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Antidepressant exposure in pregnancy and child sensorimotor and visuospatial development

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ABSTRACT

Motor development underlies many aspects of education and learning. There has been uncertainty about the impact of exposure of antidepressant medication in pregnancy on child motor outcomes. This paper examines whether exposure to antidepressants *in utero* increases the risk of poorer motor development in two areas: sensorimotor and visuospatial processing. Data were obtained from 195 women and children across 3 groups: women with untreated depression in pregnancy, women treated with antidepressants and control women. Data were collected across pregnancy, postpartum and until 4 years for mother and child. Maternal depression was established at baseline with the Structured Clinical Interview for DSM-IV. Antidepressant exposure, including type, dose and timing, was measured through repeated self-report across pregnancy and the postpartum, medical records at delivery and in cord blood samples collected at delivery. Child sensorimotor and visuospatial outcomes were assessed at 4 years of age with four subtests from the NEPSY-II. Our study found for sensorimotor development, visuomotor precision completion time was associated with better performance for antidepressant-exposed children compared to those with mothers with untreated depression. Yet another measure of sensorimotor development, motor manual sequences, was poorer in those exposed to antidepressants. One subtest for visuospatial processing, block construction, was associated with poorer performance in antidepressant-exposed children who had poor neonatal adaptation and those exposed to a higher dose of antidepressant. These findings suggest an inconsistent association between sensorimotor development and antidepressant use in pregnancy. However, the findings for visuospatial processing would support further exploration of antidepressant associated poor neonatal adaption and later motor development.

1. Background

The serotonin system has a role in regulating both muscle tone and motor output, and this has led to a concern that the developing motor system may be vulnerable to exposure to serotonergic antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and serotonin and noradrenalin reuptake inhibitors (SNRIs) (Galbally et al., 2012). In addition, alteration in serotonin levels for the fetus may also have wider neurodevelopmental effects, including for motor development, through serotonin acting as a molecular signal for neuronal growth and differentiation.

There have been animal studies, which have shown that SSRI exposure in pregnancy may specifically impact motor development (Bairy et al., 2007; Lee, 2009; Zusso et al., 2008). For example, in a study in postnatal rats, fluoxetine exposure altered cerebellar development through the activation of serotonin 5-HT_{1A} receptors (Zusso et al., 2008). In another study, rats exposed to fluoxetine had a delay in motor development (Bairy et al., 2007), and a third study found reduced locomotor activity in the context of an altered structure of the somatosensory cortex (Lee, 2009). These animal studies have led to human

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studies investigating the relationship between pregnancy exposure to antidepressants and children's motor development.

A recent systematic review and meta-analysis specifically examined associations between antidepressant exposure in pregnancy and child motor development outcomes (Grove et al., 2018). In total, 18 studies were included in the meta-analysis. The overall results of this meta-analysis found a small pooled effect size of 0.22 (95% confidence interval [CI] = 0.07 to 0.37) for antidepressant exposure on subsequent poorer motor development. However, subgroup analysis showed differences in effect size due to measurement type, specifically parent or clinician report on brief screening measures (7 studies) compared to standardized neuropsychological measures of motor development, such as the Bayley's Scales of Infant Development (11 studies) were more varied and the pooled effect was lower ($d = 0.10$, 95% CI -0.05 to 0.24) (Grove et al., 2018).

A general feature of many studies of developmental outcomes for children exposed *in utero* to antidepressants has been the limited length of follow up for child developmental outcomes. The consequence of such limited follow up in the case of child motor development is the limited investigation of related aspects of cognitive neurodevelopment. Infant motor development is an important precursor of later cognitive neurodevelopment, particularly sensorimotor and visuospatial abilities in early childhood (Davis et al., 2011; Wilson et al., 2013). Given the increasing emphasis on cognition as embodied, it is necessary to test developmental outcomes within a dynamic model in which brain, body and environment interact over time (Smith, 2005).

In 2020, Fitton and colleagues published a systematic review examining studies on antidepressant exposure *in utero* on a range of infant and child outcomes (Fitton et al., 2020). This important review addressed a common criticism of previous studies, the authors restricted their review to studies that compared controls to not only a group where the fetus had been exposed to SSRIs, but also an untreated depressed group (to account for confounding by indication with maternal depression) (Fitton et al., 2020). This review identified only 6 studies that examined longer-term child outcomes, including only two prospective studies. None of the identified studies included examination of motor or cognitive development.

Given the need for a more robust model of development and the uncertainty of current findings on the relationship between cognitive-motor development and antidepressant exposure (Grove et al., 2018), we selected specific aspects of both cognitive and motor development using subtests measuring specifically sensorimotor and visuospatial development within a neuropsychological measure, the NEPSY-II (A Developmental NEuroPSYchological Assessment, 2nd Edition). We included a study design with three groups: children exposed to antidepressants in pregnancy, those with mothers with depression in pregnancy who did not take antidepressants and those with mothers who were healthy in pregnancy. Furthermore, in addition to self-reported antidepressant use and dose over pregnancy, we also examined the relationship to cord blood concentration of antidepressants and the specific neuropsychological subtests.

2. Methods

This study draws on participants from the Mercy Pregnancy Emotional Wellbeing Study, a prospective, selected cohort pregnancy study where women recruited before 20 weeks of pregnancy and their children followed are up until 4 years postpartum. This study utilizes data from 195 women and their children who have complete data on the study variables from pregnancy until 4 years of age. Study participants comprised three groups: those with maternal depression at recruitment verified with a diagnostic measure, but not on antidepressant medication (Untreated, Currently Depressed; $n = 21$), those on antidepressant medication (AD Exposed; $n = 33$) and control women (Control; $n = 141$). Further details of the study are described in the published study protocol (Galbally et al., 2017b). The Mercy Health Human Research Ethics Committee approved this study and all participants provided informed, written consent.

2.1. Measures

2.1.1. Maternal mental health

At recruitment, the Structured Clinical Interview for DSM-IV (SCID-IV) Mood disorders schedule was undertaken by trained administrators (First et al., 1997).

2.1.2. Antidepressant use

Antidepressant type, dosage and timing during pregnancy was self-reported by women in early pregnancy and again in third trimester, as well as verified against hospital records at delivery (Galbally et al., 2017a). As the majority of participants were on sertraline, all doses of antidepressants were converted to a sertraline-equivalent dosage (SED) using a conversion chart (Procyshyn et al., 2015). The average dose across pregnancy was used in the analyses. As previously described, cord blood was collected at delivery, centrifuged and plasma stored at −80 °C (Galbally et al., 2017a). The SSRIs citalopram, escitalopram, fluoxetine, norfluoxetine, paroxetine and sertraline were analyzed with liquid chromatography–mass spectrometry (LC–MS) and the SNRIs duloxetine, venlafaxine and desvenlafaxine were analyzed with ultra-high performance liquid chromatography–tandem mass spectrometry (UHPLC–MS–MS) (Galbally et al., 2017a). In order to compare concentrations across the various antidepressants, a drug level measured within a sample was standardized by relating it to the middle of the therapeutic reference range of that drug (Hiemke and Hartter, 2000). Thus, the degree of fetal exposure could be estimated regardless of the specific antidepressant taken in pregnancy by the mother.

2.1.3. Neonatal adaptation

Poor neonatal adaptation (PNAS) was measured only in antidepressant-exposed neonates using the Neonatal Abstinence Scoring System (NASS). The NASS measure, developed by Finnegan for opiate withdrawal in neonates, was undertaken twice daily from birth for up to 6 days. At 24 h post-birth, a pediatrician administered the NASS at the same time as the midwife, however, they were blinded to each other's scores. The further details for this sample are presented in a previous publication (Galbally et al., 2017a). Other relevant variables including other pregnancy exposures (pharmaceutical, drug, alcohol and smoking), pregnancy and neonatal complications, mode of delivery, gestational age at birth, birth weight and Apgar scores were all also collected (Galbally et al., 2017a, 2017b).

2.1.4. Child motor development

NEPSY-II is a clinician-administered neuropsychological test validated for 3–16 years old (Brooks et al., 2009). For this study, we utilised those subtests thought to have the strongest relationship to motor development, including sensorimotor and visuospatial processing. These subtests under the sensorimotor domain were i) Manual Motor Sequence, ii) Visuomotor Precision (Combined, Total Errors and Completion Time). Manual motor sequence involves the child replicating demonstrated movement sequences with each and both hands. Visuomotor precision assesses graphomotor speed and accuracy through the speed and accuracy of a child being able to draw lines inside a track. For visuospatial processing the subtests were iii) Design Copying and iv) Block Construction. Design copying involves the child copying a two dimensional figure. Block construction requires a child to reproduce a three dimensional block model from each another model or a two dimensional drawing of a model. All of these subtests are associated with assessment of motor delays and disorders (Brooks et al., 2009). In this study, we utilise scaled scores, where higher scores reflect better and/or faster performance on subtests. The trained psychologists who administered the NEPSY were blind to the group status of participants.

2.1.5. Maternal cognition

To assess maternal cognition, the Test of Premorbid Functioning (TOPF) was undertaken. This is a validated screening test for cognitive ability in adults, and consists of a test of 70 atypical words (Wechsler, 2011).

2.2. Statistical analyses

For NEPSY-II subtests with only percentile ranks, we converted the raw scores to comparable scaled scores (*Mean* = 10, *Standard Deviation* = 3) by first converting raw scores to z-scores, then multiplying by 3 and adding 10. In analyses using the above scaled score conversion (i.e., Manual Motor Sequence, Design Copying and Visuomotor Precision Total Errors), we control for child's age at the time of neurocognitive testing (Rosenqvist et al., 2016). We first conducted a MANCOVA to test for differences in NEPSY-II subtests between the three groups (Untreated, Currently Depressed, AD Exposed, Control). In the MANCOVA model, we also adjusted for the effects of maternal cognitive Test of Premorbid Function (TOPF) scores and the child's gestational age at birth. To assess for dose effects, we conducted ANCOVA models using a subsample of only the children in the AD Exposed group to examine the effect of higher reported SED (daily dose $\geq$ 100 mg/d SED) compared to lower SED (daily dose $<$ 100 mg/d SED) on NEPSY-II subtests. In these ANCOVA models, we adjusted for maternal TOPF scores and child's gestational age.

We then estimated bivariate associations (*Spearman's rho*) between antidepressant concentration detected in cord plasma and NEPSY-II subtests. Due to a zero-inflated, non-normal distribution of relative cord plasma antidepressant concentrations, a constant was added (i.e. $x + 1$) and the variable was transformed using the natural logarithm, which improved the non-zero part of the distribution. Finally, using NASS latent intercept factor scores from an intercept-only model of change in NASS scores (separate models for CNS, gastrointestinal, and other symptoms, as well as total symptom scores, more details are published (Galbally et al., 2017a) measured at days 1, 2, 3 and 4 following delivery, we estimated bivariate *Spearman's rho* correlations between these NASS factor scores and cord plasma antidepressant concentrations and between NASS factor scores and performance on the NEPSY-II subtests.

Power analysis were conducted to determine how small an effect (*partial* η^2) the sample (n = 195) is powered to detect, using an alpha level of 0.05 and power level of 0.80. For the MANCOVA models adjusted for 3 covariates and including 6 outcome variables, the 195 sample is powered to detect an effect for the multivariate main effect for group (i.e., untreated currently depressed, AD exposed, and control) as small as *partial* $\eta^2 < 0.02$. For the univariate models, the 195 sample is powered to detect an effect for the main effect for group as small as *partial* $\eta^2 = 0.06$. For tests using subsets of the full sample, statistical power is limited; however, we report these findings as exploratory and include observed effect sizes, which will contribute to future meta-analyses on this topic.

3. Results

3.1. Sample characteristics

Table 1 displays sociodemographic characteristics of the sample who completed the NEPSY-II at 4 years old. Table 2 presents summary statistics for antidepressant use during pregnancy. Sertraline was the most prescribed antidepressant. Two women commenced taking antidepressant in third trimester, and one woman who was taking antidepressants in early pregnancy had ceased by third trimester. Seven women reported a lower dose and one woman reported a higher dose in third trimester compared to early pregnancy. Two women changed agents from early pregnancy to third trimester: paroxetine to fluoxetine and citalopram to sertraline, respectively.

Table 1
Sociodemographic and Other Key Variable Descriptive Statistics for the MPEWS Sample who Completed the NEPSY-II at 4 Years of Age, by Group (N = 195).

	Control (n = 141)	Untreated, Currently Depressed (n = 21)	AD Exposed (n = 33)	p-value
	n (Valid %)	n (Valid %)	n (Valid %)	
Caucasian	125 (89.3)	19 (90.5)	30 (90.9)	.955
Nulliparous	136 (96.5)	21 (100.0)	31 (93.9)	.505
Tertiary education	99 (70.7)	14 (66.7)	16 (48.5)	.052
Full-time employment	101 (73.2)	11 (57.9)	17 (54.8)	.079
Married, de facto, or otherwise stable relationship	135_a (96.4)	21_a (100.0)	27_b (81.8)	.002
SGA	14 (9.9)	1 (4.8)	2 (6.1)	.617
Apgar < 7 at 5 min	4 (2.8)	1 (4.8)	2 (6.3)	.618
Male	79 (56.0)	14 (66.7)	15 (45.5)	.298
MOD				.723
SVD	62 (44.0)	6 (28.6)	15 (45.5)	
Assisted VD	30 (21.3)	5 (23.8)	7 (21.2)	
CS	49 (34.8)	10 (47.6)	11 (33.3)	
	M (SD)	M (SD)	M (SD)	p-value
Maternal age at recruitment (y)	31.72 (4.39)	30.86 (4.77)	33.00 (5.11)	.203
Maternal Test of Premorbid Functioning	55.22 (11.53)	54.80 (7.68)	54.58 (9.18)	.498
Gestation at birth (weeks)	39.50 (1.71)	39.41 (1.88)	38.71 (1.38)	.053
Birthweight (kg)	3.41 (.50)	3.46 (.59)	3.31 (.49)	.514
Scaled NEPSY-II Subtests				
Block Construction	11.39 (3.33)	11.35 (1.93)	10.33 (3.61)	.245
Design Copying^	10.07 (2.15)	10.04 (3.05)	9.77 (3.30)	.895
Manual Motor Sequences^	10.21_a (2.99)	$10.57_{a,b}$ (3.46)	8.77_b (2.42)	.021^^
Visuomotor Precision Total Errors^	9.85 (2.77)	9.78 (3.34)	10.78 (3.62)	.260
Visuomotor Precision Completion Time	10.98_a (2.44)	9.71_a (2.17)	11.82_b (2.28)	.008
Visuomotor Precision Combined	8.85 (2.72)	8.10 (3.03)	9.00 (2.98)	.466

Note. Cells with different sub-script letters have significantly different group parameters at p < .05 using pairwise comparison tests. MOD, mode of delivery; SVD, spontaneous vaginal delivery; VD, vaginal delivery; CS, caesarean section; PR, percentile rank; y, years; kg, kilogram; SGA, small for gestational age; M, Mean; SD, Standard Deviation; AD, antidepressant.^ Scaled score = z raw NEPSY sub-test score*3 + 10.^^ Robust Welch F Test due to unequal variances; pairwise comparisons conducted using Dunnett C post-hoc tests. Missing data handled using casewise exclusion, with valid percentages presented.

3.2. NEPSY-II performance by group

Table 1 displays scaled means for the NEPSY-II subtest and accompanying significance of unadjusted F tests. There were no differences in the scaled means for Block Construction, Design Copying and the Visuomotor Total Errors and Combined subtests. However, there were significant group differences for the Manual Motor Sequence and Visuomotor Precision Completion Time subtests. For the Manual Motor Sequence subtest, pairwise comparisons demonstrated that children whose mothers were taking antidepressants during pregnancy scored significantly lower than children whose mothers were in the control group. Conversely, pairwise comparisons demonstrated that children whose mothers were depressed during pregnancy but did not use

Table 2
Summary Descriptive Statistics for the 33 Patients Using Antidepressants During Pregnancy in this MPEWS Sample.

Antidepressant Class and name	Early Pregnancy ($n = 32$)				Third Trimester ($n = 31$)			
	n	%	Sertraline-equivalent Dose (mg/d)		*n*	%	Sertraline-equivalent Dose (mg/d)	
			Median	Min - Max			Median	Min - Max
SSRI								
Fluoxetine	3	9.4	100	–	4	12.9	50	12.5–100.0
Sertraline	8	25	75	50.0–200.0	10	32.3	75	50.0–150.0
Escitalopram	5	15.6	87.5	50.0–100.0	5	16.1	100	50.0–400.0
Citalopram	4	12.5	37.5	25.0–50.0	3	9.7	50	25.0–50.0
Paroxetine	2	6.3	34.4	18.8–50.0	1	3.2	50	–
SNRI								
Venlafaxine	4	12.5	56.3	37.5–75.0	2	6.5	65.6	56.3–75.0
Desvenlafaxine	3	9.4	37.5	25.0–50.0	3	9.7	25	–
Duloxetine	2	6.3	100	–	2	6.5	100	–
Other								
Mirtazapine	1	3.1	16.7	–	1	2.3	–	–

Note. SSRI, Selective Serotonin Reuptake Inhibitor; SNRI, Serotonin and Noradrenaline Reuptake Inhibitor. Min-Max is not given (–) if the dose was the same in all subjects or if $n = 1$.

antidepressants scored significantly lower on the Visuomotor Precision Completion Time subtest than children whose mothers were taking antidepressants during pregnancy.

Fig. 1 displays the estimated marginal means adjusted for covariates at the sample means for the MANCOVA model using the linear multivariate combination of the six NEPSY-II subtests. None of the covariates were significant in the multivariate model (maternal TOPF, $F[6, 154] = 1.34$, $p = .243$, *partial* $\eta^2 < 0.05$; gestational age at birth, $F[6, 154] = 1.68$, $p = .130$, *partial* $\eta^2 = 0.06$; and child's age at neurocognitive assessment, $F[6, 154] = 1.63$, $p = .233$, *partial* $\eta^2 = 0.05$). The effect of group in the multivariate model was significant, $F(12, 310) = 2.13$, $p = .015$, *partial* $\eta^2 = 0.08$. Univariate *F*-tests showed a significant effect of group for Visuomotor Precision Completion Time only, $F(2, 165) = 5.59$, $p = .004$, *partial* $\eta^2 = 0.06$; pairwise comparison tests demonstrated that the AD Exposed group scored significantly higher than the Untreated, Currently Depressed group ($p = .003$).

3.3. Associations between antidepressant dose/concentration and NEPSY-II performance

Using only children exposed to antidepressants during pregnancy, a series of univariate ANCOVA models were run comparing SED groups (daily dose < 100 mg/d SED and daily dose ≥ 100 mg/d SED) on the child's NEPSY-II performance. Fig. 2 displays the estimated marginal means for the SED groups. There were no significant differences between SED groups on the Design Copying ($F[1, 23] = 0.44$, $p = .515$, *partial* $\eta^2 = 0.02$), Manual Motor Sequences ($F[1, 23] = 1.62$, $p = .218$, *partial* $\eta^2 = 0.07$), Visuomotor Precision Total Errors ($F[1, 23] = 2.25$, $p = .147$, *partial* $\eta^2 = 0.08$), and Visuomotor Precision Combined ($F(1, 24) = 0.16$, $p = .693$, *partial* $\eta^2 < 0.01$) subtests. However, significantly higher Visuomotor Precision Completion Time scores were observed among children in the higher SED compared to the lower SED group, $F(1, 24) = 4.62$, $p = .042$, *partial* $\eta^2 = 0.16$. Conversely, significantly lower Block Construction scores were observed for children in the higher SED group compared to the lower SED group, $F(1, 24) = 7.57$, $p = .011$, *partial* $\eta^2 = 0.24$.

Fig. 3 illustrates the bivariate associations between relative cord plasma antidepressant concentration and scaled NEPSY-II subtest scores. Only the positive correlation between cord plasma antidepressant concentration and performance on the Visuomotor Precision Completion Time subtest was significant (*rho*[28] = 0.42, $p = .028$; see Fig. 3[e]), i.e., higher antidepressant cord drug concentrations were associated with shorter completion time on the Visuomotor Precision subtest. Although not significant at $p < .05$, there was a trending negative correlation between cord plasma antidepressant concentration and performance on the Manual Motor Sequences subtest (*rho*[28] = -.38, $p = .054$; see Fig. 3 [c]), i.e. higher antidepressant cord drug concentrations may be associated with poorer performance.

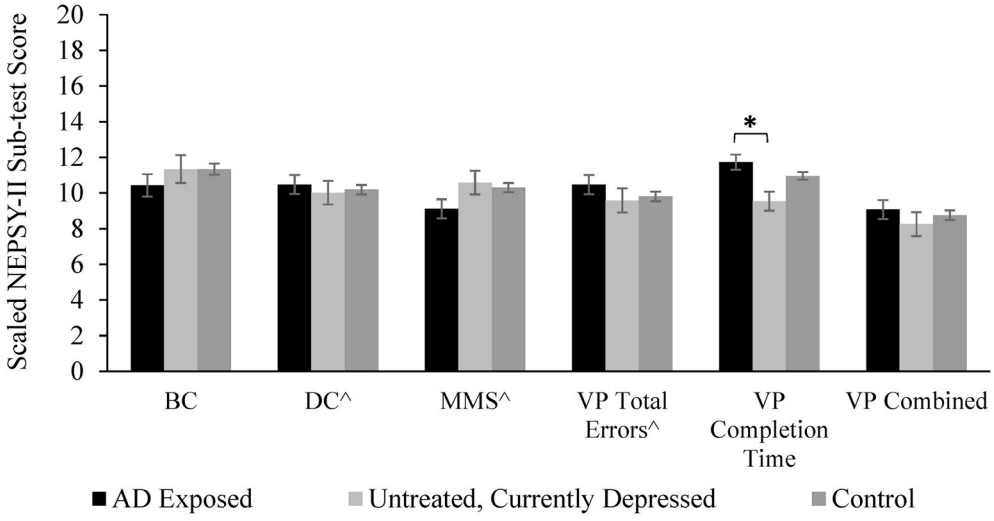

Fig. 1. Univariate Estimated Marginal Means (and standard errors as error bars) for MPEWS groups for the selected scaled NEPSY-II subtests as outcomes. Estimates are adjusted for maternal TOPF scores, gestational age at birth and child's age at time of NEPSY-II assessment. BC, Block Design; DC, Design Copying; MMS, Manual Motor Sequences; VP, Visuomotor Processing; AD, antidepressant. ^ Scaled score = $z_{raw\ NEPSY\ sub\text{-}test\ score}$*3 + 10. * Denotes significant pairwise comparison test ($p < .05$) with Bonferroni adjustment for multiple pairwise comparisons within univariate tests.

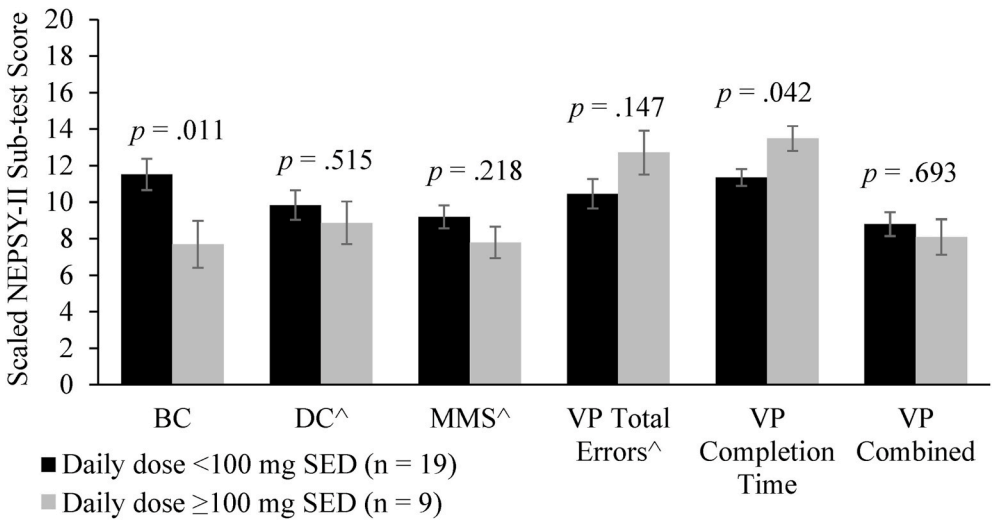

Fig. 2. Univariate estimated marginal means (and standard errors as error bars) across SED groups for the selected scaled NEPSY-II subtests as outcomes in children exposed to antidepressants *in utero*. Estimates are adjusted for maternal TOPF scores and gestational age at birth^. BC, Block Design; DC, Design Copying; MMS, Manual Motor Sequences; VP, Visuomotor Processing; SED, sertraline-equivalent dose. ^ Scaled score = $z_{\text{raw NEPSY sub-test score}}$*3 + 10. Child's age at time of neurocognitive testing also included in models as covariate.

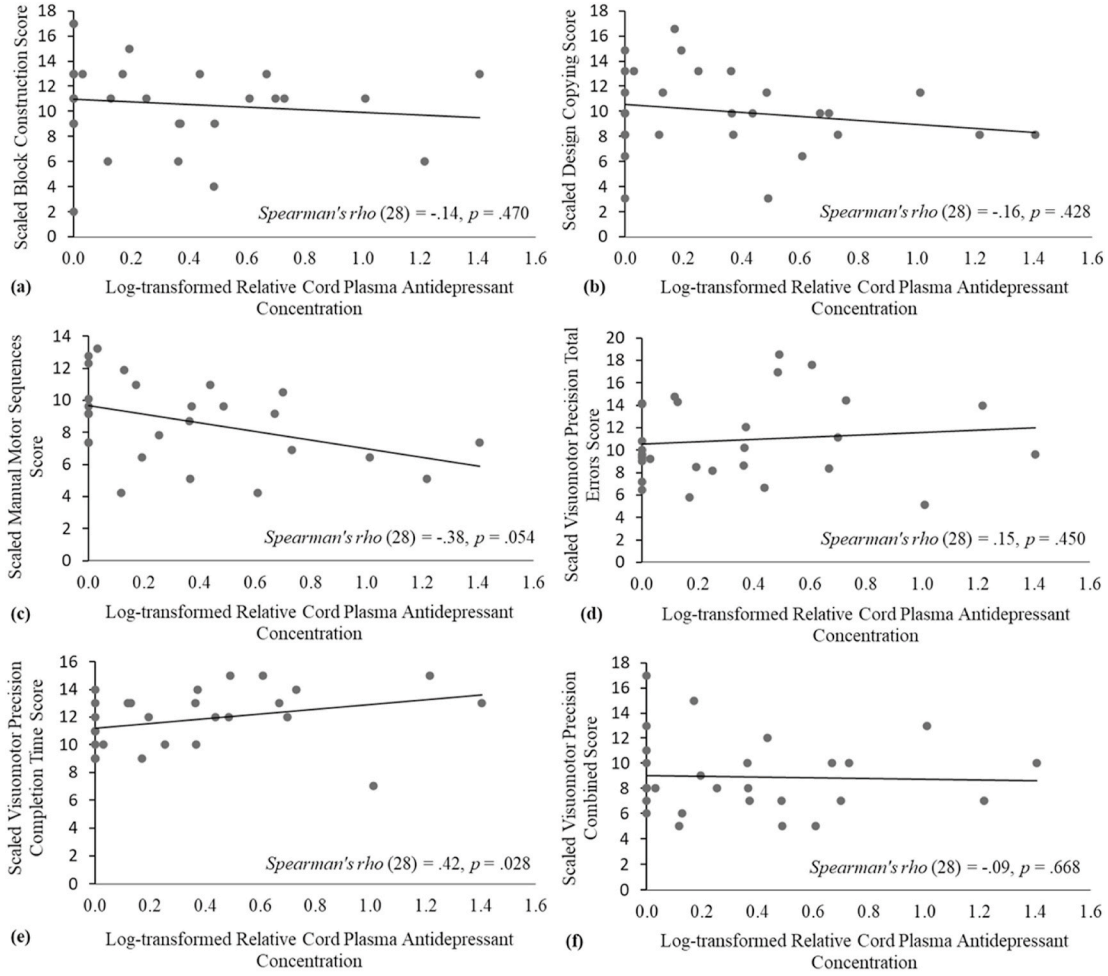

Fig. 3. Scatterplots displaying the bivariate associations between the antidepressant concentration in cord plasma and the selected scaled NEPSY-II Subtest scores.

3.4. Associations between NASS and antidepressant concentrations and NEPSY-II performance

There were no significant bivariate associations between cord plasma antidepressant concentration and any of the NASS factors scores (*p*'s > 0.05). A comprehensive analysis between cord plasma antidepressant concentrations with the NASS using MPEWS data is published (Galbally et al., 2017a). Only the NASS total factor score was associated with the specific subtests on the NEPSY-II. Specifically, there was a marginally negative association between NASS total factor score and the Block Construction scaled subtest (*rho*[28] = -.36, $p = .052$), suggesting that higher total scores on the NASS during the first 4 days of

life was associated with lower scaled Block Construction subtest scores.

4. Discussion

This study found an inconsistent pattern of associations with antidepressant exposure across the neuropsychological subtests of sensorimotor and visuospatial processing. Within the assessments of sensorimotor development, the visuomotor precision subtest was associated with better performance in children exposed to antidepressants than those exposed to untreated current depression; furthermore, this higher performance was associated with both higher reported antidepressant dose and higher cord blood levels. Whereas on another test of sensorimotor development, manual motor sequences, children whose mothers reported antidepressant use in pregnancy scored lower than children in the control group; however, there was no significant association between manual motor sequences with antidepressant dose or cord blood levels. For the subtest assessing visuospatial processing, block construction, there was no association with reported antidepressant use in pregnancy; however, higher symptoms of PNAS and higher reported antidepressant dose were both associated with poorer performance on this subtest. There were no other significant differences for antidepressant exposed children on the other subtests examined. It is also important to consider the magnitude of effects identified. The standard deviation for subtest scaled scores is 3 and the observed statistical significance demonstrated relative small differences between groups as it was within the region of one standard deviation.

This study builds on the recommendations from two recent relevant reviews for future research and with improved methodology when examining antidepressant exposure and child motor and neurodevelopmental outcomes (Fitton et al., 2020; Grove et al., 2018). These recommendations included using a three-group design that incorporates a group that has current depression not treated with antidepressants to control for the effect of underlying maternal depression. Furthermore, inclusion of a measure of maternal cognition and other important confounding factors, and careful characterisation of exposure to antidepressants were proposed. We included multi-method data collection on exposure to antidepressants using self-report, verified with hospital records, and cord blood concentrations, and collected timing, type and dose of antidepressant.

Motor development has been consistently linked to cognitive and language development (Oudgenoeg-Paz et al., 2015, 2017). As such, understanding any deleterious impact from antidepressant exposure or maternal depression on motor development is important, not only to understand this impact, but also for understanding the potential implications for broader developmental outcomes. However, this also has implications for measuring motor development with many tests overlapping in multiple domains of neurodevelopment. Our study chose four subtests, which examined sensorimotor development and visuospatial processing. Our findings indicated antidepressant exposure was associated with both poorer and improved performance across these specific subtests, and also not consistent across antidepressant dose and cord levels. For a clear neuroteratogenic finding, there is a requirement to demonstrate not only an association with use but also dose and timing, as well as a clear explanatory mechanism that underpins the relationship between exposure on the specific developmental outcome (Cicchetti and Walker, 2003). Our findings do not support a neuroteratogenic model but suggest that longer term follow up should continue to examine both motor and cognitive development, as well as their complex and subtle interplay.

Another interesting aspect of our findings were those relating to PNAS, as an association between antidepressant exposure in pregnancy and PNAS has been a consistent finding in studies, although the mechanism remains elusive. For instance, there is no current evidence to support PNAS as either a discontinuation syndrome or due to serotonergic toxicity (Grigoriadis et al., 2013). While in the short term it appears these symptoms resolve, there have been three previous studies examining longer term sequalae including motor development following PNAS associated with antidepressant exposure and this includes reported previous findings from this study (Galbally et al., 2015, 2017a; Klinger et al., 2011). Our findings suggest further research is warranted examining PNAS and longer-term child development.

Previous research focusing on maternal depression as such has found an association with poorer motor outcomes in children, including a recent study that found only an impact for current antenatal depression on motor development outcomes in children but not a history of depression without current symptoms (O'Leary et al., 2019). Our findings suggest that antenatal depression may influence motor development and in particular visuomotor development and treatment may be protective of this, but our findings are not conclusive and require further research.

Although not significant at 0.05 ($p = .052$), fewer women in the AD Exposed group compared to the control and untreated, currently depressed groups, reported having completed a tertiary education. With larger numbers, this effect may be significant and should be considered as a confounding factor between antidepressant exposure *in utero* and offspring neurocognitive development in future studies. A strength of the current study, however, is the inclusion of a measure of maternal intelligence, using the TOPF, which is considered a stable measure of intellectual functioning regardless of the presence of illness or impairment. Despite including this brief screening measure for maternal cognition, rather than relying on education to infer functioning, more comprehensive testing of maternal and paternal cognition would be preferable.

While the methodological strengths of this study have been mentioned, the limitations include the relatively low numbers of children both exposed to antidepressants and with mothers with untreated depression in pregnancy. Furthermore, while this study utilised a specific neuropsychological measure there are more specific and comprehensive measures of child motor development such as the Movement ABC (Ellinoudis et al., 2011). Further testing at an older age would be also useful to further understand the dynamics of motor development.

We have considered the antidepressants included in this study as a group. Although they exhibit somewhat different mechanisms of action, increasing synaptic levels of serotonin is a common feature. Moreover, in about two thirds of the cases, the drug was an SSRI. Mirtazapine, which is the drug with the most separate mechanism of action, contributes with one case only. Our results could therefore be considered more valid for the SSRI and SNRI groups than for mirtazapine. Adjusting doses by using the SED may introduce bias, although methods of standardising doses of different drugs within the same class are widely used to be able to study dose/effect relationships and thereby increase the credibility of the results. It is also a methodological limitation that the time interval between the last intake of the drug and sampling was – for obvious reasons – not possible to standardise. Therefore, in an unknown proportion of the cases, when this interval was short, the measured concentration would be higher than if the sample had been obtained 12 to 24 hours after intake, for which the therapeutic reference ranges are related to. However, as there is no reason to believe that it should be more samples obtained shortly after drug intake in cases with higher or lower scores in any of the outcomes studied, the misclassification would be non-differential and therefore only cause bias towards the null. Therefore, we consider that our statistically significant correlations involving plasma concentrations are valid in this perspective, but it could have happened that some true associations have not been revealed.

Although our study was unable to provide conclusive outcomes, it does point to a new path for research in understanding antidepressant exposure and child developmental outcomes. The findings demonstrate the importance of a true depressed comparison group – our untreated depressed sample met current diagnostic criteria for depression, including careful measurement of exposure to delineate potential biological effects of exposure from potential silent confounders and

nuanced and specific measures of child developmental outcomes. Ultimately, the aim of research examining child outcomes following antidepressant exposure in pregnancy is to provide women and clinicians with clarity on risks and benefits of treatment and also inform options in terms of agent, dose and timing of antidepressant treatment in pregnancy. It will only be with the expansion of knowledge through research that is carefully and specifically designed that the question of the impact of antidepressant medication on child outcomes will be answered.

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CRediT authorship contribution statement

Megan Galbally: Writing - original draft, Writing - review & editing, designed the original and overall study protocol and MG undertook the ethics application, drafted this manuscript and all authors critically reviewed and revised for content and gave approval to the final to be published version of the manuscript. **Stuart J. Watson:** Formal analysis, Writing - original draft, Writing - review & editing, undertook the statistical analysis, drafted this manuscript and all authors critically reviewed and revised for content and gave approval to the final to be published version of the manuscript. **Olav Spigset:** Formal analysis, undertook the antidepressant blood levels analysis and described this for the paper. **Andrew J. Lewis:** Writing - original draft, designed the original and overall study protocol and MG undertook the ethics application.

Declaration of competing interest

The authors declare that they have no competing interests.

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