Original Article
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Obesity

Weight-Related Differences in Salience, Default Mode, and Executive Function Network Connectivity in Adolescents

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

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

Results: Adolescents with obesity compared with those with lean weight showed stronger within-SN connectivity among the medial orbitofrontal cortex, olfactory tubercle, and pallidum; however, they 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 with those with lean weight showed lower connectivity between SN (medial orbitofrontal cortex) and EFN (ventrolateral prefrontal cortex) regions.

Conclusions: Obesity appears to be related to stronger connectivity within and between regions implicated in determining the 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 "off-line" when salience and reward-processing regions are engaged in adolescents who have obesity.

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Study Importance

What is already known?

- 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.

What does this study add?

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

How might these results change the focus of clinical practice?

- 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.

Introduction

Obesity prevalence is 13.9% among 2- to 5-year-olds and 20.6% among 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 with 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

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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 with 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 making up each of these networks and their 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, the 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 participants aged 10 to 14, participants with obesity had greater rsFC between the EFN (left middle frontal gyrus, left ventromedial prefrontal cortex) and SN (left orbitofrontal cortex [OFC]) (17). In a larger sample of 115 adolescents aged 12 to 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 to 18, excess weight (BMI ≥ 85th percentile) was associated with greater within-SN connectivity (lateral hypothalamus, OFC, striatum, and insula) and lower connectivity between the SN (medial hypothalamus) and EFN (middle frontal gyrus) and DMN (precuneus) (19). This could indicate a greater propensity to find rewarding stimuli particularly salient and a lower propensity to exert executive control in the context of rewards.

In sum, the current rsFC literature on adolescent obesity is inconsistent and further research in sufficiently powered studies is required. 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) and 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 to 16 whose weight status ranged from lean to obesity. To clarify the directionality of rsFC patterns associated with obesity, we employed seed-based analyses to test hypothesized connections between specific regions of interest (ROIs) included in the DMN, SN, and EFN, on the basis of prior findings that connectivity in these networks differs with weight status (13-14,17-19). We also attempted to standardize prescan 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

TABLE 1 Regions and theorized functions of canonical neural networks

Network	Sample regions	Theorized functions
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
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
SN (10,11)	Limbic and paralimbic regions (e.g., insula, caudate, orbitofrontal cortex)	Processing of information related to emotion, reward, and homeostatic regulation

DMN, default-mode network; EFN, executive-function network; SN, salience network.

investigation of how overweight was associated with rsFC differences in adolescence.

Methods

Participants

Participants were 186 adolescents aged 13 to 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, BMI percentile <5%, or fMRI contraindicators (e.g., presence of metal implants). Nine participants did not complete the resting-state scan; thus, they were not included in the current rsFC analyses. Nine participants were excluded because of excessive motion during the resting-state scan (i.e., less than 5 minutes of usable data). Participants excluded for excessive motion did not differ significantly in weight status from those included in the final sample ($\chi^2 = 0.02$, $P = 0.99$). Four participants were excluded because of problems in imaging data following preprocessing (e.g., unsuccessful coregistration) detected during quality assurance (QA) checks. Thus, the final sample included in these analyses comprised 164 adolescents (87 female, 77 male; mean age = 14.3 [SD 1.0], range: 13-16 years; mean BMI = 24.1 [SD 5.4]; BMI *z* score [*z*BMI] = 0.86 [0.9]) with lean weight ($n = 88$ [53.7%]), overweight ($n = 40$ [24.4%]), or obesity ($n = 36$ [22.0%]). Table 2 provides 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 underwent a high-resolution anatomical scan and an rsFC paradigm followed by a functional task investigating neural response to different types of advertising (21).

Participants were asked to eat typical meals but were asked not to consume any food or drink other than water between their last meal and the scan procedure. Scans occurred prior to typical mealtimes, with 87% of the scans occurring between 3 PM and 6 PM and the remaining scans occurring between 10:30 AM and 2 PM. Participants who rated their hunger at 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

BMI. Age- and sex-adjusted *z*BMI was used to assess adiposity. Height in centimeters and weight in kilograms were measured in the laboratory using an O'Leary Acrylic Stadiometer (Ellard Instrumentation LLD, Monroe, Washington) and Detecto Portable Scale (Cardet, Webb City, Missouri), respectively. Participants were asked to remove shoes, socks, and heavy clothing before having their height and weight measured. BMI (kilograms per meter squared) was calculated using height and weight measured in the laboratory and

TABLE 2 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 χ^2	P	η^2 or φ
Sex, *n* (%)					1.62	0.45	0.10
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)			
Race, *n* (%)					4.54	0.34	0.17
White	112 (68.3)	63 (71.6)	25 (62.5)	24 (66.7)			
Nonwhite	43 (26.2)	19 (21.6)	12 (30.0)	12 (33.3)			
Age, mean (SD)	14.30 (1.03)	14.14 (1.04)	14.40 (1.01)	14.58 (0.97)	2.73	0.07	0.03
Prescan hunger, mean (SD)	23.76 (21.28)	26.76 (20.50)	18.68 (19.64)	22.06 (24.05)	2.16	0.12	0.03
*z*BMI, mean (SD)	0.83 (0.94)	0.14 (0.61)	1.35 (0.17)	2.06 (0.32)	233.14	0.00	0.74

χ^2 test statistics (χ^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 race; thus, percentages for race variable do not add to 100%.
*z*BMI, BMI *z* score.

then converted to *z* scores using age- and sex-adjusted BMI growth curves (22). Weight status was classified as overweight, with a *z*BMI cutoff of >+1 SD, and as obesity, with a *z*BMI cutoff of >+2 SD.

Hunger. Hunger was assessed immediately before the scan. Participants rated their hunger using a visual analog scale 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 that they had not fallen asleep.

Analysis

fMRI scanner and data acquisition. MRI images were acquired using a GE Discovery MR750 3-T scanner (GE Healthcare, Chicago, Illinois) with an eight-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 scanning and the functional paradigm. Spiral imaging was used to measure the blood oxygen level–dependent (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 uses a high-readout bandwidth and a shorter echo time. Functional data were acquired with the following parameters: repetition time = 2,000 milliseconds, echo time = 30 milliseconds, inversion time = 500 milliseconds, flip angle = 90°, field of view = 22 × 22 cm^2, acquisition matrix = 64 × 64, 3-mm section thickness with no gap, and 43 axial sections. Anatomical scans were acquired using a high-resolution longitudinal relaxation time (T1)-weighted spoiled gradient–recalled acquisition (repetition time = 12.3 milliseconds, echo time = 5.2 milliseconds, inversion time = 500 milliseconds, flip angle = 15°, field of view = 22 × 22 cm^2, section thickness = 1.0 mm). Sections were prescribed parallel to the anterior commissure/posterior commissure (AC-PC) line (same locations as structural scans). Images were reconstructed into a 64 × 64 matrix. Sections were acquired contiguously, which optimized the effectiveness of the movement postprocessing algorithms. Images were reconstructed off-line using processing steps to remove distortions caused by magnetic field inhomogeneity and other sources of misalignment of the structural data, which yielded excellent coverage of subcortical areas of interest.

Preprocessing of neuroimaging data. fMRI data were preprocessed using SPM12 (Wellcome Department of Imaging Neuroscience; Institute of Neurology, University College of London, London, UK) and the CONN toolbox (www.nitrc.org/projects/conn) (23). Functional images were realigned to the scan immediately preceding the anatomical T1 image, and section time was corrected. Anatomical and rsFC images were coregistered and normalized to the Montreal Neurological Institute T1 template brain (24). Functional images were smoothed with a 6-mm full-width-at-half-maximum (FWHM) isotropic Gaussian kernel. We used Artifact Detection Tools (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 >0.2-mm motion. During denoising, white matter, cerebral spinal fluid (CSF), motion parameters plus first-order temporal derivatives, and the censored frames were all regressed out of the data prior to band-pass filtering. Mean imputation was conducted to interpolate the censored time points. A high-pass filter (128 seconds) and band-pass filter (0.01-0.1 Hz) were applied to remove low-frequency noise and signal drifts. Participants were excluded if the retained frames (motion < 0.2 mm) resulted in less than 5 minutes of usable data (i.e., movement > 0.2 mm). 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 0.10 mm. On completion of the above spatial preprocessing steps, QA plots were examined to confirm successful coregistration of structural and functional images and normalization to the template. QA plots showing voxel-to-voxel functional connectivity values and BOLD time series 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 six planes (*x*, *y*, *z*, pitch, roll, yaw) detected by Artifact Detection Tools and their derivatives were included as nuisance covariates. In second-level analyses, we used a general linear model to examine how rsFC strength within and among 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 (Table 3 provides a list of all ROIs tested) (9-11). ROIs were defined using masks derived from the Montreal Neurological Institute automated anatomical labeling (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 correction at $P < 0.05$ at the analysis level (25). Significant connectivity coefficients were extracted for each participant. Next, rsFC correlation maps were converted to *z* scores using Fisher *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 on the basis of 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 with those with lean weight showed greater within-SN connectivity, specifically between the bilateral

TABLE 3 Networks and source ROIs

Network	Source ROIs	MNI coordinates (left)			MNI coordinates (right)		
		x	*y*	*z*	*x*	*y*	*z*
DMN (9,11)	Hippocampus	−25	−22	−11	29	−21	−12
	IPL	−43	−47	45	46	−48	48
	MFG	−34	31	34	37	32	33
	Parahippocampus	−21	−17	−22	25	−16	−22
	PCC	−5	−44	23	7	−43	20
	Precuneus	−8	−57	47	10	−57	42
	vlPFC	−45	30	3	46	30	3
	vmPFC	−22	47	12	23	47	12
SN (10,11)	Amygdala	−24	2	−18	27	−1	−19
	ACC	−4	34	13	8	36	14
	Caudate	−12	10	8	14	11	8
	Insula	−35	5	2	39	5	1
	NAcc	−13	7	−12	12	9	−11
	Olfactory tubercle	−8	14	−13	10	15	−13
	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)	dlPFC	−33	34	30	34	34	30
	vlPFC	−45	30	3	46	30	3

ACC, anterior cingulate cortex; dlPFC, dorsolateral prefrontal cortex; DMN, default mode network; EFN, executive function network; IPL, inferior parietal lobe; MFG, middle frontal gyrus; MNI, Montreal Neurological Institute; NAcc, nucleus accumbens; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; ROI, region of interest; SN, salience network; vlPFC, ventrolateral prefrontal cortex; vmPFC, ventromedial prefrontal cortex.

caudate and the 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 with those with lean weight showed lower within-SN connectivity between the right amygdala and the right nucleus accumbens (NAcc) and bilateral thalamus and between the right amygdala and the right putamen. Adolescents with overweight compared with those with lean weight showed lower connectivity between the right amygdala and the right NAcc (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 with those with obesity.

Between-network connectivity

Adolescents with obesity compared with those with lean weight showed lower connectivity between the DMN and SN, specifically between the right parahippocampus and the left ACC, left amygdala, left olfactory tubercle, and left NAcc and between the bilateral caudate and the right hippocampus. Adolescents with obesity compared with those with lean weight showed lower connectivity between the SN and EFN, specifically between the right medial OFC and the left and middle ventrolateral prefrontal cortex (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 with either those with lean weight or those 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- to 16-year-old adolescents (n = 164). Adolescents with obesity compared with 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 an 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 middle vlPFC) in adolescents with obesity compared with 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 SN engagement.

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	0.032
	R parahippocampus	−3.38	0.015
	R putamen	−3.34	0.015
	Thalamus	−2.68	0.045
	Caudate		
	Precuneus	3.14	0.029
	R hippocampus	−4.12	0.002
	Hippocampus		
	Caudate	−4.12	0.002
	Medial OFC		
	Olfactory tubercle	3.69	0.009
	L pallidum	3.12	0.029
	L vlPFC	−3.01	0.029
	Middle vlPFC	−2.85	0.035
	Olfactory tubercle		
	R medial OFC	3.69	0.009
	Parahippocampus		
	L NAcc	−2.83	0.037
	L olfactory tubercle	−2.87	0.037
	L ACC	−3.03	0.037
	L amygdala	−3.38	0.025
	Putamen		
	R amygdala	−3.34	0.029
Adolescents with overweight > adolescents with lean weight	Amygdala		
	R NAcc	−3.25	0.040
	R NAcc		
	R amygdala	−3.25	0.040

ACC, anterior cingulate cortex; NAcc, nucleus accumbens; L, left; OFC, orbitofrontal cortex; *p*FDR, false discovery rate correction at $P < 0.05$; ROI, region of interest; SN, salience network; R, right; rsFC, resting-state functional connectivity; vlPFC, ventrolateral prefrontal cortex.

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 with those with lean weight showed greater connectivity between the caudate and the 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 the 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 the precuneus in the context of food stimuli.

In contrast to stronger rsFC between the caudate and the precuneus, we found obesity to be associated with lower connectivity among several areas in the DMN (hippocampus, parahippocampus) and the SN (caudate, amygdala, ACC). This may be due to differing functions among the specific DMN regions. The precuneus is activated in response to cues (36,37), whereas 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, whereas 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

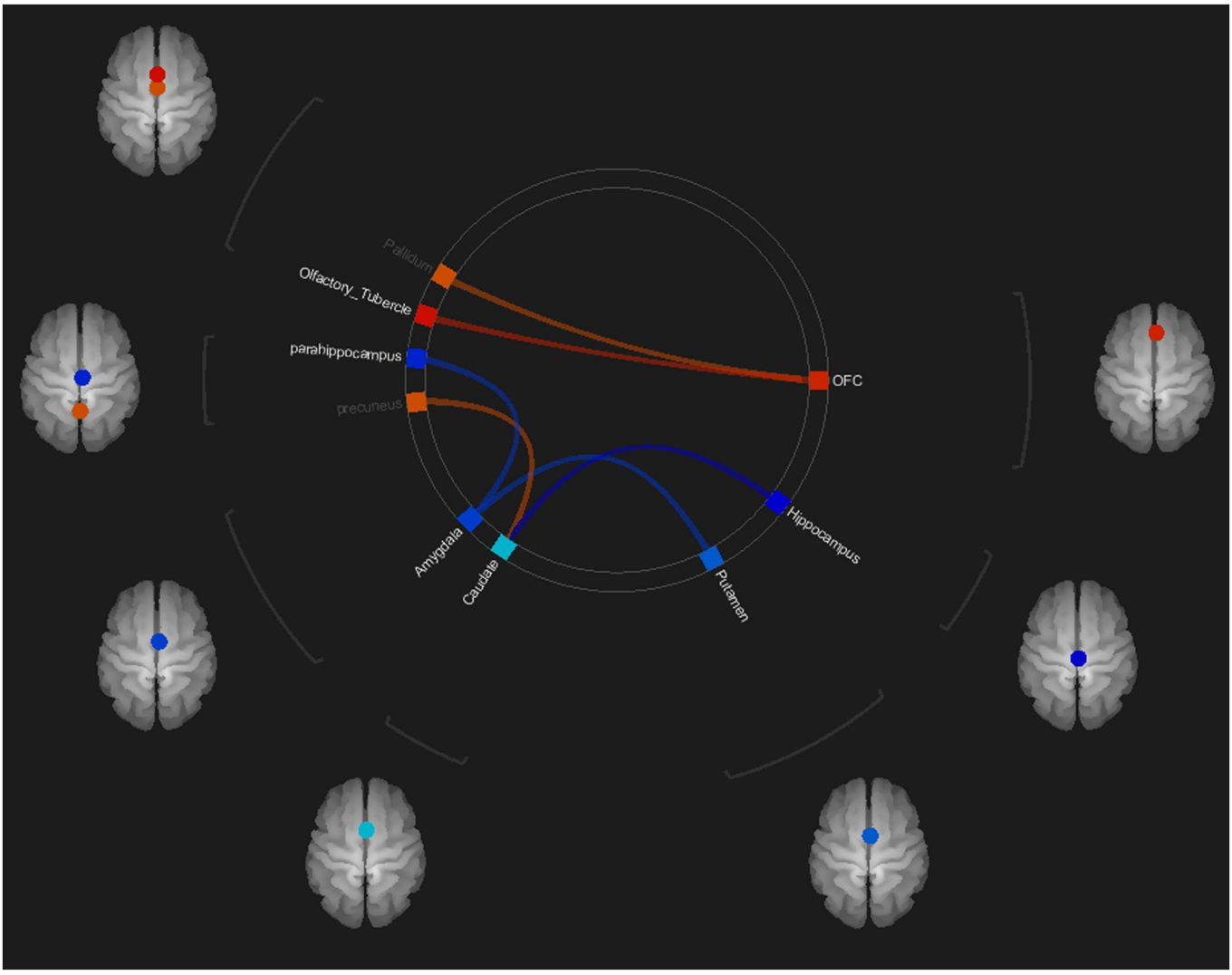

Figure 1 ROI-to-ROI connectivity patterns that significantly differed between adolescents with obesity and those with lean weight. OFC, orbitofrontal cortex; ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

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 years), reward regions are relatively well developed, and executive-function regions are relatively underdeveloped (5). In a younger sample, reward regions may also be relatively underdeveloped (40), thus not yet building strong connections among one another. In a sample with a wider age range, developmental differences within the sample may impact the relative contribution of reward and EFN 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.

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

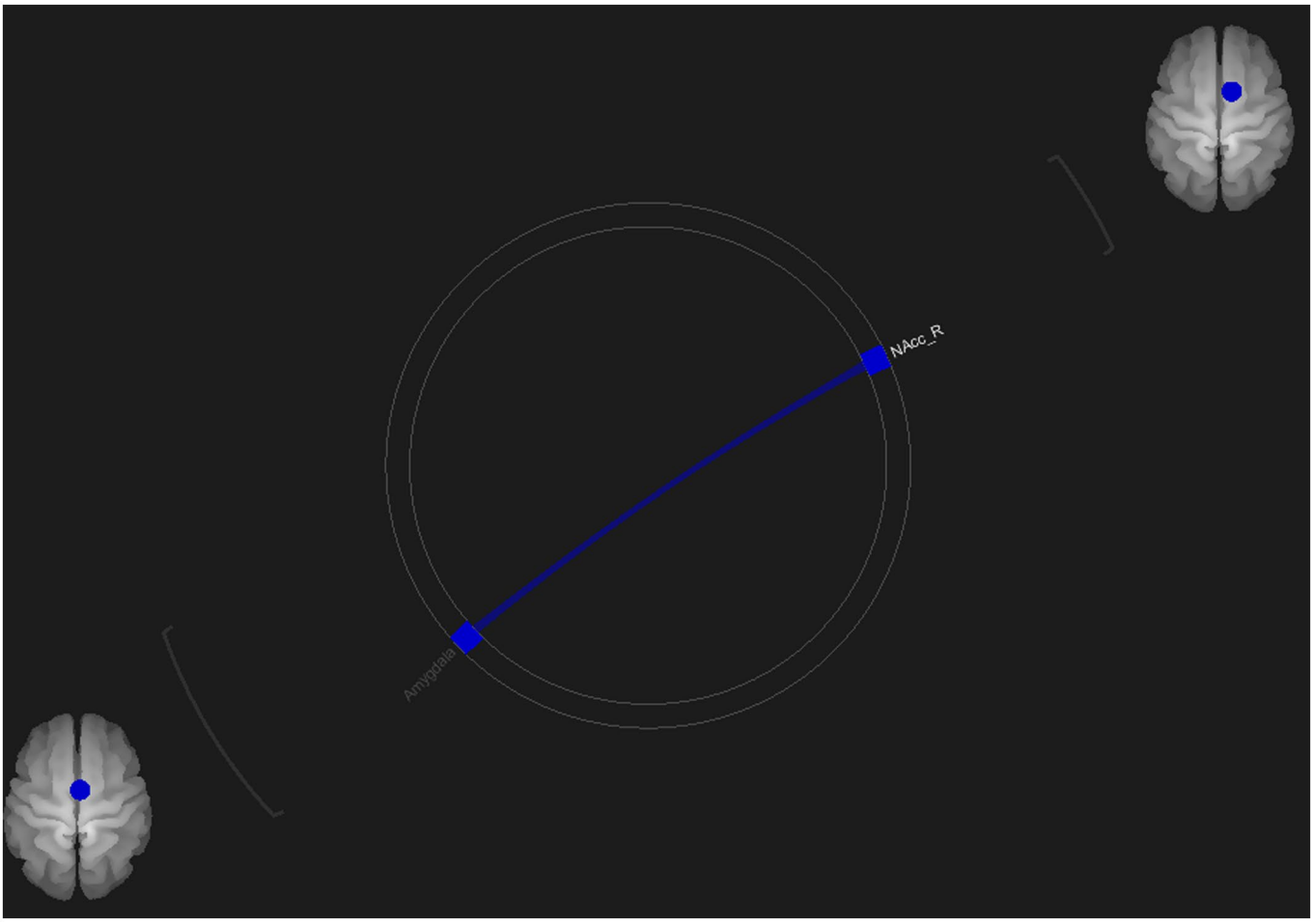

Figure 2 ROI-to-ROI connectivity patterns that significantly differed between adolescents with overweight and those with lean weight. NAcc_R, right nucleus accumbens; ROI, region of interest. [Color figure can be viewed at wileyonlinelibrary.com]

performance, will further elucidate the impact behavior may have on functional organization and could inform the development of potential interventions. Although 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-minute) 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 is 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 our findings with those of existing literature. However, this approach limited our 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 used 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). Although neural-network results in individuals with obesity 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 found only limited differences between those with overweight and those with lean weight. In the current study, we calculated weight status using *z*BMIs 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 *z*BMIs, that may particularly impact those in the overweight category (45). For example, individuals who are particularly

muscular for their age may be categorized as having overweight, along with those with excess body fat. This combination of body composition within the same category may limit the 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.

Conclusion

The current study provides support for the hypothesis that obesity in adolescence is associated with differences in functional organization in areas of the SN and DMN. Stronger connectivity within the SN (medial OFC, olfactory tubercle, and pallidum), stronger connectivity 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 among 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. O

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