Research paper

Maternal depression during pregnancy alters infant subcortical and midbrain volumes.

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ABSTRACT

Background: Maternal depression in pregnancy increases the risk for adverse neurodevelopmental outcomes in the offspring. The reason for this is unknown, however, one plausible mechanism may include the impact of maternal antenatal depression on infant brain. Nevertheless, relatively few studies have examined the brain anatomy of infants born to clinically diagnosed mothers.
Methods: A legacy magnetic resonance imaging (MRI) dataset was used to compare regional brain volumes in 3-to-6-month-old infants born to women with a clinically confirmed diagnosis of major depressive disorder (MDD) during pregnancy ($n = 31$) and a reference sample of infants born to women without a current or past psychiatric diagnosis ($n = 33$). A method designed for analysis of low-resolution scans enabled examination of subcortical and midbrain regions previously found to be sensitive to the parent-child environment.
Results: Compared with infants of non-depressed mothers, infants exposed to maternal antenatal depression had significantly larger subcortical grey matter volumes and smaller midbrain volumes. There was no association between gestational medication exposure and the infant regional brain volumes examined in our sample.
Limitations: Our scanning approach did not allow for an examination of fine-grained structural differences, and without repeated measures of brain volume, it is unknown whether the direction of reported associations are dependent on developmental stage.
Conclusions: Maternal antenatal depression is associated with an alteration in infant brain anatomy in early postnatal life; and that this is not accounted for by medication exposure. However, our study cannot address whether anatomical differences impact on future outcomes of the offspring.

1. Introduction

Maternal depression in pregnancy ('antenatal depression' hereafter) is common with estimates ranging from 9-14% in women experiencing clinically significant levels of depression in pregnancy (Evans et al., 2001; Woody, Ferrari, Siskind, Whiteford, & Harris, 2017). Several studies have reported that offspring exposed to antenatal depression are at increased risk of poorer neurodevelopmental outcomes – including for

example, lower new-born neurobehavioral functioning, higher infant cortisol response (Osborne et al., 2018) and less optimal cognitive development (Stein et al., 2014). Moreover, maternal antenatal depression is an independent risk factor for offspring depression in adolescence and early adulthood (Pawlby et al., 2009; Plant et al., 2015). The mechanism underlying the association between antenatal depression and adverse outcomes of offspring is not well understood and is likely to be complex. It is plausible that shared genes and/or

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intra-uterine (e.g. hormonal) environmental influences alter outcomes through their influence on infant brain development (Bock et al., 2015; Osborne et al., 2018). That is, the infant brain is an 'intermediate phenotype' on the pathway between gene and environmental influences involved in antenatal depression and offspring outcomes.

There is preliminary evidence to support this suggestion from several studies. For instance, the level of maternal antenatal depression has been linked to the structure and functional connectivity of their offspring's amygdala during early infancy (for reviews, please see Duan et al., 2019; Goodman, 2020). Links between severity of ongoing maternal depressive symptoms across the perinatal period and smaller gray and white matter volumes of offspring, during middle childhood, have also been reported (Zou et al., 2019). These studies were valuable first steps. However, many did not include a clinical diagnostic assessment. Additionally, their findings may be confounded by sample characteristics – such as, the inclusion of preterm-born infants (Scheinost et al., 2016) or exposure to postnatal factors, such as maternal sensitivity and postnatal depression, when scanning older children (e.g. Zou et al., 2019).

Those studies that did include mothers with a clinical diagnosis of depression have reported conflicting results. Some studies have reported no differences in global or regional brain volumes in infants born to women with a diagnosis of major depressive disorder (MDD), regardless of exposure to selective serotonin reuptake inhibitors (SSRIs) during pregnancy (Jha et al., 2016), while others have shown that prenatal exposure to SSRIs was linked to larger gray matter volumes (Lugo-Candelas et al., 2018). Taken together, it remains unclear whether clinical depression and/or SSRI treatment impact upon infant brain development.

Thus, the current investigation is an opportunistic study of a legacy dataset from a study of the impact of maternal depression on infant development. The volumetric data available to us were of low resolution but permitted examination of 'bulk' regional brain volumes. The participants were 3-to-6-month-old infants born to women with a clinically confirmed diagnosis of MDD during pregnancy and a reference sample of infants of women without a psychiatric diagnosis during or prior to the postnatal period. We applied a method designed for analysis of low-resolution scans which maximizes the information obtained from valuable cohorts of infants scanned in natural sleep. Our regions of interest were subcortical and midbrain volumes, for several reasons.

First, there is accumulating evidence for their key role in higher cognitive and emotional processes crucial to successful development (Arnsten and Rubia, 2012; Radoman et al., 2019). Second, evidence from studies including depressed child and adolescent samples have documented alterations in both the function and structure of these regions (Bessette et al., 2014; Matsuo et al., 2008). Such findings in older samples raise the possibility that alterations in subcortical and midbrain regions at earlier time-points may be indicative of a depression-related risk factor. Third, subcortical regions are especially sensitive to perinatal exposures (Okereafor et al., 2008; Shalak and Perlman, 2004). We have previously reported that anatomy of the infant subcortical region is linked to the parent-child environment (Sethna et al., 2017). Fourth, these regions can be reliably measured using our in-house protocols for low-resolution scans. [At the time of data collection, the acquisition protocol prioritized fMRI in the brief time that infants were asleep during daytime (Craig et al., in press). It precluded measurement of smaller regions-of-interest (such as amygdala) (Sethna et al., 2017)]. We predicted that infants of antenatally depressed women would exhibit volumetric alterations in subcortical grey matter and midbrain volumes, compared to infants of non-depressed women. Furthermore, we expected that the extent of any differences would be correlated with the severity of depressive symptoms.

We also incorporated exploratory analyses investigating whether there were differences in brain volumes between infants born to antenatally depressed women on antidepressant medication during pregnancy and medication naive depressed women. Population studies have identified a potential link between antidepressant (SSRI) use in pregnancy and adverse neurodevelopmental outcomes (Homberg et al., 2010). However, the interpretation of any such relationship is confounded by the likelihood that only clinically depressed mothers are offered medication in pregnancy. Accordingly, any correlation could be driven by the severity of antenatal depression (hence need for medical treatment) and not SSRI exposure directly. Moreover, even though preclinical animal studies indicate that antenatal SSRIs influence the brain development of offspring, these studies have been conducted in typical laboratory rodent strains not animals modelling 'depression' (for a review, see Ornoy and Koren, 2019). Thus, the influence of SSRIs on human infant brain development in offspring whose mothers are clinically depressed during pregnancy remains an open question.

2. Methods

The sample for the current study was drawn from a prospective cohort fMRI study aimed to explore the response to emotional sound of infants born to mothers with and without a diagnosis of prenatal maternal depression (Craig et al., in press).

In the current longitudinal investigation mothers were approached, predominantly during their second and third trimester, from antenatal clinics and perinatal psychiatric services within the same community in South London. Diagnostic status was confirmed using The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (First, Spitzer, Gibbon, & Williams, 1997) at 32 weeks of gestation, and depressive symptoms were further quantified in all mothers using the Beck Depression Inventory (BDI) (Beck & Steer, 1993). Antidepressant medication use was confirmed via medical records.

MRI assessments were conducted in infants aged 3-6 months. Infants were scanned during natural sleep at the Centre for Neuroimaging in the Institute of Psychiatry, Psychology, and Neuroscience at King's College London. During the visit, mothers completed a demographic questionnaire, and maternal sensitivity was also assessed using a standard assessment protocol (Murray et al., 1996) (usually on the same day, or within 2-weeks of the MRI scan).

2.1. Sample

Participants were initially 81 mother-infant dyads – 11 participants were excluded from the analysis as they had experienced depression prior to pregnancy ($n = 10$) and/or anxiety disorder ($n = 1$). Hence, 34 women with clinically significant MDD in pregnancy and 36 women without a current diagnosis of clinical depression in pregnancy were eligible to take part in the study.

Clinically depressed women recruited (during the second and third trimester) from perinatal services across South London served as the exposed group (i.e., women diagnosed with Major Depressive Disorder in pregnancy). A diagnosis of Major Depressive Disorder (MDD) was established by a perinatal psychiatrist from South London and Maudsley (SLAM) NHS Foundation Trust. Non-depressed women were recruited from the local community in South London to serve as the unexposed group (i.e., women without a current or past clinical diagnosis of MDD). A trained researcher independently evaluated women in both groups to detect the presence of current or previous psychiatric diagnoses using the Structured Clinical Interview for DSM-IV-TR Axis I disorders (SCID-I).

Inclusion criteria for the study comprised women having a working knowledge of the English language and being free from any antenatal or obstetric complications potentially altering infant development (e.g., gestational diabetes, placental anomalies). Infants in both groups were free from any congenital abnormalities. Exclusion criteria included contraindications for MRI scanning (e.g., metallic implants or pacemakers). The study was approved by the UK National Research Ethics Committee (REC 07/H0807/70 and 12/LO/2017) and written informed consent for participation was obtained from all women.

MRI assessments were available for 64 infants – 6 scans were

excluded from the analysis due to motion artefacts ($n = 5$) and an incidental anatomical brain anomaly found at MRI scanning ($n = 1$). Therefore, the final sample comprised 64 mother-infant dyads with complete data on maternal antenatal depression measures and infant structural MRI collected at 3-to-6 months – 31 participants in the clinically depressed group and 33 participants in the non-depressed group. Of the total sample, mother's had a mean age of 33 years ($SD = 5$ years) and the majority held a higher education certificate (78%). Infants had a mean age of 147 days ($SD = 40$ days) and 58% were male. There was no difference in infant (age at MRI, gestational age, birth weight, or sex) or maternal (age at MRI and education level) characteristics between exposed and non-exposed groups (Please see Table 1).

3. Measures

3.1. Maternal depression (Exposure)

: The Structured Clinical Interview for DSM-IV Axis 1 Disorders (SCID-I) (First et al., 2002) was used to assess the presence or absence of Major Depressive Disorder (MDD) in pregnancy and administered by a clinically trained professional. The SCID-I is a semi-structured interview for making clinical DSM-IV Axis I diagnoses. The diagnostic interview focused on MDD occurring during the current antenatal period. Furthermore, the SCID-I has demonstrated high reliability and validity in producing accurate diagnoses according to the DSM (Basco et al., 2000).

The Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) was used to measure the severity of current depressive symptoms in pregnancy and the postnatal period. The BDI-II is a self-report scale comprising of 21-items. Each item represents a particular symptom of depression which corresponds to the diagnostic criteria listed in the DSM-IV (American Psychiatric Association, 1994). Respondents are asked to choose the statement that best reflects the way they have been feeling over the course of the last 2 weeks. Each item is rated on a 4-point scale – ranging from an absence of symptoms (0) to severe or persistent expression of symptoms (3). Estimates of internal consistency reliability demonstrate that the BDI-II has good internal consistency in both clinical and non-clinical populations (Beck et al., 1988).

3.2. Structural magnetic resonance imaging (Outcome)

MRI acquisition and segmentation protocol are previously reported in: Blasi et al., 2011; Sethna et al., 2017. A summary of acquisition and segmentation is outlined below:

3.2.1. MRI data acquisition

A 1.5T General Electric TwinSpeed MRI scanner (GE Medical Systems, Milwaukee, WI, USA), equipped with an 8-channel head coil was used. Infants were scanned in natural sleep with no sedation.

A T2-weighted (T2w) fast spin echo (T2w) sequence was acquired with the following imaging parameters: number of slices = 20; slice thickness = 4mm; slice gap = 2mm; repetition time = 3000/4500ms; echo time = 115ms; field of view = 180mm; flip angle 90°; matrix size = 256 × 224. All MRI scans were assessed by a radiologist.

3.2.2. Image pre-processing and volumetric segmentation

Scans were analysed blind to family characteristics using an in-house developed protocol for low resolution images (Sethna et al., 2017). T2w MR images were skull-stripped, and the masked images were then segmented using an atlas-based method, which adapted the Statistical Parametric Mapping software (v. SPM8) and a probabilistic neonatal brain atlas (Kuklisova-Murgasova et al., 2011) as an input to the software. The SPM segmentation model unifies tissue classification, image bias correction, and non-linear atlas registration (Ashburner and Friston, 2005). Following this, the segmented cerebrospinal fluid (CSF) was refined, and partial volume misclassifications corrected based on tissue

Table 1
Infant and maternal demographic characteristics for the total sample, and split by clinical depression status [a].

Demographic characteristics	Total	Clinical depression status (SCID diagnostic groups)		
$n = 64$	Clinically depressed			
$n = 31$	Non-depressed			
$n = 33$	Statistic[a]			
Infant demographics: *mean (SD)*				
Infant's age at MRI scan (days)	147 (40)	146 (44)	149 (36)	$t (62) = 0.37, p = 0.712$
Infant's gestational age (weeks)[b]	40 (2)	40 (2)	40 (2)	$t (61) = 0.40, p = 0.694$
Infant's birth weight (grams)[b]	3279 (626)	3260 (551)	3297 (698)	$t (60) = 0.23, p = 0.819$
Infant sex: *n (%)*				$\chi^2 = 1.11, p = 0.293$
Female	27 (42%)	11 (36%)	16 (49%)	
Male	37 (58%)	20 (64%)	17 (51%)	
Maternal demographics: *mean (SD)*				
Age (years): *mean (SD)*	33 (5)	32 (5)	33 (5)	$t (62) = 0.82, p = 0.414$
Education level: *n (%)*				$\chi^2 = 3.88, p = 0.143$
GCSE's and A levels	8 (13%)	6 (19%)	2 (6%)	
Diploma	6 (9%)	4 (13%)	2 (6%)	
Higher education	50 (78%)	21 (68%)	29 (88%)	
Antidepressant medication use: *n (%)*				$\chi^2 = 26.66, p < 0.001$
During pregnancy	18 (28%)	18 (58%)	-	
Medication-naïve	46 (72%)	13 (42%)	33 (100%)	
BDI score: *mean (SD)*				
Antenatal BDI	15 (12)	22 (13)	7 (4)	$t (62) = -5.77, p < 0.001$
Postnatal BDI[b]	11 (11)	18 (13)	7 (8)	$t (49) = -3.36, p = 0.003$

SD, standard deviation; *M*, mean; *t,* independent-samples t-test; χ^2, Chi Square; **BOLD*,** significant mean difference < 0.05.
[a] Major depressive disorder assessed using the SCID.
[b] There was missing data for infant gestational age ($n = 1$) and birth weight ($n = 2$), and maternal postnatal BDI scores ($n = 49$).

connectivity using second order Markov random fields. All images were examined in a final manual editing process using ITK-SNAP (v. 2.2).

This study included subcortical grey (including the caudate, putamen, globus pallidus and thalamus) and midbrain volumes (including the cerebral peduncle, substantia nigra, brainstem and pons). These regional brain volumes were expressed as proportions of intracranial volume and 'corrected' proportions were used in the analyses.

Intra-rater intra-class correlations (ICC) were performed between the final segmentations and a repeat measurement of a randomly selected

20% of the automatically segmented images. For the intracranial volume, ICC = 0.998 (p < 0.001), midbrain (ICC = 0.918, p < 0.001) and subcortical grey matter (ICC = 0.923, p < 0.001), indicating excellent reproducibility.

3.3. Statistical analysis

Descriptive statistics were computed for the exposure (diagnostic groups – antenatally depressed and non-depressed women and severity of current depressive symptoms in pregnancy – BDI scores) and outcomes (subcortical grey matter and midbrain volumes), as well as for potential confounder variables (i.e. infant sex, gestational age (weeks) and birthweight (grams), maternal sensitivity during mother-infant interactions, postnatal depressive symptoms (BDI scores) and antenatal antidepressant use). Continuous (means / standard deviations) and categorical (frequencies / percentages) data were summarized. Bivariate correlations between potential confounders with exposure variables were tested.

Inferential statistics included three steps: (i) *t*-tests to examine mean differences in infant brain volumes between antenatally depressed and non-depressed women. Where a significant difference was observed, separate multiple linear regression models were used to test the adjusted associations. Potential confounders were included in multivariate models, if they were associated with maternal depressive indices at a threshold of at least a moderate effect size ($r \geq 0.3$) or reached cut-off level at *p* value threshold set at < 0.25 (Chowdhury & Turin, 2020). Given that individual variables may be weakly associated with the

exposure, but contribute significantly when combined, a higher significance threshold was set to allow more variables to illustrate significance in univariate analysis (Chowdhury & Turin, 2020). Effect sizes were calculated using Cohen's f^2 (Cohen, 1988) for multiple linear regression models; (ii) Analysis of variance (ANOVA) tests to examine subcortical and midbrain volume differences in three groups: depressed women on medication; medication naïve depressed women; non-depressed women; (iii) Partial correlations (adjusting for diagnostic group status) to test associations between BDI scores for maternal depressive symptoms in pregnancy and infant subcortical and midbrain brain volumes in the total sample.

4. Results

4.1. Descriptive analyses

As expected, maternal antenatal medication use was associated with both diagnostic status ($\chi 2 = 26.66$, $p < 0.001$) and depressive symptoms in pregnancy ($r (62) = 0.60$, $p < 0.001$). Clinically depressed women and those with higher BDI scores in pregnancy were more likely to be on medication. Moreover, women with elevated depressive symptoms in pregnancy were more likely to present with postnatal depressive symptoms ($r (47) = 0.65$, $p < 0.001$). Moreover, infant sex was associated with depressive symptoms in pregnancy at *p* value threshold set to < 0.25 ($r (62) = -0.18$, $p = 0.147$). Hence, antenatal medication use, postnatal depressive symptoms and infant sex were included as covariates in multivariate analyses.

Table 2
Descriptive statistics and associations between exposure, outcome and potential confounding variables (N = 64)

Study variables	Mean (SD) / N (%)	1	2	3	4	5	6	7	8	9	10	11	12
Exposure													
1. Clinical depression status (antenatally depressed)	31 (48%)	-											
2. Depressive symptoms in …pregnancy (BDI scores)	14.52 (12.15)	0.60											
(*p* <.001)*		-	-										
Outcome													
3. Subcortical grey matter . . . volumes (cm³)	35.93 (4.39)	0.42											
(*p* = .001)*		0.28											
(*p* = .023)*		-											
4. Midbrain volumes (cm³)	12.71 (2.24)	-0.51											
(*p* <.001)*		-0.22	0.13	-									
5. Total brain matter volume (cm³)	703.47 (89.25)	0.05	0.09	0.70									
(*p* < .001)*		0.63											
(*p* < .001)*		-											
Potential confounders													
6. Infant age at MRI scan (days)	147 (40)	-0.05	0.11	-0.22									
(*p* = .079)ᶜ		-0.11	0.30										
(*p* = .015)		-											
7. Infant birth weight (grams)	3279 (626)	-0.03	0.14	-0.04	0.10	0.07	0.05	-					
8. Infant sex (male)	37 (58%)	1.11	-0.18										
(*p* = .147)ᶜ		-0.14	0.00	0.10	0.02	-0.18	-						
9. Infant gestational age (weeks)	40 (2)	-0.05	0.01	-0.02	0.01	0.18	0.01	0.40					
(*p* = .001)*		0.10	-										
10. Postnatal depression,,,,,,(BDI scores)	10.94 (11.18)	0.48											
(*p* <.001)*		0.65											
(*p* <.001)*		0.30											
(*p* = .036)*		-0.12	0.14	0.15	0.04	-0.26	-0.18	-					
11. Maternal sensitivity ….(GRS scores)	3.49 (0.52)	0.01	-0.09	0.26	-0.04	0.03	-0.16	0.00	0.03	-0.06	-0.11	-	
12. Antidepressant medication …..(during pregnancy)	18 (28%)	26.66											
(*p* <.001)*		0.60											
(*p* <.001)*		0.26											
(*p* = .041)*		-0.26											
(*p* = .042)*		0.02	0.10	-0.07	2.13	-0.18	0.36						
(*p* = .011)*		-0.12 -											

SD = Standard Deviation; **BOLD*** = significant correlation (< 0.05)
ᶜ = correlation reached cut-off *p* value threshold set at < 0.25 (Chowdhury & Turin, 2020); subcortical grey matter, midbrain and total brain matter volumes expressed as proportions of intracranial volume were used in the analyses including depression indices and potential confounders; BDI = Beck Depression Inventory, BDI scored on a scale from 0-4 with higher scores indicating increased levels of depressive symptoms.

None of the other potential confounders (i.e., infant age at MRI scan, birth weight and gestational age; and maternal sensitivity) were associated with the exposure under investigation (please see Table 2).

4.2. Inferential analyses

There was no significant difference in total brain matter volume in infants born to antenatally depressed women ($M = 0.82$, $SD = 0.03$) and non-depressed women ($M = 0.82$, $SD = 0.04$); $t (62) = -0.42$, $p = 0.678$).

4.2.1. Relationship between maternal antenatal depression and infant subcortical grey matter volumes

Infants of mothers in the clinically depressed group had significantly larger subcortical grey matter volumes ($M = 0.044$, $SD = 0.003$), compared to infants of mothers in the non-depressed group ($M = 0.041$, $SD = 0.004$), $t (62) = -3.63$, $p = 0.001$. The association remained statistically significant ($\beta = 0.42$, $p = 0.036$; medium effect size (Cohens $f^2 = 0.22$)) when adjusting for maternal antenatal medication use, postnatal depressive symptoms, and infant sex.

Next, analysis of variance showed a main effect of diagnostic group status on subcortical grey matter volumes ($F (2, 63) = 6.49$, $p = 0.003$). Post-hoc analyses using Tukey's HSD indicated that infant subcortical grey matter volumes did not significantly differ between antenatally depressed women who were on antidepressant medication ($M = 0.044$, SD = 0.004) and medication naïve depressed women ($M = 0.044$, SD = 0.003) ($p = 0.987$) (see Fig. 1).

Finally, there was no evidence of an association between the severity of depressive symptoms in pregnancy and subcortical grey matter volumes in the total sample ($r_{xy.z} = 0.04$, $p = 0.736$), adjusting for diagnostic group status.

4.2.2. Relationship between maternal antenatal depression and infant midbrain volumes

Infants of mothers in the clinically depressed group had significantly smaller midbrain volumes ($M = 0.014$, $SD = 0.002$), compared to infants of mothers in the non-depressed group ($M = 0.016$, $SD = 0.002$), $t (62) = 4.64$, $p < 0.001$. When adjusting for covariates (i.e., antenatal

medication use, postnatal depressive symptoms, and infant sex), this association remained significant ($\beta = -0.62$, $p = 0.002$) with a medium to large effect size (Cohens $f^2 = 0.30$).

Next, analysis of variance showed a main effect of diagnostic group status on midbrain volumes ($F (2, 63) = 11.07$, $p < 0.001$). Post-hoc analyses using Tukey's HSD indicated that infant midbrain volumes did not significantly differ between antenatally depressed women who were on antidepressant medication (M = 0.014, SD = 0.002) and medication naïve depressed women (M = 0.013, SD = 0.002) ($p = 0.665$) (see Fig. 2).

Moreover, the severity of depressive symptoms in pregnancy was not associated with midbrain volumes in the total sample ($r_{xy.z} (62) = 0.13$, $p = 0.329$), adjusting for diagnostic group status.

5. Discussion

In this study of a valuable legacy data set we compared bulk regional brain volumes in infants born to women with a clinically confirmed diagnosis of depression during pregnancy and a reference group of infants born to women without depression in pregnancy. In addition, the association between severity of maternal depressive symptoms and infant regional brain volumes was examined. Finally, we explored whether there were differences in brain volumes between infants born to antenatally depressed women on antidepressant medication during pregnancy and medication naive depressed women.

Infants born to mothers with MDD during pregnancy had significantly larger subcortical grey matter volumes, but smaller midbrain volumes, relative to infants of non-depressed women. However, the extent of the subcortical and midbrain volume differences was not correlated with the severity of depressive symptoms in pregnancy. Additionally, our findings did not provide support for a link between gestational antidepressant medication exposure and the infant regional brain volumes examined in this study – i.e., subcortical and midbrain volumes did not differ between antenatally depressed women on antidepressants and medication naïve depressed women.

Our findings add to the evidence that subcortical structures are particularly susceptible to the *in utero* environment (Shalak and
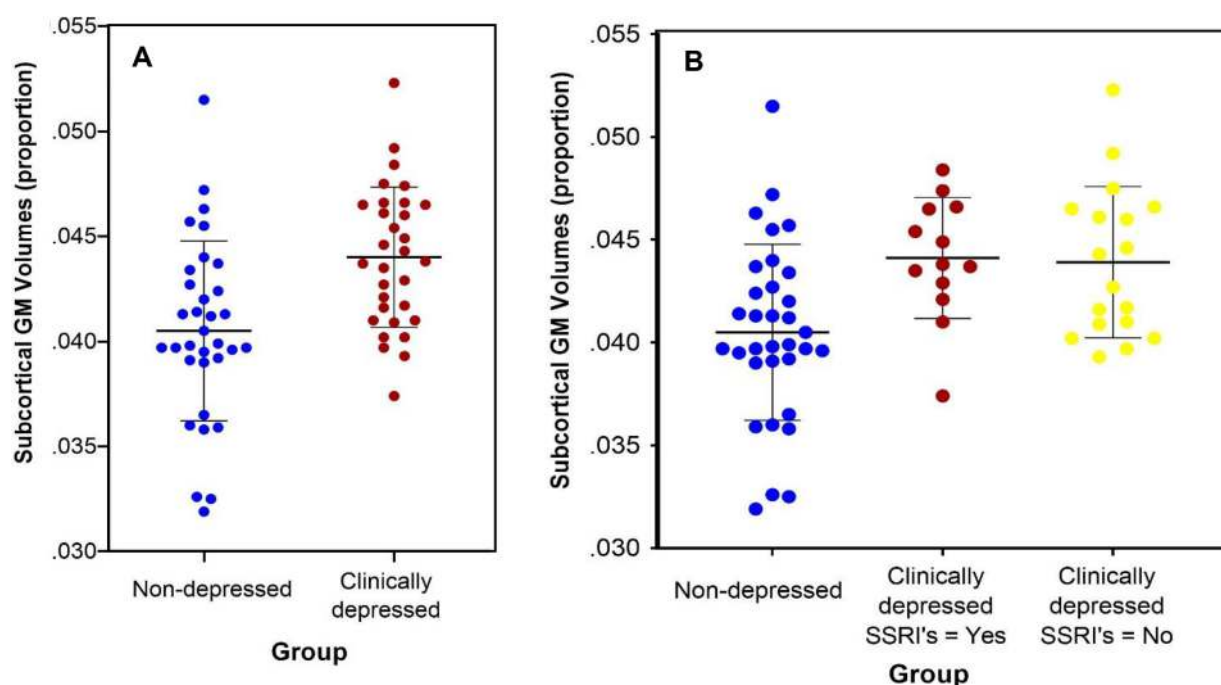

Fig. 1. Scatter dot plots of individual data points and mean and SD error bars showing (A) subcortical gray matter (GM) volumes in infants of mothers in the clinically depressed and non-depressed groups; and (B) further stratified according to maternal mediation status.
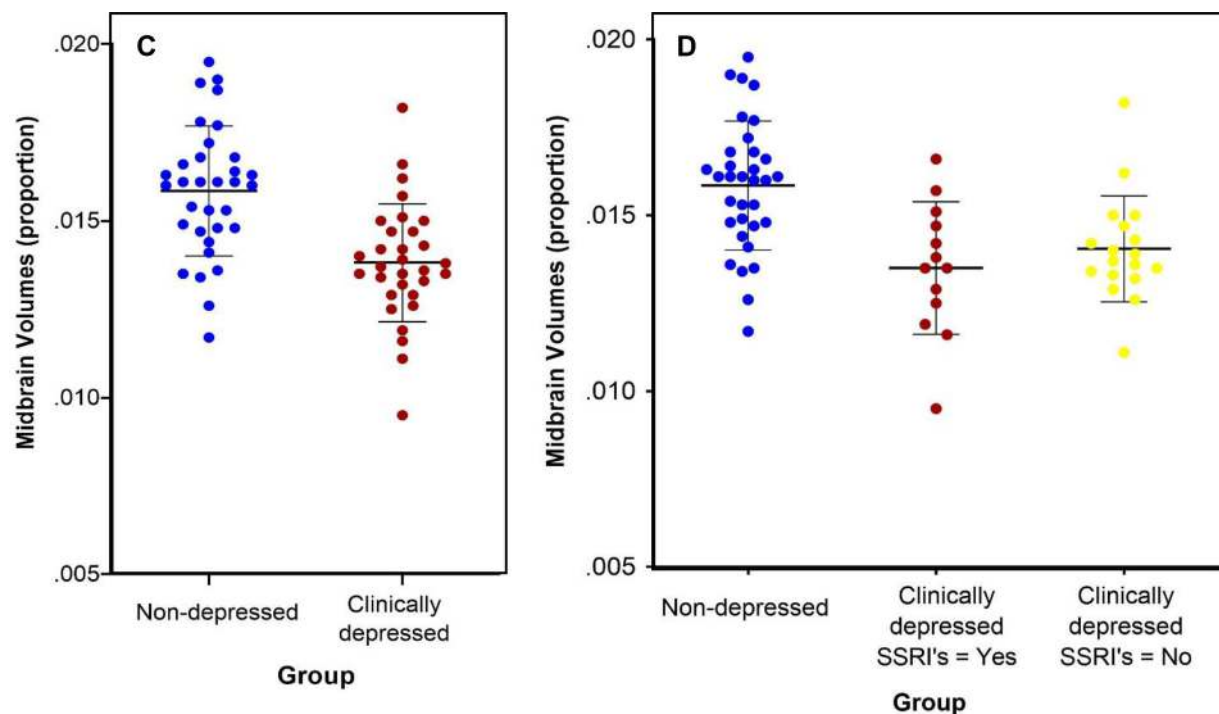
Fig. 2. Scatter dot plots of individual data points and mean and SD error bars showing (C) midbrain volumes in infants of mothers in the clinically depressed and non-depressed groups; and (D) further stratified according to maternal mediation status.

Perlman, 2004) – including, for example, antenatal exposure to hypoxic events and substance abuse (Akyuz et al., 2014; Varghese et al., 2016). Here we provide new evidence in support of an impact of exposure to maternal antenatal depression on infant subcortical brain development.

Given that subcortical structures start to develop very early on in foetal development and follow an inverted U-shaped developmental trajectory (Giedd et al., 2008; Sussman et al., 2016), it is possible that prenatal exposure to maternal stress may disrupt the normal pattern of brain growth in the foetus. Thus, potentially leading to an overgrowth of subcortical grey matter during early periods of rapid growth, as reported here.

Our results in infants exposed to maternal stress echo evidence of larger subcortical structures in children with high levels of depressive symptoms (Merz et al., 2018), as well as in adult samples with clinically diagnosed depression (Ahn et al., 2016; Zeng et al., 2015). However, we cannot say whether larger subcortical volumes in infants exposed prenatally to maternal depression is a result of their *in utero* environment or a familial transmission of a neural phenotype. We also do not know the outcomes of our cohort in later childhood or adulthood and whether subcortical enlargement in infancy is associated with a vulnerability for the development of depression later in life (Qiu et al., 2015).

Of note, however, the direction of the association we report between maternal antenatal MDD and infant subcortical volumes – i.e., larger subcortical grey matter volumes in infants of antenatally depressed women – may stand in contrast to other prior findings from older samples with similar prenatal exposures. These include significantly smaller putamen volumes reported in children aged 4-years, born to women with increased psychopathology (Bjørnebekk et al., 2014), and reductions in the caudate nucleus, putamen and thalamus (structures which comprise the subcortical grey) reported in healthy adolescents exposed to increased levels of negative personal early-life events (before 5-years of age) (Tyborowska et al., 2018). It is possible that varied stressors may differentially impact neurodevelopmental trajectories (Glover, 2015). Furthermore, such studies have examined specific subregions of the subcortex (i.e., caudate, putamen, globus pallidus, thalamus), and not the overall subcortical volume as we did here. It is likely

that specific regions of interest follow differential patterns of either progressive or regressive anatomical growth depending on the developmental timepoint (Lenroot et al., 2007). However, since our protocol precluded measurement of these smaller regions-of-interest, we cannot say which subregion(s) might be driving our results.

Our finding of an association between maternal antenatal depression and midbrain development is not surprising given the midbrain's role in stress regulation (Myers, Scheimann, Franco-Villanueva, & Herman, 2017). For instance, adults diagnosed with depression have significantly smaller volumes in the midbrain, relative to non-depressed adults (Hwang et al., 2010; Lee et al., 2011). However, the direction of this relationship between depression and mid-brain volume, whether it is a vulnerability marker or a consequence of exposure to stress, is not known, either in older samples or in our study.

Taken together, our findings extend existing research to suggest that the *in utero* milieu (genetic and/or environmental) plays an important role in infant subcortical and midbrain anatomy. From an evolutionary perspective, such alterations in brain development linked to an earlier prenatal period may prepare the foetus, at least in the short-term, for a particular environment (for example, maternal postnatal depression) in which it may find itself in, to ensure survival (Talge et al., 2007). However, this notion needs be tested with larger samples and at different stages of development.

The mechanisms underlying links between antenatal depression and offspring brain development are just starting to be explored. One candidate mechanism in which maternal antenatal stress might exert impact on the offspring brain is through alterations in the filtering capacity of the placenta; thus moderating the exposure of the foetus to specific biological products (Glover, 2015). Antenatal stress is linked to a downregulation of the placental enzyme 11β-hydroxysteroid dehydrogenase 2 (11β-HSD2), which metabolises cortisol to inactive cortisone. In turn, higher levels of cortisol cross the placenta in amounts sufficient enough to affect the development of the foetal brain (Talge et al., 2007). Another possible mediator is immunological changes in the mother linked to elevated levels of inflammation (Osborne et al., 2018). Increased stress during pregnancy has been associated with an

imbalance of cytokine expression – specifically pro-inflammatory cytokines – which cross the placenta, and consequently, expose the foetus to changes in immune responses early on in development. It is possible that such adaptations may influence early brain development. Additionally, genetic transmission of brain size from the mother to the child is plausible – i.e., depressed women could have had larger subcortical volumes in infancy and then have biological children with larger volumes. Finally, the quality of parenting may also explain the link between antenatal depression and the infant brain (Stein et al., 2014). Taken together, longitudinal designs, including genetic and maternal antenatal stress-related biology from pregnancy, as well as the postnatal environment may be helpful for future research in this area.

Our findings do not provide support for a link between gestational medication exposure and the infant regional brain volumes examined here. Literature on prenatal SSRI exposure in humans is limited. Serotonin (5-hydroxytryptamine [5-HT]) plays an important role in brain development (Hyttel, 1994). While there is some evidence to suggest that atypical serotonergic signalling resulting from antenatal SSRI exposure can alter foetal neurodevelopment and subsequent functioning (for a review, see Ornoy & Koren, 2019), structural neuroimaging evidence supporting a link between foetal exposure to SSRI's and alterations in infant brain development is scarce and inconsistent (e.g., Lugo-Candelas et al., 2018; Jha et al., 2016). Nevertheless, due to the scarcity of research in volumetric studies of infants exposed to gestational SSRI's, the clinical significance of our findings remains unknown. Future research is needed, including repeated measures of brain volumes, before firm conclusions can be drawn.

The findings reported must be viewed in the context of limitations. First, (given the challenges of pursuing scanning for research during Covid) we turned our attention to existing datasets which were not optimized for more detailed study. Although scanning sequences have since moved on, our analysis method was however especially designed for analysis of such low-resolution scans. This meant that we cannot avoid type II error (false negatives) as our approach will have missed fine-grained structural differences that might be detectable with more sophisticated imaging procedures. Second, and in line with previous studies in early infancy (Hazlett et al., 2012), gray and white matter tissue classes were not further segmented. Third, our sample size was modest, and results need to be viewed cautiously until further replication. Fourth, without repeated measures of brain volume, it is unknown, whether the direction of the relationships reported are dependent on the developmental stage. Fifth, considering the sexual dimorphism in both subcortical and midbrain development (Lenroot et al., 2007; Sussman et al., 2016), sex differences on the association between antenatal depression and subcortical and midbrain volumes also require investigation. Finally, we cannot rule out the prospect that postnatal factors associated with maternal emotional state might influence children's brain structure (for example, maternal postnatal anxiety symptoms (Adamson, Letourneau, & Lebel, 2018). Moreover, the structural volumes we observed in relation to antenatal depression could also be the result of a combination of maternal and paternal factors – e.g., transgenerational epigenetic effects through the paternal germ line (for a review, please see Soubry, 2018). Also, since our group have documented links between father-infant interactions and infant brain volumes (Sethna et al., 2019), future research should consider the impact of both parents jointly.

To our knowledge, this is the first MRI study to report subcortical and midbrain volume differences in infants aged 3-6 months born to women with a clinical diagnosis of depression in pregnancy. However, further investigation is warranted to establish how maternal stress during pregnancy influence developmental trajectories of brain maturation and behaviour in offspring.

Author's contribution

Vaheshta Sethna contributed to implementation of the research

protocol, statistical analyses, and writing the paper including the first draft of the manuscript. Jasmine Siew contributed to volumetric segmentation of MRI data, statistical analyses, writing the paper, including the first draft of the manuscript. Maria Gudbrandsen contributed to implementation of the research protocol, data management and has critically revised and approved the final manuscript. Inês Pote, Siying Wang, Eileen Daly and Maria Deprez contributed to image processing and volumetric segmentation of MRI data, and have critically revised and approved the final manuscript. Carmine Pariante and Trudi Seneviratne have contributed to designing the study and have critically revised and approved the final manuscript. Declan G.M. Murphy and Michael Craig have contributed to designing the study, research implementation and have critically revised and approved the final manuscript. Grainne McAlonan has contributed to designing the study, overseen image processing and volumetric segmentation of MRI data, and has contributed critical revisions and suggestions to the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of Competing Interest

The authors report no competing interests.

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