Title: Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity – implications for individuals born small for gestational age

Authors: Amanda B Mucellini[a], Patrícia M Miguel[c,e], Roberta Dalle Molle[b], Danitsa M Rodrigues[c], Tania D Machado[b], Roberta S Reis[b], Rudinéia Toazza[c], Giovanni A Salum[a], Andressa Bortoluzzi[c], Alexandre R Franco[d], Augusto Buchweitz[d], Barbara Barth[e], Marilyn Agranonik[f], Marouane Nassim[e], Michael J Meaney[e,g], Gisele G Manfro[a,c] , Patrícia P Silveira[c,e,g]

Affiliations: [a]Graduate Program in Psychiatry and Behavioral Sciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [b]Graduate Program in Child and Adolescent Health, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [c]Graduate Program in Neuroscience, Institute of Basic Health Sciences, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS, Brazil; [d]Brain Institute of Rio Grande do Sul, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil; [e]Ludmer Centre for Neuroinformatics and Mental Health, Douglas Mental Health University Institute, McGill University, Montreal, Quebec, Canada; [f]Fundação de Economia e Estatística Siegfried Emanuel Heuser, Porto Alegre, Brazil; [g]Department of Psychiatry, McGill University, Montreal, Quebec, Canada.

Corresponding author: Patricia Pelufo Silveira, Department of Psychiatry, Faculty of Medicine, McGill University. Douglas Hospital Research Centre, 6875 Boulevard LaSalle, Montreal, QC, H4H 1R3, Canada. Phone: 514-761-6131 (ext.2776). E-mail: patricia.silveira@mcgill.ca

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

Abstract: While classically linked to memory, the hippocampus is also a feeding behavior modulator due to its multiple interconnected pathways with other brain regions and expression of receptor for metabolic hormones. Here we tested whether variations in insulin sensitivity would be correlated with differential brain activation following exposure to palatable food cues, as well as with variations in implicit food memory in a cohort of healthy adolescents, some of whom were born small for gestational age (SGA). Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) was positively correlated with activation in the cuneus, and negatively correlated with activation in the middle frontal lobe, superior frontal gyrus and precuneus when presented with palatable food images versus non-food images in healthy adolescents. Additionally, HOMA-IR and insulinemia were higher in participants with impaired food memory. SGA individuals had higher snack caloric density and greater chance for impaired food memory. There was also an interaction between the HOMA-IR and birth weight ratio influencing external eating behavior. We suggest that diminished insulin sensitivity correlates with activation in visual attention areas and inactivation in inhibitory control areas in healthy adolescents. Insulin resistance also associated with less consistency in implicit memory for a consumed meal, which may suggest lower ability to establish a dietary pattern, and can contribute to obesity. Differences in feeding behavior in SGA individuals were associated with insulin sensitivity and hippocampal alterations, suggesting that cognition and hormonal regulation are important components involved in food intake modifications throughout life.

Keywords: Intrauterine growth restriction; Small for gestational age; HOMA-IR index; Feeding behavior; Food memory; MRI.

Abbreviations: BWR: birth weight ratio; MRI: magnetic resonance imaging; fMRI: functional magnetic resonance imaging; HOMA-IR: homeostatic model assessment of insulin resistance; AGA: adequate for gestational age; SGA: small for gestational age; BMI: body mass index; IQ: intelligence quotient; WASI: *Wechsler abbreviated scale of intelligence*; NEUPSILIN-INF: child brief neuropsychological assessment battery; DEBQ: Dutch eating behaviour questionnaire; GLM: general linear model; FWE: family-wise error; ANOVA: analysis of variance; NPY: neuropeptide Y; AgRP: agouti-related protein.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

1. Introduction

While the hippocampus is classically associated with memory, this region is also recognized as a feeding behavior modulator due to its multiple interconnected pathways with other brain regions. There is evidence that memory plays a role in the control of hunger and food intake, as the memory of food consumed is used to process subsequent decisions about what, when and how much to eat [1, 2]. Memory, even without conscious awareness, decreases the impact of recent reward and environmental cues on choices, with enhanced connectivity between the hippocampus and prefrontal cortex contributing to reward based decision-making [3].

The hippocampus is sensitive to signals of hunger and satiety, helping to inhibit the ability of food cues to evoke appetite and eating behavior [2, 4]. Hippocampal damage impairs this food inhibitory control system, leading to an altered food intake and increased risk for obesity [5-7]. The hippocampus is the brain region with the larger expression of insulin receptors [8], and insulin action in in this region is associated with cognitive function [9] [10]. Genetic individual variations in the expression of the insulin receptor gene network in the hippocampus predict risk for Alzheimer's disease in adults, but most importantly, are associated with variations in cognitive capacity in young, healthy children [11].

Human fMRI studies show a positive correlation between fasting plasma insulin levels and hippocampal activity after stimulation with high-caloric food images, which suggests a link between insulin signaling pathways, hippocampal activation, and eating behavior in humans [12-15]. Hippocampal neighboring gyri (parahippocampal and fusiform gyri) are particularly sensitive to insulin and responsive to visual food cues [16, 17]. These findings corroborate the idea that the hippocampus participates in the identification of external signs of food and that insulin is closely linked with that role of the hippocampus in feeding behavior, even in healthy, non-insulin resistant individuals [18].

Variations in early growth trajectories during development – essentially an insulin-dependent process [19] – are associated with differences in childhood executive function [20]. A clinically relevant entity in this context is poor fetal growth, reflected in being born small for a certain gestational age. Subjects born small for gestational age (SGA) are vulnerable to develop type II diabetes as a consequence of inadequate insulin secretion that begins at birth and is followed by a progressive decrease in insulin sensitivity throughout life [21-27]. Interestingly, and in agreement with the notion that central insulin action modifies cognitive and eating behavior outcomes, SGA individuals demonstrate greater preference for hyperpalatable foods (foods high in energy, fat, sugar or salt/sodium) [28-39], and have a higher incidence of cognitive impairments when compared to the general population [40-50]. Cognitive impairments in individuals born with low birth weight have been associated with a reduced volume in the hippocampus [51-57], a brain region vulnerable to neonatal insults [58-63].

In this study, we tested if variations in insulin sensitivity correlate with hippocampal morphometry and brain activation in response to palatable food images [15], as well as if these variations are associated with the ability to retrieve implicitly learned food choices in adolescents [64]. In agreement with previous findings, we hypothesized that poor insulin sensitivity would also contribute to energy intake imbalance and obesogenic behavior [18]. Being born SGA is the most prevalent and clinically significant feature associated with

variations in insulin sensitivity early in life [65], and this condition is linked to altered behavior towards palatable foods at different ages, which contributes to their increased risk for chronic metabolic disease later in life [28-39]. To investigate a potential clinical relevance of this work, a secondary aim of this study was to understand if the behaviors linked to variations in insulin sensitivity are also prominent in SGA individuals compared to normal birth weight adolescents. Considering the metabolic programming effects of poor fetal growth[27, 66], we also investigated if the birth weight status modified the relationship between HOMA-IR on the eating behavior outcomes.

2. Materials and Methods

2.1 Sample

Subjects included in this study were recruited as part of a prospective cohort, whose details can be found elsewhere [67]. Participants were recruited from six schools around the area of a family health clinic that was part of Hospital de Clínicas de Porto Alegre, Porto Alegre, Brazil. In 2008, children and adolescents from these schools were invited to participate in the study, which included psychiatric and nutritional assessments. A total of 242 individuals completed the assessment in 2008 and from this initial group, 75 participated in a more in-depth re-evaluation that included psychiatric and nutritional assessments, DNA collection and functional Magnetic Resonance Imaging (fMRI) in 2013/2014. To test our hypotheses, 52 individuals (31 female, 17±2 years) were evaluated (Supplemental figure 1).

The study was approved by the Institutional Ethics Committee of Hospital de Clínicas de Porto Alegre and the Research Ethics Committee of Pontifícia Universidade Católica do Rio Grande do Sul. Ethics approval was based on guidelines for research involving humans and included Resolution 196/96 from the National Health Council and the Declaration of Helsinki. Local ethics committee approval and written informed consent (either from the subjects or from their guardians) were obtained from all participants before entering the study.

2.2 Measurements

The anthropometric measurements were taken in the morning, in the fasted state, by trained researchers. Weight and height were measured in duplicate (the average value was used in analyses) using accurate and calibrated equipment, including a digital platform balance (Toledo, São Paulo, Brazil) and a vertical stadiometer (Harpenden, Holtain Limited, Crymych, UK). Body mass index (BMI) was calculated as weight (kg) divided by height (m2) and used as BMI *z*-scores.

Blood samples were collected in the morning after fasting for 12 h and the samples were then centrifuged at 4000 rpm for 10 min. Glucose, was measured using an enzymatic colorimetric method and insulin levels were measured using chemiluminescence ADVIA 1800 and an ADVIA Centaur insulin assay (Siemens Healthcare Diagnostics Inc., Tarrytown, NY, USA). Homeostasis Assessment Model-Insulin Resistance Index (HOMA-IR) was calculated using fasting serum insulin (mU/mL) × fasting serum glucose (mmol/L))/22.5.

Socioeconomic status was based on the subject's education level, the presence of certain items in the household and the education level of the household's head occupant according to Brazilian Research Companies Association score points. This scale sorts participants into standardized subgroups labeled from A (highest economic strata) to E (lowest economic strata). Intelligence quotient (IQ) was calculated using the *Wechsler Abbreviated Scale of Intelligence* (WASI) [68]. Phonemic and semantic verbal fluency (number of valid words) was evaluated using the Child Brief Neuropsychological Assessment Battery (NEUPSILIN-INF) [69].

Fetal growth was based on the birth weight ratio (BWR), which is the ratio between the infant's birth weight and the mean birth weight, sex- and gestational age-specific birth weights for the local population [70]. BWR was categorized into adequate for gestational age ("AGA", two superior tertiles of the BWR distribution) or small for gestational age ("SGA", those in the lower tertile).

2.2.1 Food choices and feeding behavior

After anthropometric measures and blood collection were completed, participants received a voucher to purchase a snack of their choice at the research center's cafeteria (Figure 1A). The chosen foods were displayed in a tray and photographed. In a new assessment 6 months later, 4 photos of different snacks were shown to the participants, who were fasted at the time, including the photograph from their own previous food choice. Upon the presentation of these photographs, the participants were asked the following question: "If you could eat now, which one of the following snacks would you choose?". Choices for both composition (Figure 1B) as well as spatial arrangement (Figure 1C) of the snack chosen were investigated. Our intention in this snack choice test was to evaluate implicit, non-declarative food memory, which is known as a category of mnemonic processes involved in automatic behavior [3], that is linked to decision-making that affects food choices thus modulating eating behavior [71, 72]. Food preference choices are one of the best examples of implicit memory because this behavior is not consciously and intentionally learned, and it is resistant to change [73]. Food intake was estimated using the nutritional composition of the selected snack in the first visit. The quantitative analysis of macro- and micronutrients consumed in the selected snack was calculated using the USDA National Nutrient Database [74]. After completing their chosen snack at the research centre's cafeteria, the participants completed the Dutch Eating Behaviour Questionnaire (DEBQ) [75, 76] that classified eating behavior into restrained, emotional, and external traits according to the questionnaire's subscales.

2.2.2 Structural and functional MRI

<u>fMRI acquisition parameters</u>: Of the 52 participants, 40 were eligible for structural and functional MRI (list of exclusion criteria is presented in supplemental figure 1). Participants were fasted for at least 4h and 30min before MRI acquisition, they received a standard snack consisting of a cereal bar and a box of juice containing a total of 174kcal consisting of 39g carbohydrates (90% of total calories), 0.9g protein (2% of total calories) and 1.6g of fats (8% of total calories).

MRI data were acquired using echo planar imaging sequences with a GE 3-Tesla scanner (GE Healthcare Signa HDxT, Waukesha, WI, USA) equipped with an eight-channel head coil. The following parameters were used for structural images: T1 with voxels in isotropic spatial resolution of $1mm^3$, 170 contiguous slices and matrix images of 256*256

with inversion recovery type including TE = 2.18 ms and TR = −6.1 ms, and for functional images: 26 axial slices interspersed with a slice thickness of 4.0 mm and gap of 0.4 mm, FOV of 240 mm X 240 mm and matrix size of 80 X 64, TE = 30 ms, TR= 2.000 ms, and a flip angle of 90°.

fMRI design and stimuli: Our fMRI paradigm was described in detail in a previous publication from our lab[77]. It was adapted from [78], and set to investigate brain activation in response to images of palatable and healthy food and other non-food related items (e.g. a chair). Figures were selected from a database of images [79, 80]. A pilot study including adolescents from the same age range as the current study population was performed to establish which food images were perceived as 'palatable' or 'healthy'. The figures were presented using E-Prime software (version 2, Psychological Software Tools, Pittsburgh, PA, USA), with 3 blocks of approximately 7 min each. Each block included 21 randomized images (seven hyperpalatable foods, seven healthy foods and seven non-food objects). Each food trial consisted of image presentation (4 s) followed by two probe questions: 'How much do you like the food?' (5 s) and 'How much do you want to eat the food now?' (5 s). Participants had responded, by pressing buttons, to a scale that ranged from 1 (zero) to 4 (very much) using an fMRI compatible button box. Inter-trial interval ranged from 3 to 9 s.

Structural and fMRI data analysis: Data were pre-processed and analyzed with SPM8 (SPM8, http://www.fil.ion.ucl.ac.uk/spm) and implemented in MATLAB (MathWorks, Inc., Natick, MA, United States). For each participant, pre-processing analyses included slice timing correction, realignment of functional time series, co-registration of functional and anatomical images, spatial normalization in Montreal Neurological Institute space, spatial smoothing with an 8mm full-width half-maximum Gaussian smoothing kernel, and high- and low-pass filtering. Data from participants who moved over 4mm during imaging were excluded from analyses (3 subjects).

For the structural MRI, we measured regional hippocampal volumes using the well validated multiple automatically generated templates (MAGeT-Brain, https://github.com/CobraLab/MAGeTbrain), a multi-atlas approach that improves segmentation over regular atlas-based approaches [81]. Our focus on the hippocampus was related to the research question of the relationship between variations in insulin resistance, memory and eating behavior in adolescents [18]. MAGeT-Brain minimizes the number of input atlases needed by creating a template library from a sample of the subject images, differently from the voxel-based morphometry (VMB), which is performed by first spatially normalizing all subjects into a common atlas space [82, 83]. Using MAGeT-Brain, volumes for the hippocampus and its subfields (total hippocampal volume, CA4 and DG, CA2 and CA3, CA1, subiculum and *stratum radiatum, lacunosum and moleculare*, right and left) were extracted for each participant for statistical comparisons (please see statistical analysis section below).

While the structural analysis was focused on the hippocampus to be aligned with the rationale of the study, a whole brain analysis of the functional responses to palatable food images seemed to be more interesting than focusing only on hippocampal functional responses. Therefore, for subject level analyses from fMRI, a general linear model (GLM) was used to estimate changes in brain region responses using four regressors: palatable food, healthy food, and non-food object images and baseline periods (combined with an ideal homodynamic response curve). A two-level hierarchical model was conducted using multiple

regression model analyses in which the HOMA-IR index was used as a predictor. Whole-brain analysis was conducted to identify the brain areas responses to the presentation of images of hyperpalatable food, healthy food, and non-food objects. Correlations between the HOMA-IR index and brain activation were performed with a family-wise error (FWE) correction for multiple comparisons (pFWEcorr<0.05), using the HOMA-IR index as a continuous variable. In an attempt to disentangle the effect of HOMA-IR from BMI differences, we repeated the analysis using zBMI as the predictor, and residualized HOMA-IR (after removing the shared variance with BMI). All t-maps were calculated for the entire cortical volume. We used XJVIEW 8.14 software (http://www.alivelearn.net/xjview/) to display anatomical locations.

2.3 Statistical analyses

Analysis using GPower (GPower Version 3.1.9.2) showed that we could detect an association of moderate effect size (f2=0.15) in our models with a power of 80%. We used Levene's test to evaluate homogeneity of variances. Descriptive statistics are shown in mean ± standard deviation (continuous variables) or percentages (categorical variables). Linear regression analysis was performed to evaluate the main effect of HOMA-IR on the volumes of hippocampal subfields, adjusted by sex and the total brain volume. For the behavioral outcomes, linear regression analysis to evaluate the main effect of HOMA-IR on food preference and feeding behavior were adjusted by sex. When involving memory outcomes between the two time points, ANOVAs were adjusted by sex, age, time between visits and verbal fluency (comparison between participants who chose vs. did not choose their own snack were compared on insulin, HOMA-IR, glucose and BMI z scores).

In order to compare baseline characteristics and metabolic outcomes between groups according to birth weight (SGA or AGA), we used Pearson Chi-squared and Student's T tests. Linear regression analysis to evaluate the main effect of birth status (SGA or AGA) on food preference and feeding behavior were adjusted by sex, and also the interaction between birth weight status and HOMA-IR on the same outcomes, followed by post-hoc simple slope analysis when indicated. Statistical significance was set at p<0.05.

3. Results

3.1 Sample characteristics

The sample was composed by 21 males and 31 females (59.6% females), 63.5% Caucasian ancestry, at a mean age of 17±2 years, mean IQ of 123.0±24.7 (WASI total) and phonemic and semantic verbal fluency of 42.3±10.7 (number of valid words NEUPSILIN-INF). Participants were mostly from socioeconomic classes B and C (medium SES, 65.4% of the participants). The mean time between the two visits was 6.6±2.4 months. Fifty-one subjects completed the entire snack choice test, while one participant did not answer the question about the snack's spatial arrangement.

3.2 Structural and functional MRI

Table 1 describes the main effects of HOMA-IR on hippocampal total and subfields volumes. There was no statistically significant association between HOMA-IR and total

hippocampal volumes, as well as most of its subfields. However, HOMA-IR was statistically significantly associated with right CA4 and dentate gyrus volume (Table 1).

When analyzing eligible participants for fMRI acquisition, we found a negative correlation between the HOMA-IR index and the activation of the left middle temporal gyrus, left middle frontal gyrus, left superior and inferior frontal gyrus, as well as the right precuneus (Figure 2B) using the contrast "images of palatable foods *versus* non-food objects". In addition, we observed a positive correlation between the HOMA-IR index and activation of the right cuneus and left superior occipital gyrus. Details of the activated areas and anatomical location in the different contrasts are listed in Supplemental table 1. When we evaluated the contrast "images of palatable *versus* healthy foods", there was a significant negative correlation between the HOMA-IR index and activation in the right precentral and postcentral gyrus and right superior frontal gyrus. Moreover, we found a positive correlation between the HOMA-IR index and activation in the right cuneus (Supplemental table 1). The same activated areas were also observed for the zBMI score and residual HOMA-IR.

3.2 Food choices and feeding behavior

Table 2 demonstrates that there were no statistically significant main effects of HOMA-IR on feeding behavior (DEBQ), total calories, percentage of calories derived from carbohydrates, fats and proteins of the snack they chose at the research centre's cafeteria. However, higher HOMA-IR values were significantly associated with lower snack caloric density (Table 2). Increased insulinemia [$F(1,50)=4.193$, $p=0.046$] and increased HOMA-IR index [$F(1,50)=4.405$, $p=0.041$] were seen in participants who did not choose their first original snack as compared to those who chose their own snack (Figure 2). The two groups did not differ in other variables such as z score BMI [chose own snack 0.29 ± 1.15 kg/m2, chose other snack 0.86+1.17, $F(1,50)=1.407$, $p=0.242$] or glycemia [chose own snack 83.06 ± 6.66 mg/dl, chose other snack 84.87 ± 7.61, $F(1,50)=1.133$, $p=0.293$].

3.3 Associations with birth status (main effects of SGA/AGA and interactions with HOMA-IR)

From the 52 subjects, 34 (65.4%) were classified as AGA, 15 (28.8%) were classified as SGA and 3 (5.8%) had no birth weight data available. The mean gestational age was similar between AGA and SGA adolescents (AGA 38.3 ± 2.6 weeks gestation, SGA 39.6 ± 1.2 weeks gestation, Student's T Test $p=0.07$). There were no statistically significant differences regarding baseline characteristics such as sex, age, verbal fluency, intelligence quotient, ethnicity, maternal education or socioeconomic status between AGA and SGA groups (Supplemental Table 2). They also did not differ in terms of BMI, BMI z-score, glucose, insulin or HOMA-IR index levels. The only difference observed between the groups was related to the weight at birth, as expected (Supplemental Table 2).

Table 3 demonstrates that there were no statistically significant main effects of birth weight status on feeding behavior (DEBQ), total calories, percentage of calories derived from carbohydrates, fats and proteins of the snack they chose at the research centre's cafeteria. However, being born SGA was significantly associated with higher snack caloric density (Table 3). Participants classified as SGA chose with less frequency their own snack based on the snack's spatial arrangement in comparison to participants classified as AGA (Own snack based on special arrangement, SGA = 40%, AGA =80%, $\chi2=1.051$, $p=0.01$). There were no differences in choice based on food composition (Own snack SGA = 80%, AGA =64.7%,

$\chi 2$=1.146, p=0.336). Moreover, there is a statistically significant interaction effect between the HOMA-IR index and the BWR on external eating behavior, in which in SGA individuals, a higher HOMA-IR is associated with increased external eating (although the simple slope fails to reach significance, B=0.469, p=0.07). There is no association between HOMA-IR and external eating in AGA individuals (simple slope B= - 0.293, p=0.09).

4. Discussion

In this study we found that (1) diminished insulin sensitivity was correlated with activation in areas of visual attention and inactivation in areas associated with inhibitory control in healthy adolescents, when presented with images of hyperpalatable food contrasted with non-food objects. Insulin sensitivity was also associated with less consistency regarding implicit memory related to a consumed meal. Furthermore, (2) subjects who were born SGA showed implicit food memory inconsistency, and their external eating behavior was directly related to their insulin sensitivity.

When presented with images of palatable food contrasted with non-food objects, a higher insulin resistance index associated with lower palatable food activation in brain regions that influence inhibitory control, stimulus-driven attentional control and self-regulation [84-86]. Furthermore, as the insulin resistance index increased, there was higher activation in the cuneus, an area implicated in visual processing, valuation, and that influences the saliency of cues during decision-making [87]. This suggests that subjects who exhibited increased HOMA-IR index scores were more susceptible to tempting food cues [86] and they were more likely to identify palatable food cues as visually salient and rewarding [88]. When facing palatable food compared to healthy food images, the participants with higher insulin resistance index scores showed lower activation in sensorimotor areas related to the saliency of food cues and eating behavior [87], and they also demonstrated higher activation in the cuneus, reinforcing the hypothesis that subjects with increased HOMA-IR index scores had altered value and saliency to food. We also observed that HOMA-IR was associated with the volume of right CA4 and DG, and hippocampal subregion particularly sensitive to the damaging effects of early life adversity [89]. The results were very similar when using z-BMI or residualized HOMA-IR, suggesting that it is difficult to disentangle the effects of insulin resistance from obesity, at least at this young age.

Interestingly, individuals who did not choose their own snack had increased insulinemia and decreased insulin sensitivity. This behavioral outcome is in agreement with the imaging data, as poor insulin sensitivity associated with altered brain activation when presented with images of palatable food and there was modified attentional control to food cues. The altered implicit learned food preference in participants with decreased insulin sensitivity is interpreted as these individuals showing impaired food habituation, which is a memory phenomenon, that may be involved in the development of obesity [90, 91]. Altered stability in feeding patterns is associated with poor food choices, increased energy intake and greater weight gain [92, 93], probably because food choices are influenced by external cues, without attention to the individual's current state of satiety or hunger. Therefore, implicit food memory impairment seems to be an early behavioral sign associated with changes in insulin sensitivity and, most importantly, precedes obesity [94]. Impaired implicit food memory may contribute to increased food intake [2, 95], leading to overeating, obesity and higher insulin resistance in the long-term, supporting the "vicious cycle" model proposed by

Martin & Davidson [96]. Our findings are also in agreement to studies showing that deficits in episodic memory are related to uncontrolled eating [97]. It has been shown that females with obesity have significantly poorer performance on source memory for both food and non-food cues than females with healthy weight [98], which is aligned to the suboptimal food-related decision theoretical model and to our results.

Anthropometric and biochemical measures in participants classified as SGA were not significantly different from participants classified as AGA, and this is likely due to the young age of the participants involved. We did find though that participants classified as SGA chose a snack with a higher caloric density than participants classified as AGA, suggesting that SGA subjects are at greater risk to develop obesity over time. A higher HOMA index score in SGA participants was also associated with increased external eating behavior. Individuals with a high external eating trait have an increased sensitivity to external reward cues and they have a reduced capacity to regulate their cognitive responses to food, showing a tendency to exhibit impulsive behavior when exposed to food-related motivational stimuli [99]. These results are in agreement with human studies and animal models that showed that food restricted subjects consume more food and are more impulsive eaters especially when presented with high-carbohydrate or high-fat foods [29, 30, 32, 34, 35, 38, 39, 77, 100, 101]. Insulin has traditionally been considered an important signaling molecule in regulating energy homeostasis and feeding behavior. Impaired insulin sensitivity associates with overeating and impairments in regulating food intake. Interestingly, binge eating behavior, besides being caused by psychological reasons is also influenced by increases and decreases in blood glucose levels following the consumption of carbohydrate rich foods [102]. Our findings are in accordance with the “thrifty phenotype” hypothesis wherein low birth weight is associated with long-term insulin resistance and this phenomenon is adaptive as long as food supplies remain scarce. In an environment where food supplies are abundant though, insulin resistance becomes a risk factor for the development of metabolic syndrome [27, 38].

Furthermore, individuals born small for gestational age were more likely not to choose the same snack consumed months earlier when the spatial arrangement was modified. This finding implies that these SGA individuals had an impaired memory related to a visual food cue and this may be related to altered eating behavior. Food variety, including variety in visual cues, affects palatability and energy intake [103-106] and not having a pattern in food plating may be one of the reasons for the increased consumption of food observed in individuals born SGA. The relevance of food arrangement has been previously demonstrated, indicating that individuals "eat first with their eyes", and they are willing to pay more for certain foods, to increase their liking for certain foods, to increase their intent to eat more of these foods when these foods are presented in a visually more appealing manner [107-109]. Meal layout planning also helps to decide on the kind and quantity of food to be eaten and is an adequate dietary intervention to reduce metabolic risk factors, including the glycemic index [110-112]. Besides that, implicit learned food preferences can contribute to susceptibility to metabolic syndrome if valenced attitudes toward foods are developed [71]. Displaying healthy foods in a more varied and attractive way or helping in the formation of a more rigid pattern of plating using implicit valenced cues, especially for palatable foods,

The hippocampus is suggested to be a discriminatory retention brain region for food cues and memories related to eating [5, 113]. Furthermore, the inhibitory control of food intake and appetitive behavior depends on the functional integrity and structure of the hippocampus, thus this region is associated with what, when and how much to eat [114,

115]. Considering that being born SGA persistently modifies insulin sensitivity from birth [20, 27] the relationships between HOMA-IR and hippocampal function and structure reported here may explain the altered feeding habits, impaired food memory (no platting pattern) and poor inhibitory control (higher intake and external eating related to insulin resistance) found in SGA individuals compared to individuals born AGA.

Insulin modulates feeding behavior through alterations in different brain circuitries. Insulin sensitivity correlates with the activity of dopaminergic neurons [116] and modulates feeding preferences in mesocorticolimbic pathways [117]. Insulin signaling also has been found to regulate dopamine neurotransmission, working together to orchestrate both the motivation to engage in consummatory behavior and to calibrate the associated level of reward [118], and these mechanisms could be playing a role in the described findings. Moreover, the hippocampus is involved in explicit food-related memory acquisition and recall, in the internal perception of satiety, in estimating time and meal length, in cued-food associations learning and in the control of stress-related eating [4], which are potential effects modified by insulin function in this structure. The difference in time (6 months) between lab visits [119, 120] and the type of food presentation (actual food versus photos of food items) [121] between the two lab visits should be taken into account when interpreting these results.

Our main limitation is the small sample size, which may affect our ability to detect differences between the groups. Future investigations using a larger sample size and other neuro-endocrine and eating related behavioral measures are necessary to further support our findings. The use of HOMA-IR as a marker of insulin sensitivity has also some limitations, as an OGTT-derived index of insulin sensitivity or an euglycemic hyperinsulinemic clamp would have been more robust measurements [122]. One of the strengths of this study was our ability to introduce a behavioral measure that could distinguish between individual variations in the HOMA-IR index and insulinemia. Previous behavioral studies about eating investigated hindbrain and midbrain circuits involved in the homeostatic and hedonic control of food intake [123, 124]. Our study demonstrated an altered mechanism that controls a cognitively related aspect of food intake, that is poorly explored in adolescents and had not been previously studied in individuals born SGA.

In conclusion, our work has contributed to highlight a mechanism involved in risky feeding behavior that could be associated with the development of obesity and metabolic syndrome. This mechanism is associated with insulin sensitivity and implicit food memory. Our findings also suggest a possible role for insulin sensitivity and the hippocampus in modulating feeding behavior in individuals born small for gestational age. Considering the significant incidence rates of intrauterine growth restriction found across many countries, furthering our understanding of the altered neurobiology associated with being born small for gestational age will help in the development of intervention and management programs that can improve risky eating behavioral patterns in this vulnerable population.

5. Acknowledgements

We thank the participants for their time and support. The authors report no conflicts of interest related to this work. The current study was supported by the National Council for Technological and Scientific Development (CNPq) (PPS, 478820/2010), Research and Event Incentive Fund of Hospital de Clínicas de Porto Alegre (FIPE/HCPA) (12-0254), Foundation for the Coordination of Higher Education and Graduate Training (CAPES), Canadian

Institutes of Health Research (CIHR, PJT-166066, PI Silveira PP) and the JPB Foundation through a grant to the JPB Research Network on Toxic Stress: A Project of the Center on the Developing Child at Harvard University. Sources of financial support played no role in the design and analysis of this study or in the writing of this manuscript.

ABM, GGM and PPS were responsible for the study concept and design. ABM, RDM, DMR, TDM, RSR, RT, GAS and AB contributed to the acquisition of clinical data. ARF, AB, PMM, BB and MN assisted with MRI data acquisition and/or analysis. MA contributed to the statistical analysis of the study. ABM and PMM drafted the manuscript and GGM, PPS and MJM provided critical revisions on the manuscript for important intellectual content. All authors critically reviewed and approved the final version of the manuscript.

1. Brunstrom, J.M., et al., *Episodic memory and appetite regulation in humans.* PLoS One, 2012. **7**(12): p. e50707.
2. Parent, M.B., J.N. Darling, and Y.O. Henderson, *Remembering to eat: hippocampal regulation of meal onset.* Am J Physiol Regul Integr Comp Physiol, 2014. **306**(10): p. R701-13.
3. Wang, J.X., N.J. Cohen, and J.L. Voss, *Covert rapid action-memory simulation (CRAMS): a hypothesis of hippocampal-prefrontal interactions for adaptive behavior.* Neurobiol Learn Mem, 2015. **117**: p. 22-33.
4. Stevenson, R.J. and H.M. Francis, *The hippocampus and the regulation of human food intake.* Psychol Bull, 2017. **143**(10): p. 1011-1032.
5. Davidson, T.L., et al., *A potential role for the hippocampus in energy intake and body weight regulation.* Curr Opin Pharmacol, 2007. **7**(6): p. 613-6.
6. Davidson, T.L., et al., *Memory inhibition and energy regulation.* Physiol Behav, 2005. **86**(5): p. 731-46.
7. Kanoski, S.E. and H.J. Grill, *Hippocampus Contributions to Food Intake Control: Mnemonic, Neuroanatomical, and Endocrine Mechanisms.* Biol Psychiatry, 2017. **81**(9): p. 748-756.
8. De Felice, F.G. and C. Benedict, *A Key Role of Insulin Receptors in Memory.* Diabetes, 2015. **64**(11): p. 3653-5.
9. Bomfim, T.R., et al., *An anti-diabetes agent protects the mouse brain from defective insulin signaling caused by Alzheimer's disease- associated Abeta oligomers.* J Clin Invest, 2012. **122**(4): p. 1339-53.
10. Benedict, C., et al., *Impaired insulin sensitivity as indexed by the HOMA score is associated with deficits in verbal fluency and temporal lobe gray matter volume in the elderly.* Diabetes Care, 2012. **35**(3): p. 488-94.
11. Hari Dass, S.A., et al., *A biologically-informed polygenic score identifies endophenotypes and clinical conditions associated with the insulin receptor function on specific brain regions.* EBioMedicine, 2019. **42**: p. 188-202.
12. Avena, N.M., P. Rada, and B.G. Hoebel, *Evidence for sugar addiction: Behavioral and neurochemical effects of intermittent, excessive sugar intake.* Neuroscience and Biobehavioral Reviews, 2008. **32**(1): p. 20-39.
13. Hargrave, S.L., S. Jones, and T.L. Davidson, *The Outward Spiral: A vicious cycle model of obesity and cognitive dysfunction.* Curr Opin Behav Sci, 2016. **9**: p. 40-46.
14. Pelchat, M.L., et al., *Images of desire: food-craving activation during fMRI.* Neuroimage, 2004. **23**(4): p. 1486-93.
15. Wallner-Liebmann, S., et al., *Insulin and hippocampus activation in response to images of high-calorie food in normal weight and obese adolescents.* Obesity (Silver Spring), 2010. **18**(8): p. 1552-7.
16. Kullmann, S., et al., *Functional network connectivity underlying food processing: disturbed salience and visual processing in overweight and obese adults.* Cereb Cortex, 2013. **23**(5): p. 1247-56.
17. van der Laan, L.N., et al., *The first taste is always with the eyes: a meta-analysis on the neural correlates of processing visual food cues.* Neuroimage, 2011. **55**(1): p. 296-303.
18. Mucellini, A.B., et al., *Hippocampal insulin resistance and altered food decision-making as players on obesity risk.* Neurosci Biobehav Rev, 2017. **77**: p. 165-176.
19. Soto, N., et al., *Insulin sensitivity and secretion are related to catch-up growth in small-for-gestational-age infants at age 1 year: results from a prospective cohort.* J Clin Endocrinol Metab, 2003. **88**(8): p. 3645-50.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

20. Silveira, P.P., et al., *Birth weight and catch up growth are associated with childhood impulsivity in two independent cohorts.* Sci Rep, 2018. **8**(1): p. 13705.
21. Barker, D.J., *The fetal origins of type 2 diabetes mellitus.* Ann Intern Med, 1999. **130**(4 Pt 1): p. 322-4.
22. Barker, D.J., *The developmental origins of insulin resistance.* Horm Res, 2005. **64 Suppl 3**: p. 2-7.
23. Barker, D.J., et al., *Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth.* Diabetologia, 1993. **36**(1): p. 62-7.
24. Boehmer, B.H., S.W. Limesand, and P.J. Rozance, *The impact of IUGR on pancreatic islet development and beta-cell function.* J Endocrinol, 2017. **235**(2): p. R63-R76.
25. Gatford, K.L. and R.A. Simmons, *Prenatal programming of insulin secretion in intrauterine growth restriction.* Clin Obstet Gynecol, 2013. **56**(3): p. 520-8.
26. Gatford, K.L., et al., *Review: Placental programming of postnatal diabetes and impaired insulin action after IUGR.* Placenta, 2010. **31 Suppl**: p. S60-5.
27. Hales, C.N. and D.J. Barker, *Type 2 (non-insulin-dependent) diabetes mellitus: the thrifty phenotype hypothesis.* Diabetologia, 1992. **35**(7): p. 595-601.
28. Ayres, C., et al., *Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants.* Int J Pediatr, 2012. **2012**: p. 657379.
29. Barbieri, M.A., et al., *Severe intrauterine growth restriction is associated with higher spontaneous carbohydrate intake in young women.* Pediatr Res, 2009. **65**(2): p. 215-20.
30. Crume, T.L., et al., *The long-term impact of intrauterine growth restriction in a diverse U.S. cohort of children: the EPOCH study.* Obesity (Silver Spring), 2014. **22**(2): p. 608-15.
31. Dalle Molle, R. and P.P. Silveira, *Small for gestational age children have specific food preferences.* J Pediatr, 2015. **166**(6): p. 1547.
32. Kaseva, N., et al., *Diet and nutrient intake in young adults born preterm at very low birth weight.* J Pediatr, 2013. **163**(1): p. 43-8.
33. Laureano, D.P., et al., *Intrauterine growth restriction modifies the hedonic response to sweet taste in newborn pups – Role of the accumbal μ-opioid receptors.* Neuroscience, 2016. **322**: p. 500-508.
34. Lussana, F., et al., *Prenatal exposure to the Dutch famine is associated with a preference for fatty foods and a more atherogenic lipid profile.* Am J Clin Nutr, 2008. **88**(6): p. 1648-52.
35. Perala, M.M., et al., *Body size at birth is associated with food and nutrient intake in adulthood.* PLoS One, 2012. **7**(9): p. e46139.
36. Portella, A.K., et al., *Effects of in utero conditions on adult feeding preferences.* J Dev Orig Health Dis, 2012. **3**(3): p. 140-52.
37. Rotstein, M., et al., *Facial Expression in Response to Smell and Taste Stimuli in Small and Appropriate for Gestational Age Newborns.* J Child Neurol, 2015. **30**(11): p. 1466-71.
38. Silveira, P.P., et al., *Preliminary evidence for an impulsivity-based thrifty eating phenotype.* Pediatr Res, 2012. **71**(3): p. 293-8.
39. Stein, A.D., et al., *Associations of gestational exposure to famine with energy balance and macronutrient density of the diet at age 58 years differ according to the reference population used.* J Nutr, 2009. **139**(8): p. 1555-61.
40. Allen, M.C., *Developmental outcome and followup of the small for gestational age infant.* Semin Perinatol, 1984. **8**(2): p. 123-56.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

41. Bickle Graz, M., J.F. Tolsa, and C.J. Fischer Fumeaux, *Being Small for Gestational Age: Does it Matter for the Neurodevelopment of Premature Infants? A Cohort Study.* PLoS One, 2015. **10**(5): p. e0125769.
42. Chaudhari, S., et al., *Pune low birth weight study - birth to adulthood - cognitive development.* Indian Pediatr, 2013. **50**(9): p. 853-7.
43. El Ayoubi, M., et al., *Impact of fetal growth restriction on neurodevelopmental outcome at 2 years for extremely preterm infants: a single institution study.* Dev Med Child Neurol, 2016. **58**(12): p. 1249-1256.
44. Geva, R., et al., *Neuropsychological outcome of children with intrauterine growth restriction: a 9-year prospective study.* Pediatrics, 2006. **118**(1): p. 91-100.
45. Grantham-McGregor, S.M., *Small for gestational age, term babies, in the first six years of life.* Eur J Clin Nutr, 1998. **52 Suppl 1**: p. S59-64.
46. Guellec, I., et al., *Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction.* Pediatrics, 2011. **127**(4): p. e883-91.
47. Kutschera, J., et al., *[Small for gestational age - Somatic, neurological and cognitive development until adulthood].* Z Geburtshilfe Neonatol, 2002. **206**(2): p. 65-71.
48. Martorell, R., et al., *Intrauterine growth retardation, body size, body composition and physical performance in adolescence.* Eur J Clin Nutr, 1998. **52 Suppl 1**: p. S43-52; discussion S52-3.
49. Morsing, E., et al., *Cognitive function after intrauterine growth restriction and very preterm birth.* Pediatrics, 2011. **127**(4): p. e874-82.
50. Starcevic, M., et al., *Early functional and morphological brain disturbances in late-onset intrauterine growth restriction.* Early Hum Dev, 2016. **93**: p. 33-8.
51. Abernethy, L.J., et al., *Magnetic resonance imaging and T2 relaxometry of cerebral white matter and hippocampus in children born preterm.* Pediatr Res, 2003. **54**(6): p. 868-74.
52. Camprubi Camprubi, M., et al., *Learning and memory disabilities in IUGR babies: Functional and molecular analysis in a rat model.* Brain Behav, 2017. **7**(3): p. e00631.
53. de Bie, H.M., et al., *Using fMRI to Investigate Memory in Young Children Born Small for Gestational Age.* PLoS One, 2015. **10**(7): p. e0129721.
54. Gimenez, M., et al., *Hippocampal gray matter reduction associates with memory deficits in adolescents with history of prematurity.* Neuroimage, 2004. **23**(3): p. 869-77.
55. Isaacs, E.B., et al., *Brain morphometry and IQ measurements in preterm children.* Brain, 2004. **127**(Pt 12): p. 2595-607.
56. Isaacs, E.B., et al., *Hippocampal volume and everyday memory in children of very low birth weight.* Pediatr Res, 2000. **47**(6): p. 713-20.
57. Leitner, Y., et al., *Deficits in spatial orientation of children with intrauterine growth retardation.* Brain Res Bull, 2005. **67**(1-2): p. 13-8.
58. Cintra, L., et al., *Effects of protein undernutrition on the dentate gyrus in rats of three age groups.* Brain Res, 1990. **532**(1-2): p. 271-7.
59. Debassio, W.A., et al., *Prenatal malnutrition effect on pyramidal and granule cell generation in the hippocampal formation.* Brain Res Bull, 1994. **35**(1): p. 57-61.
60. Kuchna, I., *Quantitative studies of human newborns' hippocampal pyramidal cells after perinatal hypoxia.* Folia Neuropathol, 1994. **32**(1): p. 9-16.
61. Lodygensky, G.A., et al., *Intrauterine growth restriction affects the preterm infant's hippocampus.* Pediatr Res, 2008. **63**(4): p. 438-43.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

62. Schmidt-Kastner, R. and T.F. Freund, *Selective vulnerability of the hippocampus in brain ischemia.* Neuroscience, 1991. **40**(3): p. 599-636.
63. Sizonenko, S.V., et al., *Impact of intrauterine growth restriction and glucocorticoids on brain development: insights using advanced magnetic resonance imaging.* Mol Cell Endocrinol, 2006. **254-255**: p. 163-71.
64. Docteur, A., et al., *Implicit and explicit memory bias for words related to food, shape and body parts in obese and normal weight females.* Current psychology letters, 2008(Vol. 24, Issue 2, 2008).
65. Xu, Y., et al., *Decreased insulin sensitivity and abnormal glucose metabolism start in preadolescence in low-birth-weight children—Meta-analysis and systematic review.* Primary Care Diabetes, 2019. **13**(5): p. 391-398.
66. Dorner, G. and A. Plagemann, *Perinatal hyperinsulinism as possible predisposing factor for diabetes mellitus, obesity and enhanced cardiovascular risk in later life.* Horm Metab Res, 1994. **26**(5): p. 213-21.
67. Salum, G.A., et al., *The multidimensional evaluation and treatment of anxiety in children and adolescents: rationale, design, methods and preliminary findings.* Braz J Psychiatry, 2011. **33**(2): p. 181-95.
68. Koekkoek, P.S., et al., *Cognitive function in patients with diabetes mellitus: guidance for daily care.* Lancet Neurol, 2015. **14**(3): p. 329-40.
69. Miranda, M.C., et al., *Neupsilin-Inf em um Modelo de Avaliação Neuropsicológica Breve para Centros de Saúde.* Psico-USF, 2018. **23**(1): p. 95-108.
70. Pedreira, C.E., et al., *Birth weight patterns by gestational age in Brazil.* An Acad Bras Cienc, 2011. **83**(2): p. 619-25.
71. Legget, K.T., et al., *Harnessing the power of disgust: a randomized trial to reduce high-calorie food appeal through implicit priming.* Am J Clin Nutr, 2015. **102**(2): p. 249-55.
72. Parma, V., et al., *Selecting food. The contribution of memory, liking, and action.* Appetite, 2014. **76**: p. 186-96.
73. Köster, E.P., *Diversity in the determinants of food choice: A psychological perspective.* Food Quality and Preference, 2009. **20**(2): p. 70-82.
74. USDA. *USDA National Nutrient Database for Standard Reference*. 2013.
75. van Strien T, F.J., Bergers GPA, Defares PB, *The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior.* Int J Eat Disord, 1986. **5**(2): p. 295–315.
76. Viana V, L.S., *Estilo alimentar: adaptação e validação do questionário holandês do comportamento alimentar.* Psicol Teor Investig e Prática, 2003. **XXVI**(1): p. 59–71.
77. Reis, R.S., et al., *Impulsivity-based thrifty eating phenotype and the protective role of n-3 PUFAs intake in adolescents.* Transl Psychiatry, 2016. **6**: p. e755.
78. Page, K.A., et al., *Circulating glucose levels modulate neural control of desire for high-calorie foods in humans.* J Clin Invest, 2011. **121**(10): p. 4161-9.
79. Deluchi, M., et al., *Attentional bias to unhealthy food in individuals with severe obesity and binge eating.* Appetite, 2017. **108**: p. 471-476.
80. Lang P, B.M., Cuthbert B, *International affective picture system (IAPS): Affective ratings of pictures and instruction manual.* Technical Report A-8, 2008.
81. Pipitone, J., et al., *Multi-atlas segmentation of the whole hippocampus and subfields using multiple automatically generated templates.* Neuroimage, 2014. **101**: p. 494-512.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

82. de Flores, R., R. La Joie, and G. Chetelat, *Structural imaging of hippocampal subfields in healthy aging and Alzheimer's disease.* Neuroscience, 2015. **309**: p. 29-50.
83. Min, R., et al., *Multi-atlas based representations for Alzheimer's disease diagnosis.* Hum Brain Mapp, 2014. **35**(10): p. 5052-70.
84. Behary, P. and A.D. Miras, *Brain responses to food and weight loss.* Exp Physiol, 2014. **99**(9): p. 1121-7.
85. McCaffery, J.M., et al., *Differential functional magnetic resonance imaging response to food pictures in successful weight-loss maintainers relative to normal-weight and obese controls.* Am J Clin Nutr, 2009. **90**(4): p. 928-34.
86. van Meer, F., et al., *Developmental differences in the brain response to unhealthy food cues: an fMRI study of children and adults.* Am J Clin Nutr, 2016. **104**(6): p. 1515-1522.
87. Litt, A., et al., *Dissociating valuation and saliency signals during decision-making.* Cereb Cortex, 2011. **21**(1): p. 95-102.
88. Rodrigues, D.M., et al., *Decreased comfort food intake and allostatic load in adolescents carrying the A3669G variant of the glucocorticoid receptor gene.* Appetite, 2017. **116**: p. 21-28.
89. Teicher, M.H., C.M. Anderson, and A. Polcari, *Childhood maltreatment is associated with reduced volume in the hippocampal subfields CA3, dentate gyrus, and subiculum.* Proceedings of the National Academy of Sciences, 2012. **109**(9): p. E563-E572.
90. Epstein, L.H., et al., *Food reinforcement, delay discounting and obesity.* Physiol Behav, 2010. **100**(5): p. 438-45.
91. Raynor, H.A., et al., *Amount of food group variety consumed in the diet and long-term weight loss maintenance.* Obes Res, 2005. **13**(5): p. 883-90.
92. McCrory, M.A., et al., *Dietary variety within food groups: association with energy intake and body fatness in men and women.* Am J Clin Nutr, 1999. **69**(3): p. 440-7.
93. Raynor, H.A. and L.H. Epstein, *Dietary variety, energy regulation, and obesity.* Psychol Bull, 2001. **127**(3): p. 325-41.
94. Kullmann, S., et al., *The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity.* Hum Brain Mapp, 2012. **33**(5): p. 1052-61.
95. Davidson, T.L., et al., *Inter-relationships among diet, obesity and hippocampal-dependent cognitive function.* Neuroscience, 2013. **253**: p. 110-22.
96. Martin, A.A. and T.L. Davidson, *Human cognitive function and the obesogenic environment.* Physiol Behav, 2014. **136**: p. 185-93.
97. Martin, A.A., T.L. Davidson, and M.A. McCrory, *Deficits in episodic memory are related to uncontrolled eating in a sample of healthy adults.* Appetite, 2018. **124**: p. 33-42.
98. Leng, X., et al., *Episodic memory for food and non-food cues in females with obesity.* Eat Behav, 2021. **40**: p. 101472.
99. Hou, R., et al., *External eating, impulsivity and attentional bias to food cues.* Appetite, 2011. **56**(2): p. 424-7.
100. Dalle Molle, R., et al., *Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats.* Brain Res, 2015. **1618**: p. 41-9.
101. Reis, R.S., et al., *Poor infant inhibitory control predicts food fussiness in childhood - A possible protective role of n-3 PUFAs for vulnerable children.* Prostaglandins Leukot Essent Fatty Acids, 2015. **97**: p. 21-5.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

102. Herpertz, S., et al., *Relationship of weight and eating disorders in type 2 diabetic patients: a multicenter study.* Int J Eat Disord, 2000. **28**(1): p. 68-77.
103. Friis, R., et al., *Comparison of three nudge interventions (priming, default option, and perceived variety) to promote vegetable consumption in a self-service buffet setting.* PLoS One, 2017. **12**(5): p. e0176028.
104. Kongsbak, I., et al., *Increasing fruit and vegetable intake among male university students in an ad libitum buffet setting: A choice architectural nudge intervention.* Food Quality and Preference, 2016. **49**: p. 183-188.
105. Wadhera, D. and E.D. Capaldi-Phillips, *A review of visual cues associated with food on food acceptance and consumption.* Eat Behav, 2014. **15**(1): p. 132-43.
106. Zampollo, F., et al., *Food plating preferences of children: the importance of presentation on desire for diversity.* Acta Paediatr, 2012. **101**(1): p. 61-6.
107. Cavazza, N., M. Guidetti, and F. Butera, *Ingredients of gender-based stereotypes about food. Indirect influence of food type, portion size and presentation on gendered intentions to eat.* Appetite, 2015. **91**: p. 266-72.
108. Zellner, D.A., et al., *It tastes as good as it looks! The effect of food presentation on liking for the flavor of food.* Appetite, 2014. **77**: p. 31-5.
109. Zellner, D.A., et al., *Neatness counts. How plating affects liking for the taste of food.* Appetite, 2011. **57**(3): p. 642-8.
110. Camelon, K.M., et al., *The Plate Model: a visual method of teaching meal planning. DAIS Project Group. Diabetes Atherosclerosis Intervention Study.* J Am Diet Assoc, 1998. **98**(10): p. 1155-8.
111. Jayawardena, R., et al., *Effects of the "plate model" as part of dietary intervention on modification of selected cardiometabolic risk factors in post-myocardial infarction patients: study protocol for a randomized controlled trial.* Trials, 2017. **18**(1): p. 314.
112. Raidl, M., et al., *The healthy diabetes plate.* Prev Chronic Dis, 2007. **4**(1): p. A12.
113. Higgs, S., *Cognitive processing of food rewards.* Appetite, 2016. **104**: p. 10-7.
114. Hebben, N., et al., *Diminished ability to interpret and report internal states after bilateral medial temporal resection: case H.M.* Behav Neurosci, 1985. **99**(6): p. 1031-9.
115. Rozin, P., et al., *What Causes Humans to Begin and End a Meal? A Role for Memory for What Has Been Eaten, as Evidenced by a Study of Multiple Meal Eating in Amnesic Patients.* Psychological Science, 2016. **9**(5): p. 392-396.
116. Heni, M., et al., *Nasal insulin changes peripheral insulin sensitivity simultaneously with altered activity in homeostatic and reward-related human brain regions.* Diabetologia, 2012. **55**(6): p. 1773-82.
117. Portella, A.K., et al., *Litter size reduction alters insulin signaling in the ventral tegmental area and influences dopamine-related behaviors in adult rats.* Behav Brain Res, 2015. **278**: p. 66-73.
118. Daws, L.C., et al., *Insulin signaling and addiction.* Neuropharmacology, 2011. **61**(7): p. 1123-1128.
119. Epstein, L.H., et al., *Long-term habituation to food in obese and nonobese women.* The American Journal of Clinical Nutrition, 2011. **94**(2): p. 371-376.
120. Thrailkill, E.A., L.H. Epstein, and M.E. Bouton, *Effects of inter-food interval on the variety effect in an instrumental food-seeking task. Clarifying the role of habituation.* Appetite, 2015. **84**: p. 43-53.
121. Spence, C., et al., *Eating with our eyes: From visual hunger to digital satiation.* Brain and Cognition, 2016. **110**: p. 53-63.
122. Rebelos, E., et al., *Insulin Resistance Is Associated With Enhanced Brain Glucose Uptake During Euglycemic Hyperinsulinemia: A Large-Scale PET Cohort.* Diabetes Care, 2021. **44**(3): p. 788-794.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

123. Bischoff AR, D.R., Silveira PP, *Fetal Programming of Food Preferences and Feeding Behavior*, in *Diet, Nutrition, and Fetal Programming*. 2017, Springer International Publishing. p. 453–70.
124. Dalle Molle, R., et al., *The fetal programming of food preferences: current clinical and experimental evidence.* Journal of Developmental Origins of Health and Disease, 2015. **7**(3): p. 222-230.

Table 1. Association between HOMA-IR and the volume of the hippocampus and its subfields (mm^3).

Brain structure	Main effect HOMA-IR		
	β	*p*	95% CI
Right hippocampus	0.172	0.203	(-16.792; 76.234)
Left hippocampus	0.115	0.402	(-28.771; 70.171)
Right CA4 and DG	0.301	0.028	(1.516; 24.406)
Left CA4 and DG	0.232	0.075	(-1.280; 24.982)
Right CA2 and CA3	0.293	0.053	(-0.075; 10.002)
Left CA2 and CA3	0.302	0.064	(-0.361; 12.137)
Right CA1	0.110	0.453	(-10.933; 24.018)
Left CA1	-0.014	0.928	(-18.787; 17.170)
Right str. rad. l-m.	0.069	0.639	(-10.763; 17.313)
Left str. rad. l-m.	0.051	0.734	(-12.078; 16.993)
Right subiculum	0.065	0.587	(-5.345; 9.301)
Left subiculum	0.045	0.713	(-5.875; 8.500)

Linear regression adjusted for total brain volume and sex; DG: dentate gyrus; Str. rad. l-m: *stratum radiatum*, *lacunosum* and *moleculare*.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

Table 2. Association between HOMA-IR and feeding behavior (Dutch Eating Behavior Questionnaire) and analysis of the food choices during the Snack Test at the cafeteria.

Outcome	Main effect HOMA-IR		
	β	*p*	95% CI
Total Energy snack (kcal)	0.065	0.651	(-32.028; 50.768)
Energy from protein snack (%kcal)	-0.076	0.596	(-1.157; 0.672)
Energy from carbohydrate snack (%kcal)	-0.080	0.572	(-2.750; 1.536)
Energy from fat snack (%kcal)	0.165	0.238	(-0.666; 2.621)
Caloric density snack (kcal/g)	-0.310	0.028	(-0.172; -0.010)
DEBQ restrictive eating (score points)	0.243	0.072	(-0.168; 3.724)
DEBQ emotional eating (score points)	-0.183	0.183	(-3.691; 0.723)
DEBQ external eating (score points)	-0.080	0.575	(-1.515; 0.850)

Linear regression adjusted for sex.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

Table 3. Association between birth status (SGA/AGA) main effect as well as interaction with HOMA-IR on feeding behavior (Dutch Eating Behavior Questionnaire) and analysis of the food choices during the Snack Test at the cafeteria.

Outcome	Main effect of birth status (SGA=0, AGA=1)		
	β	*p*	95% CI
Total Energy snack (kcal)	0.132	0.371	(-76.012; 199.765)
Energy from protein snack (%kcal)	0.146	0.321	(-1.522; 4.545)
Energy from carbohydrate snack (%kcal)	-0.178	0.222	(-11.236; 2.680)
Energy from fat snack (%kcal)	0.156	0.284	(-2.442; 8.063)
Caloric density snack (kcal/g)	-0.303	0.036	(-0.538; -0.019)
DEBQ restrictive eating (score points)	-0.170	0.231	(-10.621; 2.630)
DEBQ emotional eating (score points)	0.031	0.830	(-6.675; 8.280)
DEBQ external eating (score points)	-0.133	0.367	(-5.753; 2.166)
	Interaction birth status * HOMA-IR		
	β	*p*	95% CI
Total Energy snack (kcal)	-0.167	0.730	(-131.931; 93.143)
Energy from protein snack (%kcal)	-0.152	0.753	(-2.875; 2.093)
Energy from carbohydrate snack (%kcal)	-0.434	0.361	(-8.228; 3.057)
Energy from fat snack (%kcal)	0.623	0.183	(-1.364; 6.952)
Caloric density snack (kcal/g)	-0.029	0.946	(-0.200; 0.187)
DEBQ restrictive eating (score points)	0.108	0.811	(-4.623; 5.876)
DEBQ emotional eating (score points)	-0.056	0.903	(-6.390; 5.660)
DEBQ external eating (score points)	-1.062	0.023	(-6.610; -0.507)

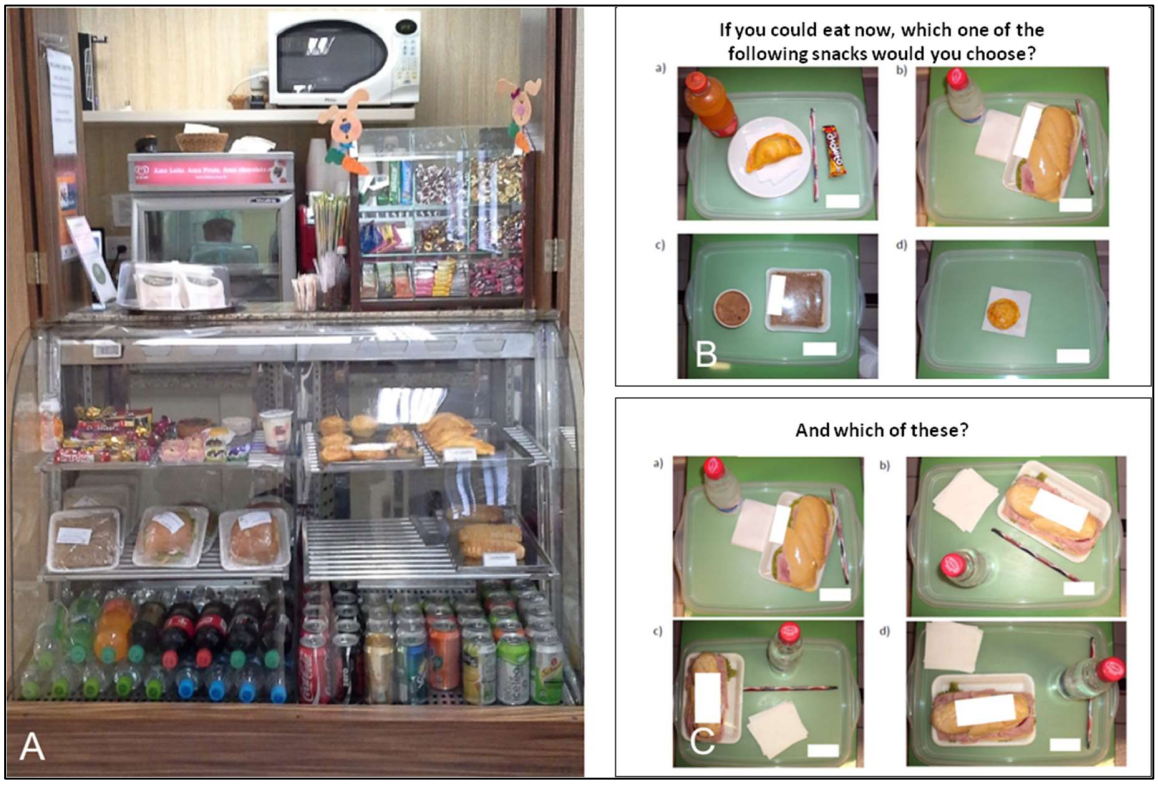
Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799

Figure legends

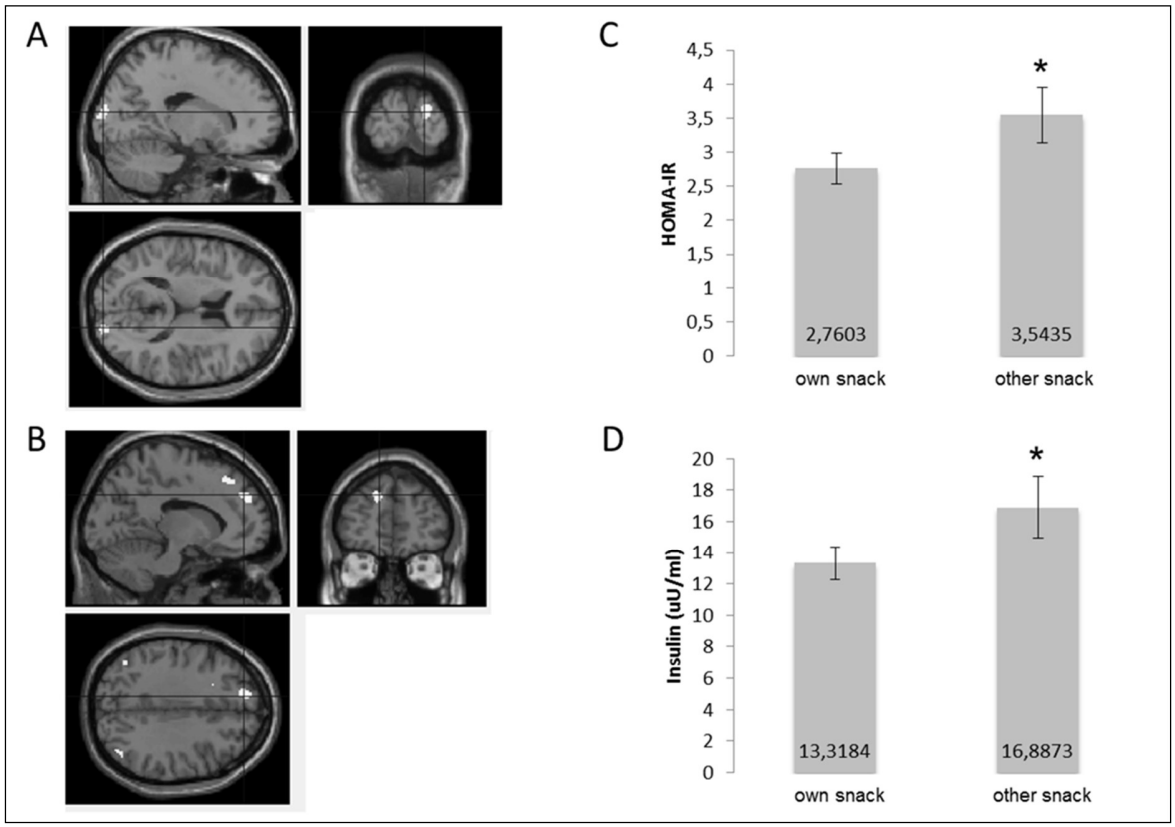
Figure 1. Research center's cafeteria. Individuals received an equal sum of money to choose and buy a snack (A). The snack was photographed and in the subsequent visit, participants were asked which snack they would choose at that moment. Choices for both composition (B) as well as spatial arrangement (C) were investigated. In both cases, one of the pictures was of the original snack chosen and eaten by the participant.

Figure 2. Main results in the whole sample. (A) Positive correlation between the HOMA-IR index and right cuneus activation when presented with the contrast "images of palatable *versus* healthy foods " (SPM multiple regression analyses using HOMA-IR as regressor, $p_{FWR\ corr}<0.001$); (B) Negative correlation between the HOMA-IR index and left middle frontal gyrus activation when presented with the contrast "images of palatable foods *versus* non-food objects" ($p_{FDR\ corr}=0.001$); (C) Participants who chose another snack had an increased HOMA-IR index (ANOVA, p=0.044) and (D) Plasma insulin (p=0.045) when compared to those individuals who chose their own snack.

Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799



Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799



Mucellini AB, Miguel PM, Dalle Molle R, Rodrigues DM, Machado TD, Reis RS, Toazza R, Salum GA, Bortoluzzi A, Franco AR, Buchweitz A, Barth B, Agranonik M, Nassim M, Meaney MJ, Manfro GG, Silveira PP. Diminished insulin sensitivity is associated with altered brain activation to food cues and with risk for obesity - Implications for individuals born small for gestational age. Appetite. 2022 Feb 1;169:105799. doi: 10.1016/j.appet.2021.105799