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Abstract: This study was aimed to examine if adolescent obesity is associated with alterations of insula function as indexed by differential correlations between insula activation and perception of interoceptive feedback versus external food cues. We hypothesized that, in healthy weight adolescents, insula activation will positively correlate with interoceptive sensitivity, whereas in excess weight adolescents, insula activation will positively correlate with sensitivity towards external cues. Fifty-four adolescents (age range 12-18), classified in two groups as a function of BMI, excess weight (n=22) and healthy weight (n=32), performed the Risky-Gains task (sensitive to insula function) inside an fMRI scanner, and completed the heartbeat perception task (measuring interoceptive sensitivity) and the Dutch Eating Behavior Questionnaire (measuring external eating as well as emotional eating and restraint) outside the scanner. We found that insula activation during the Risky-Gains task positively correlated with interoceptive sensitivity and negatively correlated with external eating in healthy weight adolescents. Conversely, in excess weight adolescents, insula activation positively correlated with external eating and negatively correlated with interoceptive sensitivity, arguably reflecting obesity related neurocognitive adaptations. In excess weight adolescents, external eating was also positively associated with caudate nucleus activation, and restrained eating was negatively associated with insula activation. Our findings suggest that adolescent obesity is associated with disrupted tuning of the insula system towards interoceptive input.

HIGHLIGHTS

- Insula activation negatively correlates with interoceptive sensitivity and positively correlates with external eating in adolescents with excess weight.
- Caudate nucleus activation positively correlates with external eating in adolescents with excess weight.
- In adolescents with overweight and obesity, the function of brain interoceptive and reward systems is not associated with perception of bodily feedback, and conversely correlates with maladaptive eating tendencies.

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TITLE

Insula tuning towards external eating versus interoceptive input in adolescents with overweight and obesity

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ABSTRACT

This study was aimed to examine if adolescent obesity is associated with alterations of insula function as indexed by differential correlations between insula activation and perception of interoceptive feedback versus external food cues. We hypothesized that, in healthy weight adolescents, insula activation will positively correlate with interoceptive sensitivity, whereas in excess weight adolescents, insula activation will positively correlate with sensitivity towards external cues. Fifty-four adolescents (age range 12-18), classified in two groups as a function of BMI, excess weight (n=22) and healthy weight (n=32), performed the Risky-Gains task (sensitive to insula function) inside an fMRI scanner, and completed the heartbeat perception task (measuring interoceptive sensitivity) and the Dutch Eating Behavior Questionnaire (measuring external eating as well as emotional eating and restraint) outside the scanner. We found that insula activation during the Risky-Gains task positively correlated with interoceptive sensitivity and negatively correlated with external eating in healthy weight adolescents. Conversely, in excess weight adolescents, insula activation positively correlated with external eating and negatively correlated with interoceptive sensitivity, arguably reflecting obesity related neurocognitive adaptations. In excess weight adolescents, external eating was also positively associated with caudate nucleus activation, and restrained eating was negatively associated with insula activation. Our findings suggest that adolescent obesity is associated with disrupted tuning of the insula system towards interoceptive input.

KEYWORDS: Insula, Interoception, External Eating, Decision-making, Adolescence.

INTRODUCTION

The current food environment is full of cues that keep thoughts of palatable, energy-dense food almost constantly in mind (Swinburn et al., 2011). Therefore, individual differences in the relative value given to external food cues versus current homeostatic needs (e.g. hunger, satiety) may contribute to understand the increasing prevalence of obesity (Carnell, Benson, Pryor, & Driggin, 2013). In this context, obesity is viewed as a condition characterised by difficulties in resisting the urge to respond to external food cues, which may override homeostatic control of food intake (Blundell & Finlayson, 2004). The insula is the brain hub that integrates homeostatic feedback with external information and expected outcomes (Craig, 2009), and therefore it is key to understand the neural balance between interoceptive and external information. Recent research suggests that during adolescence insula function is sensitised towards external reward cues and comparatively less sensitive to risk (Smith, Steinberg, & Chein, 2014). It is however yet unclear whether this pattern translates into greater insula weighing of external versus interoceptive information in adolescents with overweight and obesity. This question is relevant as in that case insula related adaptations may contribute to the establishment and maintenance of a highly palatable yet unhealthy (hence risky) diet.

Risky decision-making involves cognitive evaluation of potential rewards and outcomes, but it is also critically modulated by homeostatic signals that project to the insula cortex (Paulus, 2007). The insula receives the major sources of interoceptive input (i.e., gut, hormonal) and gives rise to awareness of homeostatic states, which guide behaviour in the direction of satisfying body needs (Craig, 2009). The insula is centrally involved in

basic functions related to perception of physiological needs such as thirsty and hunger as evidenced by animal (Hollis et al., 2008; Saker et al., 2004) and human studies (Craig, 2009; Frank, Kullmann, & Veit, 2013). In relation to food intake, the insula cortex receives gut motility and hormonal signals of appetite and satiety, processes sensory and gustatory aspects of food and guides food related decisions (Frank, Kullmann, & Veit, 2013; Volkow, Wang, & Baler, 2011). Moreover, the insula is typically engaged when subjects make risky decisions involving gains and potential losses (Preuschoff, Quartz, & Bossaerts, 2008) and specifically involved in signaling the probability of aversive outcomes (Bossaerts, 2010; Venkatraman, Payne, Bettman, Luce, & Huettel, 2009). Therefore, it is reasonable to assume that the insula plays a relevant role on food decisions involving reward, but potentially associated with health related costs.

Adolescents with excess weight have decreased activation of the insula during anticipation of higher rewards in the Risky-Gains task, which opposes a less rewarding safe choice with more rewarding risky choices (Delgado-Rico, Soriano-Mas, Verdejo-Roman, Rio-Valle, & Verdejo-Garcia, 2013). The insula also plays a crucial role in interoceptive sensitivity, which is decreased in individuals with excess weight (Herbert & Pollatos, 2014). Importantly, individual differences in interoceptive sensitivity modulate decision-making processes regarding food intake. Higher interoceptive sensitivity has been shown to predict adaptive eating behaviours (guided by awareness of internal cues of hunger or satiety), which indeed is negatively associated with BMI levels (Herbert, Blechert, Hautzinger, Matthias, & Herbert, 2013). Conversely, poor interoceptive sensitivity in the face of the current obesogenic environment may predispose obese individuals to rely on external cues rather than on internal feedback on physiological states

(e.g., hunger and satiety) (Schachter, 1968).

In this study, we used functional magnetic resonance imaging to examine whether insula activation during risk-based decision-making is associated with sensitivity towards external food cues versus perception of interoceptive feedback in adolescents with excess weight. Decision-making was challenged using the Risky-Gains task (Paulus, Rogalsky, Simmons, Feinstein, & Stein, 2003), which reliably induces recruitment of insula activation (Delgado-Rico et al., 2013). The perception of interoceptive feedback was measured by a heartbeat perception task (Schandry, 1981). It has been demonstrated that cardiac interoception is strongly correlated with gastric interoception, which indicates this is a general index of interoceptive sensitivity (Herbert, Muth, Pollatos, & Herbert, 2012). Sensitivity towards external food cues was measured by the external eating subscale of the Dutch Eating Behaviour Questionnaire (Van Strien, Frijters, Bergers, & Defares, 1986). We hypothesized that in excess weight adolescents insula activation would positively correlate with external eating, at difference with positive correlations with interoceptive sensitivity in healthy weight controls.

METHODS

PARTICIPANTS

Fifty-four adolescents (age range 12-18) participated in this study. They were classified in two groups (excess weight [n=22] or healthy weight [n=32]) according to their age- and sex-adjusted BMI percentile, following the criteria of the International Obesity Task Force (IOTF) defined by Cole (Cole & Lobstein, 2012). The demographic data, BMI,

percentage of fat and the biochemical parameters are summarized in Table 1. The two groups did not differ significantly in age, sex or any biochemical parameter. Participants were recruited from the pediatrics and endocrinology services of the Hospital "Virgen de las Nieves" in Granada, Spain, and from schools located in the same geographical area. The inclusion criteria were as follows: (i) aged between 12 and 18 years old, (ii) BMI values falling within the intervals categorized as excess weight or healthy weight according to the IOTF, (iii) absence of history or current evidence of neurological or psychiatric disorders, assessed by participants and parents interviews and the Eating Disorder Inventory (Garner, 1994), (iv) absence of significant abnormalities on MRI (Magnetic Resonance Imaging) or any contraindications to MRI scanning (including claustrophobia and implanted ferromagnetic objects) and (v) absence of history of brain injury involving loss of consciousness (LOC) for longer than 5 minutes. All of them had normal or corrected-to-normal vision. The study was approved by the Ethics Committee of the University of Granada. All participants and their parents were briefed about study aims and detailed procedures, and both signed an informed consent form certifying their voluntary participation.

TABLE 1: Socio-demographic characteristics, biometric and biochemical parameters of the study groups. SINGLE COLUMN FITTING IMAGE

fMRI TASK

We used the Risky-Gains task described by Paulus (Paulus et al., 2003). In each trial, participants are presented with the numbers 20, 40 and 80 in a fixed order. The task requires the participant to acquire as many points as possible by choosing between safe

(20 points) and risky (40, 80 points) options. Each number (20, 40 or 80) is presented on the screen for 1 s, and the participant is instructed to press a button while the selected number is on the screen in order to win the corresponding amount of points. If participants fail to press the button within the required time, a 'too late' message is displayed on the screen and they miss the points for that trial.

The first number in the sequence (20) is always a safe choice. Participants are told that if they choose to press the bottom while the 20 is on the screen they would always receive 20 points. Moreover, participants are told that they have the option to wait and select one of the two subsequent choices (40 and 80); in that case they could win either 40 or 80 points, but that there would a chance (i.e., the probability is uncertain) that these options lead to loses 40 or 80 points, respectively. Thus, although the subject may gain more points per trial by waiting until the 40 or 80 choices appear on the screen, there is also a risk of losing 40 or 80 points. Points accumulate from trial to trial and the stake is shown at the top of the screen, being continuously updated. Participants received feedback immediately after making a response, so they could adapt their behavior to the feedback received.

The task consisted of 96 trials of 5 seconds. Fifty-four trials were non-punished trial type, where participants could get as much as 80 points, while 24 trials were -40 punished and 18 were -80 punished trial types. The expected value of the three options (20, 40 and 80) is the same (i.e., the penalties are set in a way that there is no advantage in selecting the 40 and 80 options). Therefore, there is no advantage in selecting the risky response (40 or 80) over the safe response (20).

IMAGING DATA ACQUISITION AND PROCESSING

A 3.0 T clinical MRI scanner (Intera Achieva, Philips Medical Systems, Eindhoven, The Netherlands), equipped with an eight-channel phased-array head coil, was used during task performance to obtain a T2*-weighted echo-planar imaging (EPI) sequence with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 35 ms, field of view (FOV) = 230 x 230 mm, 96 x 96 matrix, flip angle = 90º, 21 4 mm axial slices, 1 mm gap, 243 scans. A sagittal three-dimensional T1-weighted turbo-gradient-echo sequence (3D-TFE) (160 slices, TR= 8.3 ms, TE = 3.8 ms, flip angle = 8°, FOV = 240 x 240, 1 mm^3 voxels) was also obtained in the same experimental session for anatomical reference. Stimuli were presented through magnetic resonance-compatible liquid crystal display goggles (Resonance Technology Inc., Northridge, California, USA), and responses were recorded through Evoke Response Pad System (Resonance Technology Inc., Northridge, California, USA).

The brain images were analyzed using Statistical Parametric Mapping (SPM8) software (Wellcome Department of Cognitive Neurology, Institute of Neurology, Queen Square, London, United Kingdom), running under Matlab R2009 (MathWorks, Natick, Massachusetts, USA). Preprocessing steps were slice timing correction, reslicing to the first image of the time series, normalization (using affine and smoothly nonlinear transformations) to an EPI template in the Montreal Neurological Institute (MNI) space, and spatial smoothing by convolution with a 3D Gaussian kernel (full width at half maximum = 8 mm).

INSIDE SCANNER BEHAVIOURAL MEASURES

The main performance measures were safe and risky choice rates (proportion of safe/risky election by total trials) and safe and risky choice rates after punishments (proportion of safe/risky election after a punishment trial).

OUTSIDE SCANNER BEHAVIOURAL MEASURES

HEARTBEAT PERCEPTION TASK

We used the heartbeat perception task (Schandry, 1981), as described by Ehlers and Breuer (Ehlers & Breuer, 1992). In each trial participants were required to count how many heartbeats they felt over a period of time while the real number of heartbeats were measured by electrocardiogram (ECG). In order to determine whether subjects could calculate their number of heartbeats by simply estimating the time interval of the trial, a time estimation test was included. Participants completed three heartbeat trials (35, 25 and 45 sec.), three time trials (23, 56 and 40 sec.) and then three further heartbeat trials (23, 56 and 40 sec.). Prior to testing, participants were asked to remove their watch and instructed not to take their pulse with their fingers or to hold their breath. Time and heartbeat perception inaccuracy was calculated by taking the modulus of the actual value minus the estimated value, dividing this by the actual value and multiplied by 100 to express the inaccuracy as a percentage: $(|AV\text{-}EV|) / (AV) * 100$, where AV is the actual value, and EV is the estimated value.

Electrocardiogram (ECG) was recorded at rest and during performance of the heartbeat perception task at a sampling rate of 2000 Hz through a Biopac MP150 (Biopac Systems Inc., USA). Electrodes (Ag/AgCl) were placed according to Einthoven□ s II derivation

attaching them to the participant's right and left ankles and wrist of the non-dominant hand. The ECG raw signal was processed using the software AcqKnoledge 3.8.1.

DUTCH EATING BEHAVIOR QUESTIONNAIRE

The Dutch Eating Behavior Questionnaire (DEBQ) (Van Strien et al., 1986) was used to measure trait-eating behaviours. It is a 33-item questionnaire consisting of three subscales measuring the constructs of emotional eating (13 items), external eating (10 items) and restrained eating (10 items). Responses are made via a 5-point Likert scale ranging from "Never (1) to "Very often (5). It has good reliability and internal and discriminant validity (van Strien, 1986).

DATA ANALYSIS

BEHAVIOURAL ANALYSIS

Behavioural data were analyzed with the Statistical Package for the Social Sciences version 19 (SPSS 19; Chicago, IL, USA). We conducted independent-sample t-tests (two-tailed) to compare the two groups on relevant sociodemographic variables, and inside and outside scanner behavioural measures.

NEUROIMAGING ANALYSIS

The time series were convolved with the SPM8 canonical hemodynamic response function and a high-pass filter was used to remove low-frequency noise (1/128 Hz). We defined 2 conditions of interest: (i) safe response (20 points trials), (ii) risky response (40, -40, 80 and -80 points trials). Conditions were modeled as the time elapsed from the beginning of the trial to the participants' response or punishment feedback appears. Our contrast of

interest was defined to study risky related brain activations: risky versus vs. safe choices.

One-sample t-test was conducted to assess intra-group activations (healthy weight and excess weight) in the contrasts of interest. Between-group comparisons were conducted using a two-sample t-test, masking results by the activation maps derived from the one-sample t-tests. The statistical threshold used for creating this mask was $p<0.005$, with a minimum cluster size extent (KE) of 10 contiguous voxels. Regarding brain-behaviour associations, voxel-wise correlation analyses with our variables of interest (i.e., percentage of error in heartbeat perception and eating behaviour scores) were masked by two anatomical masks of the insular cortex and caudate nucleus, corresponding to the regions activated by risky choices in our study groups (see below). Such masks were created using the automated anatomical labelling (Tzourio-Mazoyer et al., 2002) from the WFU Pick Atlas Tool, version 3.0, integrated into SPM8 (Maldjian, Laurienti, Kraft, & Burdette, 2003). Within this masks we conducted within group correlations as well as between-group comparisons of correlation values (i.e., interactions).

All these analyses were corrected for multiple comparisons with a combination of voxel intensity and cluster extent thresholds. The spatial extent threshold was determined by 1,000 Monte Carlo simulations using AlphaSim as implemented in the SPM REST toolbox (Song et al., 2011) (Ward, 2013). The input parameters included an insula and a caudate mask of 5383 and 1239 voxels, respectively, an individual voxel threshold probability of 0.005 and a cluster connection radius of 5 mm, considering the actual smoothness of data after estimation. A minimum cluster extent (KE) of 34 voxels was estimated to satisfy a Family-wise error (FWE) corrected P value of $P_{FWE} <0.05$.

Finally, in order to calculate the correlation coefficients (r) and depict correlation plots, the beta eigenvalues from each cluster of significant brain differences between groups were extracted for each participant, and then correlated with behavioural measures in SPSS. We performed fisher r- to-z transformation to calculate between-group interactions in these correlations.

RESULTS

BEHAVIOURAL RESULTS

There were no between-group differences in any of the behavioural measures.

TABLE 2: Behavioural measures.

SINGLE COLUMN IMAGE

NEUROIMAGING RESULTS

RISKY-SAFE CONTRAST: One-sample t-tests showed that both groups commonly activated the caudate nucleus and a cluster comprising inferior frontal gyrus and anterior insula bilaterally. Excess weight group additionally activated the midbrain. We did not observe significant differences between the groups at the selected threshold.

TABLE 3: Brain activations observed in risky versus safe choices in within-group (one-sample) whole-brain analyses. DOUBLE COLUMN FITTING IMAGE.

MAIN ANALYSIS – CORRELATIONS BETWEEN BRAIN ACTIVATION PATTERNS AND BEHAVIOURAL MEASURES: A negative correlation between percentage of errors in the heartbeat perception task and bilateral posterior insula activation was found in healthy weight participants (x, y, z = 40, -4, 8, z score= 3.61; x, y, z = -36, -10, 12, z score= 3.52). Conversely, the percentage of errors in the heartbeat perception task (x, y, z = -36, 6, -12, z score= 3.54; x, y, z = 32, 6, -12, z score= 2.81) and external eating scores (x, y, z = -46, 2, -10, z score= 3.61) were positively correlated with posterior insula activations in excess weight participants (see Figure 1).

Results showed significant between-group (normal weight vs. excess weight) interactions in the correlations between errors heartbeat perception and external eating scores and posterior insula activation (z score=3.84, p=0.0001, and z score=2.77, p=0.0056, respectively) (see Figure 1).

Figure 1: Significant interaction between heartbeat perception error and external eating scores and posterior insula activation during Risky > Safe contrast. Y denote coordinate in standard MNI space. Right hemisphere is displayed on the right. DOUBLE COULMN FITTING IMAGE IN COLOUR.

Moreover, bilateral insula activation correlated positively with Restrained Eating scores in normal weight participants (x, y, z = -40, -20, -2, z score= 3.27; x, y, z = 34, -22, 14, z score= 3.27) whereas this correlation was negative in excess weight participants (x, y, z = 36, 4, 12, z score= 3.08) The direct comparison between these correlations revealed a significant difference (z score=4.13, p<0.0001) (see Figure 2).

Figure 2: Significant interaction between restrained eating scores and posterior insula activation during Risky > Safe contrast. Y denote coordinate in standard MNI space. Right hemisphere is displayed on the right. DOUBLE COLUMN FITTING IMAGE IN COLOUR.

Finally, although there were no significant correlations between caudate activation and any of the behavioural measures in the healthy weight group, a significant and positive correlation with external eating (x, y, z = -6, 8, 10, z score= 3.10) was observed in the excess weight group (see Figure 3).

Figure 3: Correlation between external eating scores (X axis) and caudate activation during Risky > Safe contrast (Y axis). Y denote coordinate in standard MNI space. Right hemisphere is displayed on the right. DOUBLE COLUMN FITTING IMAGE IN COLOUR.

DISCUSSION

In agreement with the initial hypothesis, we found that insula activation during risk-based decision-making is positively associated with external eating and negatively associated with interoceptive sensitivity in adolescents with excess weight. The opposite pattern was observed in adolescents with healthy weight. Therefore, the distinctive insula tuning towards external compared to internal information likely reflects neurocognitive adaptations associated with obesity. In excess weight adolescents, external eating was also positively associated with caudate nucleus activation, and restrained eating - which refers to an effort to restrict food intake for the purposes of

maintenance or weight loss - was negatively associated with insula activation. These correlations emerged in the absence of significant between-group differences on brain activations or behavioural measures.

Our findings indicate that adolescents with excess weight have an altered association between insula function and processing of interoceptive information. This neuroimaging finding resonates with previous behavioural results showing that obesity is associated with poorer perception of interoceptive signals in adults (Herbert & Pollatos, 2014). The insula is the key brain system for interoceptive processing, but growing evidence suggests that adiposity may interfere with the normal perception of interoceptive input. For instance, adult obese patients display reduced posterior insula activation in response to mechanically-induced gastric distention (Tomasi et al., 2009). Therefore, adolescents with excess weight may have decreased insula sensitivity towards interoceptive stimuli (i.e., signals of hunger and satiety, bodily representations of the risk of aversive outcomes) and comparatively increased sensitivity towards external rewards (Smith, Steinberg, & Chein, 2014). In agreement with this notion, our findings suggest that adolescent obesity is associated with disrupted tuning of the insula system towards interoceptive input. At the same time, insula activity correlates with external eating patterns, which speculatively suggest that adolescents with excess weight might have a distinctive insula tuning towards external eating cues. This is consistent with previous neuroimaging studies showing that adolescents with excess weight and adolescents at risk of obesity (by virtue of family history) have increased insula activation in response to food images (Batterink, Yokum, & Stice, 2010) and monetary rewards (Stice, Yokum, Burger, Epstein, & Small, 2011), during reallocation of

attention to appetizing food images (Yokum, Ng, & Stice, 2011), and during anticipation and actual consumption of milkshakes (Stice, Spoor, Bohon, Veldhuizen, & Small, 2008). Obese men have been shown to activate the posterior and middle insula upon exposure to a meal whereas lean individuals deactivate the middle insula and show no response in the posterior insula (DelParigi et al., 2004). The insula sensitivity towards external cues has important public health implications as insula activation in response to food cues has been shown to predict ensuing consumption of high energy foods (Mehta et al., 2012) and weight gain (Demos, Heatherton, & Kelley, 2012). Furthermore, postprandial insula activation is associated with subsequent selection of high energy foods in an "ad libitum" buffet (Mehta et al., 2012).

In addition, in adolescents with excess weight, caudate nucleus activation (related to the reward - impulsive system) was positively correlated with external eating and insula activation was negatively correlated with restrained eating (related to the goal-monitoring systems). Collectively, our findings suggest that obesity may be associated with a disruption of the interoception system involved in ongoing mapping of homeostatic signals and subsequent moderation of reward-impulsive versus goal-monitoring systems (Noel, Brevers, & Bechara, 2013). Specifically, engaging the insula system during risk-based decision-making in obesity might increase the vulnerability to eat in response to external food cues (regardless of physiological needs) by exacerbating activity within the reward-impulsive system and weakening activity of the goal-monitoring systems. Sensitization of the dopaminergic reward-impulsive system might serve to increase the salience of food cues in the environment and make them more attractive (Robinson & Berridge, 1993). This is consistent with the finding that

obese versus healthy weight individuals show increased brain activation in the caudate nucleus while viewing appetizing versus bland food (Nummenmaa et al., 2012). The caudate nucleus also shows increased connectivity with the posterior insula in obese individuals while they are seeing appetitive versus bland food (Nummenmaa et al., 2012). Moreover, a recent systematic review of the literature suggests that the striatum and the amygdala (reward-impulsive system) and the insula are hyper-reactive to visual food cues in obese individuals, paralleled by decreased response in the lateral and medial prefrontal areas (goal-monitoring system) (Garcia-Garcia et al., 2013).

The main conclusion of this study is that insula activation during risky versus safe choices is positively associated with external eating and negatively associated with interoceptive sensitivity in adolescents with excess weight, which is opposite to the "normal" pattern predicted by theory and observed in healthy weight controls. Moreover, in excess weight adolescents, the activation of the caudate nucleus also positively correlates with external eating, and the activation of the insula also negatively correlates with restraint. Collectively these findings suggest that, in excess weight adolescents, both interoceptive and reward related regions are tuned towards external cues, which may hamper efforts to restrain excessive eating behaviour. These findings give therefore support to cognitive interventions focused on enhancing appraisal of internal body signals as well as hunger and satiety awareness (Bloom, Sharpe, Mullan, & Zucker, 2013). These findings should be however interpreted in the context of relevant limitations. First, the data is correlational and therefore cannot speak of the causality of these alterations. Second, the correlations between brain activations and behavior

362 emerged in absence of significant group differences in brain or behavior, likely
363 because at difference with previous studies (Delgado- Rico et al., 2013), the present
364 study was not adequately powered to detect such between-group differences. Future
365 studies using longitudinal designs, larger samples sizes and ecologically valid food choice
366 tasks are warranted to validate our findings and to examine their public health
367 implications. In essence we speculatively propose that altered insula tuning towards
368 external rather than interoceptive cues may underlie unhealthy ("risky") food choices in
369 adolescents with overweight and obesity.

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TABLE 1: Socio-demographic characteristics, BMI, percentage of fat and biochemical parameters for each group

	Excess weight (n=22) Mean (SD[b])	Healthy weight (n=32) Mean (SD)	p-value
Demographic variables			
Age	15.14 (2.03)	15.53 (1.70)	0.443
Sex (male/female)	11/21	10/12	0.412
BMI[a]	29.40 (3.00)	21.17 (2.24)	<0.001
Fat (%)	33.14 (8.85)	19.01 (6.73)	<0.001
Biochemical parameters			
Insulin	45.58 (59.90)	39.13 (38.69)	0.635
Basal glucose	92.34 (3.91)	92.17 (7.19)	0.91
Triglycerides	71.70 (31.80)	65.15 (29.05)	0.437
HDL[c]	55.15 (13.13)	56.88 (10.81)	0.6
Total cholesterol	154.64 (27.77)	146.00 (18.34)	0.174

aBody Mass Index

bStandard deviation

cHigh-density lipoprotein

TABLE 2: Behavioural measures

	Healthy weight (n=32) Mean (SD[a])	Excess weight (n=22) Mean (SD)	p-value
Body perception task			
Error in heartbeat perception (%)	33.74 (16.17)	36.35 (18.02)	0.581
Error in time perception (%)	17.94 (15.96)	18.32 (13.57)	0.928
Dutch Eating Behavior Questionnaire			
Emotional Eating	23.13 (7.52)	22.86 (8.91)	0.908
Restrained Eating	20.50 (8.61)	24.68 (8.28)	0.081
External Eating	30.06 (7.40)	28.68 (7.01)	0.494
Risky Gains Task			
Safe choices (%)	50.39 (17.04)	53.66 (13.96)	0.46
Risky choices (%)	49.61 (17.04)	46.34 (13.96)	0.46
Safe choices after punishment (%)	61.69 (26.97)	65.41 (24.44)	0.607
Risky choices after punishment (%)	38.31 (26.97)	34.59 (24.44)	0.607

aStandard deviation

TABLE 3: Brain activations observed in risky versus safe choices in within-group (one-sample) whole-brain analyses

			MNI coordinates				
	BA[a]	Side	X	Y	Z	Ke[b]	T-value
Healthy weight							
Inferior frontal gyrus /Insula	47/13	L	-30	26	-10	384	6.77
Caudate		R/L	-8	12	-6	1261	6.7
Inferior frontal gyrus / Insula	47/13	R	30	28	-8	21	3.36
Excess weight							
Inferior frontal gyrus/Insula	47/13	L	-34	26	-2	234	4.47
Midbrain		R/L	-2	-18	-28	241	4.39
Caudate		R/L	8	10	-4	473	4.31
Inferior frontal gyrus/Insula	47/13	R	32	24	-8	60	3.99

[a]Brodmann area

[b]Cluster extent in voxels

FIGURE 1

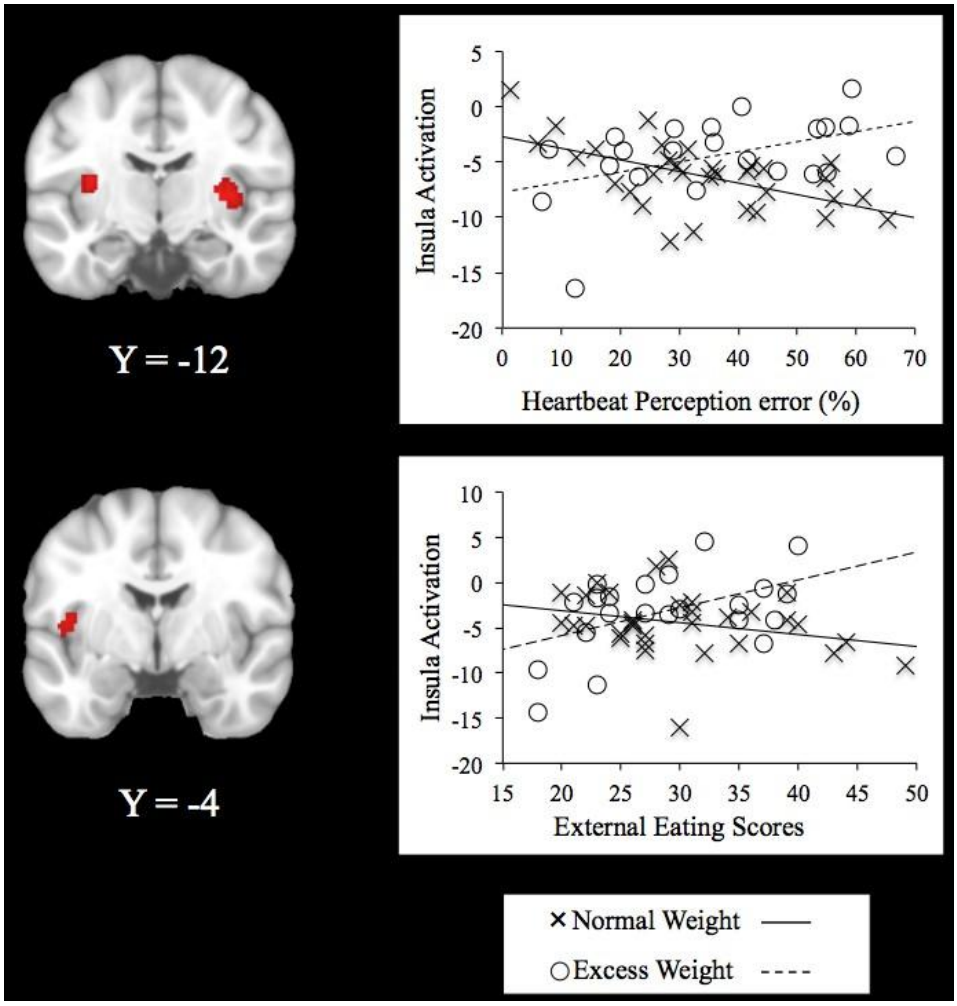


FIGURE 2

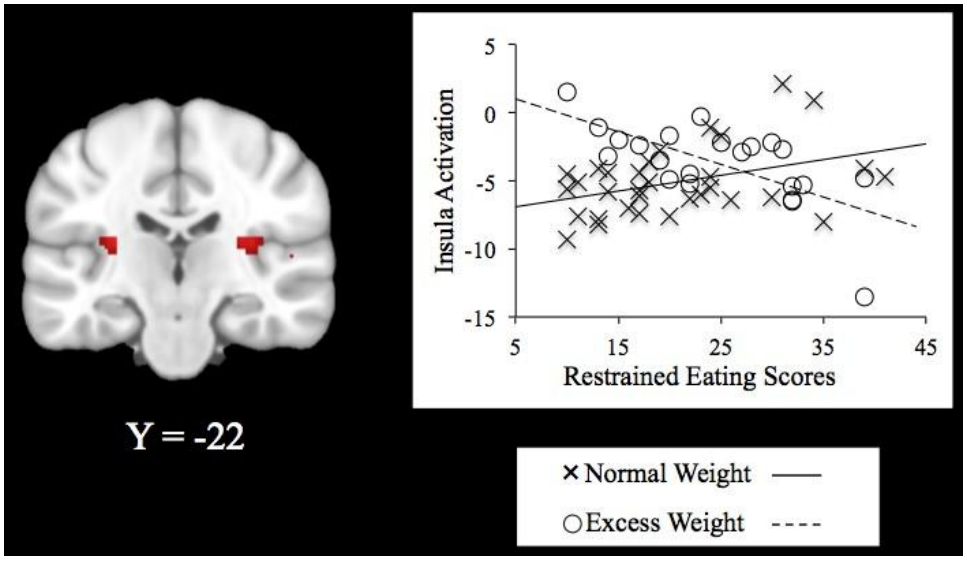
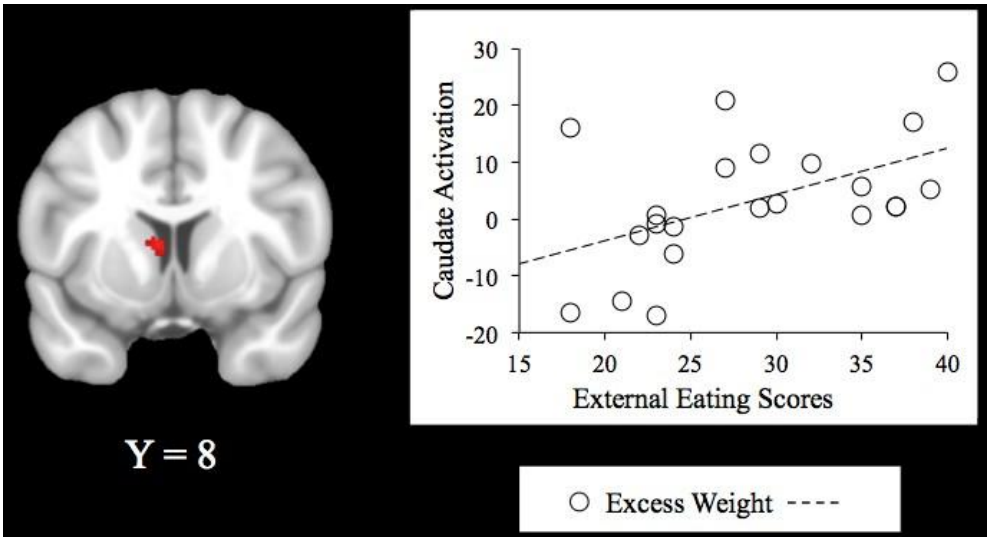


FIGURE 3


Y = 8
Caudate Activation
30
20
10
0
-10
-20
15
20
25
30
35
40
External Eating Scores
Excess Weight ----