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Child overweight and obesity are associated with reduced executive cognitive performance and brain alterations: a magnetic resonance imaging study in Mexican children

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Summary

Background: Overweight and obesity in childhood is associated with negative physical and psychological effects. It has been proposed that obesity increase the risk for developing cognitive deficits, dementia and Alzheimer's disease and that it may be associated with marked differences in specific brain structure volumes.

Objective: The purpose of this study was a neurobiopsychological approach to examine the association between overweight and obesity, brain structure and a paediatric neuropsychological assessment in Mexican children between 6 and 8 years of age.

Methods: We investigated the relation between the body mass index (BMI), brain volumetric segmentation of subcortical gray and white matter regions obtained with magnetic resonance imaging and the Neuropsychological Assessment of Children standardized for Latin America. Thirty-three healthy Mexican children between 6 and 8 years of age, divided into normal weight (18 children) and overweight/obese (15 children) groups.

Results: Overweight/obese children showed reduced executive cognitive performance on neuropsychological evaluations (i.e. verbal fluidity, $P = 0.03$) and presented differences in brain structures related to learning and memory (reduced left hippocampal volumes, $P = 0.04$) and executive functions (larger white matter volumes in the left cerebellum, $P = 0.04$ and mid-posterior corpus callosum, $P = 0.03$). Additionally, we found a positive correlation between BMI and left globulus pallidus ($P = 0.012$, $\rho = 0.43$) volume and a negative correlation between BMI and neuropsychological evaluation scores ($P = 0.033$, $\rho = -0.37$).

Conclusions: The findings contribute to the idea that there is a relationship between BMI, executive cognitive performance and brain structure that may underlie the causal chain that leads to obesity in adulthood.

Keywords: executive cognitive function, hippocampus, neuropsychological assessment, volumetric MRI.

Introduction

Childhood obesity has been rising dramatically over the past three decades (1). Currently, more than 30% of children in the North American World Health Organization (WHO) regions are overweight or obese (body mass index [BMI] ≥ 85th centile), and almost 80% of these children live in developing countries (2). Specifically for Mexico, it has been predicted that by 2050 there will be more obese and overweight than normal weight people (3); this would mean that about 12 million diabetes and 8 million heart disease cases are expected in 2050 alone (3). Similarly, it has been proposed that the diseases accompanying obesity increase the risk for developing cognitive deficits, dementia and Alzheimer's disease with additional worldwide impact on public health, tremendous suffering, lost productivity, disability and early death (4).

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While the physiological burden of obesity in childhood has received much attention, the consequences of obesity for mental health and cognitive development are not established to the same degree (5). Nevertheless, some studies have reported higher prevalence of psychiatric disorders, negative physical self-perception, diminished sense of general self-worth and behavioural and cognitive problems (5,6). Furthermore, evidence shows that the persistence of obesity from childhood into adulthood develops adverse psychosocial, socioeconomic and health sequelae (7). Mexico has the highest prevalence of obesity in the world; 26% of children and 31% of adolescents are overweight or obese (8). In the quest to understand the pathophysiology of obesity commencing in childhood in a more integrative way, the neural basis for self-regulation of food intake has received increased attention. For example, using a neurobiological approach, Riggs *et al.* (9) suggest that a key factor of behavioural dysregulation is high-calorie food intake and energy imbalance as a result of inadequate executive cognitive function skills, which are higher-order cognitive processes necessary for goal-directed problem solving. Accordingly, executive cognitive function skills are critical for correct childhood behavioural development and have been associated with prefrontal cortical integration and with emotional processes in the limbic system related to accurate inhibitory control, emotional control, planning and working memory. Furthermore, the executive cognitive function adequate to healthy controlled food intake varies depending on the type of food. Accordingly, high-calorie snacks may exert a craving effect analogous to certain drugs upon the child's labile and highly plastic cognitive systems, generating exceptional reinforcing and highly rewarding, motivational and emotional effects similar to the ones present in drug addicts (10,11). This model for explaining overeating and obesity at a neurobiological level is absolutely critical and in need of further validation. The concept of food addiction must thus be approached in an integrative and multidisciplinary way. Hitherto viewed from a neurobiological approach, obesity has been associated with atrophy in the frontal lobes, the anterior cingulate gyrus, the hippocampus and the thalamus relative to individuals with normal body mass index (BMI) (12). These brain regions are associated with attention, memory and the control of cognition. Accordingly, overweight and obesity may be associated with marked differences in specific brain structure volumes and could provide a greater understanding of the underlying causes of the obesity-related decline in cognitive function among overweight and obese individuals (13). The present work was designed to evaluate cognitive performance using a standardized neuropsychological test and to assess the brain structures previously hypothesized to be involved in obesity with magnetic resonance imaging (MRI) in 33 otherwise healthy Mexican children between 6 and 8 years of age.

Subjects and methods

Subjects

Thirty-three healthy children (21 female) between 6 and 8 years old who were of comparable socioeconomic status as measured with a variation of the CAPSES (14) and currently enrolled in a primary school in the metropolitan area of Querétaro City, Mexico participated in the study. Inclusion criteria were pregnancy to term, clinically healthy, no neurological and/or neurodevelopmental damage, learning, and/or language deficiencies as assessed by a psychological and general medical examination. Additionally, both parents participated in a clinical interview and gave informed consent. The protocol and all procedures were Institutional Review Board approved and in line with the Helsinki Declaration of 1975 as revised in 1983.

Neuropsychological battery

The *Bender-Gestalt Test*, which estimates visual motor development and reflects the mental development of the child (15), was used as an initial selection filter. Next, a clinical and psychological evaluation was conducted together with the *Mini-International Neuropsychiatric Interview (M.I.N.I. Kid) for children and adolescents*, a structured, diagnostic interview that explores the main psychiatric disorders of childhood based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV).

Neuropsychological assessment of children

The Neuropsychological Assessment of Children (ENI, for Evaluación Neuropsicológica Infantil) is a recent tool developed by Matute *et al*. (16); it is standardized with Mexican and Colombian children. It is different from the more widely used Wechsler Intelligence Scale for Children, although the results of both tests show high correlation. The ENI has been widely used in Mexico, the rest of Latin America, as well as with Hispanic children in the United States (17). It provides information on neuropsychological characteristics of children and youth aged 5–16 years old,

Table 1 Neuropsychological assessment for children

Test domain	Subcategory	Sample task
Cognitive functions	Construction abilities	
	With objects	Build with sticks four figures that are presented on cards
	Graphical	Draw a human figure
	Memory	
	Verbal	Remember the most words of a 9-item list
	Visual	Remember and draw from nine object list
	Perception	
	Tactile	Recognize eight objects put in either hand
	Visual	Recognize eight incomplete drawings
	Auditory	Recognize eight environmental sounds
	Language	
	Repetition	Repeat eight verbally presented words
	Expression	Recount a 307 word text previously read
	Comprehension	Point to the object on a drawing which the examiner has mentioned
	Metalanguage	Spell eight words
	Spatial abilities	Identifying parts of the left or right hemibody
	Attention	
	Visual	On a drawing with 44 small and big rabbits, cancel out all the big ones
	Auditory	Repeat six numbers of series between two and eight numbers
	Conceptual abilities	From eight figures presented, the child has to identify the missing part and choose among the possible options to complete it
Academic performance	Reading	
	Precision	Read out loud sentences without mistakes
	Comprehension	Read a 98-word text and answer eight questions
	Writing	
	Precision	Dictation of eight individually presented salables
	Narrative	Dictation of three full sentences
	Composition	Copy of a full text
	Speed	Copy a full text within 5 min
	Arithmetic	
	Counting	Count the number of visually presented objects
	Numerical management	Order eight presented numbers in descendent order
	Calculus	resolve 12 mentally presented arithmetic problems
	Logic	From two groups of numbers identify which is larger
	Reasoning	Starting from one add three until reaching 31
Executive cognitive functions*	Cognitive fluidity	
	Verbal	State the most number of animals in one minute
	Graphic	Draw the most number of different figures within a specific area
	Cognitive flexibility	
	Perseverance	
	Category	Similar to the Wisconsin Sorting Task
	Organization	
	Planning and organizing	Build with three blocks and the minimum movements the required buildings

Neuropsychological Assessment of Children (ENI) with sample tasks of different domains of cognitive abilities and subcategories. *Behavioural dysregulation in obese/overweight children has been reported to alter executive cognitive functions (9).

and is based on the assumption that cognitive and behavioural abilities reflect the integrity of the central nervous system. The ENI evaluates cognitive abilities grouped in three large domains, namely, cognitive functions, academic performance and executive cognitive functions with following sections: constructional abilities, memory, perception, language, spatial abilities, attention, reading, writing, arithmetic, cognitive fluidity and flexibility and capacity for planning and organizing (see Table 1 for sample questions). Rosselli *et al.* (17) presented a description of ENI in English. The ENI is regularly administered over a 300-min period, on average, per subject. As our hypothesis is focused on executive function differences, only this domain was taken into consideration for the statistical analysis.

Body mass index estimation

BMI is defined as body weight in kilograms divided by height in meters squared. BMI is the commonly accepted index for classifying adiposity in adults, and it is recommended for use with children and adolescents (18). Classification of children was calculated according to the International Obesity Task Force (18) and using the cut-off points for BMI for overweight/obesity by sex and between 2 and 18 years (with 6 months step subgrouping), defined to pass through BMI of 25 kg m^2 at age 18, corresponding to a *z* score of +1.19 and the 88th centile in females, and a *z* score of +1.30 and the 90th centile in males. All children had a medical examination before the MRI session. Weight and height were obtained for all children.

Procedure of data collection

After initial subject selection, the ENI was administered on two different days within the same week. Individual sessions lasted approximately 180 min with 10-min rest periods every 30 min. The assessment was individual and carried out by two psychologists in a Gesell chamber with the parents observing the session. After completion of the ENI, appointment for the MRI session was arranged for the following week.

Magnetic resonance imaging and statistical analysis

Whole brain imaging was performed on a 3.0 T GE MR750 (General Electric, Waukesha, WI, USA). High-resolution structural 3D-T1-weighted images were acquired (resolution of $1 \times 1 \times 1$ mm^3, repetition time (TR) = 2.3 s, echo time (TE) = 3 ms) covering the whole brain. The images were obtained with an 8-channel head coil using parallel imaging with an acceleration factor = 2.

Volumetric segmentation of subcortical gray and white matter regions was performed using the Freesurfer image analysis suite (http://surfer.nmr.mgh.harvard.edu/) with additional individual quality control; Fig. 1 shows examples of gray and white matter segmentation done in Freesurfer and yielding results expressed in mm^3. All the cortical and subcortical region volumes for each subject were normalized to the subject's total brain volume estimated by the Freesurfer segmentation process. Shapiro–Wilk testing was performed on all data to verify normality. The means of the two groups' (NLw vs. Ow/Ob according to BMI) individual brain segments were confirmed to be normally distributed and thus compared for *statistical* difference using a Student's *t*-test; conversely, the parameters obtained in the ENI for executive cognitive functions were not normally distributed and hence, they were compared for statistical differences using the Wilcoxon signed-rank test. Results with $P < 0.05$ were considered significant. Additionally, we performed correlation analyses between BMI, brain segments and ENI scores. These analyses did not include correction for multiple comparisons. Finally, to investigate if the different brain segments in combination with BMI score can predict the ENI scores, we performed a multiple linear regression.

Results

The children in this study had a mean age of 7.6 years (standard deviation [SD] = 0.42) and a mean BMI rating of 18.16 (SD = 4.73), ranging from 12.94 to 34.10. According to the International Obesity Task Force classification (see Subjects and methods section), we obtained 18 normal BMI children (NLw, 11 female < 88th centile, seven male < 90th centile, mean BMI = 15.29, SD = 1.3) and 15 overweight/obese children (Ow/Ob, 10 female > 88th centile, five male > 90th centile, BMI = 21.61, SD = 5.0). The default Freesurfer configuration generated 49 different brain segmentations from which 30 were operational. Figure 1 presents the structures which revealed significant volume differences: larger volumes were observed in Ow/Ob as compared with NLw children in the left cerebellar white matter ($P = 0.044$, Fig. 1a) and mid-posterior corpus callosum ($P = 0.034$, Fig. 1b), whereas a reduced volume was observed in the left hippocampus ($P = 0.046$, Fig. 1c). Figure 2 shows the scores for the assessed executive cognitive functions of the ENI. A significant group difference was observed in verbal fluidity ($P = 0.039$), where Ow/Ob children scored lower. Next, Fig. 3a presents the significant correlation between brain segments and BMI, where the left globulus pallidus shows a positive correlation ($P = 0.012$, $\rho = 0.43$) with BMI. Additionally, the left ($P = 0.084$, $\rho = 0.305$) and right cerebellar white matter ($P = 0.091$, $\rho = 0.299$) showed positive tendencies with BMI. Figure 3b shows the significant correlation between ENI scores and BMI where *conceptual abilities* ($P = 0.033$, $\rho = -0.3705$) showed a significant negative correlation with BMI. Additionally, *verbal fluidity* ($P = 0.079$, $\rho = -0.3093$) showed a negative tendency. Finally, the stepwise multiple linear regressions yielded significant values for *language repetition* ($P = 0.049$, $F(2,30) = 3.34$, $r^2 = 0.127$) and *reading precision* ($P = 0.023$, $F(2,30) = 4.268$, $r^2 = 0.169$).

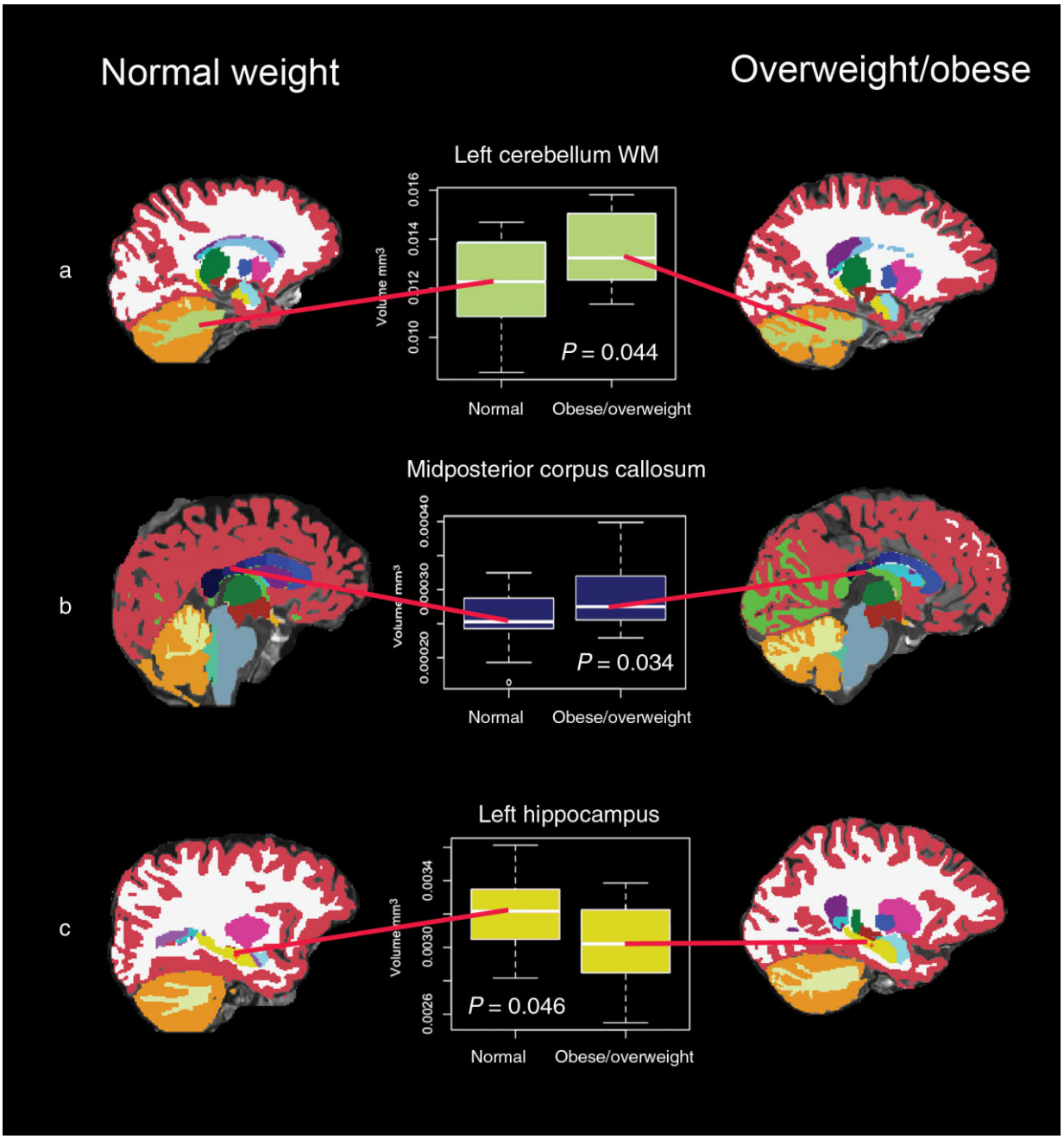

Figure 1 Normal weight and overweight/obese children's brain segmentations produced with the Freesurfer Tool. Presented are the significant Student's *t*-test comparisons between a representative normal weight (left) and overweight/obese (right) child's brain: (a) left cerebellum white matter, (b) mid posterior corpus callosum and (c) left hippocampus. Images are presented in radiological convention.

Discussion

Obesity is increasing rapidly worldwide, and it threatens to become the foremost cause of chronic disease in the world (1). Because of its public health importance, efforts should be directed at understanding the causal chain that leads to obesity in adulthood. Here, we took a neurobiological approach towards this public health problem, trying to elucidate its most fundamental aspects. The present study demonstrated an association between BMI and differences in certain specific brain structures in a sample of cognitively normal, 6- to 8-year-old Mexican children. Higher BMI was associated with larger white matter volumes in the

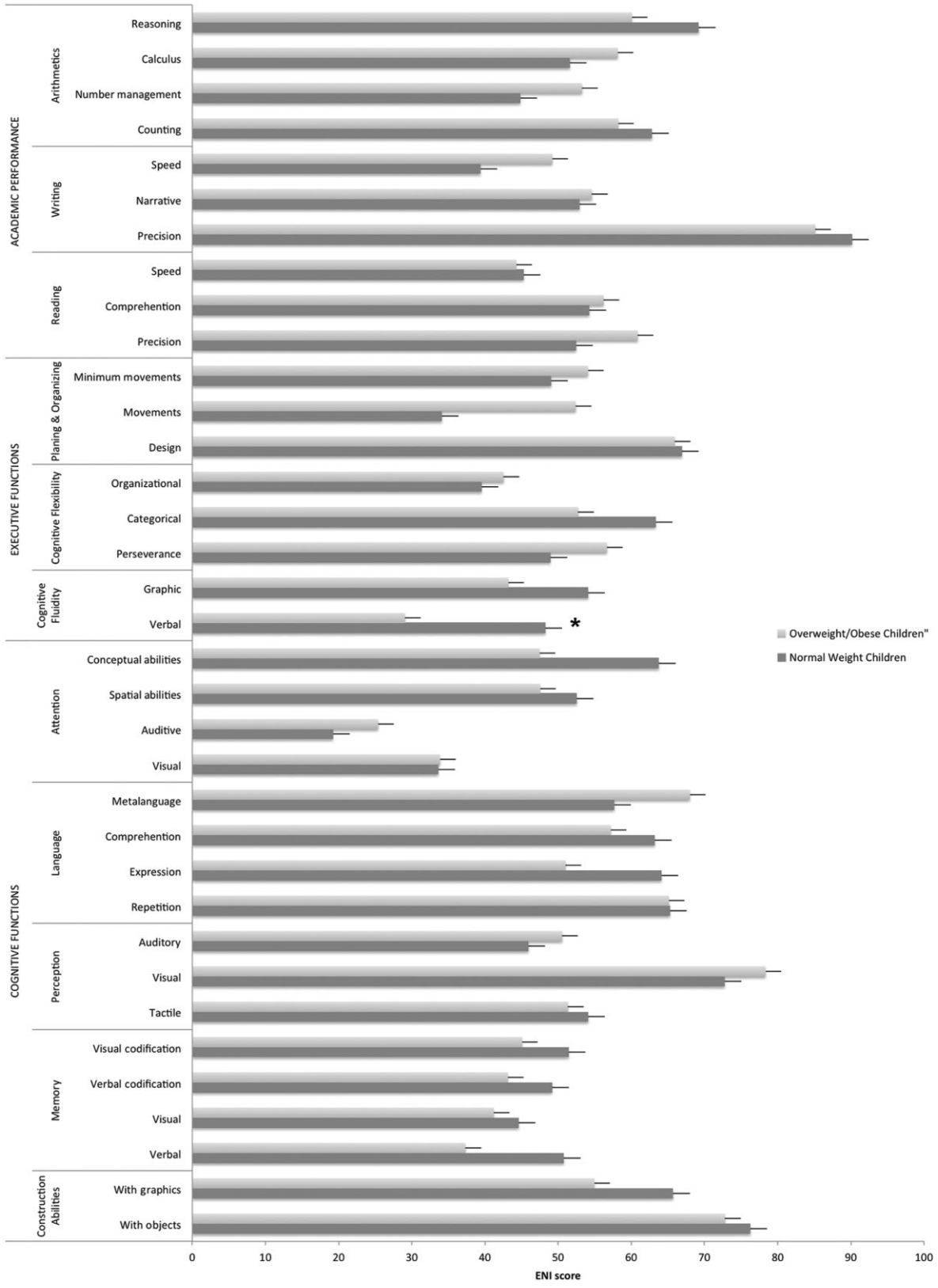

Figure 2 Scores of the Executive Cognitive Functions part in the Neuropsychological Assessment of Children (ENI). A significant group difference was observed only in verbal fluidity (*$P = 0.039$) where Ow/Ob children scored lower.

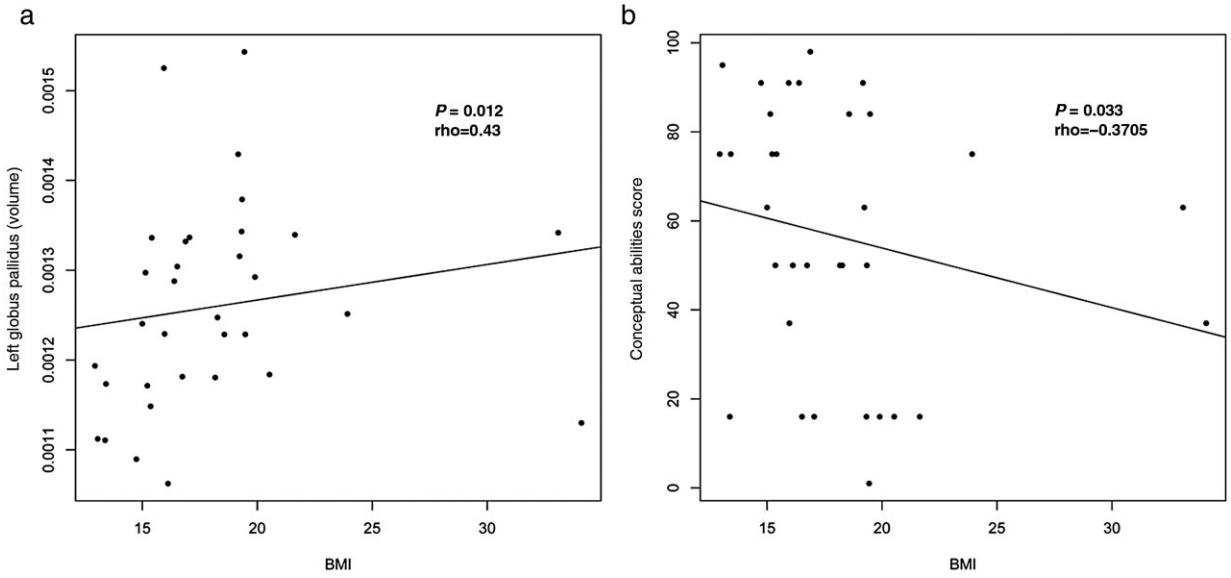

Figure 3 Correlation between brain segments, ENI scores and BMI. (a) Shows the significant positive correlation of the left globulus pallidus with body mass index (BMI) ($P = 0.012$, $\rho = 0.43$). (b) Shows the significant negative correlation of *conceptual abilities* with BMI ($P = 0.033$, $\rho = -0.3705$).

left cerebellum and mid-posterior corpus callosum, reduced left hippocampus volume and a positive correlation with the volume of the left globulus pallidus. Equally, higher BMI was associated with lower executive cognitive function and a negative correlation with attention performance. These results agree with previous studies, one by Bruce *et al.* (19) showing that obese children display hyperactivation in brain networks linked to motivation, reward and cognitive control, and another by Maayan *et al.* (20) where obese adolescents were found to have significantly higher ratings of disinhibition, lower performance on the cognitive tests and lower orbitofrontal cortex volume. In line with this, Berridge *et al.* (21) and Volkow *et al.* (11) have suggested that a dysfunction in reward circuits might contribute to obesity and eating disorders. In their view, brain mechanisms that participate in 'craving' for food include hedonic circuits that connect forebrain limbic structures such as ventral pallidum and nucleus accumbens with larger opioid networks in nucleus accumbens, striatum and amygdala that extend beyond hedonic circuits, as well as mesolimbic dopamine systems and corticolimbic glutamate signals that interact with those systems and cause at least some cases of overeating.

The present study demonstrated larger white matter volumes in the left cerebellum and mid-posterior corpus callosum in obese/overweight children, areas that have been found to be involved in frontal-subcortical network connections of the brain responsible for executive cognitive function. For example, Haltia *et al.* (22) showed a positive correlation between white matter volume and BMI, although no cognitive tests were performed. Similarly, Stanek *et al.* (23) reported a direct association between obesity and abnormal white matter tract integrity in the fornix and genu of the corpus callosum in otherwise healthy adults. These authors suggest that the white matter alterations probably result from several pathophysiological processes related to elevated adiposity, including endothelial dysfunction that translates into abnormal white matter tract integrity and larger white matter volumes. Furthermore, reduced white matter integrity has been related to cognitive instability mediated by frontal-subcortical circuits that form the principal network mediating motor activity and behaviour in humans. These frontal-subcortical circuits originate in the supplementary motor area, frontal eye field, dorsolateral prefrontal region, lateral orbitofrontal region and anterior cingulate portion of the frontal cortex, all of which have important roles in human behaviour. Dysfunction of orbitofrontal, medial and dorsolateral prefrontal lobes is associated with a variety of neuropsychiatric syndromes related to the executive cognitive functions implicated in increased impulsivity, which would cause the inability to control eating behaviour (24). Although the differences in white matter volume strongly suggest an underlying neurobiological cause for the low scores of obese/overweight children in executive cognitive functions (9,22,23), these must be explored further with focused research and larger groups.

We also found a positive correlation between BMI and left globulus pallidus volume. This structure has been found to be a hotspot within the forebrain limbic hedonic circuits strongly linked with the 'liking' mechanisms for food where opioid/endocannabinoid/orexin signals can amplify sensory pleasure (21). What is more, this amplified sensory pleasure triggers 'wanting' mechanisms that include larger opioid networks in nucleus accumbens, striatum and amygdala that extend beyond the hedonic hotspots (globulus pallidus and nucleus accumbens), as well as mesolimbic dopamine systems and corticolimbic glutamate signals that interact with those systems and might increase somewhat similar to the addiction-related phenomenon of incentive-sensitization (21).

Additionally, we found that a higher BMI was associated with a reduced left hippocampal volume. This structure is strongly implicated in learning and memory mechanisms; it also translates neurohormonal signals of energy balance into adaptive behavioural outcomes thought to be involved in further executive functions that inhibit food intake (25). Metzler-Baddeley *et al.* (25) found that obesity is related to atrophy and dysfunction of the hippocampus and that hippocampal lesions may lead to increased appetite and weight gain. Similarly, reduced hippocampal volume (12) and abnormal hippocampal activation in response to food stimulation or feeding manipulations have been related to obesity. This theory follows from the fact that the hippocampus, a medial temporal lobe structure, is fundamental for learning and memory (12). The hippocampus has classically been identified with the encoding and retrieval of spatial relations among objects in the environment (i.e. spatial memory), the formation and recall of memories about events and facts (i.e. declarative memory) and the formation of taste-related memories (12). In this sense, the hippocampus is needed to resolve 'predictable ambiguities' that exist when a single stimulus reliably signals different outcomes, depending on the presence or absence of other cues (26). A study conducted by Holland *et al.* (26) showed that inhibitory learning is highly dependent on the hippocampus and is involved in learning to resolve predictable ambiguities. The authors observed that rats with hippocampal lesions exhibit impaired inhibitory learning and thus failed to inhibit responses related to food intake. In addition, hippocampal lesions have been found to result in increased appetitive behaviour and weight gain, for example, there is evidence that amnesic human patients with hippocampal damage show impaired inhibitory control of food intake and appetitive behaviour (27). These patients, after eating a full meal, will eat a full second meal that is offered only minutes later (27), thus showing that inhibitory control of food intake strongly depends on the structural integrity of the hippocampus. A study by Higgs (28) demonstrated that for neurologically intact humans, memories of a prior meal help to inhibit subsequent intake, further suggesting that hippocampal damage might interfere with satiety signalling by both interoceptive and exteroceptive cues.

Study limitations

The main limitation of the present work is the relatively small number of children studied. Although the number of participants is sufficiently powerful in terms of brain segmentation using Freesurfer (29), the neuropsychological assessment is underpowered to find further significant differences. Additionally, this study could benefit with additional biological variables such as blood parameter and genetic profiling.

Conclusions

Our findings contribute to the hypothesis that overweight/obesity affects frontal-subcortical brain structures and circuits which are related to the executive system, the hypothesis that the hippocampus is involved in the regulation of food intake and that the globulus pallidus is a hotspot within the forebrain limbic hedonic circuit contributing to the 'liking' mechanisms for food and the amplification of sensory pleasure. They also provide additional evidence to the proposal that increased body weight results from the abundant availability of food in the environment interacting with a brain-reward system that probably lacks an effective executive system to create adequate 'stop' signals. Nevertheless, to better understand the 'wanting' and 'liking' mechanisms for food and the interaction with the cognitive executive system that controls behaviour, additional and more focused studies are needed. Furthermore, the question of causality remains: Do these structural differences cause overweight/obesity, or does overweight/obesity cause(s) these brain structural differences? Longitudinal follow-up studies may serve to gain further insight into the causal role of these structures in obesity and to find adequate therapeutic strategies.

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Conflict of Interest Statement

No conflict of interest was declared.

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