DR. MICHELLE AMBER BOROWITZ (Orcid ID : 0000-0003-4865-3273)
DR. ASHLEY N GEARHARDT (Orcid ID : 0000-0003-3843-5731)

Article type : Original Article

Weight-related differences in salience, default mode, and executive function network connectivity in adolescents

Michelle A. Borowitz, Sonja Yokum, Elizabeth R. Duval & Ashley N. Gearhardt

Department of Psychology, University of Michigan (MAB, ANG, & ERD)

Oregon Research Institute (SY)

Department of Psychiatry, University of Michigan (ERD)

Keywords: obesity, adolescents, brain, eating behaviors

Corresponding Author

Michelle A. Borowitz, 1465 East Hall, 530 Church Street, Ann Arbor, MI, 48109, majoyn@umich.edu, 925.783.9223

Word Count: 3999

Funding: This work was supported by a grant from the National Institute on Diabetes and Digestive and Kidney Diseases: R01 DK102532 (PI: Gearhardt).

Disclosure: The authors declare no conflict of interest.

Author contributions: MAB, ANG and SY designed and conducted research; MAJ, ERD, and SY analyzed data; MAB wrote the paper; MAB had primary responsibility for final content. All authors read and approved the final manuscript.

- Current research shows that differences in the relative development of neural regions implicated in reward processing and executive function may put adolescents at increased risk for overconsumption of palatable foods and the development of obesity.
- Resting state functional connectivity (rsFC) analysis allows us to observe how intrinsic neural networks are associated with other outcomes (e.g., weight status).
- To date, rsFC research on adolescents with obesity has yielded inconsistent findings.

- The current study found that, in adolescents, obesity is associated with stronger salience network connectivity, and lower connectivity between the salience network and the default mode and executive function networks.
- The current study found the amygdala to show lower connectivity with other salience network areas in adolescents with obesity.

- Understanding weight-related differences in network connectivity can guide prevention and intervention efforts, and the current findings highlight the importance of targeting response to salient and rewarding food-related stimuli.
- In adolescents, interventions that promote executive function efforts in the context of salience and reward processing may be especially effective.

Abstract

Objective: The current study examined whether adolescents with weight ranging from lean to obese showed weight-related differences in the default mode network (DMN), executive function network (EFN) and the salience network (SN).

Methods: One-hundred sixty-four adolescents participated in a resting-state functional connectivity (rsFC) scan. A general linear model (GLM) was used to examine differences in rsFC patterns between adolescents with lean weight, overweight, and obesity.

Results: Adolescents with obesity compared to those with lean weight showed stronger within-SN connectivity between the medial orbitofrontal cortex (OFC), olfactory tubercle, and pallidum, however showed lower connectivity between the amygdala and SN regions (nucleus accumbens, thalamus, putamen). Those with obesity also showed lower connectivity between SN (amygdala, caudate) and DMN (parahippocampus, hippocampus, precuneus) regions. Adolescents with obesity compared to those with lean weight showed lower connectivity between SN (medial OFC) and EFN (ventrolateral prefrontal cortex) regions.

Conclusions: Obesity appears to be related to stronger connectivity within and between regions implicated in determining salience of stimuli, which may have implications for reward processing. Lower connectivity between SN and EFN regions may suggest that executive control efforts are going "offline" when salience and reward processing regions are engaged in adolescents who are obese.

Obesity prevalence is 13.9% among 2- to 5-year-olds and 20.6 % in 12- to 19-year-old adolescents.[1] Obesity in adolescence is a strong predictor of mental health concerns,[2] adult obesity, and diet-related disease.[3] Understanding contributors to adolescent obesity is essential to reducing this health burden. Neural development at this stage may put adolescents at especially high risk for overconsumption of palatable foods.[4] Compared to adults, adolescents show an imbalance between relatively fully developed regions implicated in reward processing and relatively less developed frontal regions implicated in executive function.[5] Thus, the relative influence of reward processing versus executive functioning in adolescents could result in

increased propensity for engaging in behaviors that provide short-term rewards, despite having longer-term negative consequences (e.g., excess consumption of calorie-dense foods).[5] Obesity in adolescence may be associated with individual differences in underlying functional neural organization, highlighting possible mechanistic targets for interventions.[6]

Resting state functional connectivity (rsFC) analysis provides a tool to investigate whether the fundamental functional organization of the brain is associated with obesity in adolescents. Compared to task-based functional magnetic resonance imaging (fMRI), which provides information about neural responses to specific stimuli, rsFC provides an evaluation of how intrinsic neural networks generally function.[7] Research using rsFC has identified canonical networks of functionally related neural regions that are frequently activated together.[8] Several of these networks are involved in functions relevant to the occurrence of obesity in adolescence. The salience network (SN), executive function network (EFN), and default mode network (DMN) consist of regions involved in processing salience and reward, cognitive control, and internal self-focus and mental imagery, respectively.[9,10] Table 1 shows regions comprising each of these networks and theorized functions.[9-11] Within-network differences in connectivity may represent intrinsic differences related to the basic functional organization of the brain.[10] For example, stronger within-SN connectivity may indicate more frequent engagement in processing of salient or rewarding stimuli.[10]

Differences in these neural networks have been associated with a wide range of disorders, including depression, addiction, schizophrenia, and dementia.[12] However, the use of rsFC as a tool to investigate underlying differences in the functional organization associated with overweight and obesity is just beginning. The majority of research has been conducted in adults, finding that obesity is associated with rsFC differences within the SN and among regions implicated in homeostatic processing and cognitive control.[13-16] However, direction of rsFC findings and the networks involved have been inconsistent across studies. Fewer studies have used rsFC to examine differences in functional organization related to obesity during adolescence, and these results have also been inconsistent. In a sample of 18 subjects aged 10-14, participants with obesity had greater rsFC between the EFN (left middle frontal gyrus, left ventromedial prefrontal cortex [vmPFC]) and SN (left orbitofrontal cortex [OFC]).[17] In a larger sample of 115 adolescents aged 12-17, obesity was associated with greater rsFC connectivity between the EFN (left middle temporal cortex) and SN (bilateral OFC) and lower within-SN

connectivity (insula, right dorsal anterior cingulate cortex [ACC]).[18] Greater EFN/SN connectivity could suggest that in children and adolescents with obesity, greater effort is required to execute self-control in the context of rewarding stimuli.[17] Other rsFC research in adolescents, however, has found obesity to be related to the opposite pattern. In a sample of 118 children and adolescents aged 10-18, excess weight (BMI $\geq 85^{th}$ percentile) was associated with greater within-SN connectivity (lateral hypothalamus, OFC, striatum, and insula) and lower connectivity between the SN (medial hypothalamus) and the EFN (middle frontal gyrus) and DMN (precuneus).[19] This could indicate a greater propensity to find rewarding stimuli particularly salient, and lower propensity to exert executive control in the context of rewards.

In sum, the current rsFC literature on adolescent obesity is inconsistent and requires further research in sufficiently powered studies. Existing studies have varied substantially in their methodology, making identification of a consistent pattern of findings challenging. Sample sizes have varied, with some being very small, (e.g., 18[17]). Several studies have combined children and adolescents into the same sample (e.g., ages 10-14[17]; 10-19[19]), possibly inhibiting interpretation given the difference in relative neural development at these stages.[5] In adults, variability in hunger significantly alters the neural networks associated with obesity.[15,16] However, to our knowledge, hunger has been systematically accounted for in only one rsFC study on adolescent obesity.[19] Given the conflicting directionality of findings, wide variance in sample size and age range, and inconsistent control for variability in hunger, existing rsFC findings have not coalesced to provide a clear picture of how differences in functional organization relate to adolescent obesity.

The current study aims to address this lack of clarity by conducting a study of 164 adolescents aged 13-16 with weight ranging from lean to obese. To clarify the directionality of rsFC patterns associated with obesity, we employed seed-based analyses to test hypothesized connections between specific ROIs included in the DMN, SN, and EFN, based on prior findings that connectivity in these networks differs with weight status.[13,14,17-19] We also attempted to standardize pre-scan hunger and controlled for remaining individual differences in hunger in all analyses. We expected that adolescents with obesity relative to those with lean weight would show significant within- and between-network differences in rsFC among regions in the SN, DMN, and EFN. Given conflicting findings in the extant literature, we did not have *a priori* hypotheses about the direction of the findings. Further, prior studies in adolescents have not

investigated rsFC differences associated with overweight (relative to obesity and lean weight). Adolescents with overweight may be at particularly high risk for developing obesity.[20] Thus, in the current study, we also conducted an exploratory investigation of how overweight was associated with rsFC differences in adolescence.

Methods

Participants

Participants were 186 adolescents aged 13-16 recruited for participation in a parent study on neural response to advertising. Inclusion criteria were English-speaking adolescents within the desired age range. Exclusion criteria were current use of psychotropic medications or illicit drugs, lifetime psychiatric disorder, a body mass index (BMI) percentile of <5% or fMRI contra-indicators (e.g., presence of metal implants). Nine participants did not complete the resting state scan, thus were not included in the current rsFC analyses. Nine participants were excluded due to excessive motion during the resting state scan (i.e., less than five minutes of usable data).[1] Four participants were excluded due to problems in imaging data following preprocessing (e.g., unsuccessful coregistration) detected during quality assurance (QA) checks. Thus, the final sample included in these analyses are 164 adolescents (87 female, 77 male; mean age = 14.3 ± 1.0, range 13-16; mean BMI = 24.1 ± 5.4; BMI z-score = 0.86 ± 0.9; with lean weight: n = 88 (53.7%); overweight: n = 40 (24.4%); obesity: n = 36 (22.0%). See Table 2 for participant demographics by weight status.

Study Procedures

The University of Michigan Institutional Review Board approved this study. Parents or legal guardians provided written informed consent, and adolescent participants provided written assent. Participants completed two laboratory visits. During the baseline assessment (Visit 1), participants completed behavioral tasks pertinent to the aims of the parent study and BMI measures. During the second visit (Visit 2), participants completed a high resolution anatomical scan and a rsFC paradigm followed by a functional task investigating neural response to different types of advertising.[21]

Scan Procedures. Participants were asked to eat typical meals, however not to consume any food or drink other than water between their last meal and the scan procedure. Scans

[1] Participants excluded for excessive motion did not differ significantly in weight status from those included in the final sample ($\chi^2 = 0.02$, $p = .99$).

occurred prior to typical mealtimes, with 87% of the scans occurring between 3-6 PM, and the remaining scans occurring between 10:30 AM-2 PM. Participants who rated their hunger a 70 or higher on a scale from 1 (not hungry at all) to 100 (extremely hungry), were offered a small snack (e.g., crackers, fruit) to bring their hunger level closer to baseline before the scan. A total of 14 individuals (8.5%) received a snack. Those who received a snack then rated their hunger again.

Measures

Body mass index (BMI). Age- and sex-adjusted BMI z-scores (zBMI) were used to assess adiposity. Height in centimeters and weight in kilograms were measured in the lab using an O'Leary Acrylic Stadiometer and Detecto Portable Scale, respectively. Participants were asked to remove shoes, socks and heavy clothing before having their height and weight measured. BMI (kg/m^2) was calculated using height and weight measured in the lab, then converted to z-scores using age- and sex-adjusted BMI growth curves.[22] Weight status was classified as overweight with a zBMI cutoff of >+1SD, and obese with a zBMI cutoff of >+2SD.

Hunger. Hunger was assessed immediately before the scan. Participants rated their hunger using a visual analog scale (VAS) ranging from 0 ("Not hungry at all") to 100 ("It's all I can think about"). For participants who received a snack, their hunger rating following the snack was used.

Resting state paradigm. During the 8-minute rsFC scan, participants were instructed to focus on a fixation cross and think about nothing in particular. During the scan, participants' eyes were visible to research staff, enabling visual confirmation that their eyes were open and they had not fallen asleep.

Analysis

fMRI scanner and data acquisition. MRI images were acquired using a GE Discovery MR750 3T scanner with an 8-channel head coil located at the University of Michigan Functional MRI Laboratory (http://www.umich.edu/~fmri/). Foam padding, a vacuum pillow, and tape were used to limit head movement. Participants completed all scanning in one 60-minute session, completing the resting state paradigm followed by anatomical scan and functional paradigm. Spiral imaging was used to measure BOLD signal as an indication of cerebral brain activation. To improve BOLD signal detection and minimize susceptibility-based distortion effects for regions subject to signal distortions (e.g., OFC, amygdala), we used a protocol that utilizes a high

readout bandwidth and a shorter echo time. Functional data were acquired with the following parameters: repetition time (TR) = 2000 ms, echo time (TE) = 30 ms, TI = 500 ms, flip angle = 90^0, field of view (FOV) = 22 x 22 cm^2, acquisition matrix = 64 x 64, 3-mm slice thickness with no gap, 43 axial slices. Anatomical scans were acquired using a high-resolution T1-weighted spoiled-gradient-recalled acquisition (SPGR; TR = 12.3 ms, TE = 5.2 ms, TI = 500 ms, flip angle = 15^0, FOV = 22 x 22 cm^2, slice thickness = 1.0mm). Slices were prescribed parallel to the AC-PC line (same locations as structural scans). Images were reconstructed into a 64x64 matrix. Slices were acquired contiguously, which optimizes the effectiveness of the movement post-processing algorithms. Images were reconstructed off-line using processing steps to remove distortions caused by magnetic field inhomogeneity and other sources of misalignment to the structural data, which yields excellent coverage of subcortical areas of interest.

Preprocessing of neuroimaging data. fMRI data was preprocessed using SPM12 (Wellcome Department of Imaging Neuroscience; Institute of Neurology, University College of London, London UK) and the *CONN* toolbox.[23] Functional images were realigned to the scan immediately preceding the anatomical T1 image and slice time corrected. Anatomical and rsFC images were coregistered and normalized to the Montreal Neurological Institute (MNI) T1 template brain.[24] Functional images were smoothed with a 6mm FWHM isotropic Gaussian kernel. We used Artifact detection toolbox (ART; https://www.nitrc.org/projects/artifact_detect/), a composite movement measure derived from the linear (X, Y, Z) and rotational (roll, pitch, yaw) motion parameters, to detect and correct for motion artifacts. Censoring was performed to identify frames with >0.2mm motion. During denoising, white matter, CSF, motion parameters plus first order temporal derivatives, and the censored frames were all regressed out of the data prior to bandpass filtering. Mean imputation was conducted to interpolate the censored timepoints. A high-pass filter (128s) and band-pass filter (.01 Hz - .1 Hz) were applied to remove low frequency noise and signal drifts. Participants were excluded if the retained frames (motion <0.2mm) resulted in less than five minutes of useable data (i.e., movement > 0.2mm).[2] Upon completion of the above spatial preprocessing steps, quality assurance (QA) plots were examined to confirm successful co-registration of structural and functional images and normalization to the template. QA plots showing voxel-to-

[2] Included participants retained an average of 213.17 frames out of 240 (i.e., approximately 7.11 minutes of usable data). Average frame displacement of included participants was 0.10mm.

voxel functional connectivity values and BOLD timeseries both before and after denoising were visually examined to determine successful reduction of effects due to noise.

Statistical analyses

All analyses were conducted using the *CONN* toolbox.[23] In first-level analyses, motion parameters in all 6 planes (x, y, z, pitch, roll, yaw) detected by ART, and their derivatives were included as nuisance covariates. In second-level analyses, we used a general linear model (GLM) to examine how rsFC strength within and between ROIs belonging to the DMN, EFN, and SN differed by weight status. ROIs previously established as comprising the networks of interest (i.e., DMN, SN, EFN) were included in the current ROI-to-ROI analyses (see Table 3 for a list of all ROIs tested).[9-11] ROIs were defined using masks derived from the Montreal Neurological Institute AAL template.[24] We included sex, age, hunger, and handedness as second-level covariates. Effects were considered significant after thresholding at $p < 0.001$ and false discovery rate (FDR) corrected at $p < 0.05$ at the analysis level.[25] Significant connectivity coefficients were extracted for each subject. Then, rsFC correlation maps were converted to z-scores using Fisher's r-to-z transformation. We conducted second-level group analyses in CONN to examine rsFC strength between ROIs to test the hypothesis that rsFC patterns would differ based on the adolescent's weight status.

Results

Table 4 shows ROI-to-ROI connectivity values differing significantly by weight status. Figure 1 shows rsFC patterns differing significantly between those with obesity and those with lean weight. Figure 2 shows rsFC patterns differing significantly between those with overweight and those with lean weight.

Within-network connectivity

Adolescents with obesity compared to those with lean weight showed greater within-SN connectivity, specifically between bilateral caudate and bilateral precuneus, between the right medial OFC and the left pallidum, and between the right medial OFC and the bilateral olfactory tubercle. Those with obesity compared to those with lean weight showed lower within-SN connectivity between the right amygdala and the right NAcc and bilateral thalamus, and between the right amygdala and right putamen. Adolescents with overweight compared to those with lean weight showed lower connectivity between the right amygdala and right NAcc (see Figure 2). Within-network connectivity in the DMN and EFN did not differ significantly by weight status.

Adolescents with overweight did not show any significant within-network differences in rsFC compared to those with obesity.

Between-network connectivity

Adolescents with obesity compared to those with lean weight showed lower connectivity between the DMN and the SN, specifically between the right parahippocampus and the left ACC, left amygdala, left olfactory tubercle, and left NAcc, and between bilateral caudate and right hippocampus. Adolescents with obesity compared to those with lean weight showed lower connectivity between the SN and EFN, specifically between the right medial OFC and the left and mid-vlPFC. Connectivity between the DMN and EFN did not differ significantly by weight status. Adolescents with overweight did not show any significant between-network differences in rsFC compared to either those with lean weight or with obesity.

Discussion

The current study used rsFC to examine whether the underlying functional organization of established neural systems in the brain differed by weight status in 13-16-year-old adolescents (n=164). Adolescents with obesity compared to those with lean weight had greater within-SN connectivity between the medial OFC and the olfactory tubercle and pallidum. The medial OFC plays a role in emotional decision-making and the learning of cue-outcome associations, particularly assessing the value of a reward.[26] The olfactory tubercle and pallidum are thought to be involved in mediating the effects of rewarding stimuli.[27,28] This rsFC pattern may suggest that the rewarding properties of food stimuli are particularly salient in adolescents with obesity. Alternatively, higher within-SN connectivity at baseline in adolescents with obesity may indicate that these individuals have a more subdued response to salient and rewarding stimuli in general, and thus may seek out additional stimuli in effort to achieve a greater reward response. Theories of both hyperfunction and hypofunction of reward systems in individuals with obesity have been examined in the literature (for review, see Small, 2009).[29] Studies examining within-SN connectivity in the presence of food stimuli are necessary to provide conclusive support for either hypothesis. The medial OFC showed lower connectivity with EFN regions (left and mid-vlPFC) in adolescents with obesity compared to those with lean weight. Similar to previous research finding reduced connectivity between the SN and EFN,[19] this pattern may suggest that adolescents with obesity are exerting less executive control in the context of salience network engagement.

Interestingly, adolescents with obesity showed lower connectivity between the amygdala and several other regions in the SN and the parahippocampus, implicated in memory encoding.[30] The amygdala is typically implicated in processing the affective aspects of rewards.[31] Although speculative, adolescents with obesity may process rewards, like food, more implicitly, involving fewer affective components and triggering less encoding of emotion-related memories.

Adolescents with obesity compared to those with lean weight showed greater connectivity between the caudate and precuneus. The caudate has been suggested to play a role in goal-directed action and evaluation of reward-related outcomes.[32] The precuneus has been implicated in functions such as mental imagery and self-referential thoughts.[33] Both regions show activation in task-based studies during the processing of food-related cues.[34] The incentive-sensitization theory suggests that increased motivation to obtain and consume food is heavily influenced by increased sensitivity to rewarding cues, and the assignment of excessive reward value to food-related stimuli.[35] Stronger connectivity between the caudate and precuneus at rest may contribute not only to greater sensitivity to rewarding food cues, but also to more persistent expenditure of cognitive resources on rewarding stimuli. In other words, rewarding stimuli may become more motivationally salient and increase goal-directed action toward food consumption. Future research may test this hypothesis by examining how behavioral measures of food cue responsivity and goal-directed action are associated with connectivity between the caudate and precuneus in the context of food stimuli.

In contrast to stronger rsFC between the caudate and precuneus, we found obesity to be associated with lower connectivity between several areas in the DMN (hippocampus, parahippocampus) and the SN (caudate, amygdala, ACC). This may be due to differing functions between the specific DMN regions. The precuneus is activated in response to cues,[36,37] while the hippocampus and parahippocampus are involved in memory encoding.[30] In the case of palatable foods, an adolescent with obesity may find rewarding properties of a cookie or cupcake to be highly salient, while memories of previous times they ate such foods are less salient and factor less into decision-making regarding consumption.[38] This may reduce the likelihood that the adolescent will attempt to inhibit the urge to consume the food. Future research may further contextualize this finding by employing task-based research examining how DMN and SN connectivity are associated with memory for food salience. Interventions increasing the salience

of long-term consequences of consumption may help reduce craving and consumption in adolescents with obesity.[39]

Our findings of greater SN connectivity and lower SN/DMN connectivity in adolescents with obesity is consistent with some prior research,[19] but stands in contrast to studies showing lower SN connectivity and greater SN/EFN connectivity.[17,18] The current study found only limited association between EFN connectivity and obesity. One possible explanation for these differences may be the age range and relative developmental stage of the sample. In the age range of our sample (13-16), reward regions are relatively well-developed, and executive function regions relatively underdeveloped.[5] In a younger sample, reward regions may also be relatively underdeveloped,[40] thus not yet building strong connections between one another. In a sample with a wider age range, developmental differences within the sample may impact the relative contribution of reward and EF regions observed, resulting in varying patterns based on the age breakdown of the particular sample. By including a narrower age range consisting only of adolescents, it is hoped that the current study can provide stronger conclusions on important functions during this period of adolescence.

Limitations and Future Directions

The current study had some substantial strengths making it a useful contribution to the literature on neural correlates of adolescent obesity. The sample size was larger than many published rsFC studies in adolescents, providing sufficient power to observe effects that may not be visible in a smaller sample. The current study also had participants across a wide BMI range, allowing for the observation of differences across weight status groups. Still, some limitations of the current study provide ideas for future research. The current analyses employed a cross-sectional design, preventing us from making conclusions about how the observed effects may change over time. Examining changes in rsFC over time, particularly as related to task performance, will further elucidate the impact behavior may have on functional organization and could inform the development of potential interventions. Though we controlled for individual differences, we did not specifically manipulate hunger and satiety in the current study. Given that a state of hunger versus satiety has been shown to impact the association between rsFC and obesity in adult samples,[15,16] manipulating this in adolescent samples would be an important future direction. The current study employed a relatively short (8-min) rsFC scan duration.

Research replicating these results in a paradigm employing multiple rsFC scans totaling a longer duration may help confirm the current findings.

The current findings can inform hypotheses about how individuals with obesity, overweight, and lean weight may respond differently to food stimuli. However, given that the current paradigm examined connectivity outside the context of any particular stimuli, we cannot definitively conclude that individuals with obesity find food stimuli specifically (i.e., versus a variety of stimuli) more salient than do those with lean weight. Further research examining rsFC in the presence of food stimuli are necessary to confirm this interpretation. The hypothesis-driven approach of the current analyses allowed us to examine ROIs important in obesity, and more directly compare with existing literature. However, this approach limited ability to identify other regions and their connections that may be important to assess in obesity despite not yet being studied. Data-driven approaches should be utilized in future research to replicate and extend current findings. The current study employed the commonly-used AAL parcellation, allowing for more direct comparisons to prior literature.[41,42] While neural network results in obese individuals were found to be reproducible using AAL templates,[43] the AAL parcellation has shown lower homogeneity than others.[44] Future research should replicate these results with alternative parcellations.

We found no significant differences between adolescents with overweight and those with obesity, and only limited differences between those with overweight and those with lean weight. In the current study, we calculated weight status using zBMI to limit variability stemming from rapid developmental changes in this age range.[4] Still, pubertal and muscle development in adolescents results in wide variability, even using zBMI, that may particularly impact those in the overweight category.[45] For example, individuals who are particularly muscular for their age may be categorized as overweight, along with those with excess body fat. This combination of body composition within the same category may limit ability to observe differences between the group with overweight and that with either obesity or lean weight. Future research would benefit from the use of other measures of adiposity (e.g., waist-to-hip ratio, dual-energy X-ray absorptiometry) to more directly measure body fat percentage.

Conclusions

The current study provides support for the hypothesis that obesity in adolescence is associated with differences in functional organization in areas of SN and DMN. Stronger

connectivity within the SN (medial OFC, olfactory tubercle, and pallidum), between the SN (caudate) and DMN (precuneus), and lower connectivity between the SN (OFC) and EFN (vlPFC) were associated with adolescent obesity. These findings highlight the importance of individual differences in functional organization related to processing of salient stimuli, which often has implications for reward processing. Lower connectivity between other regions in the DMN (hippocampus, parahippocampus) and the SN (caudate, amygdala, ACC) were also associated with adolescent obesity, highlighting the potential connection of memory and reward as an important target. Future research on the association of these rsFC connections with behavioral phenotypes and the ability of targeted interventions to change rsFC connections in adolescents are important next steps.

References

1. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity among adults and youth: United States, 2015-2016. 2017.
2. Erermis S, Cetin N, Amar M, Bukusoglu N, Akdeniz F, Goksen D. Is obesity a risk factor for psychopathology among adolescents? *Pediatrics International.* 2004;46:296-301.
3. Dietz WH. Health consequences of obesity in youth: Childhood predictors of adult disease. *Pediatrics.* 1998;101:518-525.
4. Adair LS. Child and adolescent obesity: epidemiology and developmental perspectives. *Physiology & behavior.* 2008;94(1):8-16.
5. Casey BJ, Jones RM. Neurobiology of the adolescent brain and behavior. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2010;49(12):1189-1201.
6. DiFeliceantonio AG, Coppin G, Rigoux L, et al. Supra-Additive Effects of Combining Fat and Carbohydrate on Food Reward. *Cell Metab.* 2018;28(1):33-44 e33.
7. Lee MH, Smyser CD, Shimony JS. Resting-state fMRI: a review of methods and clinical applications. *AJNR Am J Neuroradiol.* 2013;34(10):1866-1872.
8. Power JD, Cohen AL, Nelson SM, et al. Functional network organization of the human brain. *Neuron.* 2011;72(4):665-678.
9. Greicius MD, Supekar K, Menon V, Dougherty RF. Resting-state functional connectivity reflects structural connectivity in the default mode network. *Cereb Cortex.* 2009;19(1):72-78.

10. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. *The Journal of neuroscience : the official journal of the Society for Neuroscience.* 2007;27(9):2349-2356.
11. Barrett LF, Satpute AB. Large-scale brain networks in affective and social neuroscience: towards an integrative functional architecture of the brain. *Curr Opin Neurobiol.* 2013;23(3):361-372.
12. Greicius M. Resting-state functional connectivity in neuropsychiatric disorders. *Current Opinion in Neurology.* 2008;21:424-430.
13. Garcia-Garcia I, Jurado MA, Garolera M, et al. Alterations of the salience network in obesity: a resting-state fMRI study. *Hum Brain Mapp.* 2013;34(11):2786-2797.
14. Kullmann S, Heni M, Veit R, 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):1052-1061.
15. Lips MA, Wijngaarden MA, van der Grond J, et al. Resting-state functional connectivity of brain regions involved in cognitive control, motivation, and reward is enhanced in obese females. *The American journal of clinical nutrition.* 2014;100(2):524-531.
16. Wijngaarden MA, Veer IM, Rombouts SA, et al. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. *Behav Brain Res.* 2015;287:127-134.
17. Black WR, Lepping RJ, Bruce AS, et al. Tonic hyper-connectivity of reward neurocircuitry in obese children. *Obesity.* 2014;22(7):1590-1593.
18. Moreno-Lopez L, Contreras-Rodriguez O, Soriano-Mas C, Stamatakis EA, Verdejo-Garcia A. Disrupted functional connectivity in adolescent obesity. *Neuroimage Clin.* 2016;12:262-268.
19. Martín-Pérez C, Contreras-Rodríguez O, Vilar-López R, Verdejo-García A. Hypothalamic Networks in Adolescents With Excess Weight: Stress-Related Connectivity and Associations With Emotional Eating. *Journal of the American Academy of Child & Adolescent Psychiatry.* 2018.
20. Reilly JJ, Kelly J. Long-term impact of overweight and obesity in childhood and adolescence on morbidity and premature mortality in adulthood: systematic review. *International journal of obesity.* 2011;35(7):891-898.

21. Gearhardt AN, Yokum S, Harris JL, Epstein LH, Lumeng JC. Neural response to fast food commercials in adolescents predicts intake. *American Journal of Clinical Nutrition.* 2020;111:493-502.
22. Kuczmarski RJ, Ogden CL, Gummer-Strawn LM, et al. *CDC growth charts: United States.* Centers for Disease Control and Prevention / National Center for Health Statistics;2000.
23. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connect.* 2012;2(3):125-141.
24. Tzourio-Mazoyer N, Landeau B, Papathanassiou D, et al. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage.* 2002;15(1):273-289.
25. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage.* 2002;15(4):870-878.
26. McDannald MA, Jones JL, Takahashi YK, Schoenbaum G. Learning theory: a driving force in understanding orbitofrontal function. *Neurobiol Learn Mem.* 2014;108:22-27.
27. Ikemoto S. Dopamine reward circuitry: two projection systems from the ventral midbrain to the nucleus accumbens-olfactory tubercle complex. *Brain Res Rev.* 2007;56(1):27-78.
28. Koob GF, Volkow ND. Neurocircuitry of addiction. *Neuropsychopharmacology : official publication of the American College of Neuropsychopharmacology.* 2010;35(1):217-238.
29. Small DM. Individual differences in the neurophysiology of reward and the obesity epidemic. *International journal of obesity.* 2009;33 Suppl 2:S44-48.
30. Eichenbaum H, Otto T, Cohen NJ. Two functional components of the hippocampal memory system. *Behavioral and Brain Sciences.* 1994;17(03):449-472.
31. Murray EA. The amygdala, reward and emotion. *Trends Cogn Sci.* 2007;11(11):489-497.
32. Grahn JA, Parkinson JA, Owen AM. The cognitive functions of the caudate nucleus. *Prog Neurobiol.* 2008;86(3):141-155.
33. Cavanna AE, Trimble MR. The precuneus: a review of its functional anatomy and behavioural correlates. *Brain.* 2006;129(Pt 3):564-583.
34. Filbey FM, Myers US, Dewitt S. Reward circuit function in high BMI individuals with compulsive overeating: similarities with addiction. *NeuroImage.* 2012;63(4):1800-1806.

35. Robinson TE, Berridge KC. The psychology and neurobiology of addiction: an incentive-sensitization view. *Addiction.* 2000;95(Suppl 2):S91-S117.
36. Burger KS, Stice E. Neural responsivity during soft drink intake, anticipation, and advertisement exposure in habitually consuming youth. *Obesity.* 2014;22(2):441-450.
37. Carnell S, Benson L, Pantazatos SP, Hirsch J, Geliebter A. Amodal brain activation and functional connectivity in response to high-energy-density food cues in obesity. *Obesity.* 2014;22(11):2370-2378.
38. Higgs S, Robinson E, Lee M. Learning and Memory Processes and Their Role in Eating: Implications for Limiting Food Intake in Overeaters. *Current obesity reports.* 2012;1(2):91-98.
39. Kober H, Kross EF, Mischel W, Hart CL, Ochsner KN. Regulation of craving by cognitive strategies in cigarette smokers. *Drug and alcohol dependence.* 2010;106(1):52-55.
40. Casey BJ, Giedd JN, Thomas KM. Structural and functional brain development and its relation to cognitive development. *Biological Psychology.* 2000;54:241-257.
41. Batterink L, Yokum S, Stice E. Body mass correlates inversely with inhibitory control in response to food among adolescent girls: an fMRI study. *NeuroImage.* 2010;52(4):1696-1703.
42. Park BY, Seo J, Yi J, Park H. Structural and Functional Brain Connectivity of People with Obesity and Prediction of Body Mass Index Using Connectivity. *PloS one.* 2015;10(11):e0141376.
43. Meng Q, Han Y, Ji G, et al. Disrupted topological organization of the frontal-mesolimbic network in obese patients. *Brain Imaging Behav.* 2018;12(6):1544-1555.
44. Gordon EM, Laumann TO, Adeyemo B, Huckins JF, Kelley WM, Petersen SE. Generation and Evaluation of a Cortical Area Parcellation from Resting-State Correlations. *Cereb Cortex.* 2016;26(1):288-303.
45. Loomba-Albrecht LA, Styne DM. Effect of puberty on body composition. *Current Opinion in Endocrinology, Diabetes and Obesity.* 2009;16(1):10-15.

Table 1

Regions and theorized functions of canonical neural networks

Network	Sample regions	Theorized functions
Default Mode Network (DMN)[9]	Regions more active at rest than during a task, e.g., posterior cingulate cortex, precuneus, medial frontal regions, inferior parietal regions	Mental imagery, mind wandering
Executive Function Network (EFN)[10]	Prefrontal regions, e.g., bilateral dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, dorsomedial prefrontal cortex	Executive functions including attention, inhibitory control, and working memory
Salience Network (SN)[10,11]	Limbic and paralimbic regions, e.g., insula, caudate, orbitofrontal cortex	Processing of information related to emotion, reward, and homeostatic regulation

Table 2

Frequencies and percentages or means and standard deviations of demographic variables by weight status.

	Total (*n*=164)	Adolescents with lean weight (*n*=88)	Adolescents with overweight (*n*=40)	Adolescents with obesity (*n*=36)	*F* or X^2	*p*	η^2 or φ
Male	77 (47.0%)	45 (51.1%)	18 (45.0%)	14 (38.9%)			
Female	87 (53.0%)	43 (48.9%)	22 (55.0%)	22 (61.1%)			
Gender					1.62	.45	.10
White	112 (68.3%)	63 (71.6%)	25 (62.5%)	24 (66.7%)			
Non-white	43 (26.2%)	19 (21.6%)	12 (30.0%)	12 (33.3%)			
Race					4.54	.34	.17
Age	14.30 (1.03)	14.14 (1.04)	14.40 (1.01)	14.58 (0.97)	2.73	.07	.03
Pre-scan	23.76 (21.28)	26.76 (20.50)	18.68 (19.64)	22.06 (24.05)	2.16	.12	.03

hunger						
zBMI	0.83 (0.94)	0.14 (0.61)	1.35 (0.17)	2.06 (0.32)	233.14	.00 .74

Note. Chi-square test statistics (X^2, φ) presented for categorical variables (i.e., gender, race). One-way ANOVA test statistics (F, η^2) presented for continuous variables. Nine participants (5.5%) did not report their race, thus percentages for race variable do not add up to 100%.

Table 3

Networks and Source ROIs

		MNI Coordinates (Left)			MNI Coordinates (Right)		
Network	Source ROIs	X	Y	Z	X	Y	Z
DMN[9,11]							
	Hippocampus	-25	-22	-11	29	-21	-12
	Inferior parietal lobe (IPL)	-43	-47	45	46	-48	48
	Middle frontal gyrus (MFG)	-34	31	34	37	32	33
	Parahippocampus	-21	-17	-22	25	-16	-22
	Posterior cingulate cortex (PCC)	-5	-44	23	7	-43	20
	Precuneus	-8	-57	47	10	-57	42
	Ventrolateral prefrontal cortex (vlPFC)	-45	30	3	46	30	3
	Ventromedial prefrontal cortex (vmPFC)	-22	47	12	23	47	12
SN[10,11]							
	Amygdala	-24	2	-18	27	-1	-19
	Anterior cingulate cortex (ACC)	-4	34	13	8	36	14
	Caudate	-12	10	8	14	11	8
	Insula	-35	5	2	39	5	1
	Nucleus accumbens (NAcc)	-13	7	-12	12	9	-11
	Olfactory tubercle	-8	14	-13	10	15	-13

	Orbitofrontal cortex (OFC)	-5	53	-9	8	50	-9
	Pallidum	-18	-1	-1	21	-1	-1
	Putamen	-24	3	1	27	4	1
	Thalamus	-13	-19	8	13	-19	8
EFN[10]							
	Dorsolateral prefrontal cortex (dlPFC)	-33	34	30	34	34	30
	Ventrolateral prefrontal cortex (vlPFC)	-45	30	3	46	30	3

Table 4

Significant Between-group ROI-to-ROI rsFC Differences

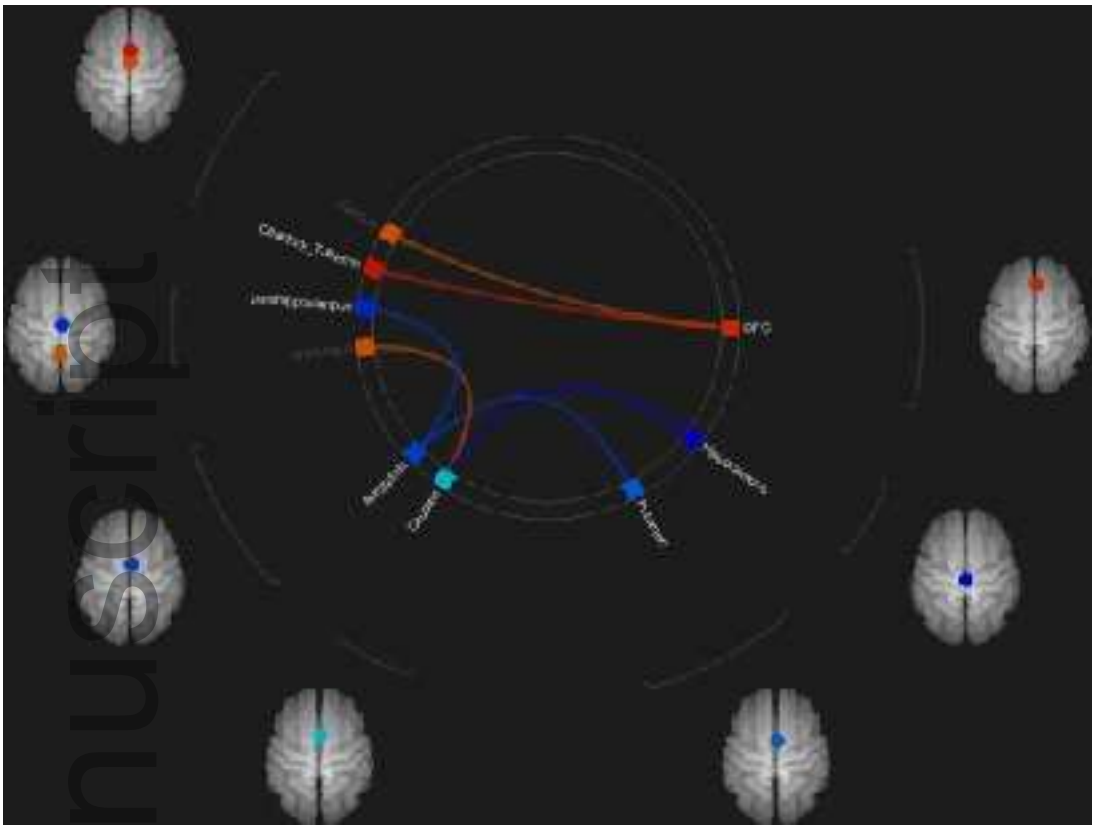
Contrast	Seed/Source	T	*p*FDR
Adolescents with obesity > adolescents with lean weight			
	Amygdala		
	R NAcc	-2.88	.032
	R Parahippocampus	-3.38	.015
	R Putamen	-3.34	.015
	Thalamus	-2.68	.045
	Caudate		
	Precuneus	3.14	.029
	R Hippocampus	-4.12	.002
	Hippocampus		
	Caudate	-4.12	.002
	Medial OFC		
	Olfactory Tubercle	3.69	.009
	L Pallidum	3.12	.029

	L VLPFC	-3.01	.029
	mid-VLPFC	-2.85	.035
	Olfactory Tubercle		
	R Medial OFC	3.69	.009
	Parahippocampus		
	L NAcc	-2.83	.037
	L Olfactory Tubercle	-2.87	.037
	L ACC	-3.03	.037
	L Amygdala	-3.38	.025
	Putamen		
	R Amygdala	-3.34	.029
Adolescents with overweight > Adolescents with lean weight			
	Amygdala		
	R NAcc	-3.25	.040
	R NAcc		
	R Amygdala	-3.25	.040

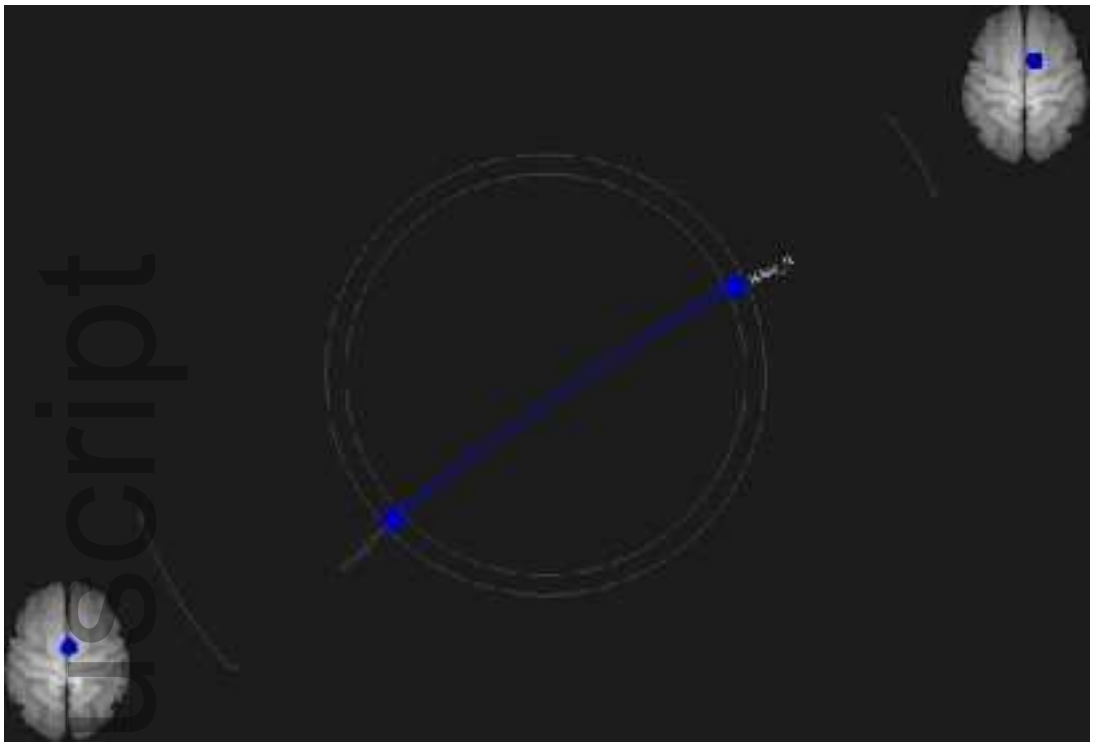
Figure legends

Figure 1. ROI-to-ROI connectivity patterns that significantly differed between adolescents with obesity and those with lean weight.

Figure 2. ROI-to-ROI connectivity patterns that significantly differed between adolescents with overweight and those with lean weight.



oby_22853_f1.png



oby_22853_f2.png