Early life factors and hippocampal functional connectivity in children with overweight/obesity

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Summary

Objective: We investigated association of anthropometric neonatal data (birth length and birth weight) and breastfeeding practices (exclusive and any breastfeeding) with hippocampal functional connectivity and its academic implication in children with overweight/obesity.

Methods: 96 children with overweight/obesity aged 8-11 years (10.01 ± 1.14) from the ActiveBrains project were included in this cross-sectional study. Anthropometric neonatal data were collected from birth records, whereas breastfeeding practices were reported by parents. A 3.0 Tesla Siemens Magnetom Tim Trio system was used to acquire T1-weighted and resting-state functional magnetic resonance images. Academic performance was assessed by the Woodcock-Muñoz standardized test. Hippocampal seed-based methods with post-hoc regression analyses were performed. Analyses were considered significant when surpassing Family-Wise Error corrections.

Results: Birth weight showed a positive association with the connectivity between the hippocampus and the pre- and postcentral gyri, and the cerebellum. In addition, breastfeeding was negatively associated with the connectivity between the hippocampus and the primary motor cortex and the angular gyrus. Any breastfeeding in turn, showed a positive association with the connectivity between the hippocampus and the middle temporal gyrus. None of the connectivity outcomes related to early life factors was coupled with better academic abilities (all $p>0.05$).

Conclusions: Our findings suggest that birth weight at birth and breastfeeding are associated with hippocampal connectivity in children with overweight/obesity. Despite this, how the results relate of academic performance remain a matter of speculation. Our findings suggest that clinicians should recognize the importance early life factors for potentially avoiding consequences on offspring's brain development.

Keywords: birth weight; brain; breastfeeding; hippocampus; cognition, obesity.

1. INTRODUCTION

Environmental factors present in early life are particularly important for brain development [1]. Early life factors such as anthropometric neonatal data (birth length and birth weight) and breastfeeding practices (exclusive and any breastfeeding) might have long lasting consequences in several key brain regions that support higher-level cognitive processes (i.e., planning, problem solving) later in life [2-4]. Specifically, the hippocampus undergoes protracted functional and structural development after birth, which likely influences everyday activities, memory and learning, and in turn academic performance during childhood [1,5-7].

There is extensive evidence of associations between early life factors and morphologic changes of the hippocampus later in childhood [5]. For example, low birth weight has been associated with smaller hippocampal shape and volume in school-aged children [8,9]. Along these lines, Anne et al. found that children that were born preterm and with very low birth weight had smaller hippocampal subfield volumes than age-matched term-born controls at 9 years [10]. Interestingly, breastfed children showed larger hippocampal volumes at term equivalent age, but this association was not evident at 7 years of age [11]. In contrast, recent evidence showed that length of exclusive breastfeeding was associated with hippocampus volume, but was not related to satiety or weight status [12]. To our knowledge, only one previous study was designed to investigate the association of a single early life factor, birth weight, and the functioning of limbic areas such as the hippocampus. This study demonstrated that birth weight was related to more efficient limbic communication (meaning that information flow is maximized between regions within a network) at rest in adolescents [13]. Thus, in contrast to the extensive literature on the relationship between early life factors and hippocampal structure [5,8-10,14], few previous studies have examined the relationship of early life factors with the function of the hippocampus in children.

There is evidence, however, that resting state functional connectivity (rsFC) of other regions, apart from the hippocampus, is sensitive to early life environment. For example, alterations in rsFC are evident at birth in networks related to motor function, language, and executive function [15]. Previous studies on early life factors and rsFC have mostly focused on the amygdala, because of its involvement in affective and cognitive processes later in life [16,17]. However, the influence of early life factors on rsFC of the hippocampus is still poorly understood [5]. This represents an important gap in our understanding of how early life environment relates to brain function because rsFC of the hippocampus has been related to different health states in childhood and adulthood, including adolescent depression [18] and schizophrenia in young adults [19,20]among others [19-22]. In addition, hippocampal functional connectivity may relate to several behavioral changes [23], such as memory deficits [24], mathematical difficulties and nonverbal learning disabilities [25], among others [26,27], which may have implications for academic performance during childhood. Further, the hippocampus is a key region implicated in the regulation of food intake by detecting learned signals [28], being specifically important in a population with overweight/obesity, especially in youth when the hippocampus is still in developments [29].

Therefore, this background highlights the importance of examining early life development of hippocampal rsFC and its academic implications in children, and particularly in children with overweight/obesity, who show altered hippocampal connectivity and worse executive function and academic performance [30-35]. In the present study, we investigated the associations of early life factors such as anthropometric neonatal data (i.e., birth length and birth weight) and breastfeeding practices (i.e., exclusive and any breastfeeding) with hippocampal rsFC, and ii) tested whether connectivity related to early life factors is associated with long-term academic performance in children with overweight/obesity.

2. METHODS

Participants

We included 96 children with overweight/obesity (categorized based on World Obesity Federation cut-off points, which consist on an extrapolation to younger ages of the established cut-points in adults, BMI 25 and 30) [36,37] aged 8-11 years from the ActiveBrains project [38] (www.profith.ugr.es/activebrains) with completed and valid measures of early life factors, brain connectivity and academic performance variables. Briefly, inclusion criteria were (a) no physical disabilities or neurological disorders; (b) absence of menstruation at the time of the baseline assessment, (c) right-handedness, and (d) no present Attention-Deficit Hyperactivity Disorder. This study is based on a cross-sectional analysis of baseline data prior to randomization to an exercise intervention. Parents or legal guardians were informed of the purpose of the ActiveBrains study and written informed consents were obtained. The project was approved by the Human Research Ethics Committee of the University of Granada, and was registered in ClinicalTrials.gov (identifier: NCT02295072).

Measures

Early life factors

Weight (kg) and length (cm) at birth were collected from health records (i.e., physical medical record that parents had with the offspring's perinatal information). In addition, parents were asked the following questions: *(i) for how long (months) did the child receive only breast milk (neither formula or other liquid or solid)?*, as an indicator of exclusive breastfeeding, and (ii) *for how long (months) did the child receive any breast milk (combined with other liquid, formula, or solid)?*, as an indicator of any breastfeeding [39]. All measure were used as continuous variables.

Academic performance

The version III of the Woodcock-Muñoz Tests of Achievement was used as a measure of academic performance (i.e., Spanish version of the Woodcock-Johnson III) [40]. A trained member of the research staff administered the test for each child. The full administration time was between 100 to 120 min. We included standard score indicators of reading, writing mathematics and total achievement in the present analysis [41].

Covariates

Gestational age (weeks) was collected from health records; peak height velocity (PHV) was used as an indicator of pubertal maturity status in childhood and was obtained through the Moore et al. equation [42]; PHV offset was computed by the difference between PHV and chronological age. Parents reported their maximum completed level of education and answers were categorized as: none of the parents had a university degree, one of the parents had a university degree or both parents had a university degree, based on our previous studies [4,39]. Children's cardiorespiratory fitness (CRF) was estimated through the 20-meter shuttle-run test and maximal oxygen consumption (VO_2max, mL/kg/min) was calculated using the Lèger equation[43].

Resting state functional MRI (rsfMRI)

MRI data acquisition and preprocessing

Images were collected using a 3.0 Tesla Siemens Magnetom Tim Trio system (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. The complete procedure was published in a previous work of the present sample [44]. High-resolution T1-weighted images

were acquired using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) protocol. The parameters were as follows: repetition time (TR) = 2300 ms, echo time (TE) = 3.1 ms, inversion time (TI) = 900 ms, flip angle = 9º, field of view (FOV) = 256 x 256, acquisition matrix= 320 x 320, 208 slices, resolution = 0.8 x 0.8 x 0.8 mm, and scan duration of 6 min and 34 s. The rsfMRI was composed of a series of 160 scans acquired using a Gradient Echo Pulse Sequence while participants rested with eyes closed. The parameters were as follows: TR = 1000 ms, TE = 25 ms, flip angle = 80º, FOV = 240 mm, acquisition matrix= 240 x 240, 35 slices, resolution = 3.5 x 3.5 x 3.5 mm, and scan duration of 5 min and 25 s.

Preprocessing steps were carried out in FMRIB's Software Library (FSL) version 5.0.7. The following steps were applied: (i) skull-stripping using brain extraction tool (BET), (ii) spatial normalization of the MPRAGE structural image to Montreal Neurological Institute (MNI) space, (iii) alignment of all rsfMRI frames to correct for head motion during the scan, (iv) co-registration to each participant's MPRAGE structural image and spatial normalization to MNI space, (v) the rsfMRI time courses were then band-pass filtered (0.1–0.01 Hz) to attenuate respiration and other physiological noise and to focus on signal frequencies associated with intrinsic connectivity, (vi) six affine transformation parameters from the alignment process, as well as the mean time courses from the brain parenchyma including white matter tissue and ventricles were included as covariates to further account for motion and physiological noise. We visually checked each individual image for acquisition artifacts, and one child was excluded due to visual image corruption.

Seed creation and resting-state functional connectivity analyses

FMRIB's Integrated Registration and Segmentation Tool (FIRST) in FSL 5.0.7 was used for seed creation. FIRST is a semi-automated model based subcortical segmentation tool that use

a Bayesian framework from shape and appearance models obtained from manually segmented images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston, MA, USA [33]. Briefly, two-stage affine registration is run to register the MPRAGE to standard MNI space using 12 degrees of freedom with 1 mm resolution and uses a subcortical mask to exclude voxels not corresponding (outside) to subcortical regions. Then, subcortical regions, including hippocampus, are separately segmented for each hemisphere. Manual volumetric region labels are parameterized as surface meshes and modeled as a point distribution model. The final segmentations of the hippocampus seeds were visually checked for quality control by one rater, and when there was any questionable segmentation, a second rater checked the images. In addition, after calculating framewise displacement, no further exclusions were performed (all framewise displacement <0.2). In a first-level (single-subject), whole-brain voxel-wise functional connectivity network maps were created for left and right hippocampal seeds, for each participant using the pre-processed rsfMRI data. The residualized parameter estimate rsFC maps were converted to z scores (via Fishers r to z transformation) to achieve normality and were entered into higher level analyses.

Statistical analysis

Descriptive data by sex are presented as mean and standard deviation (SD) for continuous variables as well as number of cases (n) and percentage (%) for categorical variables. In second-level (group) imaging analysis, the residualized parameter estimate rsFC maps were then included in two separate linear regression models to identify regions where connectivity with the right and left hippocampus was explained by each early life factors (birth weight, birth length, months of exclusive or any breastfeeding). Sex, gestational age, PHV, parental educational level and CRF were included as covariates in each of the second-level models. All the variables were mean centered prior to inclusion in the models. Correction for multiple

comparisons was performed using FSL's automatic FEAT cluster-based thresholding at an alpha of p<.05, which is a method of Family-Wise Error correction based on Gaussian Random Field Theory. To further evaluate the link with academic performance, we performed regression analyses between this variable and the signal from those regions showing a significant association with the early-life factors in the preceding analyses. Signal extraction represents the strength of the functional connectivity between the seeds (left and right hippocampus) and the voxels showing a significant association with early-life factors. A false discovery rate (FDR) was applied using the Benjamini and Hochberg method (q<. 05). Sensitivity analyses were carried out excluding children born preterm (gestational age < 37 weeks, n=17). Sensitivity analyses were carried out excluding children born preterm (gestational age < 37 weeks, n=17). Descriptive and statistical analysis corresponding to extracted rsFC signal were performed in R (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria), and statistical significance was set at $p < .05$.

3. RESULTS

Table 1 shows the descriptive characteristics of the study sample. Higher birth weight was associated with increased rsFC between the left hippocampus and 2 clusters corresponding to the left precentral and postcentral gyri **(***k*=267 and *k*=382 respectively**; Table 2, Figure 1.A)**. In addition, higher birth weight was associated with increased rsFC between the right hippocampus and 3 clusters corresponding to the left and right postcentral gyri and cerebellum **(***k* ranged from 258 to 421**; Table 2, Figure 1.A).** Birth length was not associated with connectivity of the hippocampus.

Longer and exclusive breastfeeding was associated with decreased rsFC of the left hippocampus with the left angular gyri **(***k*=369; **Table 2, Figure 1.B)** and of the right hippocampus with the primary motor cortex **(***k*=250**; Table 2, Figure 1.B)**. Any breastfeeding

was not associated with rsFC of the left hippocampus, but was positively associated with rsFC between the right hippocampus and middle temporal gyrus (*k*=329 **Table 2, Figure 1.C**). The results after excluding children born preterm from the analyses did not substantially change (see Table S1).

Post-hoc analyses

Table 3 shows the association between the early-life factor-related hippocampal rsFC and academic performance. There was a positive association between the connectivity of the right hippocampus with left primary motor cortex and mathematics (β= 0.225; p=0.019), although this association disappeared after FDR correction.

4. DISCUSSION

Our main finding suggests that early life factors were related to hippocampal connectivity in children with overweight/obesity. Specifically, birth weight, but not birth length, was associated with greater hippocampal rsFC. In addition, longer exclusive breastfeeding was associated with diminished hippocampal rsFC, and any breastfeeding was related to greater hippocampal rsFC. However, hippocampal rsFC was not coupled with better academic abilities. The present study expands the knowledge about the influence of early life factors on hippocampal structure by showing that birth weight and breastfeeding relate to hippocampal functional connectivity later in life, but its behavioral implications remain unknown.

There are several potential mechanisms for how the targeted early life factors influence rsFC in the hippocampus of school-aged children. At a molecular level, low birth weight has been previously associated with hippocampal gene expression; this is related to neuronal maturation, transcription and apoptosis, which may in turn influence connectivity [45]. Also, previous studies

suggested that the hippocampus may be highly vulnerable during fetal environment with functional consequences even at a period of hippocampal growth peak, around 9-11 years [5,46,47].

The hippocampus is a key region involved in learning and memory as well as in higher order cognitive processes. Previous structural brain studies showed that compared with term-born controls, premature-born babies had reduced hippocampal volume during childhood [8,9], and even during adulthood; and this was coupled with cognitive consequences [48,49] . Functional studies in adults showed that the activation of the hippocampus was associated with BMI and in turn, worse decision making, suggesting that body weight is closely tied to both brain function and cognitive outcomes [50]. In addition, disrupted hippocampal connectivity during adolescence, mainly within the limbic network, was partially explained by birth weight [13]. In the present study, birth weight was mainly associated with greater functional connectivity between the hippocampus and frontal and parietal regions, namely, precentral and postcentral gyri. Both precentral and postcentral gyri are related to sensorimotor and somatosensory systems, and have been recognized as being disrupted in obesity [51,52]. Specifically, while the precentral gyrus participates in planning and execution, the postcentral gyrus is a key related-obesity region involved in sensory processing and taste processing in children and adolescents with excess weight [53]. Decreased activation in the precentral and postcentral gyrus has been associated with loneliness [51] and cue reactivity scores [54], both behaviors that might be affected in obesity during childhood [55,56]. In addition, we found that birth weight was related to greater rsFC between the right hippocampus and left cerebellum, and we previously showed that both birth weight and birth length were also associated with cerebellar volume [39]. Further, the cerebellum is functionally heterogeneous, and specifically the association focused on left posterior cerebellar lobule, which is involved mainly in spatial task, emotion and executive function [57]. In this line, the hippocampal-cerebellar functional connectivity has a key role in supporting spatial navigation in different neurological disorders, suggesting a possible clinical

implication of reduced hippocampal-cerebellar connectivity [58]. Collectively, our results support the role of birth weight on functional connectivity between the hippocampus and sensorimotor and motor regions in children with overweight/obesity. However, future studies should examine the influence of anthropometric neonatal indicators (i.e., birth weight/length) on functional connectivity in larger samples using graph- based network analysis of rsfMRI to expand our understanding of early life development of the brain as a complex network.

Surprisingly, we found that exclusive breastfeeding was associated with a diminished connectivity between the hippocampus and the angular gyrus, and the primary motor cortex. Greater hippocampal-angular gyrus connectivity has been related to episodic memory, and reduced communication between these regions might lead to reduced ability to creatively think and to imagine an episodic future event in young adults (age range 19 to 26 y) [59]. However, we did not find any negative academic impact in relation to the lower hippocampal-angular gyrus connectivity in the present childhood sample. Consequently, while these unexpected results might be explained by the possible functional reorganization in response to early life adversity of offspring's, future studies including other variables (e.g., better characterization of early life stress or diet, among others) that help to understand this result are needed [60,61]. In addition, any breastfeeding was associated with greater connectivity between hippocampus and middle temporal gyrus. A recent study has shown that connectivity between the hippocampus and middle temporal gyrus is a critical neural basis for novelty and usefulness processing during concept construction, perceptual motor system (including precentral and postcentral gyrus) [62], and linguistic and nonlinguistic semantic-level processes or memory [63]. However, we did not find a relationship between hippocampal connectivity and behavior (i.e., academic performance) in this sample of children with overweight/obesity. This lack of association, however, does not preclude the possibility that these networks are implicated in other unmeasured behavioral or cognitive processes.

Collectively, we did not find any links with academic achievement indicators of the connectivity previously relate with early life factors. Similarly, a previous study with the present sample on early life factors and gray matter volume also failed to find any link with academic achievement scores [39]. Thus, it is possible that in our sample of children with overweight/obesity, the lack of variability in terms of adiposity may mask an association of functional network connectivity with academic achievement [64]. Further research examining the academic implications of the early life factors-hippocampal rsFC comparing normal-weight children and those with overweight/obesity is needed.

The present study expands the existing literature, which has mainly examined morphologic associations of the hippocampus with early life factors, by demonstrating that early life factors such as birth weight and breastfeeding practices also relate to hippocampal connectivity in children with overweight/obesity. However, some limitations of this study should be acknowledged. The retrospective cross-sectional design precludes our ability to draw causal interpretations between the targeted early life factors and rsFC of the hippocampus. In addition, parents self-report of breastfeeding practices did not clarify whether the practices were formula-fed, and parents could have potentially misunderstood the meaning of "exclusiveness" of breastfeeding [65], which may explain, in part, the unexpected association of breastfeeding practices. Also, we obtained relatively short resting-state fMRI scans. The reason for this was that children are susceptible to more movement and cannot tolerate long scanning times [66]. Despite this, similar scan time has shown to be reliable in populations with similar characteristics [66]. Lastly, we focused on a specific limited age range (i.e., children aged 8-11y) and population of children with overweight/obesity, and the lack of a normal weight group limit the extrapolation of our findings to other age or weight status groups. In addition, we did not collect information about feeding or hunger status during the MRI session, and different pattern of feeding has may alter brain connectivity [67]. Additionally, we did not collect

information about dietary patterns of mothers, stress or birth complication, which has been associated to hippocampal features of offspring [6]. The current findings provide new insights and prompt questions for future studies to further understand hippocampal functional connectivity in this population. The study has the strength in that it provides a unique contribution to the literature on early life programming of hippocampal functional connectivity in children with overweight/obesity. Clinical relevance of this findings is to help clinicians to recognize the importance of anthropometric neonatal data and infant feeding for potentially avoiding the negative consequences brain development. Therefore, interventions aiming at improving prenatal health and promoting breastfeeding in infancy may be implications for influencing hippocampal connectivity later in life.

In conclusion, our findings suggest that birth weight at birth and breastfeeding practices are associated with hippocampal functional connectivity in children with overweight or obesity at ages 8-11. Future research on the association of these changes with a greater range of behavioral outcomes is needed.

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Conflict of interest Authors declare no conflict of interest.

Consent to participate All participant signed the consent statement prior their inclusion in the study.

Ethical approval The ActiveBrains project was registered in ClinicalTrials.gov (identifier: NCT02295072) and was approved by the Ethics Committee on Human Research of the University of Granada.

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Table 1. Characteristics of study sample.

Table 2. Significant clusters in the association of early life factors associated with hippocampal connectivity in the left and right seeds.

Table 3. Associations of early-life factor-related hippocampal connectivity with academic performance*.

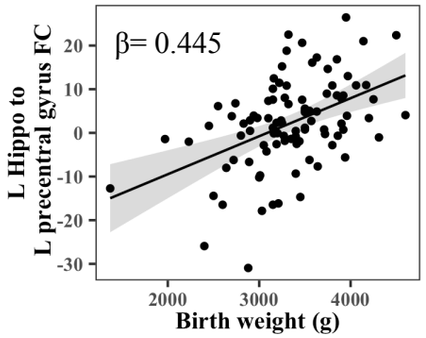
Figure. 1. **Clusters showing association between early life factors and left and right hippocampal resting state functional connectivity**. The color represent seed for left (green) and right hippocampi (yellow), as well as positive (light blue) and negative (red) association. Figures A shows birth weight cluster associated with left and right hippocampal seed. Figure B and C shows exclusive and any breastfeeding with left and right hippocampal seed, respectively. L: left, R: Right, FC: functional connectivity.

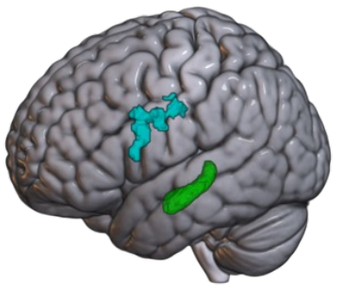
Table 1. Characteristics of study sample.

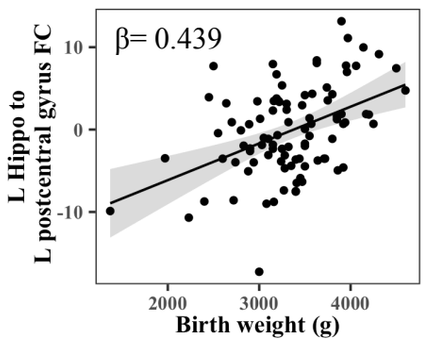
	All		*Boys*		*Girls*	
N	n		n		n	
Physical characteristics	96		60		36	
Age (yr)		10.01 ± 1.14		10.16 ± 1.14		9.78 ± 1.13
Weight (kg)		55.65 ± 11.15		56.66 ± 10.69		53.97 ± 11.85
Height (cm)		143.81 ± 8.32		144.69 ± 7.37		142.34 ± 9.64
Peak height velocity offset (yr)		-2.33 ± 0.96		-2.65 ± 0.78		-1.80 ± 1.01
Cardiorespiratory fitness (mL/kg/min)*		40.86 ± 2.77		40.84 ± 2.77		40.90 ± 2.82
Body mass index (kg/m^2)		26.70 ± 3.69		26.90 ± 3.79		26.36 ± 3.53
Body mass index category (n,%)	96		60		36	
Overweight		25 (26.0)		16 (26.7)		9 (25.0)
Obesity type I		41 (42.7)		27 (45.0)		14 (38.9)
Obesity type II		30 (31.2)		17 (28.3)		13 (36.1)
Parental education university level (n,%)	96		60		36	
None of the parents		64 (66.7)		43 (71.7)		21 (58.3)
One of the two parents		17 (17.7)		10 (16.7)		7 (19.4)
Both parents		15 (15.6)		7 (11.7)		8 (22.2)
Neonatal characteristics						
Birth weight (g) [1370-4600]	94	3343.72 ± 542.25	59	3358.98 ± 579.32	35	3318.00 ± 480.28
Birth length (cm) [40-57]	85	50.69 ± 2.68	57	50.61 ± 3.02	28	50.86 ± 1.84
Gestational age (week) [26-43]	96	38.62 ± 2.59	60	38.57 ± 2.59	36	38.70 ± 2.63
Breastfeeding practices (months)	92		59		33	
Exclusive breastfeeding† [0-16]		3.19 ± 3.24		3.53 ± 3.53		2.58 ± 2.59
Any breastfeeding‡ [0-43]		7.06 ± 8.03		6.81 ± 7.18		7.50 ± 9.44
Academic performance (standard score)**	96		60		36	
Mathematics		102.02 ± 10.68		102.37 ± 11.23		101.44 ± 9.82
Reading		108.55 ± 12.92		108.33 ± 11.08		108.92 ± 15.67
Writing		113.99 ± 11.99		112.55 ± 11.91		116.39 ± 11.91
Total Achievement		109.49 ± 11.66		108.98 ± 10.67		110.33 ± 13.25

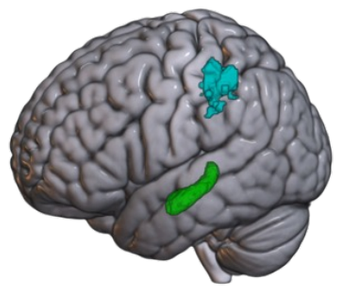
Values are mean ± SD or percentage. *Measured by the 20-m shuttle run test; †Months the child received only breast milk. †Months the child received breast milk combined with other liquid, or solid. **Measured by the Bateria III Woodcock-Muñoz Tests of Achievement.

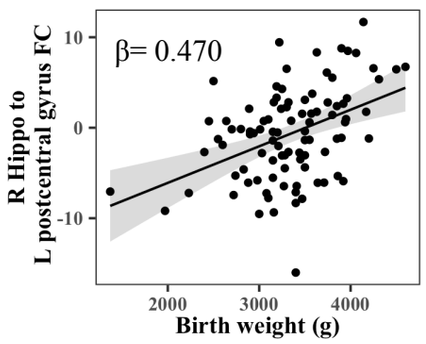
A. Birth weight

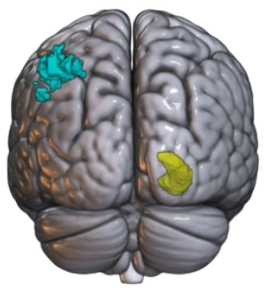


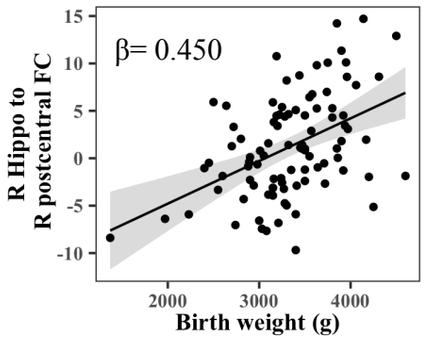


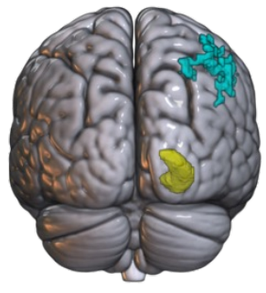


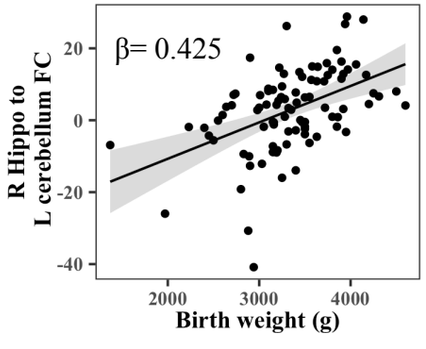


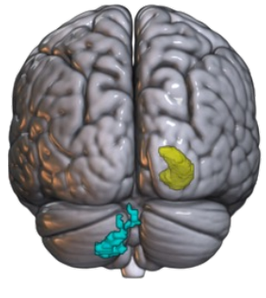




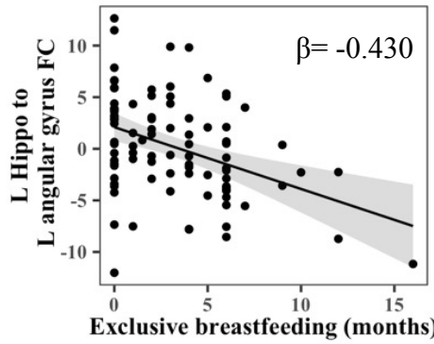


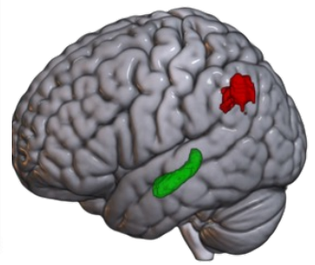


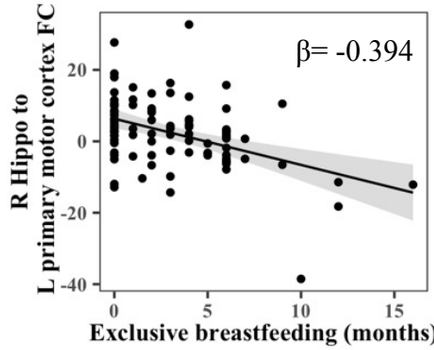


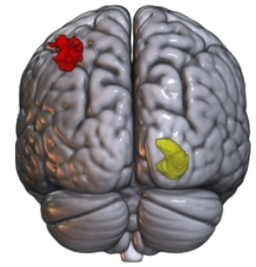


B. Exclusive breastfeeding

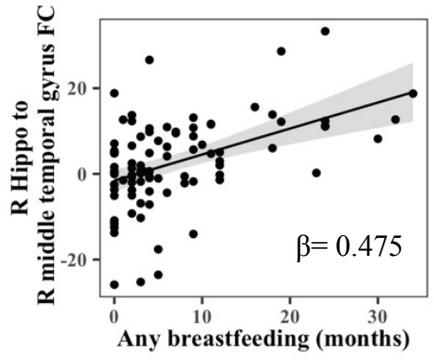








C. Any breastfeeding



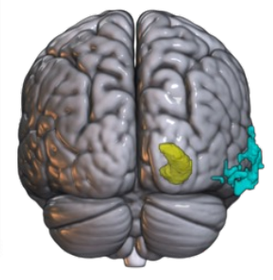


Table 3. Associations of early-life factor-related hippocampal connectivity with academic performance*.

Early life factor	Seed	Cluster location	Mathematics			Reading			Writing			Total achievement		
			β	p-value	p-FDR	*β*	p-value	p-FDR	*β*	p-value	p-FDR	*β*	p-value	p-FDR
Birth weight	L hippocampus	L precentral gyrus	-0.006	0.949	0.949	-0.05	0.614	0.702	-0.006	0.948	0.948	-0.041	0.664	0.997
		L postcentral gyrus	0.185	0.051	0.204	0.117	0.228	0.633	-0.139	0.14	0.282	0.067	0.467	0.997
	R hippocampus	L cerebellum	0.079	0.412	0.593	-0.078	0.429	0.633	-0.122	0.202	0.323	-0.059	0.525	0.997
		R postcentral gyrus	0.098	0.309	0.593	0.092	0.347	0.633	-0.142	0.134	0.282	0.02	0.832	0.997
		L postcentral gyrus	0.072	0.445	0.593	0.069	0.475	0.633	-0.147	0.116	0.282	0.00	0.997	0.997
Exclusive breastfeeding	L hippocampus	L angular gyrus	-0.05	0.608	0.695	-0.037	0.711	0.711	0.08	0.405	0.540	-0.004	0.963	0.997
	R hippocampus	L primary motor cortex	0.225	0.019[#]	0.152	0.176	0.075	0.600	0.051	0.598	0.683	0.181	0.054	0.432
Any breastfeeding	R hippocampus	R middle temporal gyrus	0.084	0.383	0.593	0.095	0.338	0.633	0.141	0.141	0.282	0.132	0.159	0.636

Values are standardized regression coefficients (β). Analyses were adjusted for sex, peak height velocity offset (years), parent education university level (neither/one/ both) and cardiorespiratory fitness (mL/kg/min). L: Left, R: Right *Measured with the Bateria III Woodcock-Muñoz Tests of achievement. FDR: False discovery rate. [#] This association disappears after FDR correction

Table 2. Significant clusters in the association of early life factors associated with hippocampal connectivity in the left and right seeds.

Explicative variable	Seed	Nature of association	Cluster location	Cluster size	Peak Z	Peak MNI coordinates
Birth weight	Left hippocampus	Positive	L precentral gyrus	267	3.81	-54, 10, 26
		Positive	L postcentral gyrus	382	4.34	-44, -36, 48
	Right hippocampus	Positive	L postcentral gyrus	421	3.86	-44, -40, 54
		Positive	R postcentral gyrus	409	4.28	54, -20, 44
		Positive	L cerebellum	258	4.02	-16, -80, -48
Exclusive breastfeeding	Left hippocampus	Negative	L angular gyrus	369	4.30	-52, -56, 40
	Right hippocampus	Negative	L primary motor cortex	250	4.21	-36, -24, 46
Any breastfeeding	Right hippocampus	Positive	R middle temporal gyrus	329	3.47	70, -26, -20

R: Right; L: Left; MNI: Montreal neurologic institute. Analyses were adjusted for sex, peak height velocity offset (years), parent education university level (neither/one/both), gestational age (weeks) and cardiorespiratory fitness (mL/kg/min). Birth length was not associated to hippocampal resting state functional connectivity.

Early life factors and hippocampal functional connectivity in children with overweight/obesity

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Table S1. Significant clusters in the association of early life factors associated with hippocampal connectivity including sensitivity analysis (Excluding preterm born, <37 weeks).

Explicative variable	Seed	Nature of association	Cluster location	Peak MNI coordinates	β	p-value	β-sens	p-value-sens
Birth weight	Left hippocampus	Positive	L precentral gyrus	-54, 10, 26	0.445	< 0.001	0.441	< 0.001
		Positive	L postcentral gyrus	-44, -36, 48	0.439	< 0.001	0.432	< 0.001
	Right hippocampus	Positive	L postcentral gyrus	-44, -40, 54	0.470	< 0.001	0.465	< 0.001
		Positive	R postcentral gyrus	54, -20, 44	0.450	< 0.001	0.400	0.001
		Positive	L cerebellum	-16, -80, -48	0.425	< 0.001	0.420	< 0.001
Exclusive breastfeeding	Left hippocampus	Negative	L angular gyrus	-52, -56, 40	-0.430	< 0.001	-0.453	< 0.001
	Right hippocampus	Negative	L primary motor cortex	-36, -24, 46	-0.394	< 0.001	-0.426	< 0.001
Any breastfeeding	Right hippocampus	Positive	R middle temporal gyrus	70, -26, -20	0.475	< 0.001	0.438	< 0.001

R: Right; L: Left; MNI: Montreal neurologic institute. Analyses were adjusted for sex, peak height velocity offset (years), parent education university level (neither/one/both), gestational age (weeks) and cardiorespiratory fitness (mL/kg/min). Birth length was not associated to hippocampal resting state functional connectivity. β-sens and p-value-sens corresponding to values of sensitivity analysis excluding preterm born (<37 weeks) children, n =17.