Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
Prenatal Maternal Distress During the COVID-19 Pandemic and Associations With Infant Brain Connectivity

Kathryn Y. Manning, Xiangyu Long, Dana Watts, Lianne Tomfohr-Madsen, Gerald F. Giesbrecht, and Catherine Lebel

ABSTRACT

BACKGROUND: The COVID-19 pandemic has caused substantially elevated distress in pregnant individuals, which has the potential to affect the developing infant brain. Our main objective was to understand how prenatal distress was related to infant brain structure and function and whether social support moderated the associations.

METHODS: The Pregnancy during the COVID-19 Pandemic (PdP) cohort study collected Patient-Reported Outcomes Measurement Information System Anxiety scale, Edinburgh Postnatal Depression Scale, and Social Support Effectiveness Questionnaire data from a population-based sample of pregnant individuals living in Canada (N = 8602). For a subsample of participants, their infants (n = 75) underwent magnetic resonance imaging at 3 months of age to examine whether prenatal maternal distress was associated with infant brain architecture, including the role of social support as a potential protective factor.

RESULTS: Overall, 33.4% of participants demonstrated clinically elevated depression symptoms and 47.1% of participants demonstrated clinically elevated anxiety symptoms. We identified lower social support as a significant predictor of clinically elevated prenatal maternal distress (t_{8598} = -22.3, p < .001). Fifty-eight diffusion image datasets (20 female/38 male, 92 ± 14 days old) and 41 functional datasets (13 female/28 male, 92 ± 14 days old) were included in our analysis after removal of poor-quality images and infants without postpartum maternal distress scores. We found significant relationships between prenatal maternal distress and infant amygdala-prefrontal microstructural and functional connectivity measures, and we demonstrate for the first time that social support moderates these relationships.

CONCLUSIONS: Our findings suggest a potentially long-lasting impact of the COVID-19 pandemic on children and show that social support acts as a possible mediator not just for pregnant individuals but also developing infants. These findings provide timely evidence to inform clinical practice and policy surrounding the care of pregnant individuals and highlight the importance of social support.

https://doi.org/10.1016/j.biopsych.2022.05.011

Prenatal maternal distress, defined as elevated symptoms of anxiety and/or depression, can have immediate negative effects on pregnant individuals as well as the rapidly developing and vulnerable fetus. Prenatal maternal distress is associated with preterm birth and long-term risks for behavioral and mental health problems in children (1–3). Alterations to the developing infant brain, especially within the limbic system, likely underlie compromised behavioral development (4–7). In particular, infants exposed to higher prenatal stress have larger amygdala volumes, disrupted white matter connectivity between the amygdala and prefrontal cortex (including the uncinate fasciculus), and functional connectivity changes between the amygdala and prefrontal regions (8–10). Further, amygdala-prefrontal pathways mediate the relationship between maternal prenatal depression and externalizing behaviors (hyperactivity, aggression) in children (11), showing that brain structure is a mechanism via which prenatal maternal distress can affect children’s behavioral development.

The COVID-19 pandemic has had a profound and prolonged effect on the mental health of pregnant individuals. Pregnant individuals have faced fear for themselves and their developing babies, disruptions to prenatal care (including lack of partner support) (12), reduced access to services, and loss of support from friends and family. Rates of psychological distress in pregnant individuals have more than tripled during the pandemic (13–15) compared with rates pre-pandemic (16,17). Previous studies of children born during natural disasters demonstrate the long-term consequences of prenatal distress on brain development (18,19) and behavior (20), raising significant concerns about how the generation of children born during the COVID-19 pandemic will be affected. Data are emerging that demonstrate deficits in early infant and child cognitive development (21).
Prenatal Distress in the Pandemic and the Infant Brain

Social support can moderate the effects of prenatal distress on maternal hypothalamic-pituitary-adrenal axis activity (22) and has been shown to reduce psychological distress during pregnancy (16,23,24). Evidence is overall highly consistent and supports the notion that social support is an important protective factor against depression (25). However, it is unclear whether social support can disrupt the transmission of prenatal maternal distress to infant brain development. Understanding how prenatal maternal distress affects brain development, including potential modifiable risk and protective factors such as social support, will aid in identifying children most at risk and inform policy recommendations to rapidly benefit families.

Here, we measured prenatal depression, anxiety, and social support in a very large sample of pregnant individuals across Canada during the COVID-19 pandemic. We hypothesized that higher prenatal maternal distress measures reported during the pandemic would demonstrate a negative relationship with measures of social support, while controlling for maternal education, household income, and ethnicity. In a subset of infants who provided imaging data, we examined how prenatal maternal distress was related to infant amygdala structural and functional connectivity at 3 months while controlling for maternal education, household income, postnatal maternal distress, child age, and sex. Furthermore, an interaction term between prenatal maternal distress and social support was included to test the hypothesis that social support moderates associations between prenatal maternal distress and the infant brain.

METHODS AND MATERIALS

Participants

The Pregnancy during the COVID-19 Pandemic (PdP) study (26) is a Canada-wide study that recruited pregnant individuals between April 2020 and April 2021 to assess life changes and physical and mental health during the pandemic. The University of Calgary Conjoint Health Research Ethics Board approved this study (REB20-0500), and participants provided informed consent. Pregnant individuals were eligible if they were living in Canada, ≥17 years of age, <35 weeks’ gestation at intake, and able to read and write in English or French (26). Here, we use data from the first intake survey. A total of 8602 participants (mean age = 32.0 ± 4.4 years, range = 17–49 years; mean gestation = 20.7 ± 8.6 weeks, range = 3–35 weeks) completed the mental health and social support measures and were included in this study. We also gathered information on maternal age, education, and ethnicity (Table S1).

PdP study participants who delivered full-term infants (≥37 weeks) in the Calgary area (390 potentially eligible, 98 examined and confirmed as eligible) were invited to participate in neuroimaging when their infants were 3 months of age. Participants received a small stipend for participating in the imaging portion of the study. Children with major birth complications (e.g., hypoxic-ischemic encephalopathy), diagnosed genetic or neurologic conditions associated with significant cognitive impairment, congenital anomalies, or contraindications to magnetic resonance imaging (MRI) were excluded.

Mental Health and Social Support

The Edinburgh Postnatal Depression Scale (EPDS) (27) was used to assess depression symptoms, and the Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety scale (28) was used to assess anxiety symptoms. The Social Support Effectiveness Questionnaire (SSEQ) (29) was used to assess the amount and quality of social support provided by a partner or close friend/family member. Clinically elevated depression symptoms were defined as a score of >12 on the EPDS (27), and clinically elevated anxiety was defined as PROMIS score >59 (28). We also obtained postpartum mental health measures through our online survey at 3 months postpartum.

Image Acquisition

We acquired brain imaging data from 75 infants (92 ± 14 days old) (Table S1) using the GE 3T MR750w MRI using a 32-channel head coil at the Alberta Children’s Hospital. Infants were scanned during natural sleep while placed in an inflatable MedVac infant scanning bed. The imaging protocol included T1-weighted imaging (repetition time = 5200 ms, echo time = 2200 ms, inversion time = 540 ms, field of view = 1900 mm, matrix = 512 × 512, bandwidth = 41.67, voxel 1 × 1 × 1 mm³, flip angle = 12°, 136 slices, total time = 3:32), diffusion tensor imaging (30 directions at b = 700 s/mm², 5 b = 0 s/mm² images, repetition time = 8500 ms, echo time = 99.4 ms, field of view = 1600 mm, matrix = 256 × 256, voxel 1.75 × 1.75 × 2 mm³, 49 slices, total time = 5:06), and resting-state functional MRI (rs-fMRI) (repetition time = 2000 ms, echo time = 30 ms, field of view = 1920 mm, matrix = 64 × 64, voxel 3.6 × 3.6 × 3.6 mm³, flip angle = 60°, 37 slices, total time = 8:10).

Image Analysis

ExploreDTI (30) was used to process the diffusion data, including signal drift, Gibbs ringing, eddy currents, and head motion corrections. Participants who awoke early during the scanning protocol and were removed from the scanner before completing the diffusion portion of the protocol or those with excessive motion and compromised diffusion data determined with manual visual check were not included in data analyses. Whole-brain white matter tractography was performed using semiautomated deterministic streamline tractography with fractional anisotropy (FA) > 0.1 and angle < 30°. We focused our analysis on the bilateral uncinate fasciculus and fiber bundles connecting the amygdala to the prefrontal cortex given previous findings (6,11), and these two tracts were generated using our previous methods (11). Mean FA and mean diffusivity (MD) were calculated within each tract for each participant.

rs-fMRI preprocessing was conducted using FSL (31) and included brain extraction, motion correction, 5-mm smoothing, and high pass temporal filtering. Participants were excluded if they awoke too early during the scanning protocol and were removed from the scan before completing the functional portion of the protocol or if they had excessive motion (>0.25-mm relative mean displacement for >120 volumes). Volumes with excessive motion (>1 mm) within individual datasets (n = 19) were truncated. Because the infants were scanned during natural sleep, motion only occurred at the beginning of the
scan (when the noise changes sometimes startled the infant) or at the end of the scan (if the infant awoke), so we were able to retain a subset of continuous data for each of these 19 participants. Independent component analysis denoising was used to regress non-neuronal components from the data, and clean images were registered to an infant atlas template for neonates (32). FEAT (33) higher-level analysis was used to create an average amygdala connectivity map. From this, the infant Automated Anatomical Labeling atlas (32) was used to identify regions (superior orbitofrontal cortex and inferior frontal gyrus) with significant functional connectivity (ρ > 2.3) with the amygdala. We tested intrahemispheric functional connectivity between these two prefrontal regions (left and right) and the amygdala (left and right) using Pearson correlation in MATLAB (version 2021b; The MathWorks, Inc.).

**Statistical Analysis**

Standard scores from the EPDS and PROMIS Anxiety measures were highly correlated (R = 0.78) and combined using a factor analysis in IBM SPSS (version 28.0.1.0) into a single factor to quantify prenatal maternal distress, similar to what has been done previously (5). This was done to determine overall prenatal maternal distress and also to decrease the number of hypotheses tested. A general linear model was used to investigate the relationship between prenatal maternal distress and social support (SSEQ) while controlling for maternal education, household income, and ethnicity. We also conducted a logistic regression analysis in MATLAB to determine if SSEQ score predicts clinically significant prenatal psychological distress, defined as >0.25 where both anxiety and depression scores were clinically significant. For the infant imaging data, a general linear model was applied in MATLAB to examine the relationship between each MRI metric (i.e., rs-fMRI functional connectivity, FA, or MD) and prenatal maternal distress. We included maternal education, household income, age of the infant at the time of the scan, infant sex, postpartum maternal distress, and SSEQ in our model as follows:

\[
\text{Infant brain measure} = \text{prenatal maternal distress} + \text{SSEQ} + \text{infant age} + \text{infant sex} + \text{maternal education} + \text{household income} + \text{postpartum maternal distress} + (\text{prenatal maternal distress} \times \text{SSEQ})
\]

where the relationship between MRI measures and prenatal maternal distress was tested for significance at \( p < .05 \). Results were corrected for multiple comparisons using false discovery rate correction based on 12 general linear models (4 FA measures, 4 MD measures, and 4 functional connectivity measures). The interaction term between SSEQ and prenatal maternal distress was included to examine whether social support moderates the relationship between prenatal maternal distress and the developing infant brain. If the interaction was significant, post hoc tests between high and low social support groups (based on the median, i.e., above and below SSEQ = 60) were used to further understand the relationships. If the interaction term was not significant, the model was re-run without it included.

**RESULTS**

**Prenatal Maternal Distress and Social Support**

Mean EPDS score was 10.4 ± 5.3 (range = 0–30), with 33.4% of participants demonstrating clinically elevated depression symptoms (score > 12). Mean PROMIS T score was 58.5 ± 8.0 (range = 36.3–82.7), with 47.1% of participants demonstrating clinically elevated anxiety symptoms. Mean SSEQ score was 50.3 ± 5.7 (range = 26–71).

Prenatal maternal distress was substantially elevated compared with pre-pandemic systematic reviews of perinatal anxiety and depression using the same measures used in our study, as well as pre-pandemic general population averages (34–37). Prenatal maternal distress was significantly related to SSEQ (\( t_{590} = −29.5, p < .001, \beta = −0.033, 95\% \text{CI} = −0.035 \) to \( −0.031 \)) while controlling for maternal education, household income, and ethnicity (Figure 1). The logistic regression was significant (\( \hat{t}_{590} = −22.3, p < .001, \beta = −0.06, 95\% \text{CI} = 0.05 \) to \( −0.05 \)) where higher SSEQ was a protective factor for clinically significant prenatal maternal distress.

**Infant Brain Structure and Function**

A total of 75 infants participated in imaging at the Alberta Children’s Hospital between August 2020 and May 2021. Mean EPDS and PROMIS Anxiety scores in this subsample were 8.6 ± 5.3 and 54.7 ± 12.4, respectively, and were normally distributed (Figure S1). These scores are significantly lower than the full survey sample (\( p < .01 \)) but still elevated compared with pre-pandemic anxiety and depression levels. During image quality control (described in Methods and Materials), 6 diffusion datasets were removed because infants awakened early and were unable to complete the protocol and 6 datasets were removed for excessive motion; we retained 63 diffusion imaging datasets (23 female/40 male, 92 ± 14 days old). Mothers of 5 infants did not provide 3-month postpartum distress scores, leaving 58 diffusion tensor imaging datasets for diffusion analysis (20 female/38 male, 92 ± 14 days old). For the functional imaging analysis, 14 datasets were removed because infants awoke early, 2 imaging datasets had a field of view error, 14 infants had excessive motion, and 4 mothers did not provide 3-month postpartum distress measures, leaving 41 rs-fMRI datasets (13 female/28 male, 92 ± 14 days old) for analysis.

The SSEQ × prenatal maternal distress interaction term was not significant for diffusion measures, so the model was run with this term removed (Table S2). Mean FA in the right uncinate fasciculus (\( t_{50} = 2.7, p = .009, \beta = 0.006, 95\% \text{CI} = 0.002 \) to 0.01) and mean MD in the right amygdala-prefrontal white matter tract (\( t_{50} = −2.3, p = .02, \beta = −0.0002, 95\% \text{CI} = −0.0003 \) to −0.00002) were significantly related to prenatal maternal distress (Figure 2).

Functional connectivity between the right amygdala and right superior orbitofrontal cortex had a significant main effect of prenatal distress (\( t_{53} = −2.9, p = .007, \beta = −0.4, 95\% \text{CI} = −0.7 \) to −0.1) with a significant SSEQ × prenatal distress interaction term.
interaction \( t_{33} = 2.6, p = .01, \beta = 0.006, 95\% \text{ CI} = 0.001 \text{ to } 0.01 \). Functional connectivity between the right amygdala and inferior frontal gyrus was significantly related to prenatal distress \( t_{33} = -3.1, p = .004, \beta = -0.5, 95\% \text{ CI} = -0.9 \text{ to } -0.2 \) with a significant SSEQ \( \times \) prenatal distress interaction \( t_{33} = 3.1, p = .009, \beta = 0.009, 95\% \text{ CI} = 0.003 \text{ to } 0.01 \) (Figure 3).

Post hoc tests revealed that pregnant individuals who reported lower quality social support (score < 60) had a significant negative correlation between prenatal maternal distress and infant amygdala and superior orbitofrontal cortex functional connectivity \( R_{40} = -0.5, p = .04, 95\% \text{ CI} = -0.8 \text{ to } -0.03 \), and those who reported higher social support did not \( R_{40} = -0.09, p = .7, 95\% \text{ CI} = -0.5 \text{ to } 0.3 \) (Figure 3). In other words, higher prenatal maternal distress was associated with weaker amygdala-prefrontal functional connectivity when social support was low, but there was no association when social support was high. Functional connectivity between the amygdala and inferior frontal gyrus also demonstrated this interaction, and the post hoc test was trending but not significant for the low SSEQ group \( R_{17} = -0.4, p = .1, 95\% \text{ CI} = -0.7 \text{ to } 0.1 \) or the high SSEQ group \( R_{20} = 0.2, p = .3, 95\% \text{ CI} = -0.2 \text{ to } 0.6 \).

Both of these functional imaging relationships also had a significant main effect of sex (Table S2), where males had significantly higher functional connectivity between the amygdala and inferior frontal gyrus \( t_{33} = -2.2, p = .04, 95\% \text{ CI} = -0.3 \text{ to } -0.01 \). Furthermore, we explored these models including an interaction term between infant sex and prenatal maternal distress, and amygdala–inferior frontal gyrus connectivity also had a significant interaction \( t_{33} = 2.7, p = .01, \beta = 0.2, 95\% \text{ CI} = 0.04 \text{ to } 0.3 \), where males tended to have a more negative relationship between functional connectivity prenatal maternal distress compared with females, who demonstrated a slightly positive relationship. However, post hoc correlation analyses between amygdala–inferior frontal gyrus connectivity and prenatal distress were not significant when grouped by sex.

---

**Figure 1.** Elevated prenatal maternal distress and social support. (A) The percentage of pregnant individuals from this study (N = 8602) that had clinically significant symptoms of anxiety or depression compared with meta-analyses of pregnant individuals pre-pandemic [1 is reference (37) and 3 is reference (34); 95% CI shown with error bars] and U.S. general population norms [2 is reference (36) and 4 is reference (35)]. (B) There was a negative relationship between Social Support Effectiveness Questionnaire (SSEQ) total score and prenatal maternal distress while controlling for maternal education, household income, and ethnicity. Higher social support was associated with lower prenatal maternal distress.

---

**Figure 2.** Prenatal maternal distress and infant brain microstructure. (A, B) Prenatal maternal distress was significantly positively correlated with mean fractional anisotropy (FA) in the right (R) uncinate fasciculus (A) and negatively correlated with mean diffusivity (MD) in the R amygdala-prefrontal tract (B).
DISCUSSION

Here, in a very large cross-Canada sample of pregnant individuals, we show substantially elevated prenatal maternal distress during the pandemic that was associated with social support measures. In a subset of participants who provided infant imaging data, prenatal maternal distress was associated with structural and functional brain connectivity alterations. One third and nearly half of pregnant individuals demonstrated clinically significant depression and anxiety symptoms, respectively. This is consistent with other studies around the world and demonstrates how substantially affected pregnant people have been during this pandemic (17). The prevalence of clinically elevated depression and anxiety symptoms among this cohort has increased substantially in comparison to pre-pandemic distress levels among pregnant individuals (34) and U.S. population norms (28,35) (Figure 1). Prenatal psychological distress was moderated by social support, where individuals with better quality and/or quantity of perceived social support reported lower symptoms of anxiety and depression. In a subsample of participants who provided imaging data, we found that prenatal distress was associated with white matter microstructure and functional connectivity in the infant brain. Furthermore, we demonstrate for the first time that the relationship between prenatal distress and functional brain connectivity is moderated by social support, suggesting that social support in pregnancy may not only support mothers but also mitigate the intergenerational transmission of prenatal stress to their infants.

In the largest sample to date of pregnant individuals during the COVID-19 pandemic, our findings affirm previous research showing that a high level of perceived social support from a partner or another supportive person may buffer the severity of psychological symptoms among pregnant individuals (16,38). Our results reflect the importance of strong social support for pregnant individuals and the role of partners and others in maintaining healthy prenatal mental health, where we identified that social support was a protective factor for clinically elevated prenatal maternal distress. Partner support may have been especially important during the COVID-19 pandemic, when individuals were isolated from family and friends, as well as from the general community, due to public health measures and fears of exposure to the virus. Partners may have had limited access to attend appointments, and some prenatal appointments were virtual instead of in person. Changes in a support person attending the birth specifically have been related to elevated symptoms of prenatal anxiety and depression in this cohort (12).

In infants born during the pandemic, we showed both structural and functional alterations in amygdala-prefrontal

Figure 3. Prenatal maternal distress and infant brain functional connectivity. (A) Mean whole-brain functional connectivity of the amygdala is shown in infants. (B) Right (R) amygdala-superior orbitofrontal cortex functional connectivity demonstrated a significant interaction between Social Support Effectiveness Questionnaire (SSEQ) score and prenatal maternal distress. (C) R amygdala-inferior frontal gyrus functional connectivity demonstrated the same interaction, but post hoc tests between high and low SSEQ groups were not significant. In general, the low SSEQ group (purple) demonstrated a significant negative correlation between maternal distress and functional connectivity and the high SSEQ (cyan) group did not.
connectivity associated with prenatal distress. Infants exposed to higher prenatal maternal distress had higher FA and lower MD. Because FA generally increases and MD generally decreases across childhood (39), our findings may reflect a more mature pattern of brain structure of the right uncinate fasciculus and amygdala-prefrontal white matter connections involved in emotion regulation. Previous studies of infant brain structural and maternal prenatal depression have demonstrated mixed findings, with some reporting higher FA and lower MD in infants and young children associated with higher maternal distress (40–42), while others report higher prenatal depressive symptoms related to lower neurite density (5) and lower FA (9) in 1-month-old and 2-week-old infants, respectively. The tracts identified in these studies vary; for example, higher pre- and postnatal depression symptoms were associated with higher FA in the genu of the corpus callosum (supporting prefrontal connections) but not in the uncinate fasciculus when averaged across both hemispheres. Our right-lateralized functional and structural results are consistent with prior findings showing that prenatal maternal depressive symptoms are associated with prefrontal white matter connections in the right hemisphere (9). Previous studies have identified right cortex structural variations in children and adolescents with or at risk of depression (43,44), and electroencephalography studies have demonstrated functional brain activity in infants and children using right frontal electrodes that relate to prenatal anxiety and depression (45). The right hemisphere is also more implicated in mental health in children (46) and adolescents (47), suggesting that functional and structural brain alterations may be an underlying mechanism via which maternal prenatal distress can lead to increased risk for mental health difficulties in adolescence.

Our results also show, for the first time, that social support plays a role not only on the impact of prenatal distress on pregnant individuals but also on the developing infant brain. Prenatal distress was negatively related to infant brain functional connectivity in mothers with low social support, but this relationship was not present in individuals with high social support. We found that reduced functional connectivity between the right amygdala and superior orbitofrontal cortex as well as the inferior frontal gyrus was related to higher prenatal distress, suggesting an alteration in the development of the functional connectome that supports emotional regulation and decision making. Previous research in 6-month-old infants demonstrated a positive relationship between amygdala functional connectivity and prenatal depression (48); negative associations have also been observed in young children (9). Our data in infants are consistent with the latter finding and demonstrate a similar pattern in infants born to mothers with low social support. Including social support measures and other important covariates may improve the reproducibility of the complex relationship between prenatal distress and the developing infant brain. These findings suggest that social support may disrupt the transmission of prenatal stress to altered functional connectivity in the developing infant brain. Maternal education significantly correlated with survey measures of prenatal distress and social support. It also played a role in the infant amygdala and orbitofrontal cortex functional connectivity model, where relatively less education was related to higher functional connectivity. Structural connectivity showed alterations associated with prenatal distress, but these were not moderated by social support. It is possible that these relationships may change in later stages of development, because the functional and structural connectome of the infant brain continues to develop and refine (39,49,50). In general, stronger structural connectivity measures and weaker functional connectivity were related to higher prenatal maternal distress. In addition, functional connectivity, but not structural connectivity, relationships were moderated by social support. At this early stage of development, structural and functional brain connectivity appear to have distinct relationships with prenatal maternal distress. Longitudinal imaging data throughout childhood will help better understand the developmental trajectories of the structural and functional connectome and how this relates to perinatal maternal distress.

Potential mechanisms linking prenatal maternal distress to infant brain alterations include epigenetic changes such as increased glucocorticoid receptor methylation in children to silence stress responses (51). Invasive animal studies often attribute heightened and sustained cortisol concentrations to changes in infant cognition and behavior; however, human literature is inconsistent, and an indirect mechanism such as regulation of enzymes may be responsible for cortisol metabolism (52). Prior research has also shown that social support can mitigate the impacts of prenatal stress on this underlying neurophysiology through normalizing the dysregulation of the hypothalamic-pituitary-adrenal axis and consequent cortisol levels (22), providing further evidence for the importance of social support for pregnant individuals and the developing infant.

While our study demonstrates the important role of social support and its relationship with prenatal maternal distress during the pandemic and the relationship with infant functional and structural connectivity measures, there are limitations and opportunities to extend our findings. Our imaging sample had slightly different educational and racial demographic profiles compared with the larger survey sample, and reaching a wider population at multiple sites could be useful to replicate our findings. The infant brain images were acquired at 3 months of age. By this time, postnatal factors may influence the relationships between infant brain and prenatal distress. We controlled for postnatal maternal distress, but infant feeding, sleep, family structure, and infection may also have influenced early brain development in this population. Infants were scanned while asleep without the use of sedatives; however, functional connectivity profiles may differ in awake states. Future studies with higher resolution measures of white matter will be able to further elucidate the nature of these relationships.

In conclusion, we show that pregnant individuals’ mental health has been especially impacted during the COVID-19 pandemic and that social support plays an important role. Furthermore, we observed a relationship between prenatal maternal distress and the developing infant brain. There may be long-lasting impacts of this pandemic-related stress on infants, and our findings will help inform health policies and identify families who may benefit from early interventions (53). The brain shows developmental plasticity in infancy and early childhood, and evidence-based interventions exist to improve
children’s behaviors and mental health risk (54). Our findings provide evidence that social support may disrupt the inter-generational transmission of stress. This highlights the pressing need for prenatal mental health screening and policies that target improving social support (54), because we have demonstrated that this may also support healthy infant brain development in early life.

ACKNOWLEDGMENTS AND DISCLOSURES
This work was supported by the Alberta Children’s Hospital Research Institute and the Owerko Centre for Neurodevelopment and Mental Health. CL receives funding from the Canada Research Chair Program. KYM was supported by the T Chen Fong Postdoctoral Fellowship in Medical Imaging Science.

ACKNOWLEDGMENTS AND DISCLOSURES

CL and KYM had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. KYM contributed through data collection, analysis, data interpretation, manuscript preparation, and revisions. XL contributed data collection, analysis, and statistical analyses. DW contributed data analysis. LT-M, GFG, and CL contributed study conception, funding acquisition, protocol design, and data interpretation. All authors participated in manuscript revisions and approved the final draft.

A previous version of this article was published as a preprint on medRxiv: https://www.medrxiv.org/content/10.1101/2021.10.04.21264536v1.

The authors report no biomedical financial interests or potential conflicts of interest.

ARTICLE INFORMATION
From the Department of Radiology (KYM, XL, CL), Hotchkiss Brain Institute (KYM, XL, CL), Department of Psychology (DW, LT-M, GFG), Department of Pediatrics (LT-M, GFG), Department of Community Health Sciences (GFG), and the Alberta Children’s Hospital Research Institute (KYM, XL, LT-M, GFG, CL), University of Calgary, Calgary, Alberta; and the Department of Educational and Counselling Psychology (LT-M), University of British Columbia, Vancouver, British Columbia, Canada.

Address correspondence to Catherine Lebel, Ph.D., at clebel@ucalgary.ca.

Received Dec 21, 2021; revised Apr 25, 2022; accepted May 9, 2022.

Supplementary material cited in this article is available online at https://doi.org/10.1016/j.biopsych.2022.05.011.

REFERENCES
1. Pearson RM, Evans J, Kounali D, Lewis G, Heron J, Ramchandani PG, et al. (2013): Maternal depression during pregnancy and the postnatal period: Risks and possible mechanisms for offspring depression at age 18 years. JAMA Psychiatry 70:1312–1319.
2. Van den Bergh BRH, van den Heuvel Mi, Lahti M, Braeken M, de Rooij SR, Entringer S, et al. (2020): Prenatal developmental origins of behavior and mental health: The influence of maternal stress in pregnancy. Neurosci Biobehav Rev 117:26–64.
3. Pawlby S, Hay DF, Sharp D, Waters CS, O’Keane V (2009): Antenatal depression predicts depression in adolescent offspring: Prospective longitudinal community-based study. J Affect Disord 113:236–243.
4. Lee A, Poh JS, Wen DJ, Guillaume B, Chong YS, Shek LP, et al. (2019): Long-term influences of prenatal maternal depressive symptoms on the amygdala-prefrontal circuitry of the offspring from birth to early childhood. Biol Psychiatry Cogn Neuroimaging 4:940–947.
5. Dean DC 3rd, Planalp EM, Wooten W, Kecskemeti SR, Adluri N, Schmidt CK, et al. (2018): Association of prenatal maternal depression and anxiety symptoms with infant white matter microstructure. JAMA Pediatr 172:973–981.
6. Lebel C, Walton M, Letourneau N, Giesbrecht GF, Kaplan BJ, Dewey D (2016): Prepartum and postpartum maternal depressive symptoms are related to children’s brain structure in preschool. Biol Psychiatry 80:859–868.
7. O’Donnell KJ, Glover V, Barker ED, O’Connor TG (2014): The persisting effect of maternal mood in pregnancy on childhood psychopathology. Dev Psychopathol 26:393–403.
8. Donnici C, Long X, Dewey D, Letourneau N, Landman B, Huo Y, Lebel C (2021): Prenatal and postnatal maternal anxiety and amygdala structure and function in young children. Sci Rep 11:4019.
9. Rifkin-Graboi A, Meaney MJ, Chen H, Bai J, Hameed WB, Tint MT, et al. (2015): Antenatal maternal anxiety predicts variations in neural structures implicated in anxiety disorders in newborns. J Am Acad Child Adolesc Psychiatry 54:313–321.e2.
10. Sandman CA, Buss C, Head K, Davis EP (2015): Fetal exposure to maternal depressive symptoms is associated with cortical thickness in late childhood. Biol Psychiatry 77:324–334.
11. Hay RE, Reynolds JE, Grohs MN, Panukov D, Giesbrecht GF, Letourneau N, et al. (2020): Amygdala-prefrontal structural connectivity mediates the relationship between prenatal depression and behavior in preschool boys. J Neurosci 40:6969–6977.
12. Groulx T, Bagshawe M, Giesbrecht G, Tomfohr-Madsen L, Hetherington E, Lebel CA (2021): Prenatal care disruptions and associations with maternal mental health during the COVID-19 Pandemic. Front Glob Womens Health 2:648328.
13. Wu Y, Zhang C, Liu H, Duan C, Li C, Fan J, et al. (2020): Perinatal depressive and anxiety symptoms of pregnant women during the coronavirus disease 2019 outbreak in China. Am J Obstet Gynecol 223:240.e1–240.e9.
14. Berthelot N, Lemioux R, Garon-Bissonnette J, Douin-Maziade C, Martel E, Maziade M (2020): Uptrend in distress and psychiatric symptomatology in pregnant women during the coronavirus disease 2019 pandemic. Acta Obstet Gynecol Scand 99:848–855.
15. Saccone G, Florio A, Aiello F, Venturella R, De Angelis ML, Locci M, et al. (2020): Psychological impact of coronavirus disease 2019 in pregnant women. Am J Obstet Gynecol 223:293–295.
16. Lebel C, MacKinnon A, Bagshawe M, Tomfohr-Madsen L, Giesbrecht G (2020): Elevated depression and anxiety symptoms among pregnant individuals during the COVID-19 pandemic [published correction appears in J Affect Disord 2021; 279:377–379], J Affect Disord 277:5–13.
17. Tomfohr-Madsen LM, Racine N, Giesbrecht GF, Lebel C, Madigan S (2021): Depression and anxiety in pregnancy during COVID-19: A rapid review and meta-analysis. Psychiatry Res 300:113912.
18. Jones SL, Dufoix R, Laplante DP, Elbegli G, Patel R, Chakravarty MM, et al. (2019): Larger amygdala volume mediates the association between prenatal maternal stress and higher levels of externalizing behaviors: Sex specific effects in Project Ice Storm. Front Hum Neurosci 13:144.
19. McLean MA, Cobham VE, Simcock G, Kildes S, King S (2019): Toddler temperament mediates the effect of prenatal maternal stress on childhood anxiety symptomatology: The QF2011 Queensland flood study. Int J Environ Res Public Health 16:1998.
20. Cao-Lei L, Dancauce KN, Elbegli G, Massart R, Szyl M, Liu A, et al. (2015): DNA methylation mediates the impact of exposure to prenatal maternal stress on BMI and central adiposity in children at age 13 1/2 years: Project Ice Storm. Epigenetics 10:749–761.
21. Deoni SCL, Beauchemin J, Volpe A, Dà Sa V, RESONANCE Consortium (2021): Impact of the COVID-19 pandemic on early child cognitive development: Initial findings in a longitudinal observational study of child health. medRxiv. https://doi.org/10.1101/2021.08.10.21262184.
22. Giesbrecht GF, Poole JC, Letourneau N, Campbell T, Kaplan BJ, AIPRON Study Team (2013): The buffering effect of social support on hypothalamic-pituitary-adrenal axis function during pregnancy. Psychosom Med 75:856–862.
23. Tomfohr-Madsen L, Cameron EE, Dunkel Schetter C, Campbell T, O’Berne M, Letourneau N, Giesbrecht GF (2019): Pregnancy anxiety and preterm birth: The moderating role of sleep. Health Psychol 38:2025–1035.
24. Demisie Z, Siega-Riz AM, Esvenson KR, Herring AH, Dodge N, Gaynes BN (2011): Physical activity and depressive symptoms among pregnant women: The PIN3 study, Arch Womens Ment Health 14:145–157.
Prenatal Distress in the Pandemic and the Infant Brain

25. Garlepy G, Honkanenri H, Quesnel-Vallee A (2016): Social support and protection from depression: Systematic review of current findings in Western countries. Br J Psychiatry 209:284–293.

26. Giesbrecht GF, Bagshawe M, van Sloten M, Mackinnon AL, Dhillion A, van de Wouw M, et al. (2021): Protocol for the Pregnancy during the COVID-19 Pandemic (PoP) study: A longitudinal cohort study of mental health among pregnant Canadians during the COVID-19 pandemic and developmental outcomes in their children. JMIR Res Protoc 10:e25407.

27. Bergink V, Kooistra L, Lambrechts-van den Berg MP, Wijnen H, Bunevicuvis R, van Baar A, Pop V (2011): Validation of the Edinburgh Depression Scale during pregnancy. J Psychosom Res 70:385–389.

28. Cella D, Choi SW, Condon DM, Schalet B, Hays RD, Rothrock NE, et al. (2019): PROMIS® adult health profiles: Efficient short-form measures of seven health domains. Value Health 22:537–544.

29. Rini C, Schetter CD, Hibel CJ, Glynn LM, Sandman CA (2006): Effective social support: Antecedents and consequences of partner support during pregnancy. Personal Relat 13:207–229.

30. Leemans A, Jeurissen B, Sijbers J, Jones DK (2009): ExploreDTI: A graphical toolbox for processing, analyzing and visualizing diffusion MR data. Proc Intl Soc Mag Reson Med 17:3537.

31. Jenkinson M, Beckmann CF, Behrens TEJ, Woolrich MW, Smith SM (2012): FSL. Neuroimage 62:782–790.

32. Shi F, Yap PT, Wu G, Jia H, Gilmore JH, Lin W, Shen D (2011): Infant brain atlases from neonates to 1- and 2-year-olds. PLoS One 6: e18746.

33. Woolrich MW, Behrens TEJ, Beckmann CF, Jenkinson M, Smith SM (2004): Multilevel linear modelling for FMRI group analysis using Bayesian inference. Neuroimage 21:1732–1747.

34. Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Brody DJ, Pratt LA, Hughes JP (2018): Prevalence of depression among adults aged 20 and over: United States, 2013–2016. NCHS Data Brief. Available at: https://www.cdc.gov/nchs/data/databriefs/db303_table.pdf#3. Accessed August 24, 2021.

35. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Gaffrey MS, Barch DM, Luby JL, Petersen SE (2021): Amygdala functional connectivity is associated with emotion regulation and amygdala reactivity in 4- to 6-year-olds. J Am Acad Child Adolesc Psychiatry 60:176–185.

36. Fischer CS, Tzeler EH, Mogg K, Bradley BP, Mai X, Louro HMC, et al. (2008): Amygdala and ventrolateral prefrontal cortex activation to masked angry faces in children and adolescents with generalized anxiety disorder. Arch Gen Psychiatry 65:568–576.

37. Qiu A, Anh TT, Li Y, Chen H, Rifkin-Graboi A, Broekman BFP, et al. (2015): Prenatal maternal depression alters amygdala functional connectivity in 6-month-old infants. Transl Psychiatry 5:e508.

38. Wang H, Ghaderi A, Long X, Reynolds JE, Lebel C, Protzner AB (2021): The longitudinal relationship between BOLD signal variability changes and white matter maturation during early childhood. Neuroimage 242:118448.

39. Long X, Benischeck A, Dewey D, Lebel C (2017): Age-related functional brain changes in young children. Neuroimage 155:322–330.

40. Oberlander TF, Weinberg M, Grunau R, Misri S, Devlin AM (2011): Validation of the Edinburgh Depression Scale during pregnancy. J Psychosom Res 70:385–389.

41. Glover V, O’Connor TG, O’Donnell K (2010): Prenatal stress and the programming of the HPA axis. Neurosci Biobehav Rev 35:17–22.

42. Gleason MM, Goldson E, Yogman MW, Council on Early Childhood; Committee on Psychosocial Aspects of Child and Family Health, Section on Developmental and Behavioral Pediatrics (2016): Addressing early childhood emotional and behavioral problems. Pediatrics 138:e20163025.

43. Tomfohr-Madsen LM, Giesbrecht G, Madsen JW, Mackinnon A, Le Y, Doss B (2020): Improved child mental health following brief relationship enhancement and co-parenting interventions during the transition to parenthood. Int J Environ Res Public Health 17:766.