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ORIGINAL RESEARCH

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Associations of sleep with gray matter volume and their implications for academic achievement, executive function and intelligence in children with overweight/obesity

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Summary

Background: Children with overweight/obesity have poorer sleep and smaller gray matter volume (GMV) than normal-weight children. No studies have investigated the associations of objectively-assessed sleep and GMV in children with overweight/obesity, or their implications for academic and cognitive outcomes.

Objectives: To explore the associations of sleep behaviors with GMV in the whole brain and particularly the hippocampus as a region of interest independent of sedentary time (SED) and physical activity; and to assess whether GMV in the associated regions was related to academic achievement, executive function and intelligence quotient (IQ).

Methods: Ninety-six children with overweight/obesity (10 ± 1 year) were included. Sleep behaviors were assessed with accelerometers. GMV was acquired by magnetic resonance imaging. Academic achievement, executive function and IQ were assessed with separate tests. Analyses were adjusted for sex, peak height velocity and parent education as well as SED and physical activity.

Results: Earlier wake time, less time in bed, wakening after sleep onset (WASO) and WASO occurrences were associated with higher GMV in eight cortical brain regions (k:56-448, P's < .001). Longer total sleep time, higher sleep efficiency and less WASO time were associated with higher GMV in the right hippocampus (β:0.187-0.220, P's < .05). The inferior temporal, fusiform, supramarginal, and postcentral gyri, the

superior parietal cortex, precuneus and hippocampus associated with academic achievement and/or IQ. Associations remained after adjustments for SED and physical activity.

Conclusions: Sleep behaviors are associated with GMV in multiple cortical regions including the right hippocampus in children with overweight/obesity, which in turn, were associated with academic achievement and IQ.

KEYWORDS

academic success, accelerometer, brain, child, cognition, sleep

1 | INTRODUCTION

Childhood academic achievement and cognition are affected by insufficient sleep duration (ie, <8 hours); a public health concern reported worldwide.[1,2] Gray matter volume (GMV) is a measure of the amount of tissue in a brain region under examination. It represents all tissue properties contained in gray matter including vasculature, glial cells, and neuronal cell bodies. GMV contributes to the processing of information in the brain. Further, greater GMV in the developing brain is positively associated with brain health outcomes such as academic achievement and cognition,[3] which are crucial characteristics for childhood success in school and throughout life. Likewise, several studies have reported that sleep behaviors, that is, those behaviors related to sleep that can be measured in free-living conditions, such as total sleep time or total time in bed, are associated with academic achievement,[4-7] executive function[8,9] and intelligence.[10] The study of the sleep behaviors and their association with GMV could provide insight into the mechanisms underlying the relationship of sleep with academic achievement, executive function and intelligence. To date, previous research suggests a positive link between sleep behaviors and GMV in several cortical regions in 14-year-old adolescents[11] and with hippocampal GMV in 5-18-year-olds.[12] Special attention should be paid to the hippocampus, which is important for memory consolidation during sleep.[13,14]

Most of the previous findings on the relationship between sleep behaviors and academic achievement, executive function and intelligence have focused on sleep onset, wake time, and total sleep time. In this regard, later sleep onset and wake times are associated with lower GMV in cortical regions[11] and poorer school performance,[6,11] including mathematics, reading and social sciences.[7,15] Total sleep time showed a small effect on school grades.[5] Previous studies hypothesized impaired attention during school hours to explain the link between reduced sleep and poorer academic achievement.[4,11] Likewise, previous studies have found modest associations between later sleep onset, shorter total sleep time and lower sleep quality with poorer executive function (ie, cognitive flexibility, inhibition and working memory[16,17]) in adolescents[8] and young adults.[9] Lastly, sleeping more than 8 hours was associated with higher IQ in male adolescents.[10]

It is noteworthy that previous research derives timing and duration variables from self-reported sleep onset and wake times (ie, asking participants what time they go to bed and wake on average).[11,12] Self-report methods have been found to be influenced by subjective inaccuracies and social desirability.[18-20] As an example, total sleep time has usually been derived from the difference between reported sleep onset and wake times, which would indicate total time in bed rather than total sleep time. Thus, previous findings based on self-reported information should be complemented via the use of objective assessments. Several algorithms have demonstrated that wrist-worn accelerometers can provide valid assessment of sleep behaviors.[21-23] Another important limitation of previous studies is the use of school grades as indicator of academic achievement,[11] which are affected by teachers' subjectivity and inter-school variability.[24] The use of accelerometer-derived sleep behaviors and standardized tests for the measurement of academic achievement are needed to investigate this relationship.

Children with overweight/obesity have been characterized as having poorer sleep behaviors,[25-27] and smaller GMV than children with a normal weight.[28-30] Furthermore, these children often engage in greater sedentary time (SED) and insufficient physical activity,[31] which may also be associated with poorer sleep behaviors.[32,33] SED and physical activity behaviors coexist with sleep in the 24-hour cycle. All of these behaviors can potentially affect one another, since increasing the time spent in one would reduce the time devoted to another of the remaining behaviors. Therefore, when studying associations between sleep behaviors and GMV, it is crucial to study the potential influence of SED and physical activity behaviors on these associations. This scenario requires investigation of sleep behaviors on GMV, academic achievement and cognition in children with overweight/obesity, as well as how SED and physical activity behaviors may influence these relationships.

Given the important issues described above this study explored: (a) the association of sleep behaviors with GMV in children with overweight/obesity using a whole-brain volumetric approach, as well as the specific association between sleep behaviors and GMV in the hippocampus using a region-of-interest (ROI) approach, independent of SED and physical activity; and, (b) whether GMV in those regions associated with sleep behaviors were also related to academic achievement, executive function and IQ. To the best of our knowledge, there has not been a clear hypothesis guiding which brain regions might underlie the association of sleep with academic

achievement, executive function or IQ. However, a main candidate could be the hippocampus, given its relationship to learning and memory.[12-14] Thus, we chose to use a whole-brain approach and further investigate the specific association with the hippocampus using a ROI approach. Based on previous research,[4-9,34] we hypothesized that sleep behaviors would be associated with GMV, and that GMV in some of these regions would be associated with academic achievement, executive function and/or IQ.

2 | METHODS

2.1 | Participants and Study Design

This study used baseline data from the ActiveBrains project (http://profith.ugr.es/activebrains). Of the 110 children who enrolled, 96 provided valid accelerometry and brain data at baseline (10 ± 1 years, 38 girls) and were included in this cross-sectional study. Since the ActiveBrains project is a randomized controlled trial aimed at discovering the effects of exercise on brain, cognition and academic achievement in children with overweight/obesity, the sample size was primarily calculated to detect moderate changes in brain outcomes after the intervention.[35] The detailed rationale and inclusion criteria are described elsewhere.[35] Briefly, inclusion criteria included: (a) overweight or obesity based on the World Obesity Federation cut-off points[36,37]; (b) 8 to 11 years old; (c) no physical disabilities or neurological disorders that affect physical performance; and, (d) in the case of females, not to have started menstruation at the time of the baseline assessment. Data were collected from 2014 to 2016 in Granada (Spain) in three different waves evaluated during the months of November, December, January and February (always during school time in the three waves). Parents were informed of the purpose of the study and parental written informed consent was obtained. The ActiveBrains project was approved by the Ethics Committee on Human Research (CEIH) of the University of Granada.

2.2 | Sleep behaviors, SED and physical activity

Participants wore ActiGraph GT3X+ accelerometers (ActiGraph, Pensacola, FL, USA) on their non-dominant wrist for seven consecutive days and reported information on the time in which they went to bed and got out of the bed every day. Raw accelerations were downloaded via the ActiLife v.6.13.3 software (ActiGraph, Pensacola, Florida) and processed in the R package GGIR[38] (v. 1.5.12, https://www.cran.r-project.org/). Detailed information on accelerometer data processing can be found elsewhere.[39] Identification of sleep onset and wake times were determined by an automatized algorithm guided by participants' reported times.[22] First, the algorithm examined potential sleep occurrences (ie, at least 5 minutes with low variability in arm angle, that is, ., <5°) throughout the 24 hours. Next, the first and last epochs classified as sleep before and after the reported times were considered the definitive sleep onset and wake times. Finally, the algorithm developed by Sadeh et al[21] was applied within the bedtime defined to classify every 1-minute epoch as "asleep" or "awake." Sleep behaviors included indicators of sleep timing (ie, wake time and sleep onset), total time in bed, total sleep time and sleep patterns (ie, sleep efficiency, wakening after sleep onset [WASO] time and number of WASO). Total time in bed is the time difference between wake and sleep onset times. Total sleep time represents the sum of all minutes classified as sleep within total time in bed. Sleep efficiency is the percentage of time classified as sleep over the total time in bed. Cut points for the non-dominant wrist proposed by Hildebrand et al[40,41] were used to classify SED, LPA and MVPA. A total of 104 met the pre-requisite of recording 4 valid days (ie, ≥ 16 hours/day); including at least 3 weekdays and 1 weekend day were required. Specifically, to consider a day valid, participants should accumulate 2/3 of the waking hours and 2/3 of night hours as wear time and altogether accumulate at least 16 hours of wear time. Sleep-related variables, SED, LPA and MVPA daily values were averaged as follows: ((school-day average * 5) + (weekend day average * 2))/7.

2.3 | Magnetic resonance imagining (MRI)

All images were collected with a 3.0 Tesla Siemens Magnetom Tim Trio scanner (Siemens Medical Solutions, Erlangen, Germany) with a 32-channel head coil. High-resolution, T1-weighted images were acquired using a 3D MPRAGE (magnetization-prepared rapid gradient-echo) protocol. The acquisition parameters were the following: repetition time = 2300 ms; echo time = 3.1 ms; inversion time = 900 ms; flip angle = 9°; field of view = 256 × 256; acquisition matrix = 320 × 320, 208 slices; resolution = 0.8 × 0.8 × 0.8 mm; and scan duration = 6 minutes and 34 seconds.

Whole-brain volumetric analyses were conducted using the Statistical Parametric Mapping software (SPM12; Wellcome Department of Cognitive Neurology, London, UK) implemented in Matlab (The MathWorks, Inc, Natick, Massachusetts). Imaging pre-processing included quality control, motion correction, spatial normalization to an MNI (Montreal Neurological Institute) template, and spatial smoothing. Detailed information about pre-processing steps is described elsewhere.[3] Hippocampal volumetric analyses were conducted using FMRIB's Software Library (FSL) version 5.0.7. Specifically, we used FMRIB's Integrated Registration and Segmentation Tool (FIRST) in FSL. FIRST is a semi-automated model-based subcortical segmentation tool which uses the Bayesian framework from shape and appearance models obtained from manually segmented images from the Center for Morphometric Analysis, Massachusetts General Hospital, Boston, Massachusetts.[42] Briefly, FIRST runs a two-stage affine registration to a standard space template (ie, MNI space) using 12 degrees of freedom and uses a subcortical mask to exclude voxels outside subcortical regions. Second, the subcortical regions, including the hippocampus, are segmented for both hemispheres separately. The manual volumetric region labels are parameterized as surface meshes and modeled as a point distribution model. In addition, the hippocampus segmentation from FIRST was then split based on the center of gravity of the region into anterior and posterior sub-regions for each

hemisphere separately. This resulted in separate anterior and posterior hippocampal segmentations for each hemisphere in each participant.[43,44] The final segmentations were visually inspected for quality. The volume of each region was obtained from FIRST in mm^3.

2.4 | Academic achievement, executive function and intelligence quotient

Academic achievement was assessed with the Spanish version of the Woodcock-Johnson III battery, which is a valid and reliable (internal consistency reliability coefficient > 0.9) measure of academic achievement in children.[45] Children completed a total of 12 tests from this battery including reading, language, mathematics and sciences during one session of 100-120 minutes. Tests were independently checked by two trained evaluators and then scores were processed in the Compuscore and profile software (v. 3.1., Riverside Publishing Company, Itasca, Illinois). We used standardized scores of broad reading, mathematics and writing components, as well as composite measures of academic skills (answers accuracy), academic fluency (processing speed), academic applications (problem solving) and total academic achievement.

Executive function domains included cognitive flexibility, inhibition and working memory as described elsewhere.[39,46] Cognitive flexibility was assessed with the second and fourth conditions of the design fluency test (DFT) and the third and fourth conditions of the trail making test (TMT).[47,48] Both the DFT and the TMT are valid and reliable for measuring cognitive flexibility in children.[47,49] The score from these tests was standardized by sex using z-scores and then averaged to obtain a unique indicator of cognitive flexibility. The Stroop test[50] was used as a valid and reliable indicator of inhibition.[47,49,51,52] Performance time for condition 3 (ie, inhibiting reading by naming color) minus condition 1 (ie, color naming) was used as previously reported.[39,46] Finally, working memory was measured from a modified version of the Delayed non-match-to-sample (DNMS) computerized task, which has been previously validated.[53] A total of 16 practice trials and 140 experimental trials were presented in two separated conditions (ie, low- and high-memory load). Response accuracy for the high-load condition was used.[54]

IQ was assessed with the Spanish version of the Kaufman Brief Intelligence Test (K-BIT).[55] The K-BIT shows a coefficient α for validity of 0.86 to 0.93 in its Spanish version.[55] Crystallized and fluid intelligence components were assessed with vocabulary and matrices sub-tests, respectively. Both sub-test scores were summed to obtain the IQ score.

2.5 | Confounders

Participants' weight, height, peak height velocity and parents' education level were obtained as part of the protocol of the ActiveBrains project.[35] Weight and height were measured twice consecutively with an electronic scale (SECA 861, Hamburg, Germany) and a stadiometer (SECA 225, Hamburg, Germany), respectively, and average values were used in analyses. Body mass index (BMI) was calculated as kg/m^2. Peak height velocity was derived from standing and sitting height as a continuous measure of maturational status[56]. Parents reported whether none, one, or both of them reached university level education. Total brain volume was derived from FreeSurfer software version 5.3.0 (http://surfer.nmr.mgh.harvard.edu) as the sum of total white matter volume and total GMV.

2.6 | Statistics

Participants' descriptive characteristics were summarized as mean and standard deviation (SD) or percentages. All variables were checked for normality. Included and excluded participants did not significantly differ in sociodemographic and anthropometric variables (all $P > .05$). Based on previous studies,[11,12] we tested sex, peak height velocity, parent university education level and total brain volume as confounders in sensitivity analyses. As all models remained similar with and without adjustment for total brain volume, we excluded it from the covariates. Thus, the association between sleep behaviors (ie, sleep onset, wake time, total time in bed, total sleep time, sleep efficiency, WASO time and WASO number) and GMV was analyzed using whole-brain voxel-wise multiple regression models, adjusted for sex, peak height velocity and parent university education level (ie, basic confounders). Sensitivity analyses were performed adding BMI as confounder to the previous model and all significant associations presented in this study remained unchanged (data not shown). Additionally, we extracted the eigenvalues from the peak coordinates of each significant cluster. The associations of the extracted mean GMV from significant clusters and academic achievement, executive function and IQ were studied with linear regression models adjusted for basic confounders. The Benjamini-Hochberg procedure was applied to account for the random effect in multiple comparisons for every dependent domain (ie, academic achievement, executive function and IQ) with $q = 0.1$. Then, we performed additional independent models adding either SED, LPA or MVPA as confounders. These covariates were not included in the same model because time spent in sleep, SED, LPA and MVPA is constrained by the day duration and, therefore, incur perfect multicollinearity when included in the same model.

The statistical threshold in the imaging analyses was calculated with AlphaSim, as implemented in Resting-State fMRI Data Analysis Toolkit toolbox (RESTplus).[57] Parameters were defined as follows: cluster connection radius (rmm) = 5 mm and the actual smoothness of the data after model estimation, incorporating a gray mask volume of 128 190 voxels. The voxel-level alpha significance (threshold, $P < .001$ uncorrected) along with the appropriate cluster size for controlling for multiple comparisons in each analysis were indicated in the results. The resulting cluster extents were further adjusted to account for the non-isotropic smoothness of structural images.[58]

Multiple linear regression models were used to study the associations between sleep behaviors and ROI hippocampal GMV adjusted for basic confounders. Additional models adjusting for SED, LPA or MVPA were performed. All statistical analyses were performed in R (v. 3.4.4, https://cran.r-project.org/), except those involving imaging data which were performed using the GLM approach implemented in SPM12.

3 | RESULTS

Sociodemographic and anthropometric characteristics, sleep behaviors, academic achievement, executive function and IQ scores of participants are reported in Table 1. Fourteen participants were excluded from analyses because they did not accumulate enough accelerometer wear time (N = 5) or had missing (N = 1) or low-quality (N = 8) MRI images. These participants were similar to the included participants in terms of age, peak height velocity, BMI and parent education level (*P*'s > .115).

TABLE 1 Descriptive characteristics of participants

	All (N = 96)	Boys (N = 58)	Girls (N = 38)
Physical characteristics, mean (SD)			
Age (years)	10.02 (1.13)	10.16 (1.15)	9.79 (1.09)
Peak height velocity (years)	−2.30 (0.96)	−2.65 (0.79)	−1.77 (0.96)
Weight (kg)	55.67 (10.69)	56.46 (10.54)	54.46 (10.95)
Height (cm)	143.95 (8.10)	144.72 (7.44)	142.78 (8.99)
BMI (z-Score)	3.04 (0.89)	3.17 (0.99)	2.82 (0.65)
Parent education university level, %			
Neither parent	66	72	58
One parent	17	16	18
Both parents	17	12	24
Physical activity, mean (SD)			
SED (min/day)	561.07 (60.09)	553.46 (60.32)	572.70 (58.62)
LPA (min/day)	275.85 (39.30)	271.39 (38.42)	282.65 (40.17)
MVPA (min/day)	54.94 (20.80)	62.01 (22.05)	43.86 (12.36)
Sleep behaviors, mean (SD)			
Wake time (hh:mm)	8:07 (0:34)	8:05 (0:33)	8:10 (0:36)
Sleep onset time (hh:mm)	23:02 (0:40)	23:01 (0:41)	23:04 (0:38)
Total time in bed (min/day)	527.24 (31.87)	526.14 (33.55)	528.93 (29.49)
Total sleep time (min/day)	457.78 (34.91)	455.39 (32.42)	461.42 (38.58)
Sleep efficiency (%)	84.53 (4.92)	84.01 (4.39)	85.34 (5.6)
WASO time (min/day)	77.14 (23.8)	79.92 (20.51)	72.89 (27.85)
Number of WASO (nr.)	23.40 (4.43)	24.04 (4.08)	22.42 (4.81)
Valid days (nr.)	6.95 (0.4)	6.97 (0.49)	6.92 (0.35)
Academic achievement, mean (SD)			
Reading (standard score)	108.17 (13.13)	108.31 (11.17)	107.95 (15.83)
Mathematics (standard score)	101.80 (10.79)	102.45 (11.42)	100.82 (9.81)
Writing (standard score)	113.60 (12.86)	112.66 (12.02)	115.05 (14.10)
Academic skills (standard score)	118.66 (16.18)	117.76 (14.77)	120.03 (18.26)
Academic fluency (standard score)	103.56 (11.92)	104.03 (10.70)	102.84 (13.69)
Academic applications (standard score)	99.31 (9.12)	99.81 (9.18)	98.55 (9.10)
Total achievement (standard score)	109.14 (11.98)	109.03 (10.85)	109.29 (13.67)
Executive function, mean (SD)			
Cognitive flexibility (z-Score)	−0.03 (0.81)	0.08 (0.82)	−0.2 (0.77)
Inhibition (s)	41.9 (17.31)	38.97 (15.31)	46.38 (19.34)
Working memory (number of correct answers)	65.54 (16.44)	67.00 (16.46)	63.31 (16.39)
Intelligence, mean *(SD)*	98.45 (12.34)	97.02 (12.14)	100.63 (12.48)

Note: Data are presented as mean ± SD or percentages.

Abbreviations: BMI, body mass index; LPA, Light physical activity; MVPA, moderate-to-vigorous physical activity; SED, sedentary time; WASO, wakening after sleep onset.

TABLE 2 Brain regions showing significant negative associations of sleep behaviors with gray matter volume (n = 96)

						Basic confounders		Basic conf. + SED		Basic conf. + LPA		Basic conf. + MVPA	
Predictors	Brain regions	X	Y	Z	Hem	Peak *t*	Cluster size	Peak *t*	Cluster size	Peak *t*	Cluster size	Peak *t*	Cluster size
Wake time (hh:mm)	Inferior temporal gyrus	−41	−12	−44	L	3.58	186	3.54	164	3.56	164	3.55	164
		47	−21	−35	R	3.76	243	3.73	218	3.71	210	3.75	222
	Fusiform gyrus	−30	−47	−18	L	3.76	138	3.78	144	3.79	149	3.80	152
	Supramarginal gyrus	−48	−50	33	L	4.00	412	3.96	375	3.94	404	3.96	402
	Superior parietal cortex	29	−75	57	R	4.12	56	4.08	52	4.09	50	4.10	52
Total time in bed (min/day)	Postcentral gyrus	−33	−42	56	L	4.22	257	4.60	420	4.41	335	4.18	267
WASO time (min/day)	Superior temporal pole	29	18	−29	R	3.61	98	3.67	132	3.59	89	3.56	86
	Precuneus	−2	−39	48	L	3.67	400	3.65	400	3.64	269	3.68	478
	Superior parietal cortex	18	−60	71	R	3.61	150	3.57	145	3.51	79	3.59	122
Number of WASO (nr.)	Medial superior frontal gyrus	12	45	42	R	3.73	448	3.69	402	3.76	287	3.69	422
	Postcentral gyrus	63	−12	23	R	3.96	418	3.90	372	3.75	283	3.96	431
		−56	−39	53	L	3.67	117	3.62	102	3.56	63	3.64	109
	Superior parietal cortex	−20	−75	54	L	3.63	125	3.61	124	3.77	161	3.61	114

Note: Whole-brain voxel-wise multiple regression models were used. Basic confounders are sex, peak height velocity (years) and parent education university level (neither/one/both). All contrasts were thresholded using AlphaSim at $P < .001$ with $k = 47$ for wake-up time, $k = 57$ for bedtime, $k = 46$ for WASO time, $k = 55$ for number of WASO for the basic confounders model, and remained similar for the rest of models, and surpassed Hayasaka correction. Anatomical coordinates (X, Y, Z) are given in Montreal Neurological Institute (MNI) Atlas space. No clusters were significatively associated with sleep onset time, sleep time or sleep efficiency.

Abbreviations: Hem, hemisphere; L, left; LPA, Light physical activity; MVPA, moderate-to-vigorous physical activity; R, right; SED, sedentary time; WASO, wakening after sleep onset.

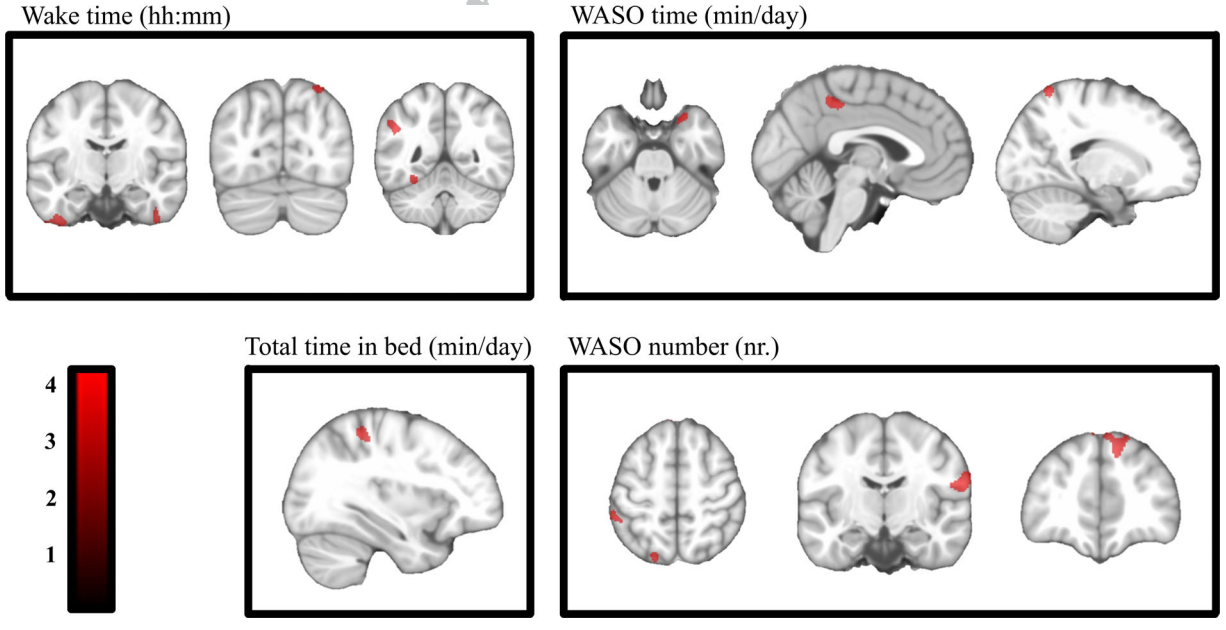

FIGURE 1 Brain regions showing negative associations of sleep behaviors with gray matter volume in children with overweight/obesity. WASO: wakening after sleep onset. Analyses were adjusted for sex, peak height velocity and parent education university level. All contrasts were thresholded using AlphaSim at $P < .001$ with $k = 47$ for wake-up time, $k = 57$ for bedtime, $k = 46$ for WASO time, $k = 55$ for number of WASO, and surpassed Hayasaka correction. Anatomical coordinates (X, Y, Z) are given in Montreal Neurological Institute (MNI) Atlas space. The color bar represents *t*-values scale

3.1 | Whole-brain associations of sleep behaviors with GMV

Table 2 presents the sleep behaviors inversely associated (no positive associations were found) with GMV in the whole-brain volumetric analyses adjusted for sex, peak height velocity, parent education level, as well as SED and physical activity behaviors. A later wake time was associated with lower GMV in 2 bilateral clusters in the inferior temporal gyrus (Left: peak t = 3.58, k = 186; Right: peak t = 3.76, k = 243), and 3 more clusters in the fusiform gyrus (peak t = 3.76, k = 138), the supramarginal gyrus (peak t = 4.00, k = 412) and the superior parietal cortex (peak t = 4.12, k = 56). A longer total time in bed was associated with lower GMV in the postcentral gyrus (peak t = 4.22, k = 257), but no association with total sleep time was found. A longer WASO time was associated with less GMV in the superior temporal pole (peak t = 3.61, k = 98), the precuneus (peak t = 3.67,

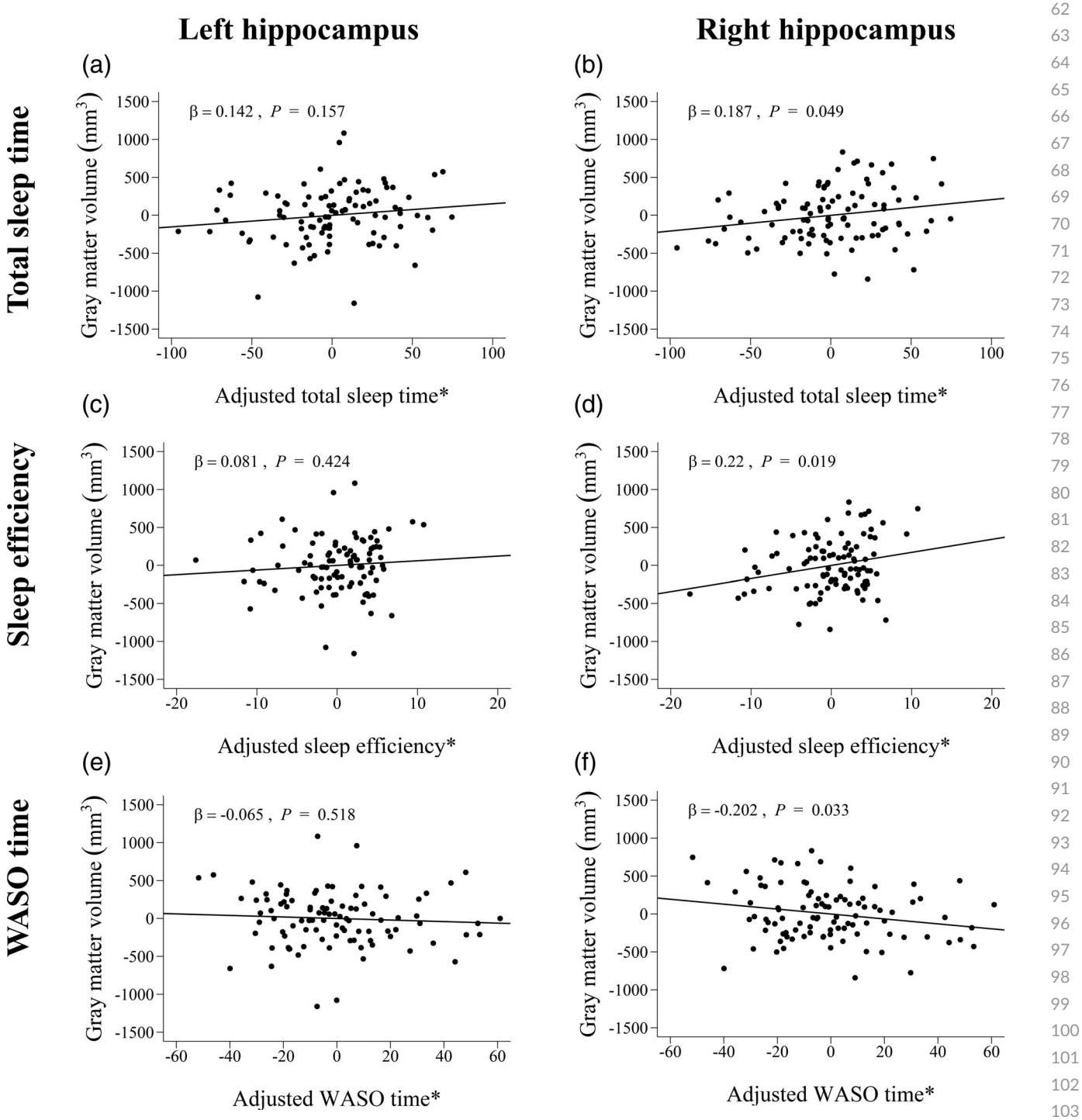

FIGURE 2 Linear regression analyses of the association of total sleep time A, B, sleep efficiency C, D, and WASO time E, F, with gray matter volume in the left and the right hippocampus. WASO: wakening after sleep onset. *Analyses were adjusted for sex, peak height velocity and parent education university level

TABLE 3 Associations of gray matter volume from regions associated with wake-up time and total time in bed with academic achievement, executive function and intelligence (N = 96)

	Wake time					Total time in bed
	L Inferior temporal gyrus	R Inferior temporal gyrus	L Fusiform gyrus	L Supramarginal gyrus	R Superior parietal cortex	L Postcentral gyrus
Academic achievement						
Reading	0.121	−0.012	0.160	0.104	0.174	**0.355****
Mathematics	0.160	0.166	**0.224***	**0.241***	**0.333****	0.216*
Writing	0.149	0.027	0.200	0.170	0.207*	0.163
Academic skills	0.097	0.006	0.150	0.120	0.152	**0.225***
Academic fluency	**0.256***	0.126	**0.231***	**0.264***	**0.294****	**0.244***
Academic applications	0.136	0.070	0.181	0.155	**0.276****	**0.281****
Total achievement	0.171	0.058	**0.217***	0.195	**0.260****	**0.296****
Executive function						
Cognitive flexibility	0.184	0.020	0.191*	0.126	−0.001	0.075
Inhibition	−0.04	−0.057	0.051	−0.192	−0.146	0.185
Working memory	−0.03	0.069	0.065	0.113	0.152	0.210*
Intelligence	0.105	0.045	0.183	**0.269***	0.102	0.209*

Note: Multiple linear regression models adjusted for sex, peak height velocity (years) and parent education university level (neither/one/both). Bolded font indicates that the specific association surpassed the Benjamini-Hochberg correction for multiple comparison tests (performed for each domain, that is, academic achievement, executive function and intelligence). L, left; R, right.

*Indicates $P < .05$.

**Indicates $P < .01$.

TABLE 4 Associations of gray matter volume from regions associated with WASO time and number of WASO with academic achievement, executive function and intelligence (N = 96)

	WASO time			Number of WASO			
	R Superior temporal pole	L Precuneus	R Superior parietal cortex	R Medial superior frontal gyrus	R Postcentral gyrus	L Postcentral gyrus	L Superior parietal cortex
Academic achievement							
Reading	0.122	**0.249***	**0.252***	0.138	0.216*	0.031	0.109
Mathematics	0.193	**0.249***	**0.309****	0.153	0.181	0.001	0.069
Writing	0.091	0.219*	0.079	−0.013	−0.031	−0.100	0.022
Academic skills	0.169	**0.241***	0.194	0.044	0.163	0.009	0.100
Academic fluency	0.050	**0.249***	0.193	0.146	0.137	−0.057	0.088
Academic applications	0.125	0.170	**0.232***	0.104	0.038	−0.065	−0.021
Total achievement	0.163	**0.274****	**0.248***	0.098	0.147	−0.028	0.074
Executive function							
Cognitive flexibility	0.009	−0.065	−0.065	−0.021	−0.104	−0.114	−0.123
Inhibition	0.037	−0.069	−0.064	0.030	−0.068	0.046	−0.094
Working memory	−0.054	0.040	0.088	0.095	0.028	0.094	0.012
Intelligence	0.105	0.233*	0.060	−0.084	−0.005	−0.076	−0.034

Note: Multiple linear regression models adjusted for sex, peak height velocity (years) and parent education university level (neither/one/both). Bolded font indicates that the specific association surpassed the Benjamini-Hochberg procedure for multiple comparison tests (performed for each domain, that is, academic achievement, executive function and intelligence).

Abbreviations: L, left; R, right; WASO, Wakening after sleep onset.

*Indicates $P < .05$.

**Indicates $P < .01$.

TABLE 5 Standardized beta coefficients for the association of gray matter volume in hippocampal regions and academic achievement, executive function and intelligence (N = 96)

	Right hippocampus	Right anterior hippocampus	Right posterior hippocampus
Academic achievement			
Reading	0.106	0.063	0.161
Mathematics	0.06	0.043	0.087
Writing	0.128	0.114	0.139
Academic skills	0.059	0.015	0.122
Academic fluency	0.164	0.156	0.16
Academic applications	0.099	0.092	0.106
Total achievement	0.116	0.085	0.155
Executive function			
Cognitive flexibility	−0.03	−0.038	−0.018
Inhibition[a]	−0.204*	**−0.222***	−0.159
Working memory	−0.03	−0.045	−0.009
Intelligence	0.059	0.046	0.08

Note: Multiple linear regression models adjusted for sex, peak height velocity (years) and parent education university level (neither/one/both). Bolded font indicates that the specific association surpassed the Benjamini-Hochberg procedure for multiple comparison tests (performed for each domain, that is, academic achievement, executive function and intelligence).

**Indicates $P < .01$.

*Indicates $P < .05$.

[a]Indicates that the score is multiplied by −1 (ie, a positive association is interpreted as higher inhibition).

k = 400) and the superior parietal cortex (peak t = 3.61, k = 150). The number of WASO was inversely associated with GMV in two bilateral clusters in the postcentral gyrus (Right: peak t = 3.96, k = 418; Left: peak t = 3.67, k = 117) and in two more clusters in the medial superior frontal gyrus (peak t = 3.73, k = 448) and the superior parietal cortex (peak t = 3.63, k = 125). All of these clusters showed $P < .001$ and they remained significant after additional adjustments for SED, LPA or MVPA. Associated clusters are visually presented in Figure 1. Table S1 shows bivariate correlation coefficients and confidence intervals between sleep behaviors (Supplementary Material).

3.2 | Associations of sleep behaviors with GMV in the hippocampus

Figure 2 depicts scatter plots for the association between total sleep time, sleep efficiency and WASO time with GMV in the left and right hippocampi. Associations with the right hippocampus were positive for total sleep time (β = 0.187, P = .049) and sleep efficiency (β = 0.220, P = .019) and negative for WASO time (β = −0.202, P = .033). Specific associations for the anterior and posterior hippocampal sub-regions can be found as Supplementary Material (Table S3).

3.3 | GMV associations with academic achievement, executive function and intelligence quotient

Higher GMV in those clusters related to wake time (ie, inferior temporal gyrus, fusiform, supramarginal gyri and superior parietal cortex) were associated with higher academic achievement scores. Specifically, four of the five clusters were associated with one or more academic achievement indicators (β ranging from 0.217 to 0.333, all $P < .028$); and one cluster (ie, supramarginal gyrus) was also associated with IQ (Table 3). GMV in the cluster related to total time in bed (left postcentral gyrus) was associated with various academic achievement indicators (ie, reading, academic skills, academic fluency, academic applications and total achievement) (β ranging from 0.225 to 0.355, P's < .032) (Table 3). Additionally, clusters in the precuneus and the superior parietal cortex, which were previously associated with WASO time, were also associated with reading, mathematics, academic skills, fluency and total achievement (β ranging from 0.232 to 0.309, P's < .028) (Table 4). The remaining clusters were not associated with academic achievement, executive function or IQ (all $P > .05$).

Finally, GMV in right hippocampus was not associated with academic achievement, executive function and IQ (Table 5). We only found a negative association with inhibition (β = −0.222 to 0.271, P = .02) surpassing the correction for multiple comparisons.

4 | DISCUSSION

Our findings support an association between certain sleep behaviors (ie, sleep timing, duration and pattern) and GMV in cortical and subcortical brain structures, including the hippocampus, in children with overweight/obesity. Specifically, earlier wake time, less total time in bed, lower WASO time and the number of WASO were associated with greater GMV in one or several brain structures. Additionally, ROI

analyses in the hippocampus depicted associations of a longer total sleep time, higher sleep efficiency and a lower WASO time with the GMV in the right hippocampus. All of these associations were adjusted for sex, peak height velocity and parent education university level. Nearly every association remained following adjustment for SED, LPA or MVPA. The identified brain structures associated with sleep behaviors were also positively associated with academic achievement and, to a lesser extent, IQ (but not with executive function). These findings should be interpreted with caution given the multiple tests performed. Further studies should investigate the brain regions reported in this study with larger samples.

4.1 | Whole-brain associations of sleep behaviors with GMV

Only two previous studies investigated the associations between sleep behaviors and GMV in children and/or adolescents using a whole-brain volumetric approach.[11,12] The whole-brain volumetric approach depicted a complete picture of sleep and GMV associations at a whole-brain level, rather than at a region-of-interest level. Thus, the whole-brain approach affords the exploration of associations not described in previous studies. These two studies focused separately on weekdays and weekend days.[11,12] Our study was the first to investigate the week as a whole (using weighted averages to account for the correspondent weight of school days and weekend days in daily life) and, therefore, consider the association with brain structure as a result of sleep behaviors during both weekdays and weekend days. This approach provided us with a unique and clear perspective on the association between sleep variables and GMV rather than assuming different associations of sleep with GMV dependent upon the day in which sleep occurs.

In regard to sleep timing, later wake times were associated with less GMV in several cortical structures, such as the inferior temporal, fusiform, and supramarginal gyri and the superior parietal cortex. Sleep onset was not associated with GMV in any brain region. The inferior temporal gyrus, the fusiform gyrus and the supramarginal gyrus are important for reading and language processing, word recognition and posture and gesture identification.[59,60] GMV in these structures was positively associated with academic fluency, mathematics, total achievement and IQ. The superior parietal cortex is important for processing spatiotemporal and visual information,[61] which is important for academic achievement as GMV in this region was associated with mathematics, academic fluency, academic applications and total achievement. One previous study found that self-reported earlier wake time during weekends was associated with greater GMV in the medial frontal orbital and the anterior cingulate cortices in 14 year-olds.[11] Diversity in the associated brain regions can respond to a different stage in brain development (pre-adolescence vs adolescence) and/or different methods of assessing sleep (ie, self-reported vs objective). Consistent with our findings, Urrila et al[11] found a positive association between GMV and school grades, which suggests that larger GMV was linked to better academic achievement. This study complements the previous one by adding a detailed study of the associations with different academic abilities and by including executive function and IQ.

Likewise, total time in bed was associated with higher GMV in the postcentral gyrus. Considering the negative association with wake time and the lack of association with sleep onset, it is logical that longer total time in bed is due to later wake times, which are both negatively associated with GMV in several brain regions. None of the previous studies[11,12] found associations with GMV in the postcentral gyrus, but differing sample characteristics and methodological inconsistencies may account for this discrepancy. The postcentral gyrus is located in the primary somatosensory cortex. Our findings suggest that those children who stay in bed longer may interact less with the environment and, in turn, may not stimulate this brain region adequately. This negatively affects academic achievement, since GMV in this specific cluster was positively associated with reading, academic skills, academic fluency, academic applications and total achievement. However, this should not be interpreted as a negative consequence of longer sleep periods. Total sleep time was not associated with GMV in any region, but total time in bed was associated, suggesting that those children who stayed in bed longer (especially when engaged in non-sleeping time activities) have smaller GMV in certain regions, which may lead to poorer academic achievement.

In regard to sleep patterns, longer WASO time was related to lower GMV in the superior temporal pole, the precuneus and the right superior parietal cortex; and a higher number of WASO with lower GMV in the superior medial frontal and the postcentral gyri, and the left superior parietal cortex. GMV in the precuneus and the right superior parietal cortex were positively associated with reading, mathematics, academic skills, fluency, applications and total achievement. Consistently, Urrila et al[11] also found sleep behaviors associated with GMV in the precuneus and, in turn, this GMV was associated with school grade average. The precuneus has been related to visuospatial perception and, together with the hippocampus, to episodic memory.[62,63] These functions are important for academic achievement. It is also noteworthy that the right superior parietal cortex was negatively associated with wake time and WASO time in our sample. Since these two sleep behaviors were not correlated with each other (see Table S1), we cannot assume that these findings are overlapping. Likewise, the left postcentral gyrus was associated with bedtime and the number of WASO, indicators which did not correlate with one another. Only the cluster related to bedtime was associated with academic achievement.

Briefly, these findings complement previous literature by confirming some specific brain regions which were associated with sleep behaviors and by describing associations which have not been previously reported. Brain development during childhood and adolescence is heavily dependent upon the age of participants, with age having a differential relationship relative to which brain areas are more or less sensitive to sleep behaviors.[64] In this regard, our sample comprised 8-11-year-old children, while previous studies were focused on older adolescents. Furthermore, all of the participants in the current study presented with overweight or obesity, which could alter the relationship between sleep and brain outcomes, including development,[28] and

may account for differences in the findings between the current study and previous research. Likewise, we found eight cortical regions associated with sleep, which resulted in a high number of statistical tests that were employed to study their association with academic achievement, executive function and IQ. Although we applied a correction for multiple comparisons, we advise caution in the interpretations and suggest further investigation of these findings.

All of the above-mentioned associations were not affected by including SED; LPA or MVPA in the models. Therefore, SED, LPA and MVPA do not appear to influence the association between sleep behaviors and GMV in our sample of children with overweight/obesity.

4.2 | Associations of sleep behaviors with GMV in the hippocampus

The hippocampus is a subcortical brain structure that is in constant communication with cortical structures and has been found to be crucial for memory consolidation during sleeping.[13,14] A major hypothesis on this link points to the memory consolidation process, which occurs predominantly during sleep.[14] Our ROI analyses of the hippocampus showed that total sleep time was positively associated with GMV in the right hippocampus. This finding agrees with Taki et al.,[12] who found similar associations using self-reported sleep behaviors in 5-18-year-old children. Specifically, they found a longer total sleep time during weekdays was associated with the hippocampus; a relationship not observed for weekend total sleep time. This study compliments their findings by objectively assessing a representative whole week, including both weekdays and weekends.

Furthermore, higher sleep efficiency and shorter WASO time were associated with greater hippocampal GMV in the right hemisphere. This is the first study to investigate the associations between these variables and GMV in children. Of note, sleep efficiency and WASO time were highly correlated in this sample (see Table S1). Our conclusion is that WASO time should be as short as possible, meaning that sleep efficiency and GMV in the hippocampus would be higher. It is noteworthy that our whole-brain volumetric analyses failed to find associations between sleep behaviors and GMV in the hippocampal regions as the ROI analysis did. The whole-brain analysis requires enough contiguous voxels associated with sleep behaviors to consider a significant association, which makes this analysis stricter than the ROI.

Further, the right hippocampus appears more sensitive to sleep behaviors than the left hippocampus in children with overweight/obesity. However, GMV in the right hippocampus was not clearly associated with academic achievement, executive function or IQ (ie, only the anterior sub-section of the right hippocampus was associated with inhibition).

4.3 | Limitations and strengths

Several limitations of this study should be acknowledged. First, the cross-sectional design does not afford a causal interpretation of the findings. Next, accelerometer-based estimates of sleep do not represent sleep itself, but rather an estimation based on movement patterns, so our findings should be interpreted with caution. However, accelerometers are a less-invasive objective method to assessing sleep behaviors in free-living settings, while also providing good validity.[21,22] Likewise, nap time cannot be accurately identified via accelerometers, and we did not collect self-report information on naps; thus, it could be that part of the daily sleep is missing in our estimates. Furthermore, some participants had missing accelerometer or MRI data and had to be excluded from analyses because of the impossibility of imputing MRI images. However, these participants were similar to those included in analyses in terms of BMI and sociodemographic characteristics. Nevertheless, strengths of this study include: the relatively large sample size (96 children with valid MRI); the consideration of SED and physical activity as potential confounding factors for sleep behaviors and GMV; the objective assessment of sleep behaviors across an entire week; the standardized tests for the measurement of academic achievement rather than school grades; and the focus on children with overweight/obesity, given the bidirectional associations between obesity and sleep behaviors, physical activity and brain development.

In conclusion, our findings indicate that sleep behaviors, including timing, duration and patterns, are associated with GMV and, subsequently, GMV is associated with academic achievement and IQ in children with overweight/obesity. The superior parietal and postcentral cortices appear to be the most consistent regions associated with sleep, given that they were also associated with academic achievement indicators. We should also highlight that WASO time was associated with GMV in both cortical structures and, subsequently, related strongly to academic achievement. Total sleep time, sleep efficiency and WASO time are specifically associated with the right hippocampus, but this subcortical region was not associated with academic achievement, executive function or IQ. Sleep behaviors are important for GMV and academic achievement and, to a lesser extent, IQ, but appeared unrelated with executive function. All these associations remained significant after considering the potential effect of SED, LPA and MVPA.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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