NeuroImage 202 (2019) 116130

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Early life factors, gray matter brain volume and academic performance in overweight/obese children: The ActiveBrains project

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ARTICLE INFO

Keywords:
Childhood
Early programming
Brain structure
Aerobic capacity
Academic achievement

ABSTRACT

Early life factors may influence brain and academic outcomes later in life, especially during childhood. Here we investigate the associations of early life factors (i.e., birth weight, birth length, and breastfeeding) with gray matter volume, adjusted for body mass index and cardiorespiratory fitness, and ii) we test whether early-life factor-related differences in gray matter volume are associated with academic performance in overweight/obese children. 96 children with overweight/obesity aged 8–11 years participated. Birth weight, birth length and gestational age were collected from birth records, and breastfeeding practices were asked to parents. T1-weighted images were acquired with a 3.0 T Magnetom Tim Trio system. Academic performance was assessed with the Bateria III Woodcock-Muñoz Tests of Achievement. Whole-brain voxel-wise multiple regressions were used to test the associations of each early life factor with gray matter volume. Higher birth weight and birth length were associated with greater gray matter volume in 9 brain regions including the middle frontal gyrus, rectal gyrus, thalamus, putamen, middle temporal gyrus, lingual gyrus, middle occipital gyrus, calcarine cortex and cerebellum bilaterally (β ranging from 0.361 to 0.539, t ranging from 3.46 to 5.62 and cluster size from 82 to 4478 voxels; $p < 0.001$); and greater duration of any breastfeeding was associated with greater gray matter volume in 3 regions including the bilateral inferior frontal gyrus and rolandic operculum (β ranging from 0.359 to 0.408, t ranging from 4.01 to 4.32 and cluster size from 64 to 171 voxels; $p < 0.001$). No associations were found for duration of exclusive breastfeeding. Additionally, none of the gray matter regions that were associated with the early life factors were associated with academic performance (all $p > 0.05$). Our results demonstrate that birth weight, birth length, and breastfeeding are predictive of gray matter volume of numerous brain structures that are involved in higher order cognition and emotion regulation, but how these results relate to measures of academic achievement remain a matter of speculation.

Abbreviations: BMI, Body mass index; CRF, Cardiorespiratory fitness; MRI, Magnetic Resonance Image; SD, Standard deviation; PHV, Peak height velocity.

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https://doi.org/10.1016/j.neuroimage.2019.116130
Received 5 April 2019; Received in revised form 24 July 2019; Accepted 23 August 2019
Available online 26 August 2019

1. Introduction

Perinatal nutrition and development are crucial factors for long-term health outcomes (Gluckman et al., 2008). Specifically, birth weight, birth length and infant feeding, which are key indicators of prenatal and perinatal nutrition (Miller et al., 2016; Nyaradi et al., 2013), are predictors of long-term physical (Barker et al., 2002; Labayen et al., 2015) and mental outcomes (Aarnoudse-Moens et al., 2009; Esteban-Cornejo et al., 2018; Hack et al., 2004). In addition, early life factors may influence brain and academic outcomes later in life, especially during childhood (Belfort et al., 2016; Esteban-Cornejo et al., 2018; Farajdokht et al., 2017).

Brain size at birth is only one quarter to one third of its adult volume and fetal development is one of the most important periods of maturation (Toga et al., 2006). Indeed, the period from conception through 2 years of age has been recognized as a critical stage of development, in which brain may be altered by various exposures, resulting in long-term consequences to both its morphology and function (Cusick and Georgieff, 2016). Specifically, the first year of postnatal life is associated with an increase of 108–149% of cortical gray matter volume, and of 14–19% in the second year, with wide variability between regions (Gilmore et al., 2012, 2018). Importantly, intrauterine growth restriction from inadequate prenatal and perinatal fetal environments can profoundly affect post-natal neurodevelopment later in life (Cusick and Georgieff, 2016; Solsnes et al., 2016).

Previous studies on prenatal environmental factors (i.e., birth weight or birth length) in childhood have mainly focused on preterm or low birth weight infants in relation to brain development. For example, school-aged children born with low birth weight have overall and regional (e.g., hippocampus, cerebellum) reductions in gray matter volume (de KIEVIET et al., 2012; Solsnes et al., 2016) that, in turn, may relate to lower academic performance (Peterson et al., 2000). Importantly, the association between these early life factors and brain development could differ according to gestational age, as these infants are exposed to different medical complications during perinatal period (Walhovd et al., 2012). While low birth weight infants (i.e., <2500 g or very low birth <1500 g) have shown lower brain health (Aarnoudse--Moens et al., 2009; Esteban-Cornejo et al., 2018), little is known about the extent to which early life across the birth weight spectrum may predict brain structure (Thompson et al., 2018; Walhovd et al., 2012). Thompson et al. found that variation in birth weight predicts brain development in all groups of gestational age (Thompson et al., 2018). Furthermore, Murray et al. found a differential effect of intrauterine growth restriction on neurodevelopment as a function of gestational age (Murray et al., 2015). However, there are not studies that have investigated the association of birth length and gray matter volume. As such, more studies are needed to examine whether birth weight and birth length separately predict brain development in children across the birth weight spectrum, since both factors have been differentially related to brain health outcomes (Mosing et al., 2018). This is important for a better understanding of the individual variability of brain development in childhood.

Postnatal environmental factors, such as breastfeeding, are potential nutritional opportunities for influencing healthy brain development (Cusick and Georgieff, 2016). Breast milk provides nutrients (e.g. docosahexaenoic acid) that are rapidly incorporated into the central nervous system during the first months of life and, in turn, could help stimulate gray matter development (Reynolds, 2001). Additionally, taurine is the major free amino acid in breast milk, which has a crucial role in the optimal development, proliferation and maturation of brain cells promoting healthy neurodevelopment (Tochitani, 2017). To date, few studies have examined the long-term effect of breastfeeding on child's gray matter volume, and in turn on their academic abilities (Belfort et al., 2016; Luby et al., 2016). Ou et al. showed that children who were breastfed had greater gray matter volume in temporal and parietal regions compared with those who were fed with cow formula (Ou et al., 2016). Belfort et al. found that those who predominantly were breastfed through the first 28 days of life had greater deep gray matter volume in the first week of life, but this association disappeared at the age of 7, and was only associated with a higher intelligence quotient and better performance in mathematics, working memory and motor function at this age (Belfort et al., 2016). Thus, whether breastfeeding has long lasting effects on gray matter and neurocognitive outcomes remain unclear.

Collectively, a better understanding of the association between early life factors and regional gray matter volume in school-age children is needed, and specifically this association has not been studied in children with overweight/obesity. This is particularly important in an overweight/obese population, since suboptimal early life factors have been associated with a higher body mass index (BMI) (Eriksson, 2016), lower cardiorespiratory fitness (CRF) (Boreham et al., 2001; Lawlor et al., 2008) and lower gray matter volume during childhood (Farajdokht et al., 2017). In turn, children with overweight/obesity have worse academic abilities compared to normal-weight children (Reinert, 2013; McCrory and Layte, 2012; Ou et al., 2015). In addition, despite the marked relevance of CRF on gray matter volume in normal weight children (Chaddock-Heyman et al., 2015) and in overweight/obese children (Esteban-Cornejo et al., 2017), previous studies have not considered CRF or BMI when examining the influence of early life factors on brain development. Therefore, the aim of the present study was twofold: i) to investigate the associations between early life factors (i.e., birth weight, birth length, and exclusive and any breastfeeding) and gray matter volume adjusting for several covariates including CRF and BMI, and ii) to test whether these early-life factor-related differences in regional gray matter volume are associated with variability in academic performance in overweight/obese children.

2. Material and method

2.1. Participants

We included 96 overweight/obese children aged 8–11 years from the ActiveBrains project (http://profith.ugr.es/activebrains) with valid measures of early life factors, brain and academic performance variables. Participants met the following inclusion/exclusion criteria to be in the study: 1) 8 to 11.9 years-old; 2) classified as overweight or obese at baseline according to sex and age specific World Obesity Federation cut-off points (Bervoets and Massa, 2014; Cole and Lobstein, 2012; Mora-Gonzalez et al., 2019); 3) an absence of physical disabilities or neurological disorders that prohibited them from exercise; 4) in the case of girls, not to have started menstruation at the moment of baseline assessments; 5) reporting no use of medications that influence central nervous system function; 6) right-handed (i.e., measured by the Edinburgh inventory) since right-handed individuals substantially differ in brain hemisphere structure (i.e., dominant and non-dominant hemisphere) from left-handed ones; and 7) an absence of attention-deficit hyperactivity disorder (ADHD) above the 85th percentile measured by the ADHD rating scale (Cadenas-Sanchez et al., 2016). The present cross-sectional analysis was carried out using baseline data prior to randomization for an exercise intervention. Measurements were carried out from November 2014 to February 2016. Parents or legal guardians were informed of the purpose of the study and written informed parental consents were obtained. The ActiveBrains project was approved by the Ethics Committee on Human Research (CEIH) of the University of Granada and was registered in ClinicalTrials.gov (identifier: NCT02295072).

2.2. Early life factors

Birth weight (kg), birth length (cm) and gestational age (weeks) were collected from birth records (parents' record with the perinatal information of each child). The duration of exclusive and any breastfeeding in months was reported by parents. Parents were asked how long (months)

the child received only breast milk (neither formula nor other liquid or solid). This answer was classified as exclusive breastfeeding. In addition, parents were also asked how long (months) the child received any breast milk (combined with other liquid, formula, or solid). This answer was classified as any breastfeeding.

2.3. Magnetic resonance imaging (MRI) acquisition and processing

MRI assessment was performed with a 3.0 T Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) equipped with a 32-channel head coil. Three-dimensional high-resolution T1-weighted images were collected using a magnetization-prepared rapid gradient-echo (MPRAGE) sequence. The sequence parameters were as follows: repetition time (TR) = 2300 ms, echo time (TE) = 3.1 ms, inversion time (TI) = 900 ms, flip angle = 9°, Field of view (FOV) = 256 × 256, acquisition matrix = 320 × 320, 208 slices, resolution = 0.8 × 0.8 × 0.8 mm, and scan duration of 6 min and 34 s.

The processing protocol was detailed in a previously published paper (Esteban-Cornejo et al., 2017). In brief, imaging pre-processing steps included quality control, alignment and segmentation into gray matter tissue, white matter tissue and cerebrospinal fluid. First, each individual image was checked for acquisition artifacts and alignment along the horizontal anterior commissure and posterior commissure plane. Then, gray matter images were spatially normalized to Montreal Neurological Institute (MNI) space and used to create a template using Diffeomorphic Anatomical Registration Through Exponentiated Lie algebra (DARTEL). Subsequently, images were normalized to the DARTEL template via non-linear transformation and modulated with Jacobian determinants. Finally, the images were smoothed by convolving them with an isotropic Gaussian kernel of 8 mm full width at half maximum (FWHM).

2.4. Academic performance

The Bateria III Woodcock-Muñoz Tests of Achievement was used to assess academic performance (i.e., Spanish version of the Woodcock-Johnson III) (Woodcock et al., 2001). A trained evaluator individually administered the tests to each child, explained the instructions and assessed the child during the session. The full administration time was between 100 and 120 min. The Bateria III Woodcock-Muñoz is a standardized test of achievement comprising several sub-tests. In this study we included four indicators: reading, writing, mathematics, and a total achievement standard score.

2.5. Covariates

Sex, gestational age, peak height velocity (PHV), parental education, BMI and cardiorespiratory fitness were used as covariates. Pubertal maturity status was determined by PHV and was obtained from the Moore et al. (2015) equation for boys and girls; PHV offset was calculated by subtracting the age of PHV from the chronological age. The difference in years was defined as a value of maturity offset. Both father and mother's educational level were considered indicators of socioeconomic status. Thus, parents were asked to report their maximum completed level of education and answers were categorized as: none of the parents had university degree, one of the parents had a university degree or both parents had a university degree (Huppertz et al., 2017). BMI was computed as weight in kilograms divided by height in meters squared (kg/m^2). CRF was assessed through the 20-m shuttle-run test and maximal oxygen consumption (VO_2max, mL/kg/min) was calculated using the Leger equation (Leger et al., 1988).

2.6. Statistical analysis

Participant characteristics are shown as mean and standard deviation (SD) for continuous variables, and percentages for categorical variables. Whole-brain voxel-wise multiple regression models were performed in SPM12 for the analyses of imaging data. The associations between each early life factor (i.e., birth weight, birth length, exclusive and any breastfeeding) and gray matter volume were tested in separate linear regressions. The model included adjustment for sex, gestational age, PHV offset, parental education level, BMI and CRF. We extracted eigenvalues of the peak coordinates of each significant cluster that showed association with each early life factor and we performed separate regression models in SPSS including eigenvalues as outcomes and each early life factor as a predictor, adjusted for covariates mentioned above. Additionally, we performed linear regression in SPSS (version 21 for Macintosh; P set at < 0.05) to test the association between each significant gray matter region using those eigenvalues as predictors and academic performance indicators as outcomes adjusting for sex, PHV offset, parental education level, BMI and CRF. The spatial extent threshold was determined using AlphaSim as implemented in Resting-State fMRI Analysis Toolkit toolbox (RESTplus). Input parameters include a brain mask of 128190 voxels and a cluster connection radius of 5 mm considering the smoothness of data after model estimation. The voxel-level alpha significance (threshold, $p < 0.001$ uncorrected) along with the appropriate cluster size for controlling for multiple comparisons in each analysis was indicated in the results. Finally, resulting cluster extents were adjusted to account for the non-isotropic smoothness of structural images, in accordance with Hayasaka et al. (2004). The clusters are reported after applying these corrections. Additionally, sensitivity analyses were performed excluding preterm children.

3. Results

Table 1 shows descriptive characteristics of the overall sample and separated by boys and girls. Table 2 presents the associations for each early life factor showing a positive association with regional gray matter volume, independently of CRF and BMI. Consistent with our predictions, higher birth weight was associated with greater gray matter volume ($p < 0.001$, $k = 45$) in seven clusters, with t values ranging from 3.46 to 5.62, a cluster size between 82 and 4445 and a standardized coefficient (β) between 0.361 and 0.539, specifically, in frontal regions (i.e., middle frontal gyrus and rectal gyrus), temporal regions (middle temporal gyrus), thalamus, and cerebellum (i.e. cerebellum III, and cerebellum crus II bilaterally) (Table 2, Fig. 1).

Similarly, higher birth length was associated with greater gray matter volume ($p < 0.001$, $k = 38$) in seven clusters, with t ranging from 3.78 to 5.44, cluster size between 97 and 4478 and a standardized coefficient (β) between 0.378 and 0.537, specifically, in putamen, temporal regions (middle temporal gyrus), occipital regions (lingual, middle occipital gyrus), calcarine cortex and cerebellum crus II bilaterally (Table 2, Fig. 2).

We also found that duration of any breastfeeding was associated with greater gray matter volume ($p < 0.001$, $k = 39$) in 3 clusters, with t ranging from 4.01 to 4.32, cluster size between 64 and 171 and standardized coefficient (β) between 0.359 and 0.408, specifically, in frontal regions (inferior frontal gyrus pars orbital bilaterally) and rolandic operculum (Table 2, Fig. 3). No significant associations were found between duration of exclusive breastfeeding and gray matter volume.

In sensitivity analysis after excluding preterm children, the associations were maintained for birth weight in four regions (i.e., middle frontal gyrus, middle temporal gyrus, cerebellum crus II left and cerebellum crus II right), for birth length in five regions (i.e., putamen, lingual, calcarine cortex, cerebellum crus II left and cerebellum crus II right) and for duration of any breastfeeding in two regions (i.e., inferior frontal gyrus pars orbital and rolandic operculum) (data not shown). These associations were also independent of BMI and CRF.

There were no negative significant relationships between early life risk factors and gray matter volume in any brain region ($p > 0.05$). Table 3 shows the association between brain regions corresponding to each early life factor and academic performance. No significant associations were found (all $p > 0.05$).

Table 1
Characteristics of study sample.

	All		*Boys*		*Girls*	
	n		*n*		*n*	
Physical characteristics	96		60		36	
Age (years)		10.0 ± 1.1		10.2 ± 1.1		9.8 ± 1.1
Weight (kg)		55.7 ± 11.2		56.7 ± 10.7		54.0 ± 11.8
Height (cm)		143.8 ± 8.3		144.7 ± 7.4		142.3 ± 9.6
Peak height velocity offset (year)		−2.3 ± 1.0		−2.7 ± 0.8		−1.2 ± 0.8
Body mass index (kg/m^2)		26.7 ± 3.7		26.9 ± 3.8		26.4 ± 3.5
Cardiorespiratory fitness (mL/kg/min)*		40.9 ± 2.8		40.8 ± 2.8		40.9 ± 2.8
Body mass index category (%)	96		60		36	
Overweight		25.0		23.3		27.8
Obesity type I		42.7		45.0		38.9
Obesity type II/III		32.3		31.7		33.3
Parental education university level (%)	96		60		36	
None of the parents		66.7		71.7		58.3
One of the two parents		17.7		16.7		19.4
Both parents		15.6		11.5		22.2
Gestational age (%)	96		60		36	
<37 weeks		17.7		16.7		19.4
37–40 weeks		64.6		68.3		58.3
>40 weeks		17.7		15.0		22.2
Neonatal characteristics						
Birth weight (g)	94	3343.7 ± 0.5	59	3359.0 ± 0.6	35	3318.0 ± 0.5
Birth length (cm)	85	50.7 ± 2.7	57	50.6 ± 3.0	28	50.9 ± 1.8
Gestational age (weeks)	96	38.6 ± 2.6	60	38.6 ± 2.6	36	38.7 ± 2.6
Exclusive breastfeeding[#] (%)	92		59		33	
Never		31.5		28.2		36.4
<3 months		17.4		20.3		12.1
3–5 months		23.9		18.6		33.3
≥6 months		27.2		32.2		18.2
Any breastfeeding[##](%)	92		59		33	
Never		20.7		20.3		21.2
<3 months		14.1		13.6		15.2
3–5 months		25.0		22.0		30.3
≥6 months		40.2		44.1		33.3
Academic performance (standard score)**	96		60		36	
Mathematics		102.0 ± 10.7		102.4 ± 11.2		101.4 ± 9.8
Reading		108.5 ± 12.9		108.3 ± 11.1		108.9 ± 15.7
Writing		114.0 ± 12.0		112.6 ± 11.9		116.4 ± 11.9
Total achievement		109.5 ± 11.7		109.0 ± 10.7		110.3 ± 13.3

Values are mean ± SD or percentage. Statistically significant values are shown in bold. *Measured by the 20-m shuttle run test; **Measured with the Bateria III Woodcock-Muñoz Tests of Achievement. [#]Months the child received only breast milk. [##]Months the child received breast milk combined with other liquid, or solid.

4. Discussion

The main finding indicates that early life factors (i.e., birth weight, birth length and any breastfeeding) were positively associated with gray matter volume in numerous cortical and subcortical brain structures in children with overweight/obesity and these associations were independent of BMI and CRF. Additionally, regional gray matter volumes of clusters associated with early life factors were not associated with academic performance. These results have important public health implications since they suggest that gray matter volume during childhood could be partially influenced by fetal or early infancy environment.

Several mechanisms might explain the present results. During pregnancy, intrauterine growth restriction profoundly and negatively influences brain development; the number of neurons, dendritic and synaptic head architecture, the concentrations of neurotransmitters and growth factors are affected in a suboptimal intrauterine environment (Cusick and Georgieff, 2016). Poor fetal environment can lead to fetal circulatory redistribution, which is considered an adaptive fetal response that preserves oxygen supplied to the brain (and other vital organs) in conditions of chronic hypoxia (Murray et al., 2015). This does not apparently ensure normal brain development, and even more, cortical gray matter volume could decrease independently of a reduction in overall brain volume (Miller et al., 2016; Nyaradi et al., 2013). Thus, poor fetal nutrition as well as other aspects of the environment reflected in lower weight and length at birth could affect brain development and subsequently gray matter volume in early childhood.

Additionally, the early postnatal period, specifically the first year of life, is crucial for gray matter growth, since during this period gray matter volume may increase more quickly than white matter volume, reaching 80% of adult capacity by the second year (Gilmore et al., 2018). From age 2, gray matter volume shows minimal absolute increases in comparison with white matter volume that increases much more gradually (Gilmore et al., 2018). Indeed, the importance of docosahexaenoic acid (an abundant ingredient in human milk) as well as taurine and iron for neurogenesis, neuronal migration, and synaptogenesis might be leading to some of these associations (Cusick and Georgieff, 2016; Wachs et al., 2014). Breastfeeding provides the essential components to infant growth and development in each period according to the personal needs of each child (Andreas et al., 2015; Deoni, 2018). Therefore, breastfeeding in the early postnatal period might be a nutritional strategy for sustaining healthy brain development (Cusick and Georgieff, 2016; Nyaradi et al., 2013).

To the best of our knowledge, there are no previous studies examining the relationship of early life factors with gray matter volume specifically in children with overweight/obesity. In infants, higher birth weight was associated with larger brain volumes and regional cortical gray matter volumes in those individuals scanned between week 41.4–42.4 of postmenstrual age (Thompson et al., 2018). Additionally, low birth weight was the most predominant predictor of lower brain volume and altered microstructure, in comparison with multiple birth, social risk or postnatal growth factors (Thompson et al., 2018). Previous systematic reviews in healthy normal-weight children support that low birth weight (i.e.,

Table 2
Brain regions showing positive associations of birth weight* (n = 94), birth length (n = 85) and any breastfeeding (n = 92) with gray matter volume in overweight/obese children.

Brain Regions (mm^3)	*x*	*y*	*z*	*t*	*Cluster size*	*Hem*	B (95% CI)	*β*
Birth weight								
Middle frontal gyrus	32	42	21	4.32	82	L	0.101 (0.055,0.148)	0.462
Rectal gyrus	2	38	−30	3.92	328	L	0.030 (0.015,0.045)	0.392
Thalamus	16	−21	12	3.46	100	L	0.023 (0.010,0.037)	0.371
Middle temporal gyrus	−45	−16	−9	3.82	180	R	0.040 (0.019,0.060)	0.390
Cerebellum III	−9	−36	−20	3.68	166	R	0.025 (0.012,0.038)	0.361
Cerebellum crus II	24	−84	−46	5.62	4445	L	0.052 (0.034,0.070)	0.539
Cerebellum crus II	−36	−78	−51	4.62	2638	R	0.030 (0.017,0.043)	0.453
Birth length								
Putamen	−21	14	−14	3.93	430	R	0.005 (0.003,0.008)	0.378
Middle temporal gyrus	−50	−27	−8	3.87	375	R	0.017 (0.008,0.026)	0.431
Lingual	22	−74	−8	4.09	97	L	0.013 (0.007,0.020)	0.439
Middle occipital gyrus	40	−76	26	3.78	150	L	0.012 (0.006,0.018)	0.408
Calcarine cortex	−10	−84	−2	3.80	283	R	0.010 (0.005,0.016)	0.425
Cerebellum crus II	33	−74	−51	5.44	4478	L	0.015 (0.010,0.021)	0.537
Cerebellum crus II	−40	−70	−54	4.76	1878	R	0.007 (0.004,0.010)	0.496
Any breastfeeding								
Inferior frontal gyrus pars orbital	16	18	−27	4.01	64	L	0.002 (0.001,0.003)	0.359
Inferior frontal gyrus pars orbital	−16	21	−27	4.26	133	R	0.002 (0.001,0.002)	0.364
Rolandic operculum	56	−2	14	4.32	171	L	0.004 (0.002,0.006)	0.408
Exclusive breastfeeding								
Non-significant association	–	–	–	–	–		–	–

Analyses were adjusted for sex, peak height velocity offset (years), parent education university level (neither/one/both), gestational age (weeks), body mass index (kg/m^2) and cardiorespiratory fitness (mL/kg/min). All contrasts were thresholded using AlphaSim at $P < 0.001$ with $k = 45$ voxels for birth weight, $k = 38$ voxels for birth length and $k = 39$ voxels for any breastfeeding, and surpassed Hayasaka correction. Anatomical coordinates (X, Y, Z) are given in Montreal Neurological Institute (MNI) Atlas space. Hem, hemisphere; R, right, L, left *Values in Kg.

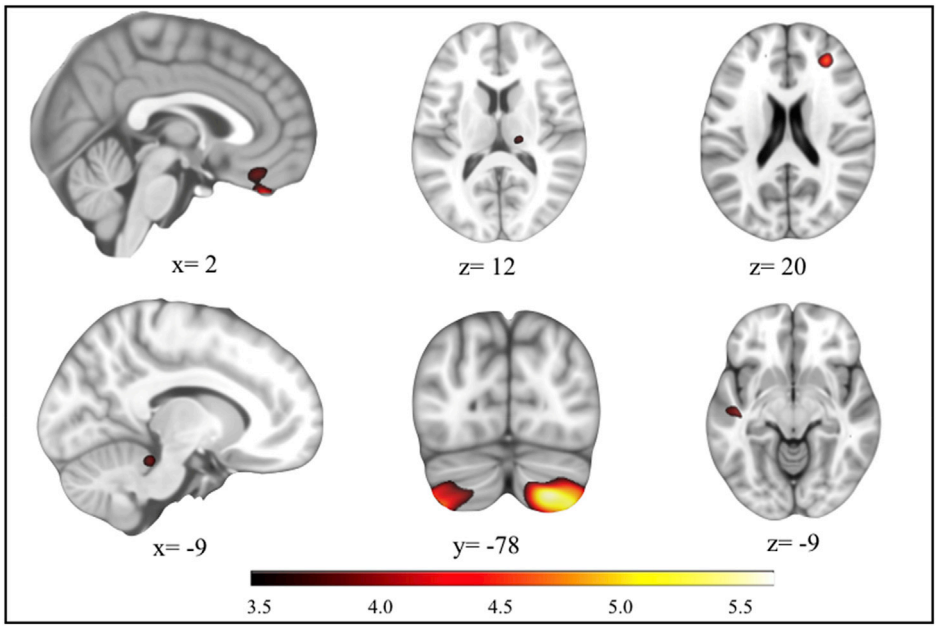

Fig. 1. Brain regions showing positive association with birth weight. Images corresponding to model adjusted for sex, peak height velocity offset (years), parental education level (neither/one/both), body mass index (kg/m^2) and cardiorespiratory fitness (mL/kg/min). Maps were thresholded using AlphaSim at $P < 0.001$ with $k = 45$ and surpassed Hayasaka correction. The color bar represents t-values, with lighter yellow color indicating higher significant association. Images are displayed according to neurological convention; therefore, the right hemisphere corresponds to the right side in coronal displays. x: indicates coordinate of sagittal view; y: indicates coordinate of coronal view; z: indicates coordinate of axial view.

<2500 g or very low birth <1500 g) negatively affects several cortical gray matter areas, cerebellar gray matter, and thalamus volume (de KIEVIET et al., 2012; Farajdokht et al., 2017; Solsnes et al., 2016). For instance, our results showed that the cerebellum was an important region associated with both body weight and length at birth. These associations remained after sensitivity analysis excluding preterm children (data not shown). Recently, the cerebellum has been related to plasticity in the cerebral cortex; it plays an important role in language, motor and cognitive maturation, and is considered a domain-general region in all motor and cognitive processes (Marek et al., 2018). These results suggest that the cerebellum might be particularly sensitive to the intrauterine environment due to its major growth and development during the second half of gestation, and sub-optimal conditions in this period could lead to smaller body size (Andescavage et al., 2017; du Plessis et al., 2018; Koning et al., 2017; Miller et al., 2016). Moreover, middle temporal gyrus was consistently associated with both birth length and birth weight. This finding is in line with previous studies showing that temporal brain regions are particularly susceptible to disruption of the gestational environment which may have long-term consequences (Pascoe et al., 2019). This region is involved in both linguistic and nonlinguistic semantic-level processes (Enrici et al., 2011; Knickmeyer et al., 2017), as well as in memory and several other cognitive processes (Cabeza and Nyberg, 2000; Onitsuka et al., 2004).

Additionally, we found that birth length was associated with greater

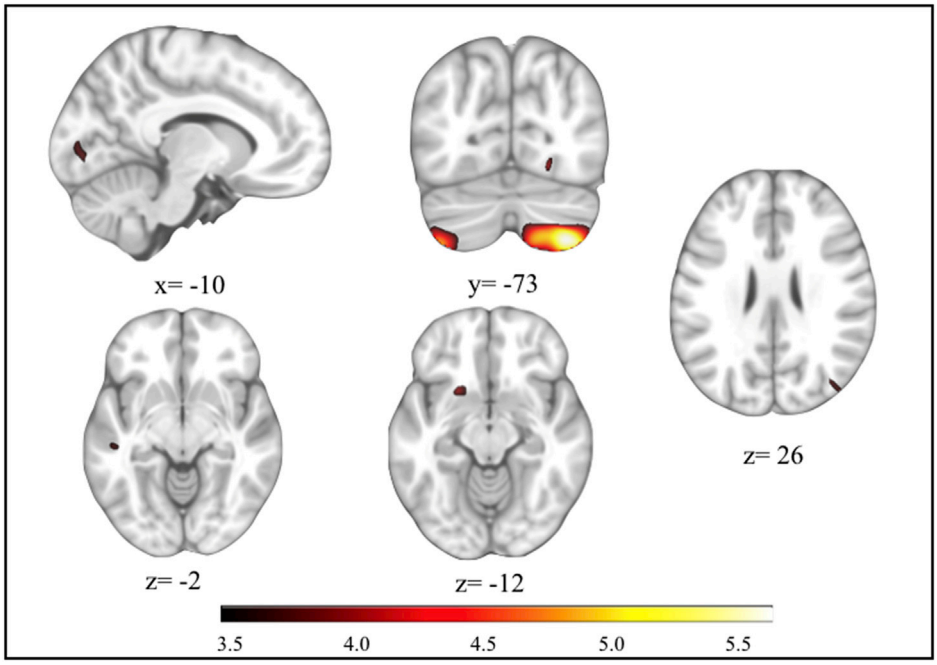

Fig. 2. Brain regions showing positive association with birth length. Images corresponding to model adjusted for sex, peak height velocity offset (years), parental education level (neither/one/both), body mass index (kg/m^2) and cardiorespiratory fitness (mL/kg/min). Maps were thresholded using AlphaSim at $P < 0.001$ with $k = 38$ and surpassed Hayasaka correction. The color bar represents t-values, with lighter yellow color indicating higher significant association. Images are displayed according to neurological convention; therefore, the right hemisphere corresponds to the right side in coronal displays. x: indicates coordinate of sagittal view; y: indicates coordinate of coronal view; z: indicates coordinate of axial view.

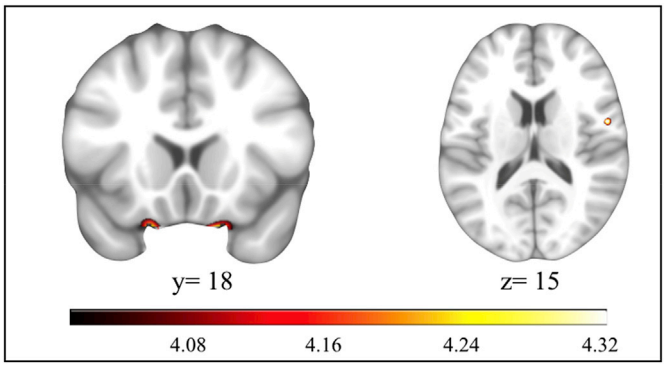

Fig. 3. Brain regions showing positive association with any breastfeeding. Images corresponding to model adjusted for sex, peak height velocity offset (years), parental education level (neither/one/both), body mass index (kg/m^2) and cardiorespiratory fitness (mL/kg/min). Maps were thresholded using AlphaSim at $P < 0.001$ with $k = 39$ and surpassed Hayasaka correction. The color bar represents t-values, with lighter yellow color indicating higher significant association. Images are displayed according to neurological convention; therefore, the right hemisphere corresponds to the right side in coronal displays. x: indicates coordinate of sagittal view; y: indicates coordinate of coronal view; z: indicates coordinate of axial view.

gray matter volume in occipital regions (e.g., lingual gyrus, middle occipital gyrus and calcarine cortex), which have a principal role in visual processing (Jacobson et al., 2018) in line with previous findings indicating that the prenatal environment has long-term consequences in these regions (Bouyssi-Kobar et al., 2018; Leung et al., 2018). Collectively, although previous studies have focused on preterm or low or very low birth weight infants, our findings across a wide range of birth weight partially concur with previous studies showing that birth size was associated with greater regional gray matter independently of important health-related factors such as CRF or BMI (Esteban-Cornejo et al., 2017; Ou et al., 2015).

Exclusive and any breastfeeding have been related to gray matter development (Belfort et al., 2016). In the present study, exclusive breastfeeding was not associated with gray matter volume; however, any breastfeeding was positively associated with regional gray matter in the inferior frontal gyrus and rolandic operculum, two regions mainly related to language (Gilmore et al., 2018). While long-term effect has been found for duration of exclusive breastfeeding in neurodevelopment outcomes, other findings have not observed an effect on executive function, behavior or social-emotional development (Gishti et al., 2016). Indeed, higher proportion of breast milk intake in the first month of life was associated with deep nuclear gray matter and hippocampus volume in the first months of life (between 3 and 42 weeks postmenstrual age), but such findings did not appear at the age of 7 years (Belfort et al., 2016). In contrast, Luby et al. found increases in cortical and subcortical gray matter volume between the ages of 9 and 14 years when comparing those who were breastfed with those who were not (Luby et al., 2016). Ou et al., using voxel-based morphometric analysis, found that breastfed infants presented greater gray matter in the inferior temporal and superior parietal lobes at age 8 compared with those fed with cow-milk formula (Ou et al., 2016). Of note, no previous studies have found associations between any breastfeeding and gray matter volume in the inferior frontal gyrus and rolandic operculum; however, the potential role of breastfeeding in speech and language during childhood has been previously reported (Smith, 2015), and it is possible that those regions may be implicated in these benefits. Thus, we highlight the importance of any long-term breastfeeding for brain development, although future studies are needed to confirm these results. While no associations were found for duration of exclusive breastfeeding, we observed a high prevalence of participants exclusively breastfed for longer than six months. This is of particular interest since obese children have been reported to have received lower duration of exclusive breastfeeding (Oken et al., 2017; Von Kries et al., 1999).

Previous studies in different populations have demonstrated that volume and integrity of gray matter volume is related to several aspects of executive function, and academic abilities (Chaddock-Heyman et al., 2015; Hair et al., 2015). In the present study, gray matter volumes (previously associated with early life factors) were not associated with academic performance in overweight/obese children. Obesity *per se* has been associated with poorer cognitive function compared with normal weight peers (Garcia-Garcia et al., 2018; Li et al., 2008; Smith et al., 2011), and this may hinder the influence of early life factors with differences in gray matter volumes on academic performance in an overweight/obese population. For example, Wang et al. examined the

Table 3
Associations of early-life factor-related changes in gray matter with academic performance*.

	Mathematics		*Reading*		*Writing*		*Total achievement*	
	β	***p***	***β***	***p***	***β***	***p***	***β***	***p***
Birth weight								
Middle frontal gyrus	0.038	0.705	0.106	0.295	0.100	0.308	0.100	0.297
Rectal gyrus	0.188	0.081	0.064	0.564	−0.134	0.209	0.041	0.698
Thalamus	0.139	0.172	0.182	0.078	−0.038	0.703	0.119	0.226
Middle temporal gyrus	0.014	0.894	0.129	0.217	−0.012	0.908	0.053	0.591
Cerebellum III	0.081	0.470	0.194	0.086	0.069	0.533	0.143	0.186
Cerebellum crus II	0.074	0.482	−0.002	0.983	−0.016	0.877	0.012	0.905
Cerebellum crus II	0.087	0.820	−0.037	0.736	0.075	0.474	0.032	0.755
Birth length								
Putamen L	0.068	0.562	0.124	0.307	−0.088	0.461	0.056	0.626
Middle temporal gyrus	−0.014	0.890	0.001	0.989	−0.057	0.575	−0.032	0.745
Lingual	−0.185	0.072	0.044	0.682	0.016	0.882	−0.035	0.729
Middle occipital gyrus	0.028	0.790	0.121	0.259	−0.053	0.614	0.052	0.609
Calcarine cortex	−0.104	0.300	0.074	0.478	−0.077	0.453	−0.028	0.772
Cerebellum crus II	−0.080	0.446	−0.018	0.867	−0.005	0.960	−0.042	0.684
Cerebellum crus II	−0.048	0.647	−0.172	0.106	−0.023	0.828	−0.115	0.256
Any breastfeeding								
Inferior frontal gyrus pars orbital	0.207	0.059	0.056	0.621	0.043	0.693	0.114	0.286
Inferior frontal gyrus pars orbital	0.220	0.053	0.054	0.644	0.067	0.554	0.124	0.267
Rolandic operculum	0.082	0.423	−0.087	0.400	0.041	0.685	0.009	0.932

Values are standardized regression coefficients (β). Analyses were adjusted for sex, peak height velocity offset (years), parent education university level (neither/one/both), gestational age (weeks), body mass index (kg/m^2) and cardiorespiratory fitness (mL/kg/min). *Measured with the Bateria III Woodcock-Muñoz Tests of achievement.

association of gray matter and academic performance in a large sample of Chinese adolescents, and found that the left dorsolateral prefrontal cortex was related to academic performance (Wang et al., 2017). In addition, consistent with our findings, Isaac et al. found that breastfeeding was not associated with cortical gray matter, but it was associated with white matter; and in turn, white matter was associated with intellectual quotient in children and adolescents (Isaacs et al., 2010). To note, we included an important confounder that was not previously considered (i.e., CRF). Several sources of evidence, including a previous study with the present sample, supported the associations of CRF with academic performance (Chaddock-Heyman et al., 2015; Esteban-Cornejo et al., 2017), brain structure (Esteban-Cornejo et al., 2017, 2018; Ortega et al., 2017) and thus, CRF has been proposed as an important moderator/mediator of cognitive function related to obesity (Chang et al., 2017). As such, the inclusion of important health-related factors as covariates, such as CRF, may attenuate the strength of the association between gray matter volume and academic performance. However, future research is needed to examine the influence of early life factors on gray matter, and in turn, on academic performance including both normal-weight and overweight/obese children.

There are several limitations that should be acknowledged. First, the use of a retrospective cross-sectional design does not allow attributing causality between variables. Second, participants potentially misunderstood the term or meaning of "exclusiveness" of breastfeeding, and such an issue may have been exacerbated by a lack of information regarding formula-fed for those who were not breastfed (van Ginkel et al., 2018), which may explain, in part, the null association related to breastfeeding practices. Third, the inclusion of only overweight and obese children limits the generalizability of our findings. Nevertheless, obesity is an important public health concern during childhood, and examining health factors in in this population is of great importance to understand factors that influence brain development. Strengths of the present study include its relatively large sample of overweight/obese children, the use of birth records to assess early life factors and the adjustment for important confounders.

5. Conclusion

Our results support the influence of early life factors (i.e., birth weight, birth length and any breastfeeding) on gray matter volume of numerous cortical and subcortical brain structures in overweight/obese children. These results were maintained despite controlling for a wide number of health-related factors such as CRF and BMI. However, there were no associations between gray matter volumes associated with early life factors and academic performance in overweight/obese children. These results might have important practical applications since obesity is epidemic in childhood and attention in prenatal nutrition during pregnancy may be necessary to avoid negative effects of early life factors on the offspring's brain development later in life. Therefore, interventions aiming at improving optimal intrauterine growth and development, and promoting breastfeeding in infancy may be of importance to achieve a healthy brain later in life.

Declarations of interest

None.

Funding

This study was supported by the Spanish Ministry of Economy and Competitiveness (DEP2013-47540, DEP2016-79512-R, and DEP2017-91544-EXP), the European Regional Development Fund (ERDF), the European Commission (No 667302), and the Alicia Koplowitz Foundation. This study was partially funded by the University of Granada, Research and Knowledge Transfer Fund (PPIT) 2016, the Excellence Actions Programme: Units of Scientific Excellence; Scientific Unit of Excellence on Exercise and Health (UCEES), the Andalusian Regional Government, the Regional Ministry of Economy, Knowledge, Entreprises and University, and the European Regional Development Fund (ERDF), ref. SOMM17/6107/UGR. PS-U is supported by a grant from CONICYT/BECAS Chile/72180543. IE-C is supported by the Spanish Ministry of Economy and Competitiveness (IJCI-2017-33642). In addition, this study was further supported by the SAMID III network, RETICS, funded by the PN I+D+I 2017–2021 (Spain) CC-S is supported by the Andalusian Regional Government, 2014–2020 Cadiz Integrated Territorial Investment (PI-0002-2017). JM-G and JHM are supported by the Spanish Ministry of Education, Culture and Sport (FPU14/06837, FPU15/02645). JV-R is supported by a grant from the Spanish Ministry of Science, Innovation and Universities (FJCI-2017-33396).

Acknowledgements

We would like to thank all the families participating in the Active-Brains. We also acknowledge everyone who helped with the data collection and all of the members involved in the field work for their effort, enthusiasm, and support. This work is part of a Ph.D. Thesis conducted in the Doctoral Programme in Biomedicine of the University of Granada, Spain. We are grateful to Ms. Ana Yara Postigo-Fuentes for her assistance with the English language.

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