NeuroImage: Clinical 12 (2016) 262–268

Contents lists available at ScienceDirect

NeuroImage: Clinical

journal homepage: www.elsevier.com/locate/ynicl

Disrupted functional connectivity in adolescent obesity

Laura Moreno-Lopez[a], Oren Contreras-Rodriguez[b,c], Carles Soriano-Mas[b,c,d], Emmanuel A. Stamatakis[a], Antonio Verdejo-Garcia[e,f,g,*]

[a] Division of Anaesthesia, University of Cambridge, Cambridge, UK
[b] Department of Psychiatry, Bellvitge Biomedical Research Institute-IDIBELL, Barcelona, Spain
[c] Centro de Investigación Biomédica en Red de Salud Mental (CIBERSAM), Barcelona, Spain
[d] Department of Psychobiology and Methodology of Health Sciences, Universitat Autònoma de Barcelona, Barcelona, Spain
[e] Red de Trastornos Adictivos, University of Granada, Granada, Spain
[f] Instituto de Neurociencias F. Olóriz, University of Granada, Granada, Spain
[g] School of Psychological Sciences & Monash Institute of Cognitive and Clinical, Neurosciences, Monash University, Melbourne, Australia

ARTICLE INFO

Article history:
Received 6 May 2016
Received in revised form 21 June 2016
Accepted 11 July 2016
Available online 12 July 2016

Keywords:
fMRI
Resting state
Functional connectivity
Obesity
Adolescents

ABSTRACT

Background/objective: Obesity has been associated with brain alterations characterised by poorer interaction between a hypersensitive reward system and a comparatively weaker prefrontal-cognitive control system. These alterations may occur as early as in adolescence, but this notion remains unclear, as no studies so far have examined global functional connectivity in adolescents with excess weight.
Subjects/methods: We investigated functional connectivity in a sample of 60 adolescents with excess weight and 55 normal weight controls. We first identified parts of the brain displaying between-group global connectivity differences and then characterised the extent of the differences in functional network integrity and their association with reward sensitivity.
Results: Adolescent obesity was linked to neuroadaptations in functional connectivity within brain hubs linked to interoception (insula), emotional memory (middle temporal gyrus) and cognitive control (dorsolateral prefrontal cortex) (pFWE < 0.05). The connectivity between the insula and the anterior cingulate cortex was reduced in comparison to controls, as was the connectivity between the middle temporal gyrus and the posterior cingulate cortex and cuneus/precuneus (pFWE < 0.05). Conversely, the middle temporal gyrus displayed increased connectivity with the orbitofrontal cortex (pFWE < 0.05). Critically, these networks were correlated with sensitivity to reward ($p < 0.05$).
Conclusions: These findings suggest that adolescent obesity is linked to disrupted functional connectivity in brain networks relevant to maintaining balance between reward, emotional memories and cognitive control. Our findings may contribute to reconceptualization of obesity as a multi-layered brain disorder leading to compromised motivation and control, and provide a biological account to target prevention strategies for adolescent obesity.

1. Introduction

Obesity is the most important health concern in the world today, as it contributes to diseases such as type-2 diabetes, cardiovascular disease, musculoskeletal conditions, some cancers and dementias (Guh et al., 2009; Whitmer et al., 2008). When obesity manifests during adolescence, the risk of developing these medical conditions during lifetime is significantly increased (Inge et al., 2013; Reis et al., 2013). Obesity has been traditionally defined as a *physiological* imbalance between energy consumption and energy expenditure, and thus most research on its neural underpinnings has been limited to homeostatic centres, such as the hypothalamus (Horvath, 2005). However, obesity is arguably linked to abnormal communication between multiple brain areas implicated in perception of homeostatic signals, reward related motivation and cognitive control (Berthoud, 2011; Jensen and Kirwan, 2015; Mata et al., 2015). Given that adolescence is characterised by a unique brain network organisation linked to a *psychological* imbalance between enhanced reward sensitivity and reduced cognitive control, (Paus et al., 2008; Van Leijenhorst et al., 2010) and thus to sensitised reactivity towards highly appetising food, (Stice et al., 2011) research on brain network organisation can provide important insights for understanding and prevention of adolescent obesity.

Resting-state connectivity approaches have successfully identified alterations in functional brain networks within populations with obesity: obese individuals compared to normal weight controls show increased connectivity between regions involved in metabolic sensing

* Corresponding author at: School of Psychological Sciences, Monash University, 18 Innovation Walk, 3800 Clayton Campus, Melbourne, Australia.
E-mail address: antonio.verdejo@monash.edu (A. Verdejo-Garcia).

http://dx.doi.org/10.1016/j.nicl.2016.07.005

and interoception (i.e., hypothalamus, insula) and regions involved in reward processing (i.e., striatum and orbitofrontal cortex or OFC) (Coveleskie et al., 2015; Kullmann et al., 2014; Wijngaarden et al., 2015). Moreover, obese individuals display decreased connectivity in brain regions involved in interoceptive processing and cognitive control (Kullmann et al., 2012). However, these studies have exclusively assessed adult samples, and therefore it remains unknown if brain connectivity alterations are manifest in adolescent populations. Only one study has previously assessed resting-state functional connectivity in obese adolescents through magnetoencephalography (MEG), showing that obese adolescents display increased connectivity in frontal, temporal and occipital regions compared to normal weight controls (Olde Dubbelink et al., 2008). However, the application of novel functional magnetic resonance imaging (fMRI) methods for measuring both global and regional connectivity can provide substantially more precise mapping of the connectivity alterations that characterises adolescent obesity.

In this study, we apply (i) a large-scale global connectivity approach to identify the key brain hubs that distinguish adolescents with obesity from normal weight controls, and (ii) data driven seed-based connectivity analyses to describe specific alterations between these networks, and their correlation with sensitivity to reward. We hypothesise that obese adolescents will have abnormal global connectivity in brain hubs implicated in interoception (insula), motivation (striatum, limbic regions, OFC) and cognitive control (dorsolateral prefrontal cortex or DLPFC), and that increased seed-based functional connectivity between regions involved in interoception and motivation, and decreased functional connectivity between regions involved in interoception/motivation and cognitive control would be associated with higher sensitivity to reward.

2. Materials and methods

2.1. Subjects

One hundred and fifteen adolescents participated in this study: 55 with normal weight (32 females, 23 males) and 60 with excess weight (38 females, 22 males) based on standard BMI cut-offs (Cole and Lobstein, 2012). Both groups had statistically similar distributions in terms of age, years of education and biochemical measures (Table 1). Participants were recruited through the Hospital Virgen de las Nieves (Granada, Spain) and through educational and community services in the same geographical area. The eligibility criteria were age between 12 and 17 years old, and BMI between 18 and 40. The exclusion criteria were as follows: (i) chronic medical conditions (i.e., diabetes, hypertension) indicated by self-reports and blood count and blood pressure measures, (ii) mental health problems indicated by the Millon Adolescent Clinical Inventory, (Aguirre, 2004) (iii) history of head trauma indicated by self-reporting, and (iv) contraindications to MRI scanning, such as claustrophobia and implanted ferromagnetic objects. This study was approved by the Human Research Ethics Committee of the University of Granada and all subjects and their parents provided written informed consent.

2.2. Procedure

Assessments were conducted during two different sessions at least 7 days apart. During the first session the participants were screened and completed the self-report questionnaires. The second session involved resting-state fMRI scanning.

2.2.1. Self-report questionnaire

The Sensitivity to Punishment and Sensitivity to Reward Questionnaire (SPSRQ) (Torrubia et al., 2001) is a 48 items self-report questionnaire comprising two subscales: Sensitivity to Punishment (e.g., “Are you often afraid of new or unexpected situations?”), and Sensitivity to Reward (e.g., “Do you sometimes do things for quick gains?”). Participants respond using a dichotomous scale (“yes” or “no”), and the score of each subscale is the result of the sum of the affirmative responses. This questionnaire has showed adequate internal consistency, and its scores hold adequate validity (Caseras et al., 2003). The outcome measure of interest was the score of sensitivity to reward, which was correlated with brain connectivity measures.

2.2.2. MRI data acquisition

All the MRI scans took place between 4 and 6 p.m., after the main meal of the day (lunch is the main meal of the day in Spain and typically occur between 2 and 3 p.m.). The resting-state sequence lasted 6 min, and participants were instructed to keep awake with their eyes closed. We used a 3.0 Tesla clinical MRI scanner, equipped with an eight-channel phased-array head coil (Intera Achieva Philips Medical Systems, Eindhoven, The Netherlands). A T2*-weighted echo-planar imaging (EPI) was obtained (TR = 2000 ms, TE = 35 ms, FOV = 230 × 230 mm, 96 × 96 pixel matrix; flip angle = 90°, 21 4-mm axial slices, 1-mm gap, 180 whole-brain volumes). The sequence included four additional dummy volumes to allow magnetization to reach equilibrium.

2.3. Imaging analyses

2.3.1. Preprocessing

Functional imaging data were preprocessed and analyzed using statistical parametric mapping (SPM8) (http://www.fil.ion.ucl.ac.uk/spm/software/spm8/) implemented in MATLAB R2007b (MathWorks, Natick, MA, USA). Preprocessing steps involved motion correction,

Table 1
Demographics, blood count based biochemical indices and self-report scores of excess weight and normal weight groups.

	Normal weight (n = 55)		Excess weight (n = 60)		Test	
	Mean	SD	Mean	SD	t	p
Age (years)	15.11	1.82	14.67	1.70	1.345	0.181
Height (m)	164.17	9.34	163.62	8.85	0.327	0.744
Weight (kg)	56.60	10.68	78.69	13.93	9.482	0.000*
BMI (kg/m^2)	20.84	2.39	29.26	3.84	−14.242	0.000*
Biochemical parameters						
Insulin	57.12	119.88	49.76	59.53	0.279	0.781
Basal glucose	92.00	6.92	93.26	5.108	−0.832	0.409
Triglycerides	63.89	27.91	71,37	29.81	−1.013	0.315
Cholesterol	145.97	19.66	158.00	28.35	−1.990	0.051
Sensitivity to punishment and reward questionnaire						
Sensitivity to reward	10.18	5.10	9.95	5.09	0.244	0.808
Sensitivity to punishment	11.44	4.15	9.58	3.72	2.527	0.013*

* $p < 0.05$.

spatial normalization to the standard SPM-EPI template and smoothing using a Gaussian filter (FWHM 8 mm). Data was resliced to $6.3 \times 7.6 \times 6.8$ mm for the global functional connectivity degree analysis and to 2 mm isotropic resolution for the seed-based analysis in Montreal Neurological Institute (MNI) space. We used a relatively large voxel size for the global functional connectivity degree analysis to optimize computational efficiency. Once broad differences were established, we decreased the voxel size to characterise in detail regional connectivity differences for each of the areas we found differences in the first analysis.

2.3.2. Global functional connectivity degree mapping

To obtain a quantitative measure of the extent each voxel is connected to every other voxel in the brain we used a global brain connectivity degree approach (Sepulcre et al., 2010; Pujol et al., 2014; Contreras-Rodríguez et al., 2014). Briefly, the analysis was restricted to the analysis of spontaneous BOLD signal fluctuations in gray matter voxels (those with >40% gray matter tissue probability in SPM8 MNI templates), while signal fluctuations in white matter, cerebrospinal fluid and the whole brain (the sum of the three tissue types) were included as nuisance covariates. Additionally, a high-pass filter set at 128 s was used to remove low-frequency drifts of less than approximately 0.008 Hz. Each voxel's fMRI signal time series was correlated with every other voxel's time series, resulting in a Pearson correlation coefficient r-matrix (2938 voxels × 2938 correlations each voxel), which was then binarized with a threshold of $|r| > 0.3$ (thus including positive and negative correlations). Connectivity degree of each voxel was finally expressed in relative values as the ratio of total supra-threshold connections over all the possible connections. Individual connectivity maps were then included in a group (second-level) random-effects analysis to assess for within and between-group effects.

2.3.3. Seed based analysis

Subsequently, significant clusters from the above group analyses were used in standard seed-based whole-brain functional connectivity analyses aimed at describing the specific pattern of connectivity underpinning the global functional connectivity degree alterations. Each seed was defined as a 3.5 mm diameter sphere (sampling approximately 25 voxels) constructed in MNI stereotaxic space using MarsBaR region-of-interest toolbox (Brett et al., 2002) and its signal value was calculated as the average signal of all the voxels included at each seed sphere. Functional connectivity maps were estimated for each of the selected seeds with regression analyses utilising the same nuisance variables used in the global connectivity analysis (white matter, cerebrospinal fluid and global brain signal fluctuations). Likewise, a high-pass filter set at 128 s was used to remove low-frequency drifts of less than approximately 0.008 Hz. Contrast images were generated for each subject by estimating the regression coefficient between the seed time series and each brain voxel signal. Resulting images were then included in a group (second-level) random-effects analyses to assess for within and between-group effects.

2.3.4. Correlation analyses with personality and clinical scores

Voxel-wise linear regression analyses were performed to assess between-group differences in the correlation between the scores of sensitivity to reward and the voxel-wise functional connectivity estimates of each seed region of interest. The correlations were conducted with each of the seeds showing significant between-group differences.

2.3.5. Statistical significance thresholding criteria

Statistical significance of all imaging comparisons and correlations was determined by 1000 Monte Carlo simulations using AlphaSim as implemented in the SPM REST toolbox (Song et al., 2011). The input parameters to AlphaSim were default parameters as defined in Ward (2000) and included a gray matter mask volume of 167,265 voxels ($2 \times 2 \times 2$ mm), an individual voxel threshold probability of 0.005, a cluster connection radius of 5 mm and the estimated smoothness of each T map after model estimation. The minimum cluster sizes were 3 voxels for the global connectivity degree analysis and 125 voxels for the seed-based functional connectivity analysis to satisfy a whole-brain family-wise error rate correction of $pFWE < 0.05$. Cluster threshold in the correlational analyses were calculated in the same manner and were considered significant if they exceeded a threshold of 125 voxels.

3. Results

3.1. Global connectivity

To obtain a quantitative measure of the extent each voxel is connected to every other voxel in the brain we used a global brain connectivity degree approach. Compared with normal weight controls, excess weight adolescents showed reduced global connectivity in a region encompassing the right insula and the frontal operculum (peak at x, y, $z = 55, 23, 9$, $t = 3.63$, 20 voxels), the left middle temporal cortex (peak at x, y, $z = -53, -8, -18$, $t = 3.65$, 3 voxels) and the right DLPFC (peak at x, y, $z = 29, 53, 23$, $t = 2.83$, 4 voxels) (Fig. 1). We used the coordinates of the brain regions showing statistical differences between groups as seeds for the subsequent seed-based connectivity analyses.

3.2. Seed-based connectivity

3.2.1. Within-group

Connectivity analyses between each seed (i.e., insula/operculum, middle temporal cortex and DLPFC) and the rest of the brain produced similar maps in the two groups (Table S1 and Fig. S1). A summary of our findings follows.

3.2.1.1. Insula/operculum seed. Both groups showed positive correlations with frontal and temporal regions, and negative correlations with the fusiform and posterior regions such as the posterior cingulate cortex and the cuneus/precuneus.

3.2.1.2. Middle temporal cortex seed. Both groups showed positive correlations with the middle temporal cortex and negative correlations with the parietal and DLPFC.

3.2.1.3. DLPFC seed. Both groups showed positive correlations with frontal regions such as the DLPFC, the insula or the supramarginal gyrus and negative correlations with posterior regions such as the cerebellum, the precuneus and the postcentral gyrus.

3.2.2. Between-groups comparisons

3.2.2.1. Insula/operculum seed. Excess weight adolescents displayed reduced connectivity between the insula/operculum and the right dorsal anterior cingulate cortex and supplementary motor area. In addition, excess weight adolescents showed increased connectivity between this seed and the left cuneus (Fig. 2A; Table 2).

3.2.2.2. Middle temporal cortex seed. Excess weight adolescents displayed reduced connectivity between the middle temporal cortex and the posterior cingulate cortex and cuneus/precuneus. In addition, excess weight adolescents showed increased connectivity between this seed and the OFC bilaterally, and the right inferior and middle frontal gyri, which in the right hemisphere also encompassed the insula (Fig. 2B; Table 2).

3.2.2.3. DLPFC seed. Excess weight adolescents displayed increased connectivity between the DLPFC and the right primary visual cortex (Fig. 2C; Table 2).

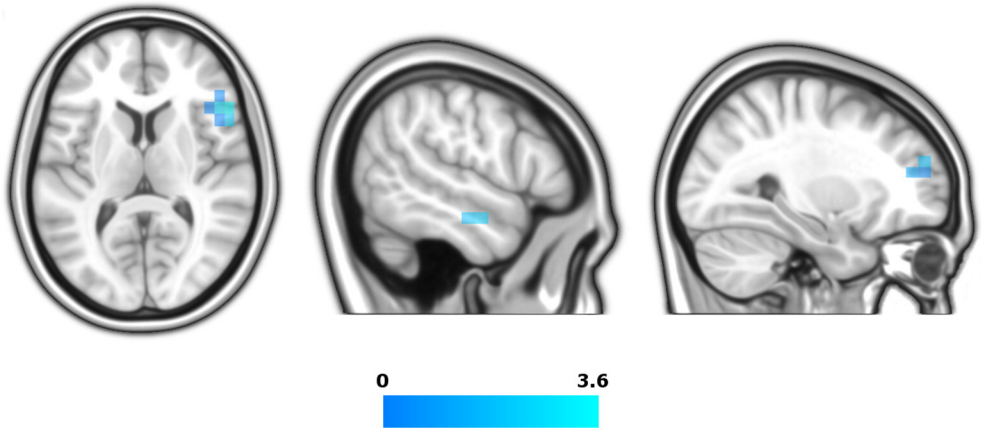

Fig. 1. Reduced global connectivity in excess weight adolescents compared with normal weight controls. The color scale represents t-values. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

3.2.3. Association between seed-based connectivity and sensitivity to reward

3.2.3.1. Insula/operculum seed. Sensitivity to reward was negatively associated with connectivity between the insula/operculum and the right superior frontal gyrus (peak at x, y, z = 22, 22, 36, t = 4.2, k = 447) in excess weight adolescents ($r = -0.406$, $p = 0.001$) whereas this association was positive in normal weight controls ($r = 0.320$, $p = 0.017$) (Fig. 3A). Despite differences in the direction of correlations, the Fisher's test of significance of the interaction effect was not significant ($p = 0.60$).

3.2.3.2. Middle temporal cortex seed. Sensitivity to reward was negatively associated with connectivity between the middle temporal cortex and the left frontal operculum (peak at x, y, z = −40, 4, 22, t = 3.6, k = 154) in excess weight adolescents ($r = -0.384$, $p = 0.002$) whereas this association was positive and non-significant in normal weight controls ($r = 0.245$, $p = 0.072$) (Fig. 3B). The Fisher's test of significance of the interaction effect was not significant ($p = 0.42$).

3.2.3.3. DLPFC seed. We did not find significant correlations in this seed.

4. Discussion

We found that adolescents who are overweight and obese display reduced global functional connectivity in the insula/operculum, the middle temporal cortex and the DLPFC, compared to normal weight controls. In addition, they show reduced regional seed-based connectivity between the insula/operculum and the dorsal anterior cingulate cortex and supplementary motor area, and between the middle temporal cortex and the posterior cingulate cortex and the cuneus/precuneus; and increased seed-based connectivity between the insula/operculum and the cuneus, between the middle temporal cortex and the OFC, and between the DLPFC seed and the primary visual cortex. Lower connectivity between the insula/operculum seed and the superior frontal gyrus and between the middle temporal cortex seed and the frontal operculum correlated with greater sensitivity to reward within the overweight and obese adolescents. These findings support our original assumptions, and suggest that adolescent obesity is linked to abnormal connectivity between brain regions involved in interoception and motivation and brain regions involved in cognitive control, in association with reward sensitivity.

Our global connectivity findings reveal a prominent role of brain hubs linked to interoception (i.e., insula), emotional memory (i.e., middle temporal gyrus) and cognitive control (i.e., DLPFC) in adolescent obesity. Overall, these findings support the notion that adolescent obesity is associated with multi-layered alterations in neural networks relevant to the detection of the motivational significance of homeostatic states, the representation of affective memories and the implementation of cognitive control over reward cues (Mata et al., 2015; Volkow et al., 2008). Since alterations were spread across different higher-order brain systems, our findings indicate that obesity is best characterised by deficits in brain networks that are relevant for coding higher-level stimulus significance and exerting top-down executive control, and not only by deficits in brain networks regulating metabolic needs (Verdejo-Garcia et al., 2010). Remarkably, these alterations are manifest in adolescence. Since the present study is cross-sectional, we cannot draw definite conclusions about the causality of these early brain alterations. However, given that excess weight participants were systematically assessed to rule out other health problems that may have a negative impact on brain health, and based on recent evidence demonstrating that adiposity is longitudinally associated with deterioration of brain health, (Chuang et al., 2015a; Chuang et al., 2015b) it is biologically plausible that the alterations in connectivity are related to obesity. Thus, they may significantly contribute to long-term obesity problems that span beyond adolescence.

Seed-based connectivity findings indicate that obese adolescents have deficits in regional networks relevant for cognitive control. Functional connectivity between the insula and the dorsal anterior cingulate cortex has been linked to attention and successful inhibitory control, (Cai et al., 2014; Cauda et al., 2012; Taylor et al., 2009) and thus reduced connectivity in this network may contribute to attentional biases towards food cues and diminished top-down control of eating in adolescents with obesity (Liang et al., 2014; Shank et al., 2015). This interpretation, related to attentional salience, is similarly supported by the finding of increased connectivity between the insula and a set of regions implicated in visual processing such as the cuneus and the primary visual cortex (Heatherton and Kelley, 2015). Since the insula is thought to maintain a pivotal role in mediating the function of other networks, (Jilka et al., 2014) our findings suggest that adolescent obesity is characterised by increased efficiency in interactions between the insula and sensory regions, at the expense of efficiency in the interactions between insula and cognitive control regions.

Seed-based connectivity findings also indicate that obese adolescents have deficits in regional networks relevant for emotional memory. Functional connectivity between the middle temporal cortex and the OFC, insula and middle frontal gyrus (increased in obese adolescents) has been linked to the generation of emotional states, (Kohn et al., 2014) whereas connectivity between the middle temporal cortex and

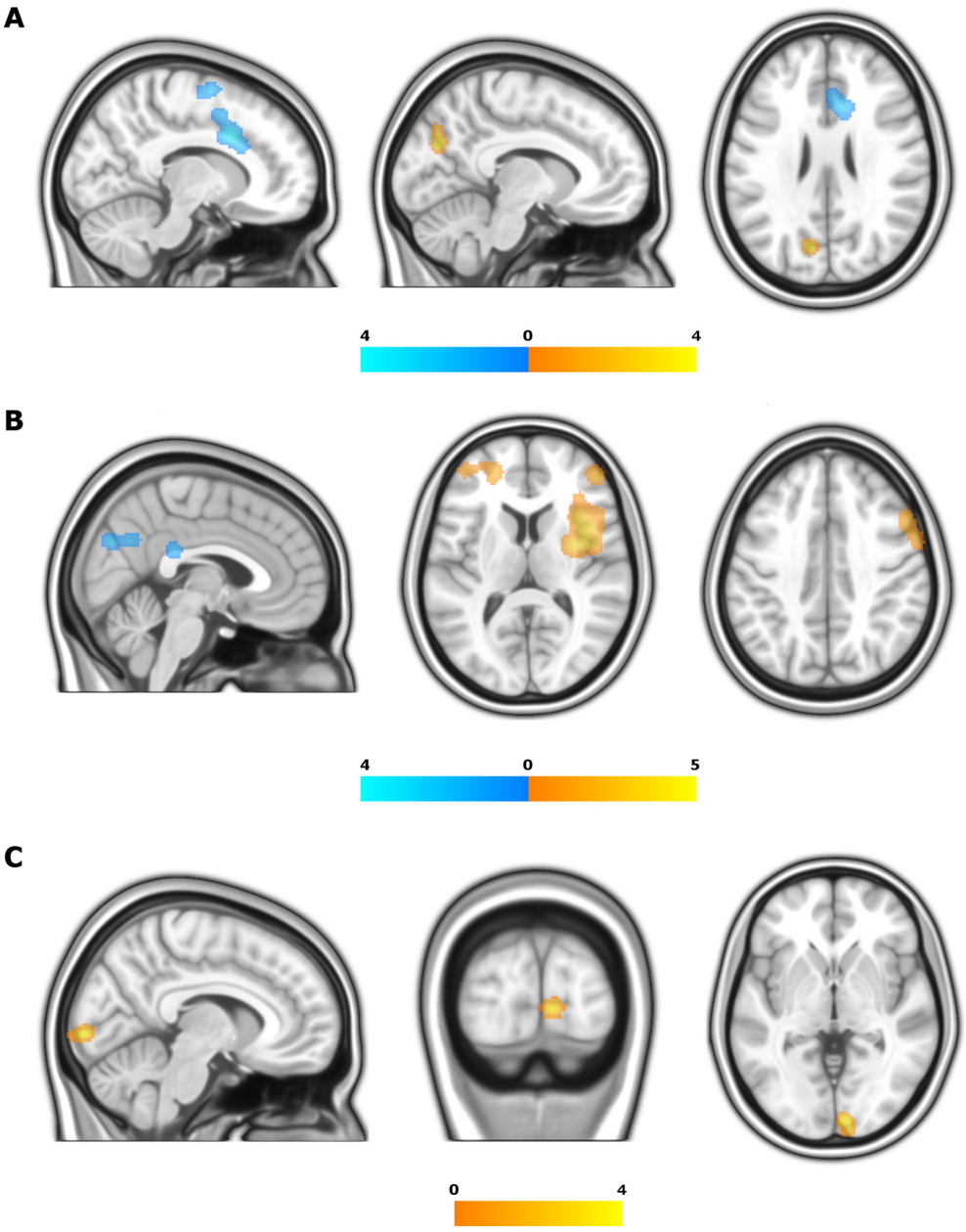

Fig. 2. Functional connectivity of the seeds found in excess weight adolescents compared with normal weight controls. A. Functional connectivity of the insula/operculum seed. B. Functional connectivity of the middle temporal cortex seed. C. Functional connectivity of the DLPFC seed. The color scale represents t-values with warm and cool colors indicating increased and reduced connectivity, respectively. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the posterior cingulate cortex and the precuneus/cuneus (decreased in obese adolescents) has been linked to encoding of new events and semantic memory (Kim, 2013; Binder et al., 2009). Since the cognitive systems controlling emotional salience and semantic memory normally interact to update memories of emotional material, (Talmi and Moscovitch, 2004) our findings suggest that adolescent obesity is linked to an imbalance between the increased function of the network tracking emotional salience and the diminished function of the network that manages semantic knowledge. Speculatively, this may contribute to the "stickiness" of cached representations of emotional (i.e., rewarding) food memories in obesity.

Correlational findings support our main hypothesis that insula and middle temporal regional networks are linked to increased reward sensitivity in adolescent obesity. Connectivity between the insula and middle frontal regions was negatively associated with sensitivity to reward, in fitting with our suggestion that lower connectivity between insula and frontal regions can sensitise reward systems versus cognitive control systems in obese adolescents, similar to what has been described in adults (Lips et al., 2014). Moreover, connectivity between the middle temporal cortex and frontal operculum gustatory aspects was also negatively associated with sensitivity to reward. Since this network has been linked to evaluation and updating of the salience of food stimuli, (Ziauddeen et al., 2012) findings are consistent with the notion that poor function of the network sensitises reward-related "cached" representations (Verdejo-Garcia et al., 2012). In contrast to negative correlations among excess weight participants, both networks (insula-middle frontal, and middle temporal-frontal operculum) had positive correlations with sensitivity to reward in healthy weight controls, although only the insula – middle frontal correlation was significant. The opposite direction of correlations suggest that obesity is linked to distortion of the normal function of these networks, i.e., normal interaction between the insula and the middle frontal gyrus would contribute to

Table 2
Between-group differences in functional connectivity.

Normal weight > excess weight	x	y	z	k	t
Insula/operculum *seed*					
R dorsal ACC	12	12	32	1069	4.03
L cuneus	−12	−74	26	131	3.30
Middle temporal cortex *seed*					
L PCC	−4	−32	28	181	3.91
R cuneus/precuneus	12	−66	30	302	3.24
R orbitofrontal cortex	36	52	−8	454	3.75
L orbitofrontal cortex	−20	44	10	199	3.44
R middle frontal gyrus	52	14	44	222	3.61
R inferior frontal gyrus/insula	46	22	0	2490	4.61
Dorsolateral prefrontal cortex *seed*					
R occipital cortex	8	−92	−2	133	3.56

Anatomical coordinates are given in Montreal Neurological Institute (MNI) Atlas space. R = right; L = left; ACC = anterior cingulate cortex; PCC = posterior cingulate cortex; OFC = orbitofrontal cortex.

interoceptive valuation of reward value, whereas this function is reversed in obesity (Mata et al., 2015). However, since the interaction effects were not significant, these findings must be interpreted with caution. Moreover, we did not found significant correlations between DLPFC connectivity and sensitivity to reward, which is consistent with the notion that this regions is primarily involved in cognitive control rather than stimulus valuation (Stice et al., 2011; Volkow et al., 2008).

In conclusion, we found that adolescent obesity is linked to disrupted organisation of functional connectivity within the insula, middle temporal cortex and DLPFC networks, which are relevant for the detection and representation of motivationally significant signals and top-down cognitive control of reward. Since these findings are manifest in early adolescence, future studies are warranted to explore whether cognitive training and brain stimulation techniques targeting these networks can shift the progression of obesity.

Conflict of interest

The authors declare no conflict of interest.

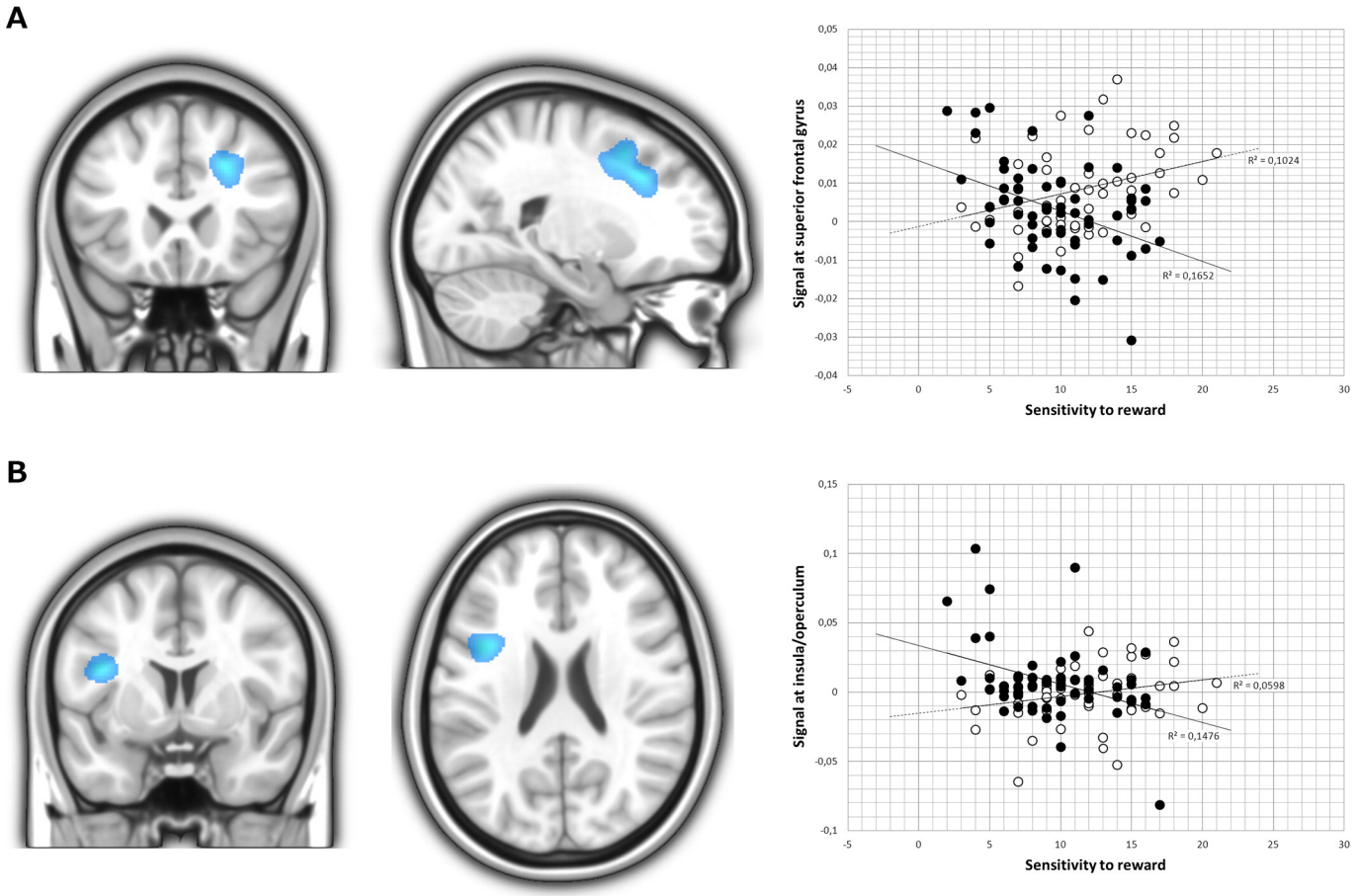

Fig. 3. Clusters and plots of the interactions found between the connectivity of the seeds and the measure of sensitivity to reward (excess weight filled circles, solid line). A. Cluster and plot of the interaction found between the measure of sensitivity to reward and the connectivity between the insula/operculum seed and the superior frontal gyrus. B. Cluster and plot of the interaction found between the measure of sensitivity to reward and the connectivity between the middle temporal cortex seed and the frontal operculum.

Acknowledgments

We would like to acknowledge Elena Delgado-Rico, Juan Verdejo-Roman and Jacqueline Schmidt Rio-Valle for invaluable help in collecting the data. We thank Jesus Pujol and Dídac Macià for kindly sharing part of the code used for data analysis. This study was funded by grants PI 0416/2008 (BRAINOBE) from the Andalusian Health Service (Consejería de Salud), PSI2010-17290 (INTEROBE) from the Ministry of Innovation and Science (MICINN) and P-10-HUM-6635 (NEUROECOBE). Dr. Laura Moreno-López was funded by a Post-Doctoral Fellowship from the University of Granada. Dr. Carles Soriano-Mas is funded by a Miguel Servet contract (CP10/00604) and Oren Contreras-Rodríguez by a Sara Borell contract (CD14/00246) from the Carlos III Health Institute. Emmanuel A. Stamatakis is funded by a Stephen Erskine Fellowship, Queens' College, Cambridge, UK.

Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.nicl.2016.07.005.

References

Aguirre, G., 2004. Inventario Clínico para Adolescentes de Millon. TEA, Madrid, Spain.
Berthoud, H.R., 2011. Metabolic and hedonic drives in the neural control of appetite: who is the boss? Curr. Opin. Neurobiol. 21, 888–896.
Binder, J.R., Desai, R.H., Graves, W.W., Conant, L.L., 2009. Where is the semantic system? A critical review and meta-analysis of 120 functional neuroimaging studies. Cereb. Cortex 19, 2767–2796.
Brett, M., Anton, J.L., Valabregue, R., Poline, J.B., 2002. Region of interest analysis using an SPM toolbox. NeuroImage 16 (Abstract).
Cai, W., Ryali, S., Chen, T., Li, C.S., Menon, V., 2014. Dissociable roles of right inferior frontal cortex and anterior insula in inhibitory control: evidence from intrinsic and task-related functional parcellation, connectivity, and response profile analyses across multiple datasets. J. Neurosci. 34, 14652–14667.
Caseras, X., Avila, C., Torrubia, R., 2003. The measurement of individual differences in behavioural inhibition and behavioural activation systems: a comparison of personality scales. Personal. Individ. Differ. 34, 999–1013.
Cauda, F., Costa, T., Torta, D.M., Sacco, K., D'Agata, F., Duca, S., et al., 2012. Meta-analytic clustering of the insular cortex: characterizing the meta-analytic connectivity of the insula when involved in active tasks. NeuroImage 62, 343–355.
Chuang, Y.F., An, Y., Bilgel, M., Wong, D.F., Troncoso, J.C., O'Brien, R.J., et al., 2015a. Midlife adiposity predicts earlier onset of Alzheimer's dementia, neuropathology and presymptomatic cerebral amyloid accumulation. Mol. Psychiatry http://dx.doi.org/10.1038/mp.2015.129 (e-pub ahead of print 1 Sep 2015).
Chuang, Y.F., Tanaka, T., Beason-Held, L.L., An, Y., Terracciano, A., Sutin, A.R., et al., 2015b. FTO genotype and aging: pleiotropic longitudinal effects on adiposity, brain function, impulsivity and diet. Mol. Psychiatry 20, 133–139.
Cole, T.J., Lobstein, T., 2012. Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatr. Obes. 7, 284–294.
Contreras-Rodríguez, O., Pujol, J., Batalla, I., Harrison, B.J., Soriano-Mas, C., Deus, J., et al., 2014. Functional connectivity bias in the prefrontal cortex of psychopaths. Biol. Psychiatry http://dx.doi.org/10.1016/j.biopsych.2014.03.007 (e-pub ahead of print 14 March 2014).
Coveleskie, K., Gupta, A., Kilpatrick, L.A., Mayer, E.D., Ashe-McNalley, C., Stains, J., et al., 2015. Altered functional connectivity within the central reward network in overweight and obese women. Nutr. Diabetes. 5, e148.
Guh, D.P., Zhang, W., Bansback, N., Amarsi, Z., Birmingham, C.L., Anis, A.H., 2009. The incidence of co-morbidities related to obesity and overweight: a systematic review and meta-analysis. BMC Public Health 9, 88.
Heatherton, T.F., Kelley, W.M., 2015. Individual differences in reward and somatosensory-motor brain regions correlate with adiposity in adolescents. Cereb. Cortex http://dx.doi.org/10.1093/cercor/bhv097 (e-pub ahead of print 20 May 2015).
Horvath, T.L., 2005. The hardship of obesity: a soft-wired hypothalamus. Nat. Neurosci. 8, 561–565.
Inge, T.H., King, W.C., Jenkins, T.M., Courcoulas, A.P., Mitsnefes, M., Flum, D.R., et al., 2013. The effect of obesity in adolescence on adult health status. Pediatrics 132, 1098–1104.
Jensen, C.D., Kirwan, C.B., 2015. Functional brain response to food images in successful adolescent weight losers compared with normal-weight and overweight controls. Obesity 23, 630–636.
Jilka, S.R., Scott, G., Ham, T., Pickering, A., Bonnelle, V., Braga, R.M., et al., 2014. Damage to the salience network and interactions with the default mode network. J. Neurosci. 34, 10798–10807.
Kim, H., 2013. Differential neural activity in the recognition of old versus new events: an activation likelihood estimation meta-analysis. Hum. Brain Mapp. 34, 814–836.
Kohn, N., Falkenberg, I., Kellermann, T., Eickhoff, S.B., Gur, R.C., Habel, U., 2014. Neural correlates of effective and ineffective mood induction. Soc. Cogn. Affect. Neurosci. 9, 864–872.
Kullmann, S., Heni, M., Linder, K., Zipfel, S., Häring, H.U., Veit, R., et al., 2014. Resting-state functional connectivity of the human hypothalamus. Hum. Brain Mapp. 35, 6088–6096.
Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H.U., et al., 2012. The obese brain: association of body mass index and insulin sensitivity with resting state network functional connectivity. Hum. Brain Mapp. 33, 1052–1061.
Liang, J., Matheson, B.E., Kaye, W.H., Boutelle, K.N., 2014. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int. J. Obes. 38, 494–506.
Lips, M.A., Wijngaarden, M.A., van der Grond, J., van Buchem, M.A., de Groot, G.H., Rombouts, S.A., et al., 2014. Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. Am. J. Clin. Nutr. 100, 524–531.
Mata, F., Verdejo-Roman, J., Soriano-Mas, C., Verdejo-Garcia, A., 2015. Insula tuning towards external eating versus interoceptive input in adolescents with overweight and obesity. Appetite 93, 24–30.
Olde Dubbelink, K.T., Felius, A., Verbunt, J.P., van Dijk, B.W., Berendse, H.W., Stam, C.J., et al., 2008. Increased resting-state functional connectivity in obese adolescents; a magnetoencephalographic pilot study. PLoS One 3, e2827.
Paus, T., Keshavan, M., Giedd, J.N., 2008. Why do many psychiatric disorders emerge during adolescence? Nat. Rev. Neurosci. 9, 947–957.
Pujol, J., Macià, D., Blanco-Hinojo, L., Martínez-Vilavella, G., Sunyer, J., de la Torre, R., et al., 2014. Does motion-related brain functional connectivity reflect both artifacts and genuine neural activity? NeuroImage 101, 87–95.
Reis, J.P., Loria, C.M., Lewis, C.E., Powell-Wiley, T.M., Wei, G.S., Carr, J.J., et al., 2013. Association between duration of overall and abdominal obesity beginning in young adulthood and coronary artery calcification in middle age. JAMA 310, 280–288.
Sepulcre, J., Liu, H., Talukdar, T., Martincorena, I., Yeo, B.T., Buckner, R.L., 2010. The organization of local and distant functional connectivity in the human brain. PLoS Comput. Biol. 6, e1000808.
Shank, L.M., Tanofsky-Kraff, M., Nelson, E.E., Shomaker, L.B., Ranzenhofer, L.M., Hannallah, L.M., et al., 2015. Attentional bias to food cues in youth with loss of control eating. Appetite 87, 68–75.
Song, X.W., Dong, Z.Y., Long, X.Y., Li, S.F., Zuo, X.N., Zhu, C.Z., et al., 2011. REST: a toolkit for resting-state functional magnetic resonance imaging data processing. PLoS One 6, e25031.
Stice, E., Yokum, S., Burger, K.S., Epstein, L.H., Small, D.M., 2011. Youth at risk for obesity show greater activation of striatal and somatosensory regions to food. J. Neurosci. 31, 4360–4366.
Talmi, D., Moscovitch, M., 2004. Can semantic relatedness explain the enhancement of memory for emotional words? Mem. Cogn. 32, 742–751.
Taylor, K.S., Seminowicz, D.A., David, K.D., 2009. Two systems of resting state connectivity between insula and cingulate cortex. Hum. Brain Mapp. 30, 2731–2745.
Torrubia, R., Avila, C., Molto, J., Caseras, X., 2001. The sensitivity to punishment and sensitivity to reward questionnaire (SPSRQ) as a measure of Gray's anxiety and impulsivity dimensions. Personal. Individ. Differ. 31, 837–862.
Van Leijenhorst, L., Gunther Moor, B., Op de Macks, Z.A., Rombouts, S.A., Westenberg, P.M., Crone, E.A., 2010. Adolescent risky decision-making: neurocognitive development of reward and control regions. NeuroImage 51, 345–355.
Verdejo-Garcia, A., Clark, L., Dunn, B.D., 2012. The role of interoception in addiction: a critical review. Neurosci. Biobehav. Rev. 36, 1857–1869.
Verdejo-Garcia, A., Pérez-Expósito, M., Schmidt-Río-Valle, J., Fernández-Serrano, M.J., Cruz, F., Pérez-García, M., et al., 2010. Selective alterations within executive functions in adolescents with excess weight. Obesity 18, 1572–1578.
Volkow, N.D., Wang, G.J., Fowler, J.S., Telang, F., 2008. Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 363, 3191–3200.
Ward, B.D., 2000. Simultaneous Inference for FMRI Data. NIMH.
Whitmer, R.A., Gustafson, D.R., Barrett-Connor, E., Haan, M.N., Gunderson, E.P., Yaffe, K., 2008. Central obesity and increased risk of dementia more than three decades later. Neurology 71, 1057–1064.
Wijngaarden, M.A., Veer, I.M., Rombouts, S.A., van Buchem, M.A., Willems van Dijk, K., Pijl, H., et al., 2015. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. Behav. Brain Res. 287, 127–134.
Ziauddeen, H., Farooqi, I.S., Fletcher, P.C., 2012. Obesity and the brain: how convincing is the addiction model? Nat. Rev. Neurosci. 13, 279–286.