

# The impact of the in utero and early postnatal environments on grey and white matter volume: A study with adolescent monozygotic twins

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Short title: The early environment and the brain in adolescence

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## ABSTRACT

Prenatal and early postnatal adversities have been shown to be associated with brain development. However, we do not know how much of this association is confounded by genetics, nor whether the postnatal environment can moderate the impact of *in utero* adversity. This study used a monozygotic (MZ) twin design to assess 1) the association between birth weight (BW) and brain volume in adolescence; 2) the association between within-twin-pair BW discordance and brain volume discordance in adolescence; and 3) whether the association between BW and brain volume in adolescence is mediated or moderated by early negative maternal parenting behaviours. These associations were assessed in a sample of 108 MZ twins followed longitudinally since birth and scanned at age 15. Total grey (GM) and white matter (WM) volumes were obtained using the DARTEL toolbox in SPM8. We found that BW was significantly associated with total GM and WM volumes, particularly in the superior frontal gyrus and thalamus. Within-twin-pair discordance in BW was also significantly associated with within-pair discordance in both GM and WM volumes, supporting the hypothesis that the specific *in utero* environment has an impact on brain development independent of genetics. Early maternal hostile parenting behaviours and depressive symptoms were associated with total GM volume, but not WM volume. Finally, greater early maternal hostility may moderate the association between BW and GM volume in adolescence, since the positive association between BW and total GM volume appeared stronger at higher levels of maternal hostility (trend). Together, these findings support the importance of the *in utero* and early environments for brain development.

Keywords: MRI, early environment, brain volume, adolescence, moderation, birth weight, parenting

## INTRODUCTION

*In utero* events can affect brain development and thus can have long-term effects on global functioning. Birth weight (BW) can be used as an overall index of the *in utero* environment [1-4]. Research has shown that individuals born with very low BW (<1500 g) have smaller brains than controls from infancy to early adulthood [5-13]. Structural associations with BW are found throughout the brain, even when BW is within a normal range, as shown in various populations and age groups [10, 14-16]. However, findings are inconsistent, with other studies finding no association between BW and brain volume [11, 17, 18]. This may be due in part to differing definitions of low BW and confounds including prematurity, genetics, and neural injury.

Adversity occurring during the first two years of life can also affect brain development. Examples of stressors that have been associated with altered brain volumes include maltreatment [19-21], socioeconomic status (SES) [22-24], maternal depression [25], and institutionalization [26]. What's more, recent studies are showing that the later environment may mediate or moderate the impact of early stressors on brain development [27]. For instance, the impact of SES on brain development, as well as emotional and cognitive outcomes, has been shown to be at least partially mediated by parental care [reviewed in [22, 24, 28]], parental education [23], stimulation from the environment and diet [24]. However, the moderating effects of early environmental factors including maternal parenting on *in utero* adversity have not been studied extensively.

Distinguishing environmental influences on brain development from genetic effects can be difficult since the two are so tightly intertwined [29]. Monozygotic (MZ) twins provide the ideal method to assess environmental factors given that they share 100% of their gene sequence. Associations found between low BW and brain volume in MZ twins should therefore be attributable to the unique environment. However, to our knowledge, the only study to have assessed the association between BW and brain structure in a MZ twin sample is by Raznahan and colleagues [15]. They assessed brain development longitudinally in MZ and DZ twin pairs, as well as in singletons, and found that lower BW, even when in the normal range, is associated with decreases in brain volume in several regions implicated in mental health problems. In addition, these findings were replicated within MZ twin pairs. The twin with lower BW had a

comparatively smaller brain volume than his/her co-twin, providing further support for the importance of the *in utero* environment for brain development into adulthood [15]. However, the sample included participants aged 3 to 30, making it difficult to assess the specific impact of BW during particular developmental time periods. Adolescence — a period of great physiological and psychosocial change, as well as brain maturation — is a particularly important time period to assess brain development following early adversity. Furthermore, the impact of the postnatal environment was not assessed.

In the present study we aimed to assess 1) the association between the *in utero* environment (as indexed by BW) and total grey (GM) and white matter (WM) volumes in adolescent MZ twins, and 2) the association between BW discordance and discordance in total GM and WM volumes. We also assessed 3) whether early negative maternal parenting behaviours mediate or moderate the association between BW and total brain GM and WM volumes.

## **METHODS**

### *Participants*

Participants were 108 fifteen-year-old adolescents (54 pairs of MZ twins: 23 male and 31 female) recruited from the Quebec Newborn Twin Study (QNTS) [30, 31]. The QNTS used the Quebec Ministry of Health and Social Services registry of new births occurring in the Province of Quebec, between April 1, 1995 and December 31, 1998 to recruit participants and followed them longitudinally. All participants who underwent scanning at age 15 were healthy and free of psychotropic medications, neurological disease, as well as current depression and substance use disorders. Out of 96 participants with reported gestation length, 10 were born with gestation less than 36 weeks. See Table 1 for the sample characteristics. Written informed consent and assent was obtained from the parents and twins, respectively, and the study protocol was approved by the appropriate ethics committees.

### *Measures*

BW was obtained from medical records and measured on a continuous scale. Maternal parenting behaviours were assessed using the Parent's Cognition and Conduct Toward the Infant Scale (PACOTIS) [30], a 23-item self-report questionnaire rated by the mother when the twins were 5, 18 and, 30 months. We retained the hostility subscale, measured by items such as "I have raised my voice or shouted at my baby when he/she is particularly fussy." Scores were continuous and averaged over time points. Maternal depressive symptoms were assessed on a continuous scale with the Symptom Checklist (SCL-90) [32, 33] when the twins were 5, 18, 30, and 48 months and averaged over time points in accordance with Levesque and colleagues [34].

Scans were acquired at the Montreal Neurological Institute (MNI) Brain Imaging Centre, with a Siemens Magnetom 3T Tim Trio scanner ([www.medical.siemens.com](http://www.medical.siemens.com)), using a magnetization-prepared rapid acquisition gradient-echo (MPRAGE) 9 min sequence (176 slices; 1 mm thickness, TR=2300 ms, TE=2.98ms, TI=900 ms, flip-angle=9°, FOV=240x256mm).

#### *Pre-processing*

Statistical Parametric Mapping version 8 (SPM8; Wellcome Department of Cognitive Neurology) implemented in MATLAB R2010a (Mathworks, Sherborn, MA) was used for image analyses. Images were pre-processed and analyzed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox in SPM8. The DARTEL toolbox uses a high dimensional warping process that increases the registration between individuals, which results in improved localization and increased sensitivity in analyses [35]. Smoothing was performed with an 8mm FWHM Gaussian kernel. We used voxel-based morphometry (VBM) to assess the voxel-wise comparison of the local concentration of GM and WM within the MZ twins. Total GM, WM, and brain volumes were obtained using SPM8.

#### *Analyses*

To assess whether the *in utero* environment, as indexed by BW, is associated with total GM volumes, we regressed total GM and WM volumes onto BW in the 108 participants, using the Statistical Package for the Social Sciences (SPSS). Then, we conducted an exploratory VBM whole-brain analysis in SPM8, in order to assess whether there was an association between BW and brain volume in specific brain regions. All reported brain regions were examined at a

threshold corrected for multiple comparisons (corrected using familywise error rate (FWE) at cluster-level,  $p < 0.05$ ). To assess the specific effect of the discordant *in utero* environment within twin pairs, we also regressed within-twin-pair total GM and WM volume discordance onto discordance in BW in SPSS (see Figure 1 for a histogram of BW discordances in our sample). Although GM and WM volumes were significantly lower in girls [ $F(1,106)=44.89$ ,  $p < 0.001$  for GM;  $F(1,106)=41.24$ ,  $p < 0.001$  for WM] compared to boys (which is consistent with the literature), since BW did not interact with sex, we collapsed the sexes together for the main analyses. However, we also report on the association between BW and total GM and WM volumes separated by sex.

We then regressed total GM and WM volumes onto early maternal hostile parenting behaviours and maternal depressive symptoms using SPSS. Then, we conducted multilevel-modelling (MLM) to confirm the associations while accounting for both between- and within-pair variability, including the following variables as fixed factors: BW, sex, maternal depressive symptoms, and maternal hostile parenting behaviours. For each outcome (total GM and WM volumes), we first assessed the null model with fixed and random effects for the intercept. We then added 1<sup>st</sup> level predictors (BW, maternal hostile parenting behaviours) one by one, first as fixed effects only, then as fixed and random effects; we kept them in the model if they contributed significantly to the model. We then added 2<sup>nd</sup> level predictors (sex, maternal depressive symptoms) one by one as fixed factors [36]. Finally, we assessed whether maternal hostile parenting behaviours might independently mediate or moderate the association between BW and GM/WM volume, in accordance with [37] and [38].

## RESULTS

### *BW and brain volume*

We found that BW was significantly associated with both total GM (standardized beta=0.32,  $t(106)=3.46$ ;  $p=0.001$ ) and WM (standardized beta=0.30,  $t(106)=3.22$ ;  $p=0.002$ ) volumes at age 15; these findings were confirmed using MLM (see Table 2) and in a sample consisting of only twins with gestation length greater than or equal to 36 weeks. Using SPM8, we found a

significant positive association between BW and the right superior frontal cortex GM (MNI coordinates 26 9 60;  $k=118$ ; peak  $T(103)=4.55$ ;  $pFWE=0.008$ ) and a significant negative association with the left thalamus GM (MNI coordinates -15 -30 0;  $k=389$ ; peak  $T(103)=4.76$ ;  $pFWE<0.001$ ), as well as a significant negative association between BW and the right superior frontal WM (MNI coordinates 30 41 30;  $k=61$ ; peak  $T(103)=3.74$ ;  $pFWE=0.004$ ). See Figures 2–4. When we repeated analyses in boys and girls independently, only the association between BW and total WM volume in girls remained significant, likely due to reduced sample size. Furthermore, within-pair analyses showed that greater within-pair BW discordance was significantly associated with both greater within-pair discordance in GM (standardized beta=0.32,  $t(52)=2.43$ ;  $p=0.02$ ) and WM (standardized beta=0.52,  $t(52)=4.41$ ;  $p<0.001$ ) volumes, and this finding held in a subsample consisting of only twin pairs with gestation length of 36 weeks or more. When analyzing boys and girls separately, the associations between BW discordance and both GM and WM discordance were still significant in girls, but not in boys.

#### *The postnatal environment and brain volume*

In regards to the postnatal environment, there was a significant negative association between maternal hostile parenting behaviours and total GM volume (standardized beta=-0.21,  $t(96)=-2.11$ ;  $p=0.04$ ), but not WM volume. There was also a trend for a positive association between maternal depressive symptoms and total GM volume (standardized beta=0.18,  $t(102)=1.85$ ;  $p=0.067$ ), but not for WM volume. Results were very similar in MLM (see Table 2). Discordance in hostile parenting behaviours was not associated with discordance in GM or WM volumes.

#### *Mediation/moderation*

We then assessed whether early maternal hostile parenting behaviours might mediate or moderate the association between BW and total GM volume. Maternal hostile parenting behaviours did not mediate the association between BW and total GM volume. We did, however, find a trend for an interaction between BW and maternal hostile parenting behaviours ( $p=0.07$ ); it appears that the positive association between BW and total GM volume tends to get stronger at higher levels of maternal hostile parenting behaviours (see Figure 5).

## DISCUSSION

The present study aimed to assess the association between the *in utero* and early postnatal environment and total grey and white matter volumes in a sample of adolescent monozygotic twins. We found that BW was associated with total GM and WM volumes, particularly in the superior frontal cortex and thalamus. Importantly, greater discordance in BW was associated with greater discordance in total GM and WM volumes within twin pairs, which highlights the importance of the unique environment, irrespective of DNA sequence. Early maternal depressive symptoms, as well as maternal hostile parenting behaviours, were also associated with total GM volume, but not with total WM volume. Together, these results highlight the importance of the *in utero* and early postnatal environment for brain volume in adolescence.

Our finding that lower BW is associated with lower total GM and WM volumes is in accordance with previous studies that found altered GM and WM volumes in infants, children, and adolescents born with low BW [39-42], and particularly with those studies that used a sample with normative BW variation [10, 14-16]. At a regional level, we found both increases and decreases in volumes in association with lower BW, which is also in accordance with previous reports (e.g., [43]). However, results across studies are somewhat conflicting in regards to direction of change. Thus, further studies that carefully control for confounds and assess volumes of subregions will be necessary.

We then assessed the association between BW discordance and brain volume discordance within MZ twin pairs during adolescence, in order to control for DNA sequence and assess the specific impact of the unique *in utero* environment. The study by Raznahan and colleagues is the only other study that has used such a design; however, they used a sample with a wide range of ranges (i.e., from 3 to 30 years of age) [15]. The present study thus corroborates that the *in utero* environment has a significant impact on brain development above and beyond genetic effects in a sample of adolescent MZ twins followed longitudinally since birth. Together, the findings of our study suggest that those born with low BW do develop differently from their heavier peers, even in the absence of neurodevelopmental impairments.

We did not find any association between discordance in early hostile parenting behaviours and brain volume of either GM or WM. This could be due to low within-family variability in



maternal parenting behaviours [30]. Alternatively, it could be that maternal parenting behaviours do not affect brain development independent of genetics. Brain development shows high heritability [44, 45], and, genetics and parenting practices are tightly intertwined and influence one another in a bi-directional manner [46]. It is possible that genetic effects simply outweigh non-shared environmental effects.

We found that early maternal hostile parenting behaviours are associated with GM volume, but not WM. Previous diffusion tensor imaging studies have found an association between early adversity, including a positive family history of major depressive disorder, parental verbal abuse, witnessing domestic violence, as well as childhood neglect and maltreatment, with lower fractional anisotropy (FA) values in several WM tracts during adolescence and young adulthood [47-50]. It should be noted, however, that these all represent severe forms of adversity and that these studies were most often conducted using participants with post-traumatic stress disorder (PTSD), thereby making it difficult to distinguish the impact of early adversity from that of having PTSD [51]. Our sample was exposed to mild forms of early postnatal adversity, and we assessed volume using a whole-brain VBM approach as opposed to WM integrity using DTI. It could be that more severe forms of early postnatal adversity have an impact on WM, or that WM integrity is affected to a greater degree than WM volume.

The main limitation of this study was the limited number of participants born with very low BW; however, our findings confirm the importance of BW even within a normal range. Moreover, with a greater sample size, the trend for the moderation of the association between BW and brain volume in adolescence by maternal hostile parenting behaviours may have been significant. Nonetheless, this is one of the few studies that controlled for genetics and isolated the impact of the unique environment on brain development by using a within-MZ-twin design. Furthermore, since this cohort has been followed longitudinally since birth, all information on the early environment is prospective.

Overall, these findings demonstrate that the *in utero* environment can have an impact on brain volumes during adolescence, independent of genetics. Given these results, it may be beneficial to target children born with low birth weight for preventive interventions early in life.

**Conflicts of interest:**

We have no conflicts of interest to report.

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Table 1. Characteristics of the sample.

| Variable   | N   | Range           | Mean (SD)     |
|--|-----|-----------------|---------------|
| Birth weight, in kilograms                             | 108 | 1.0 – 3.73      | 2.55 (0.5)    |
| BW difference score, in kilograms                      | 54  | -1.07 – 1.04    | 0.02 (0.4)    |
| Gestation length, in weeks                             | 96  | 30 – 40         | 36.92 (2.4)   |
| Maternal hostile parenting, assessed with the PACOTIS  | 98  | 0 – 8.67        | 3.49 (2.0)    |
| Maternal depressive symptoms, assessed with the SCL-90 | 104 | 34 – 70         | 55.44 (7.8)   |
| Total GM volume  | 108 | 514.06 – 928.87 | 700.85 (63.6) |
| Total WM volume  | 108 | 380.53 – 672.62 | 479.16 (57.0) |

Descriptive statistics in the sample of 108 fifteen-year-old adolescents.

SD = standard deviation; BW = Birth Weight; SCL-90 = Symptom Check List-90 items; GM = grey matter; WM = white matter.

Table 2. Within- and between-family associations with total brain volume as assessed using MLM.

| Parameters                   | Total GM volume     | Total WM volume     |
|------------------------------|---------------------|---------------------|
| <b>Fixed effects</b>         |                     |                     |
| Intercept                    | 737.44 (10.9)****   | 509.23 (10.3)****   |
| <i>Level 1</i>               |                     |                     |
| BW                           | 23.39 (8.5)***      | 22.30 (4.9)****     |
| <i>Level 2</i>               |                     |                     |
| Sex                          | -64.58 (14.2)****   | -54.12 (13.3)****   |
| Maternal depressive symptoms | 1.77 (0.9)**        | 1.43 (0.8)*         |
| <b>Random effects</b>        |                     |                     |
| Intercept                    | 2174.79 (471.9)**** | 2117.03 (426.6)**** |
| Residuals                    | 435.00 (85.4)****   | 109.02 (21.4)****   |

The best fitting models for both total GM and WM volumes included BW, sex, and maternal depressive symptoms as fixed factors, and the intercept as a random factor. There is greater variability between- than within-families, after controlling for BW, sex, and early maternal depressive symptoms.

Values for fixed and random effects represent estimates (standard error)

\*p<0.1 (trend); \*\*p<0.05; \*\*\*p<0.01; \*\*\*\*p<0.001

Table 3 has been removed



Figure 1. Intra-pair birth weight discordance.

Frequency of BW discordances in MZ twin pair, in kg.

BW = birth weight; MZ = monozygotic; GM = grey matter; WM = white matter.

Figure 2. Birth weight is associated with total grey matter volume in the superior frontal cortex.

T-Statistic map of the positive association between regional superior frontal GM volume and BW (pFWE=0.008). Hot and yellowish colors indicate volume increases are correlated with BW.

GM = grey matter; BW = birth weight

Figure 3. Birth weight is associated with total grey matter volume in the thalamus.

T-Statistic map of the negative association between regional thalamus GM volume and BW (pFWE<0.001). Hot and yellowish colors indicate volume decreases are correlated with BW.

GM = grey matter; BW = birth weight

Figure 4. Birth weight is associated with total white matter volume in the superior frontal cortex.

T-Statistic map of the negative association between regional superior frontal WM volume and BW ( $p_{FEW}=0.004$ ). Hot and yellowish colours indicate volume decreases are correlated with BW.

WM = white matter; BW = birth weight

Figure 5. Association between birth weight and total grey matter volume as moderated by early maternal hostile parenting behaviours.

Graph depicting results showing the trend for maternal hostile parenting behaviours moderating the association between BW and total GM volume.

Horizontal axis represents BW in kg and vertical axis represents total GM volume in adolescence.

BW = birth weight, GM = grey matter