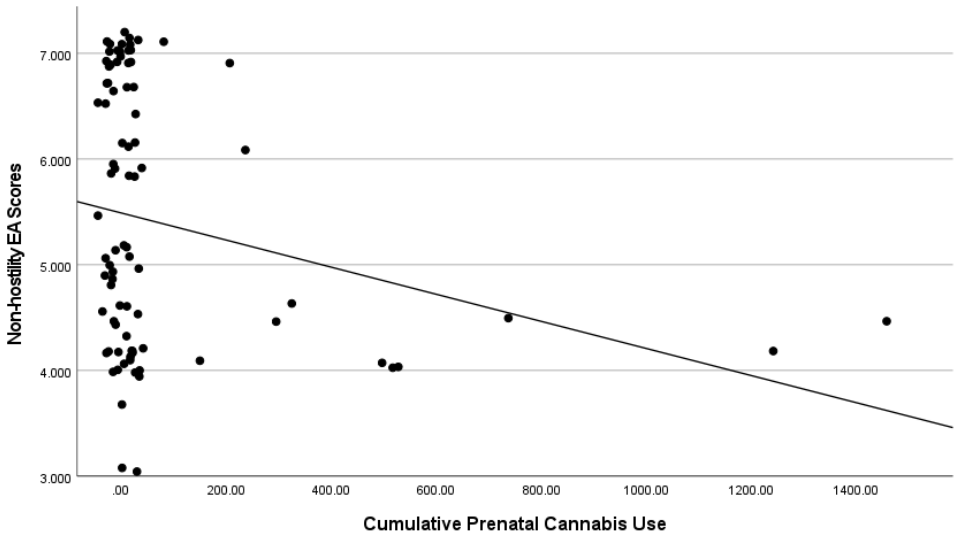

Figure 11: Correlation of the non-hostility scale with cumulative prenatal cannabis use

Note: EA = Emotional Availability Scale

CHAPTER EIGHT: STUDY TWO DISCUSSION

The present study investigated the effects of prenatal cannabis use on BOLD responses to infant faces. In the first model, this study assessed cannabis dichotomously in line with previous literature. In the second model, cannabis was assessed similarly to new literature looking at early first trimester use compared to ongoing use past the first trimester. In the third model, cannabis was assessed cumulatively for a total sum of use over the prenatal period. All models were matched to the same control group. In the first model, BOLD response to infant faces did not differ between groups. In the second model, BOLD response did not differ between groups. In the third cumulative model, cumulative prenatal cannabis use was associated with heightened activation in the inferior frontal gyrus to control (unknown) infant faces. This region is important for emotional processing and saliency of infant face cues. A heightened response in this region to own infant face is expected, and seeing heightened response to the unknown infant face could show dysregulation in emotional processing parenting networks. Contrarily to previous findings, ratings about how the baby was feeling and what parents were thinking were not associated with inferior frontal gyrus response and did not differ between groups (McCurdy et al., 2024). These findings suggest that cannabis may impact emotional processing parenting networks.

As parenting was explored previously, it was again assessed in this analysis as there was a slight change in the sample for this model. Parenting group differences were

assessed in all models and groups did not differ in any models. Higher cumulative prenatal use in the third model was associated with lower non-hostility (more negative affect and facial features) parenting scores. This should be interpreted with caution as the main larger model did not show differences and these analyses were exploratory.

4.1. Cannabis use and response to infant faces

The inferior frontal gyrus has been associated with emotional empathy. Emotional empathy, defined as sharing feelings of others, and cognitive empathy, defined as the ability to understand what others are feeling, are both important in parenting to understand infant cues (P. Kim, 2021; Shamay-Tsoory et al., 2009). Increased activation in the inferior frontal gyrus to infant faces has been thought to be associated with heightened emotional empathy response, allowing for more sensitive and attuned parenting (Endendijk et al., 2020; Rigo, Kim, et al., 2019). Overall, activation to infant faces is expected in the postpartum period, with heightened overall sensitivity to infant faces being helpful for increasing parental motivation behaviors and reward networks. The current study differs from previous substance use research in gestational parents, that found heightened response to own infant faces, and heightened response to unknown infant faces of emotional valence (happy and sad) (Rutherford et al., 2020). Cannabis in adult populations has been shown to increase approach and prosocial behaviors (Vigil et al., 2022). Potentially, this heightened response to unknown infant faces among gestational parents who use cannabis is different from other substances increasing the salience of this cue. While this prosocial behavior could increase parental motivation, the inferior frontal gyrus is important for own infant face processing. As controls are showing increased response to own infant faces in this region, this could suggest a

potential dysregulation of response that could lead to less sensitive parenting. While the sample was smaller in the cumulative total, this could be reflected in the lower non-hostility scores on the parent-child interaction.

This study provides new information different to previous reported studies. While it was hypothesized that there would be an increase in activation to own faces in reward networks of the superior medial frontal, inferior parietal, and middle temporal gyrus, this study found heightened BOLD response to unknown faces in the inferior frontal gyrus. This also contradicts previous substance use literature that found dampened response in the inferior frontal gyrus to unknown faces (McCurdy et al., 2024). There are a few possibilities for differences. First, this study assessed neural responses at one month postpartum and only showed neutral infant faces, as emotional expression at this age is limited. Previous literature looked at neural response to faces at 8 months and collapsed own and unknown images across emotion (happy and sad) (McCurdy et al., 2024). As these paradigms differ, looking at only neutral faces in the early postpartum period could elicit differing responses. Previous literature also found increased activation to own compared to unknown in happy and sad faces in the inferior frontal gyrus in gestational parents who used substances with infants at 5 months postpartum, though this same study also found dampened response in regions of the medial PFC, ventral striatum, and hypothalamus (S. Kim et al., 2017). This study that found both heightened and dampened activation did not have the presence of a control group, which could account for differences in outcomes to the present study.

This current study assessed brain activation in response to infant faces at one month postpartum, which may contribute to differences observed in neural responses

compared to previous studies that assessed brain response at later in the postpartum year. Increased brain activation to own infant faces may be particularly important and salient in this early stage of parenthood, potentially explaining why the cannabis group appears comparable to the control group in response to own infant. While responses to own faces were comparable, the inferior frontal gyrus is implicated in social information processing within parental neural networks. This heightened response to control faces in the early postpartum period could highlight a dysregulation in salience of information processing of infant faces. As these findings were unexpected, and not replicated in the main sample, future research should look at cumulative cannabis use in larger samples.

Compared to infant cries, where activation is associated with an urgent response, infant faces is a more neutral to positive cue. While not as salient as cries, infant faces should elicit a salient response. Additionally, infant cries require executive function networks and cognitive empathy, meaning gestational parents must regulate their own emotions, interpret the emotions of their child, and act on those interpretations. Unlike infant cries, infant faces elicits an emotional empathy response. In the late pregnancy period, infant faces among pregnant populations shows an attenuated response related to more sensitive parenting in the postpartum period and continued heightened response in the postpartum period has shown better parent-infant bonding (Dudek et al., 2020; Pearson et al., 2009). An additional interpretation of this is that increased salience to infant faces is important for emotional empathy in parenting. Although, previous research has suggested that own infant is a more positive emotional stimuli than an unknown infant, suggesting potentially that unknown infants could cause a stress response (Barrett et al., 2012; Rigo, Kim, et al., 2019). This could suggest that while infant faces are a

positive cue, potentially unknown neutral faces could be perceived as distressing (less so than infant cries) and have heightened response in emotional processing networks like the inferior frontal gyrus.

Additionally, this current study did not replicate previous findings in the dichotomous group, but found that the greater cumulative amount of use was associated with neural responses. This could be due to cannabis' less robust changes on reward neural circuitry compared to other illicit substances, and research that heavier monthly use and more problematic cannabis use have greater impairments in neurocognition (Scott et al., 2018). In heavy monthly use of cannabis (more than 10 times in a month) compared to more infrequent use (less than 10 times a month) there are more associated structural and functional changes in regions that are import for sensory, motor, and cognition (Hirjak et al., 2022). Taken together, this could demonstrate that higher levels of use are associated with greater effects on neural function compared to other illicit substances that lower levels may be associated with. This current study supports these implications as the dichotomous model of cannabis included a greater variety of cannabis use during the prenatal period and was not associated with neural functioning differences, but greater cumulative use was. Future research should look at the effects of more chronic cannabis use on parenting networks.

4.2. Associations with mood symptoms and cannabis use

Previous research has reported on the associations of cannabis use and depression and anxiety symptoms (Crume et al., 2022; Goodwin et al., 2020; Latuskie et al., 2019; Skelton et al., 2020b; Taylor et al., 2021; Weisbeck et al., 2021; Young-Wolff, Gali, et al., 2020). Depression and anxiety symptoms at the third trimester and postnatal visit did

not differ in the dichotomous or first trimester and beyond use models. In the third model, CESD scores differed between groups with the cumulative cannabis group having higher reported postnatal CESD scores though this was not associated with cumulative use or inferior frontal gyrus activation. Heavy cannabis use has been associated with potentially higher risk of developing depression, but depression and cannabis findings are mixed (Mammen et al., 2018). Future studies should investigate the effects of depression and anxiety symptoms on cannabis use during the prenatal and postnatal period.

4.3. Strengths, limitations, and future directions

This study contributes to the limited parental neuroimaging studies by investigating cannabis use on parental neural networks. With cannabis becoming increasingly more commonly used during pregnancy, understanding its impact on parenting neural mechanisms is essential to give better clinical insights. As reward circuitry overlaps with parenting networks, there is potential for disruption of parenting neural networks and subsequent parenting behavior. A strength of this study is looking at cannabis use in insolation of other substances besides tobacco use. Previous parenting substance use literature has looked at substances more broadly, and while valuable for understanding larger reward circuitry, cannabis could lack robustness in neural response compared to other substances of abuse. In addition, parenting substance use studies often are not in the immediate postpartum period. Another strength of this study is highlighting the immediate neural changes within one month postpartum, allowing for more direct relation of prenatal use to postpartum changes. By using own and other infant faces, and not emotional valence during the early postpartum period this study adds information to the literature on the effects of cannabis use early in the postpartum period. Additionally,

the longitudinal design of this study allows for implications of prenatal cannabis use on the early postpartum period, particularly reflecting parenting cues during this time.

While there are strengths with this study, there are a few limitations. First, while our control sample size was adequate, cumulative use in the third model was a smaller sample size. Future studies should repeat the analysis in larger samples. Additionally, a lack of immunoassay for all time points in this study is a limitation. Biological measures can provide valuable insights and future studies should look at immunoassay to detect differences in heavier prenatal cannabis use. In relation to cannabis use, pre-partum and postpartum cannabis use is a limitation. Previous studies look later in the postpartum period and often include postpartum use as a screener for participation, our study had relatively lower use in the postpartum period as reported on the TLFB. Additionally, this study did not capture pre-partum use. Long term cannabis use prior to pregnancy could affect reward circuitry. While this is also a strength to isolate prenatal use, positive immunoassay at time of the fMRI visit could also be a confounding factor. Future research should explore the intricacies of pre-partum, prenatal, postnatal cannabis use, and active THC intoxication on neural response to infant cues. As non-heavy tobacco use was allowed for this study and findings survived when accounting for tobacco use, future research should look at cannabis is isolation of any other substance, including tobacco. Additional, previous research has identified differences in relationship status in prenatal cannabis use, while this study did not have significant differences between groups. Future research should investigate how social support might be implicated in gestational parents who use cannabis. This study also completed the neuroimaging scan in the early postpartum period, and thus used neutral stimuli. As emotional valence was not included,

future research should look at emotional valence and brain response in the early postpartum period to see if it mimics the current literature on dampened response to own infant emotional faces in gestational parents who use substances. Understanding how cannabis impacts processing of emotional valence in the early and later postpartum period is important for understanding the effects cannabis has on these emotion networks. It is also important to follow up on brain differences in the later postpartum period to understand how these differences may or may not impact parent-child relationships, and infant development outcomes at a later age. Finally, this study cannot rule out additional factors that could show differences in response to neural cues such as childhood trauma, neglect, and care quality and future research should look to address these additional possibilities of involvement in neural response to infant cues and parenting.

Finally, no differences in parent-child interactions in the main sample were found. Although current literature supports coding interactions at this stage, future research should consider examining additional later timepoints to incorporate infant scales, which are essential for comprehensively understanding parenting behavior (Biringen & Easterbrooks, 2012; Clark et al., 2021; Frigerio et al., 2019)

4.4. Conclusions

In conclusion, this study sheds light on the effects of prenatal cannabis use on BOLD responses to infant faces, revealing heightened activation in the inferior frontal gyrus to unknown infant faces associated with greater total prenatal use. This finding suggests a potential dysregulation in salience of social information processing to infant faces, particularly highlighting interventions that target brain and behavioral sensitivity to own infant faces. Future research should explore these unexpected results in larger

samples and investigate the impact of cannabis use on neural response to infant faces throughout the postnatal period. Additionally, while no significant differences in depression and anxiety symptoms were found between groups, further investigation into the effects of these symptoms on cannabis use during the prenatal and postnatal periods is warranted. Finally, considering the importance of understanding parenting behavior, future studies should examine parenting behavior in the later postpartum period. While there is some education on the adverse effects of cannabis use during pregnancy on infant outcomes, increasing education in gestational parents about the potential adverse effects of cannabis use during pregnancy, and finding targeted interventions to increase saliency of own infant cues and less negative parenting behaviors is imperative.

CHAPTER NINE: SUPPLEMENTARY

Supplementary 1: Mood descriptives in the first and second trimesters for the main sample of Infant Cry

	Control (n=64)		**Cannabis (n=35)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*
CESD at first trimester visit	13.66+/-7.69	3.00—34.00	16.63+/-10.64	1.00—42.00
EPDS at first trimester visit	5.64+/-4.57	0—18.00	7.29+/-5.49	0—20.00
STAI at first trimester visit	30.75+/-11.15	20.00—75.00	31.74+/-11.47	20.00—56.00
CESD at second visit*	12.26+/-7.81 *(1 missing)*	1.00—47.00	16.42+/-10.60 *(1 missing)*	1.00—50.00
EPDS at second visit	5.86+/-4.74 *(1 missing)*	0—24.00	7.35+/-5.64 *(1 missing)*	0—21.00
STAI at second visit	30.77+/-9.93 *(1 missing)*	20.00—68.00	32.74+/-10.61 *(1 missing)*	20.00—55.00

Note: for Infant Cry 11 control subjects were recruited at the third trimester (n=64), and 4 cannabis (n=35) subjects were recruited at the third trimester. The above table shows results for subjects recruited at the 1st trimester and have data. One subject in each group did not complete their second trimester visit. Significantly different between groups based on t-test, ** $p < .001$, * $p < .05$.

Supplementary 2: Mood descriptives in the first and second trimesters for the main sample of Infant Picture

	Control (n=62)		**Cannabis (n= 36)**	
Characteristic	*μ / n*	*range / %*	*μ / n*	*range / %*
CESD at first trimester visit	13.55+/-7.74	3.00—34.00	16.72+/-10.50	1.00—42.00
EPDS at first trimester visit	5.62+/-4.64	0—18.00	7.22+/-5.42	0—2.00
STAI at first trimester visit	30.73+/-11.25	20.00—75.00	31.67+/-11.31	20.00—56.00
CESD at second visit*	12.27+/-7.92 *(1 missing)*	1.00—47.00	16.35+/-10.45 *(1 missing)*	1.00—50.00
EPDS at second visit	5.97+/-4.78 *(1 missing)*	0—24.00	7.29+/-5.57 *(1 missing)*	0—21.00

STAI at second visit	30.83+/-10.03 *(1 missing)*	20.00—68.00	32.97+/-10.55 *(1 missing)*	20.00—55.00

Note: for Infant Picture 11 control subjects were recruited at the third trimester (n=63), and 5 cannabis (n=36) subjects were recruited at the third trimester. The above table shows results for subjects recruited at the 1st trimester and have data. One subject in each group did not complete their second trimester visit. Significantly different between groups based on t-test, ** $p < .001$, * $p < .05$.

fMRIPrep Processing Pipeline:

Results included in this manuscript come from preprocessing performed using *fMRIPrep* 22.0.2 (Esteban, Markiewicz, et al. (2018); Esteban, Blair, et al. (2018); RRID:SCR_016216), which is based on *Nipype* 1.8.5 (K. Gorgolewski et al. (2011); K. J. Gorgolewski et al. (2018); RRID:SCR_002502).

Preprocessing of B_0 inhomogeneity mappings

A total of 2 fieldmaps were found available within the input BIDS structure for this particular subject. A B_0-nonuniformity map (or *fieldmap*) was estimated based on two (or more) echo-planar imaging (EPI) references with topup (Andersson, Skare, and Ashburner (2003); FSL 6.0.5.1:57b01774).

Anatomical data preprocessing

A total of 1 T1-weighted (T1w) images were found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al. 2010), distributed with ANTs 2.3.3 (Avants et al. 2008, RRID:SCR_004757), and used as T1w-reference throughout the workflow. The T1w-reference was then skull-stripped with a *Nipype* implementation of the antsBrainExtraction.sh workflow (from ANTs), using OASIS30ANTs as target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w using fast (FSL

6.0.5.1:57b01774, RRID:SCR_002823, Zhang, Brady, and Smith 2001). Brain surfaces were reconstructed using recon-all (FreeSurfer 7.2.0, RRID:SCR_001847, Dale, Fischl, and Sereno 1999), and the brain mask estimated previously was refined with a custom variation of the method to reconcile ANTs-derived and FreeSurfer-derived segmentations of the cortical gray-matter of Mindboggle (RRID:SCR_002438, Klein et al. 2017). Volume-based spatial normalization to one standard space (MNI152NLin2009cAsym) was performed through nonlinear registration with antsRegistration (ANTs 2.3.3), using brain-extracted versions of both T1w reference and the T1w template. The following template was selected for spatial normalization: *ICBM 152 Nonlinear Asymmetrical template version 2009c* [Fonov et al. (2009), RRID:SCR_008796; TemplateFlow ID: MNI152NLin2009cAsym].

Functional data preprocessing

For each of the BOLD runs found per subject (across all tasks and sessions), the following preprocessing was performed. First, a reference volume and its skull-stripped version were generated by aligning and averaging 1 single-band references (SBRefs). Head-motion parameters with respect to the BOLD reference (transformation matrices, and six corresponding rotation and translation parameters) are estimated before any spatiotemporal filtering using mcflirt (FSL 6.0.5.1:57b01774, Jenkinson et al. 2002). The estimated *fieldmap* was then aligned with rigid-registration to the target EPI (echo-planar imaging) reference run. The field coefficients were mapped on to the reference EPI using the transform. BOLD runs were slice-time corrected to 0.189s (0.5 of slice acquisition range 0s-0.378s) using 3dTshift from AFNI (Cox and Hyde 1997, RRID:SCR_005927). The BOLD reference was then co-registered to the T1w reference

using bbregister (FreeSurfer) which implements boundary-based registration (Greve and Fischl 2009). Co-registration was configured with six degrees of freedom. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. Several confounding time-series were calculated based on the *preprocessed BOLD*: framewise displacement (FD), DVARS and three region-wise global signals. FD was computed using two formulations following Power (absolute sum of relative motions, Power et al. (2014)) and Jenkinson (relative root mean square displacement between affines, Jenkinson et al. (2002)). FD and DVARS are calculated for each functional run, both using their implementations in *Nipype* (following the definitions by Power et al. 2014). The three global signals are extracted within the CSF, the WM, and the whole-brain masks. Additionally, a set of physiological regressors were extracted to allow for component-based noise correction (*CompCor*, Behzadi et al. 2007). Principal components are estimated after high-pass filtering the *preprocessed BOLD* time-series (using a discrete cosine filter with 128s cut-off) for the two *CompCor* variants: temporal (tCompCor) and anatomical (aCompCor). tCompCor components are then calculated from the top 2% variable voxels within the brain mask. For aCompCor, three probabilistic masks (CSF, WM and combined CSF+WM) are generated in anatomical space. The implementation differs from that of Behzadi et al. in that instead of eroding the masks by 2 pixels on BOLD space, a mask of pixels that likely contain a volume fraction of GM is subtracted from the aCompCor masks. This mask is obtained by dilating a GM mask extracted from the FreeSurfer's *aseg* segmentation, and it ensures components are not extracted from voxels containing a minimal fraction of GM. Finally, these masks are resampled into BOLD space and binarized by thresholding

at 0.99 (as in the original implementation). Components are also calculated separately within the WM and CSF masks. For each CompCor decomposition, the *k* components with the largest singular values are retained, such that the retained components' time series are sufficient to explain 50 percent of variance across the nuisance mask (CSF, WM, combined, or temporal). The remaining components are dropped from consideration. The head-motion estimates calculated in the correction step were also placed within the corresponding confounds file. The confound time series derived from head motion estimates and global signals were expanded with the inclusion of temporal derivatives and quadratic terms for each (Satterthwaite et al. 2013). Frames that exceeded a threshold of 0.5 mm FD or 1.5 standardized DVARS were annotated as motion outliers. Additional nuisance timeseries are calculated by means of principal components analysis of the signal found within a thin band (*crown*) of voxels around the edge of the brain, as proposed by (Patriat, Reynolds, and Birn 2017). The BOLD time-series were resampled into standard space, generating a *preprocessed BOLD run in MNI152NLin2009cAsym space*. First, a reference volume and its skull-stripped version were generated using a custom methodology of *fMRIPrep*. All resamplings can be performed with *a single interpolation step* by composing all the pertinent transformations (i.e. head-motion transform matrices, susceptibility distortion correction when available, and co-registrations to anatomical and output spaces). Gridded (volumetric) resamplings were performed using antsApplyTransforms (ANTs), configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos 1964). Non-gridded (surface) resamplings were performed using mri_vol2surf (FreeSurfer).

Many internal operations of *fMRIPrep* use *Nilearn* 0.9.1 (Abraham et al. 2014, RRID:SCR_001362), mostly within the functional processing workflow. For more details of the pipeline, see the section corresponding to workflows in *fMRIPrep*'s documentation

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