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Ventral and Dorsal Striatum Networks in Obesity: Link to Food Craving and Weight Gain

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ABSTRACT

BACKGROUND: The food addiction model proposes that obesity overlaps with addiction in terms of neurobiological alterations in the striatum and related clinical manifestations (i.e., craving and persistence of unhealthy habits). Therefore, we aimed to examine the functional connectivity of the striatum in excess-weight versus normal-weight subjects and to determine the extent of the association between striatum connectivity and individual differences in food craving and changes in body mass index (BMI).

METHODS: Forty-two excess-weight participants (BMI $>$ 25) and 39 normal-weight participants enrolled in the study. Functional connectivity in the ventral and dorsal striatum was indicated by seed-based analyses on resting-state data. Food craving was indicated with subjective ratings of visual cues of high-calorie food. Changes in BMI between baseline and 12 weeks follow-up were assessed in 28 excess-weight participants. Measures of connectivity in the ventral striatum and dorsal striatum were compared between groups and correlated with craving and BMI change.

RESULTS: Participants with excess weight displayed increased functional connectivity between the ventral striatum and the medial prefrontal and parietal cortices and between the dorsal striatum and the somatosensory cortex. Dorsal striatum connectivity correlated with food craving and predicted BMI gains.

CONCLUSIONS: Obesity is linked to alterations in the functional connectivity of dorsal striatal networks relevant to food craving and weight gain. These neural alterations are associated with habit learning and thus compatible with the food addiction model of obesity.

Keywords: Body mass index change, Excess weight, Food craving, Functional connectivity, Obesity, Striatum

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In rich societies, the ubiquitous availability of appetizing high-calorie foods has increased the relevance of brain reward systems in governing food intake (1). In this context, recent theories have proposed a food addiction model of obesity, by which sensitization of the brain centers that represent reward and habits (i.e., the striatum) can lead to food craving, inability to cut down food intake, and weight gain (2–4).

The food addiction model is grounded in neuroimaging evidence showing that obese individuals display increased food cue-evoked activation in cortical-striatal regions that code food-related reward value (i.e., ventral striatum) and hedonic properties (i.e., insula/somatosensory cortices) and food choices (i.e., medial prefrontal/orbitofrontal cortex) (5–11). Moreover, food cue-evoked activation in these regions is associated with subjective measures of craving (9–13) and body mass index (BMI) gains (14–16). These regional alterations are plausibly associated with abnormalities in a broader network between the striatum and prefrontal regions representing food value. For example, neuroimaging studies have shown that functional connectivity between the ventral striatum and the medial prefrontal cortex correlates with external food sensitivity in healthy samples (17). Moreover, positron emission tomography studies have shown that obese individuals, akin to addicts, display reduced dopamine D_2 receptors in the striatum (18) linked to lower orbitofrontal cortex metabolism (19).

The food addiction model also assumes that severity of obesity is associated with neuroadaptations in the dorsal striatum network (4). This assumption is based on preclinical studies showing that self-administration of addictive drugs leads to neuroadaptations in the dorsal striatum (2,3,20). This is further illustrated by human neuroimaging studies on drug craving: in severe substance users, drug-related cues activate dorsal striatum regions implicated in habits processing (21,22). Therefore, dorsal striatal neuroadaptations have been implicated in the transition between incentive-based and habit-based control of behavior. Hence, greater involvement of the dorsal striatum is predicted as food intake becomes addictive or compulsive (3,4). In obese patients, high-calorie food intake is subjectively perceived as less pleasurable but strongly driven by habits (23,24), and they show increased dorsal striatum activation in response to food cues (6,7,25) and reduced activation during food receipt (6,7).

Altogether, ventral and dorsal striatum networks are relevant to the pathophysiology of obesity and to the association

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between obesity and addiction-related characteristics, such as craving and persistent high-calorie food intake. We aimed to contrast the functional connectivity of ventral and dorsal striatum networks in excess-weight versus normal-weight participants and to determine the association between functional connectivity in the striatum and individual differences in food craving and weight gain. We applied a seed-based resting-state functional connectivity approach to assess ventral and dorsal striatum networks (26). Resting-state fluctuations reflect cognitive and emotional biases that contribute to shape individuals' preferences; thus, striatal connectivity measures may have predictive validity in relation to craving and food intake (27,28). We hypothesized that excess-weight participants compared with normal-weight control subjects would show increased functional connectivity in the ventral and dorsal striatum. Increased dorsal striatal connectivity would be associated with greater food craving and weight gain.

METHODS AND MATERIALS

Participants

Forty-two subjects with excess weight (BMI >25) and 39 subjects with normal weight enrolled in the study. Participants were recruited via general hospitals and community advertisement (i.e., local press, radio, and social media) and enrolled if they were aged 18 to 45 and had BMI >18. Exclusion criteria were 1) history of brain injury or diseases impacting the central nervous system; 2) history of substance use, major depression, or psychosis; 3) self-reported use of psychotropic medication; and 4) morbid obesity (BMI ≥ 40). The two groups had similar sociodemographic characteristics (Table 1). The Universidad de Granada Human Research Ethics Committee approved the study, and all participants provided informed consent.

Participants were involved in two assessment sessions. At baseline, they 1) were measured and weighed to calculate BMI via an automated scale; 2) underwent a functional magnetic resonance imaging (fMRI) scan; 3) rated their food craving immediately after fMRI scan; and 4) had a 30-minute diet counseling session with a professional dietitian who provided specific strategies to lose weight (i.e., excess-weight group only). At 12-week follow-up, excess-weight participants (n = 28, 67% of the original sample) were reassessed to calculate change in BMI relative to baseline. Twelve weeks is the standard benchmark to assess the outcome of weight loss interventions (29).

Measures

Imaging Data Acquisition and Preprocessing. All participants were scanned at the same time of the day (4:00 to 6:00 PM) and after lunch, which is typically between 2:00 and 4:00 PM. Prescanner ratings of hunger (0–100 visual analog scale [VAS]) did not differ between groups (Table 1). Participants underwent a 6-minute resting-state scan. They were instructed to lie still with eyes closed. We used a 3.0 Tesla clinical magnetic resonance imaging scanner, equipped with an eight-channel phased-array head coil (Intera Achieva Philips Medical Systems, Eindhoven, The Netherlands). A T2*-weighted echo-planar imaging was obtained (repetition time = 2000 ms, echo time = 35 ms, field of view = 230 × 230 mm, 96 × 96 pixel matrix; flip angle = 90º, 21 4-mm axial slices, 1-mm gap, 180 whole-brain volumes). The sequence included four initial dummy volumes to allow the magnetization to reach equilibrium.

Food Craving. Participants viewed six photographs of highly appetizing food stimuli, all rich in sugar and fat content (e.g., cheesecake, chocolate), and were instructed to rate their level of craving using VAS (range 0–10). The dependent measure was the mean score of the six VAS ratings. To increase the task's validity, all participants were pre-exposed to these foods in a catered tasting session conducted 1 week before the scan (Supplemental Figure S1).

Table 1. Demographics and Clinical Characteristics of the Study Groups

	Normal Weight (n = 39)	Excess Weight (n = 42)
Age (Years)	33.07 (6.73)	33.59 (6.16)
Education (Years)	18.18 (3.75)	17.50 (3.77)
Sex (Men/Women)	18 (46.2%)/21 (53.8%)	20 (47.6%)/22 (52.4%)
BMI Baseline (kg/m^2)[a,b]	22.09 (1.74)	30.51 (3.63)
BMI Change (kg/m^2)[c,d]	−.03 (.72)	−.60 (1.66)
Food Craving	5.47 (1.36)	5.93 (1.39)
Hunger Before fMRI	15.03 (19.07)	16.27 (18.72)
Hunger After fMRI	39.59 (28.62)	44.20 (25.45)
Impulsivity (Delay Discounting Area Under the Curve)[e]	.55 (.19)	.58 (.23)
Compulsivity (Reversal Learning Perseveration Error Rate)[f]	1.66 (.69)	1.67 (.74)

Except for sex, all values are mean (± SD).
BMI, body mass index; fMRI, functional magnetic resonance imaging.
[a] $p \leq .01$.
[b] BMI minimum/maximum values, normal weight 19/24.8, excess weight 25.20/38.30.
[c] Data for 24 normal-weight and 28 excess-weight participants at 12 weeks follow-up.
[d] Minimum/maximum values, normal weight −1.70/1.30, excess weight −4.60/4.70.
[e] Data from two normal-weight and two excess-weight participants are missing.
[f] Data from one excess weight are missing.

BMI Change. Changes in BMI were computed by subtracting baseline BMI from follow-up BMI, and thus positive values reflected weight gain. This change index is a standard outcome measure in obesity treatment research (30,31).

Cognitive Measures. Standard measures of impulsivity (i.e., delay discounting task) (32) and compulsivity or habit learning (i.e. reversal learning task) (33) were also assessed (see detailed procedures in the Supplement).

Analyses

Imaging Analyses and Preprocessing. The functional imaging data were processed and analyzed using MATLAB version R2008b (The MathWorks Inc., Natick, Massachusetts) and statistical parametric mapping software (SPM8; The Welcome Department of Imaging Neuroscience, London, United Kingdom). Preprocessing steps involved motion correction, spatial normalization, and smoothing using a Gaussian filter (full width at half maximum 8 mm). Data were normalized to the standard SPM echo planar imaging (EPI) template and resliced to a 2-mm isotropic resolution in Montreal Neurological Institute space. We compared both study groups for potential differences in movement for translations and rotations and found no significant differences (mean total movement [SD], normal-weight control subjects = .31 [.18], excess-weight participants = .31 [.29], $p = .34$).

Striatal Seed-Based Functional Connectivity Analyses. Following prior work (26,34), ventral and dorsal striatal subregions were distinguished using $z < 7$ mm as a marker for the ventral caudate (VC)/nucleus accumbens, $z > 7$ mm as a marker for dorsal caudate, and $z = 2$ as the boundary between the dorsal and ventral putamen per hemisphere. Respective seeds of interest were placed in VC (corresponding approximately to the nucleus accumbens) ($x = \pm 9$, $y = 9$, $z = -8$), ventral rostral putamen (VP) ($x = \pm 20$, $y = 12$, $z = -3$), dorsal caudate (DC) ($x = \pm 13$, $y = 15$, $z = 9$), and dorsal caudal putamen ($x = \pm 28$, $y = 1$, $z = 3$) using 3.5-mm-radius spheres. We included in the model two intermediate seeds (of no interest) located in the ventral caudate superior ($x = \pm 10$, $y = 15$, $z = 0$) and dorsal rostral putamen ($x = \pm 25$, $y = 8$, $z = 6$) to replicate the fine striatal parcellation method, and no seed placements were made in the globus pallidus, substantia nigra, or subthalamic nucleus considering the spatial data resolution and the smoothing.

First-level (single subject) maps were estimated in whole-brain SPM8 linear regression analyses for each striatal seed region (34) by including its mean activity time courses extracted via the MarsBaR toolbox (http://marsbar.sourceforge.net) (35) together with nuisance signals as predictors of interest and no interest. Nuisance signals included six head-motion parameters (three translations and three rotations) and time courses representing mean signal fluctuations in white matter, cerebrospinal fluid, and the entire brain. Separate first-level analyses were carried out for right and left hemisphere striatal regions. A high-pass filter (128 seconds) was used to remove low-frequency drifts. Contrast images were generated for each subject by estimating the regression coefficient between all brain voxels and each seed's time series and were then included in separate two-sample models to assess within- and between-group effects. All imaging results were considered significant with a cluster of 1960 mm^3 (245 voxels) at a height threshold of $p < .005$, which satisfied the family-wise error rate correction of $p_{\text{familywise error}} < .05$ according to Monte Carlo simulations using Alphasim within the REST toolbox (http://www.restfmri.net) (36) with a cluster connection radius of 5 mm, 12-mm full width at half maximum smoothness, and incorporating a gray matter mask volume of 128.190 voxels ($2 \times 2 \times 2$ mm). The selected threshold was deemed appropriate to control for type I error, as the targeted striatal networks have been previously defined and have anatomical specificity (26,34).

Associations With Food Craving and Prediction of BMI Change. We conducted correlations between the functional connectivity maps of the striatum and food craving in SPM8. We conducted these analyses in each group separately, as we were specifically interested in individual differences in this relationship within the excess-weight group. Analyses were considered significant at a height threshold of $p < .005$, 1960 mm^3 (245 voxels) whole brain. A multiple regression analysis was conducted in SPSS version 22.0 (IBM Corp., Armonk, NY) to examine if functional connectivity associated with craving predicted BMI change. This analysis was thresholded at $p \leq .01$ (at least 10% prediction).

RESULTS

Functional Connectivity in Ventral and Dorsal Striatum

Within-group positive and negative functional connectivity maps of the ventral and dorsal striatum networks overlapped with previously described neurofunctional maps of these networks (26,34) (Supplemental Table S1 and Supplemental Figure S2).

Between-Group Differences in Functional Connectivity

Results are displayed in Figure 1 and Table 2 and are described below.

Ventral Striatum. Excess-weight participants compared with normal-weight control subjects showed increased functional connectivity between the VC seed and the medial prefrontal cortex and between both ventral striatum seeds (VC and VP) and the parietal cortex, including posterior cingulate, angular gyrus, and somatosensory regions. Moreover, excess-weight participants showed increased anticorrelation between the VC seed and the dorsal anterior cingulate cortex and the posterior insula and between the VP seed and the lateral orbitofrontal cortex.

Dorsal Striatum. Excess-weight participants showed increased functional connectivity between the DC seed and the somatosensory cortex. Moreover, excess-weight participants showed increased anticorrelation between the DC seed and the cerebellum. There were no group differences in the dorsal caudal putamen seed at the selected threshold.

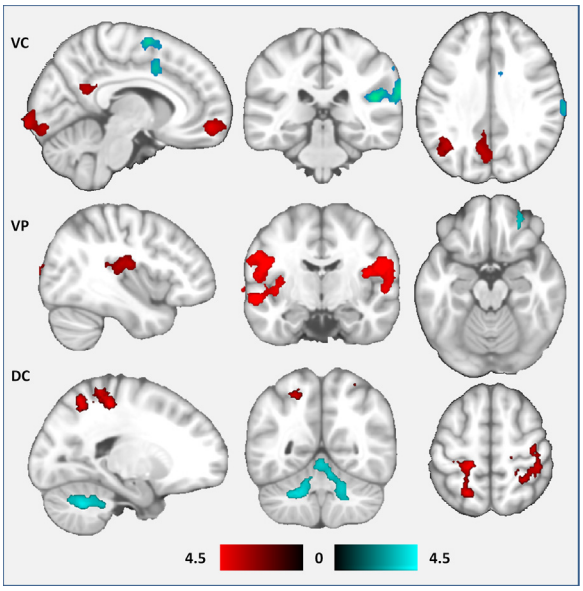

Figure 1. Brain regions showing increased connectivity (red) or increased anticorrelation (blue) with the striatum in excess-weight compared with normal-weight participants. The right hemisphere corresponds to the right side of axial views, and the sagittal images show the right hemisphere. The color bars indicate *t* values. Results are displayed at $p < .005$, uncorrected. DC, dorsal caudate; VC, ventral caudate; VP, ventral rostral putamen.

Correlations With Food Craving

In excess-weight participants, food craving was positively associated with functional connectivity between the DC seed and the somatosensory cortex (x = 46, y = −32, z = 62, $t = 3.8$, $p < .005$, 265 voxels). In normal-weight participants, in turn, food craving was positively associated with functional connectivity between the VP seed and the orbitofrontal cortex (x = −32, y = 50, z = −2, $t = 4.8$, $p < .005$, 459 voxels) (Figure 2). Fisher's tests of between-group differences were not significant (DC-somatosensory: $F = 1.32$, $p = .09$; VP-orbitofrontal cortex: Fisher's $F = 1.06$, $p = .14$). Additional correlations (i.e., functional connectivity patterns that do not map on between-group differences) are reported in Supplemental Table S2.

To further explore the link between BMI-related variation in striatum networks and food craving, we examined this association within subgroups with obesity (BMI ≥ 30, $n = 21$), overweight (BMI > 25 < 30, $n = 21$), and normal weight. Thus, we extracted the eigenvariate signal from the peak voxel in the orbitofrontal cortex cluster linked to the VP seed and food craving in normal-weight control subjects and the eigenvariate signal from the peak voxel in the somatosensory cortex cluster linked to the DC seed and food craving in excess-weight participants. We found that the positive association between VP-orbitofrontal functional connectivity and food craving was lower within participants with greater BMI (i.e., normal weight, $r = .476$, $p = .001$; overweight, $r = .313$, $p = .044$; obese, $r = .141$, $p = .373$) (Supplemental Figure S2). Conversely, the positive association between DC-somatosensory cortex functional connectivity and food craving was higher in participants with greater BMI (i.e., normal weight, $r = .073$, $p = .527$; overweight, $r = .326$, $p = .035$; obese, $r = .378$, $p = .014$).

Prediction of BMI Change

On average, BMI changed from 30.51 (SD = 3.63) to 29.95 (SD = 3.43) among excess-weight participants (1.96% change). The two networks associated with craving were included in a multiple regression model to predict the change in BMI. The functional connectivity between the VP seed and the orbitofrontal cortex was not associated with BMI change ($F_{\text{Change } 1,53} = .001$, $p = .982$, $R^2 = .000$), yet inclusion of the functional connectivity between the DC seed and the

Table 2. Between-Group Differences in Striatal Functional Connectivity

Seed	Brain Region	x, y, z	*t*	CS	Direction
VC	Medial PFC	6, 56, −10	4.5	666	Excess > Normal Weight
	PCC	−6, −68, 30	3.7	861	Excess > Normal Weight
	Angular gyrus	−40, −64, 40	3.9	443	Excess > Normal Weight
	Occipital cortex	6, −90, −12	3.6	438	Excess > Normal Weight
	Dorsal ACC-SMA	8, 0, 64	3.8	399	Normal > Excess Weight
	Posterior insula	48, −34, 18	4.2	554	Normal > Excess Weight
VP	Insula	40, −12, 16	4.0	1175	Excess > Normal Weight
		−40, −8, 2	3.7	1306[a]	Excess > Normal Weight
	Somatosensory cortex	56, −10, 24	4.5	1175	Excess > Normal Weight
		−54, −12, 30	3.8	1306[a]	Excess > Normal Weight
	Temporal	−58, −10, −8	4.5	1306[a]	Excess > Normal Weight
	Lateral OFC	−26, 20, −22	4.2	789	Normal > Excess Weight
DC	Somatosensory cortex	40, −38, 60	3.5	521	Excess > Normal Weight
		−18, −32, 56	4.2	692	Excess > Normal Weight
	Cerebellum	−22, −58, −34	3.9	1558	Normal > Excess Weight

Coordinates (x, y, z) are given in Montreal Neurological Institute atlas space.

ACC, anterior cingulate cortex; CS, cluster size; DC, dorsal caudate; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; PFC, prefrontal cortex; SMA, supplementary motor area; VC, ventral caudate; VP, ventral putamen.

[a]Part of the large cluster.

somatosensory cortex showed statistically significant effects ($F_{\text{Change } 1,53} = 6.787$, $p = .01$, $R^2 = .114$). DC-somatosensory functional connectivity was positively associated with BMI change, accounting for 11% of BMI change (Figure 3).

Sensitivity and Post Hoc Analyses

To examine if longitudinal associations between functional connectivity and BMI gain were driven by baseline correlations, we conducted bivariate correlations between the functional connectivity associated with food craving and BMI at baseline and BMI change. The functional connectivity between the DC seed and the somatosensory cortex was only associated with BMI change ($r = .33$, $p = .01$) but not with baseline BMI ($r = -.11$, $p = .33$).

To better delineate the implications of the connectivity findings, we ran post hoc correlations between the striatal connectivity patterns and cognitive measures of impulsivity and compulsivity. The functional connectivity between the DC seed and the somatosensory cortex was significantly associated with the

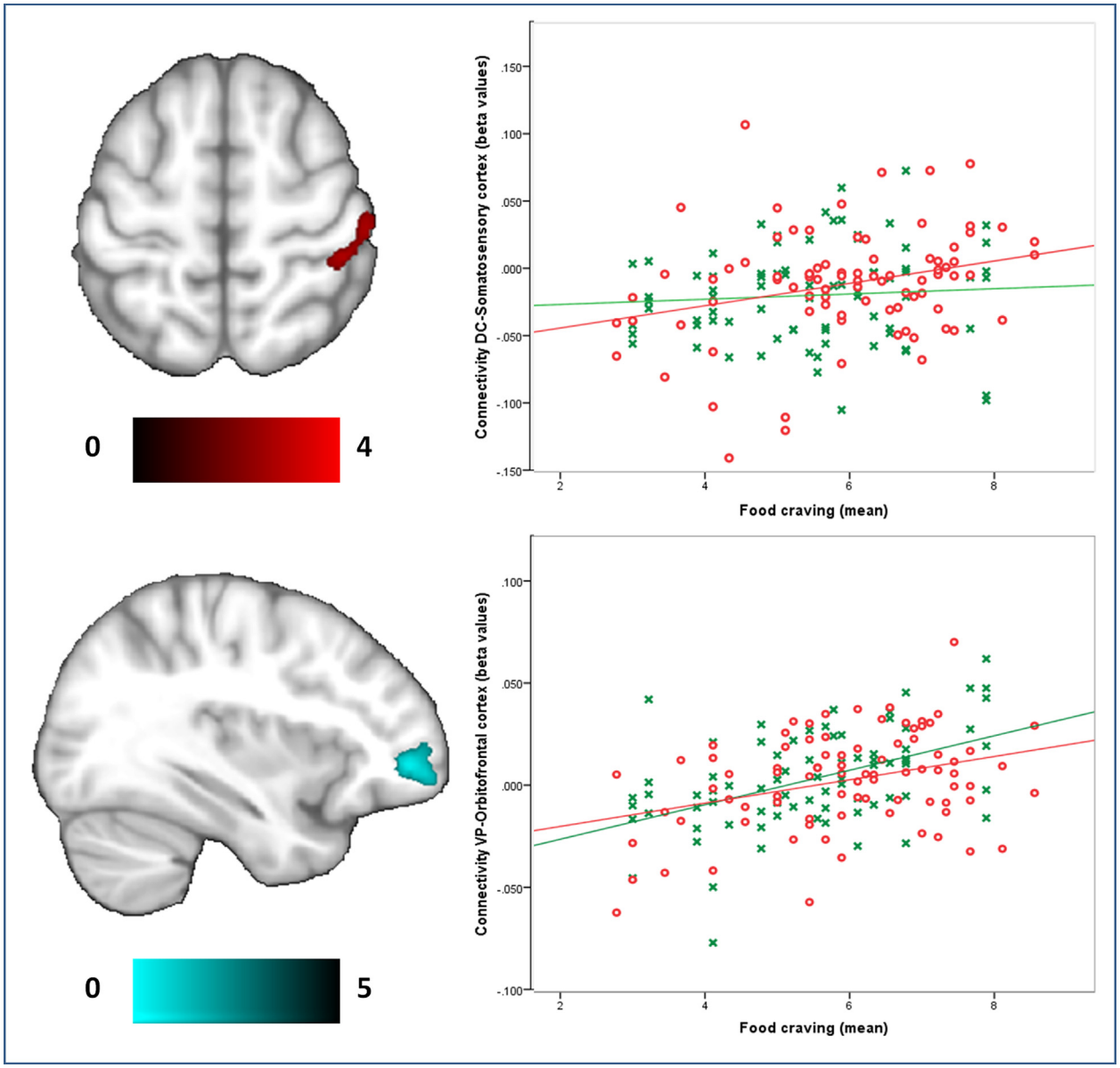

Figure 2. Correlations between food craving and the connectivity between the dorsal caudate (DC) and the somatosensory cortex in excess-weight participants (top panel, MNI coordinates, DC-Somatosensory, x = 46, y = −32, z = 62 mm) and the connectivity between the ventral putamen (VP) and the orbitofrontal cortex in normal-weight controls (bottom panel, MNI coordinates, VP-OFC, x = −32, y = 50, z = −2 mm). In plots, red corresponds to excess-weight participants, green to normal-weight controls. The right hemisphere corresponds to the right side of axial views, and the sagittal image show the left hemisphere. The color bar indicates *t* values. Results are displayed at $p < .005$, uncorrected. VP, ventral putamen.

measure of compulsivity (i.e., reversal learning perseveration error rate) in excess-weight participants (x = 52, y = −24, z = 44, t = 3.6, $p < .005$, 17,636 voxels). There were no significant correlations with impulsivity. Additional correlations between cognitive measures and functional connectivity patterns that did not overlap with the between-group differences in striatal connectivity are reported in the Supplemental Tables S3 and S4.

DISCUSSION

We found that individuals with excess weight display increased functional connectivity between the ventral striatum and medial prefrontal and parietal cortices and between the dorsal striatum and the somatosensory cortices. They also show reduced functional connectivity between the ventral striatum and the dorsal anterior cingulate cortex, the insula, and the lateral orbitofrontal cortex. Dorsal striatal connectivity positively correlates with food craving and predicts BMI gains after 12 weeks. These findings are consistent with the food addiction model, which proposes that obesity is associated with neural adaptations in the striatum and particularly within the dorsal striatum network (3,4).

Ventral striatum findings are consistent with previous studies showing functional connectivity differences between obesity and normal weight via complementary approaches. A recent study using a region-of-interest based approach showed increased functional connectivity between the ventral caudate and the medial frontal cortex in excess-weight individuals (37). Increased ventral caudate connectivity is also consistent with our findings in stimulant-addicted individuals (33). Enhanced ventral striatal connectivity aligns with the incentive sensitization theory of addiction, which proposes that addiction leads to increased dopamine excitability in this pathway (38,39). However, fMRI studies in heroin addicts have shown decreased connectivity in this network (40,41), and a recent study has shown that obesity is associated with alterations in opioid, but not dopamine, receptors (42). Therefore, more studies are needed to establish the neuropharmacologic underpinnings of these findings and the overlap between obesity and different types of addiction (e.g., psychostimulant vs. opiate). Increased connectivity between the ventral striatum and the posterior cingulate cortex and the angular gyrus is consistent with Kullmann *et al.* (43), which suggested that abnormal connectivity in the brain default network may contribute to overeating through an imbalance between reward-affective and cognitive processes. Decreased connectivity between the ventral caudate and the dorsal anterior cingulate cortex/insula accords with previous findings showing abnormal recruitment of brain regions involved in interoception in obese subjects (44).

Dorsal striatum findings are consistent with the food addiction model in relation to the components of craving and inability to cut down food intake (3,4,45). The dorsal caudate-somatosensory cortex association with food craving accords with previous studies showing increased dorsal caudate activation in response to palatable food cues in obesity (5,25). Given the role of the somatosensory cortex in taste processing (46), increased connectivity with the caudate is likely associated with enhanced valuation of high-palatable

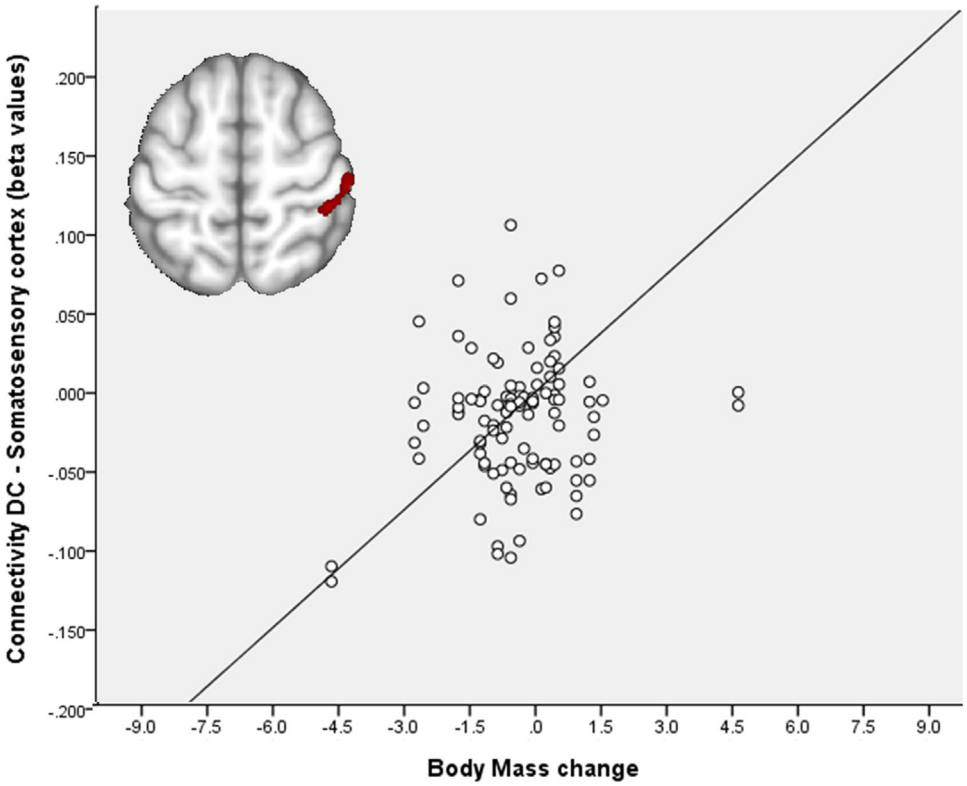

Figure 3. Plot showing change in BMI associated with increased connectivity between the dorsal caudate (DC) and the somatosensory cortex (MNI coordinates, x = 46, y = −32, z = 62 mm).

foods (47). Moreover, the link between the dorsal striatum network and food craving was significant in the excess-weight group and greater within participants with higher BMI values, in agreement with the notion of an addictive dimensionality of obesity (4). The finding that functional connectivity between the dorsal caudate and the somatosensory cortex longitudinally predicts weight gain also accords with previous neuroimaging findings showing that increased dorsal caudate activation is associated with BMI gains in obese subjects (6,7). Furthermore, caudate activation during food receipt differentiates obese subjects who gain weight relative to obese subjects who lose weight or remain stable at 6-month follow-up (6). Our functional connectivity approach extends these findings, demonstrating that a broad network linking the dorsal caudate with sensory/gustatory regions is implicated in future weight gain. Notably, this network is implicated in the coding of the energetic value of foods (48–50) and in habit learning, as indicated by correlations with reversal learning. Therefore, these findings may contribute to explain how ingrained preferences for high-calorie food can trigger eating habits beyond homeostatic needs (51,52). Future studies are needed to formally evaluate this mechanism.

We conclude that excess weight is associated with striatocortical functional connectivity alterations that are consistent with a food addiction model. Specifically, the associations with food craving and BMI gain during diet resonate with the DSM substance use disorders' criteria of craving and inability to cut down drug seeking (i.e., in this case food seeking) behavior (53). Our results should be appraised in the context of limitations. The cross-sectional design does not allow us to determine if striatum network alterations are a consequence of excessive weight or premorbid vulnerability factors. Further longitudinal research is necessary to understand the causal link between the brain reward system and obesity. The spatial resolution of fMRI did not allow us to differentiate the connectivity of medial versus lateral territories of the dorsal striatum. This dissociation is potentially relevant for human obesity, as preclinical data have shown that habit-based behaviors are supported by the anterior dorsolateral striatum (54,55). Our correlation analyses showed significant correlations between dorsal striatal connectivity and food craving within the excess-weight group, but correlations did not significantly differ between groups (i.e., Fisher's test) and thus the specificity of this finding must be interpreted with caution. Our longitudinal analyses testing the clinical meaningfulness of functional connectivity were conducted in a subgroup representing only 67% of the original sample. Nonetheless, this attrition rate is consistent with that reported in meta-analytic research on obesity interventions (56), and participants in the follow-up subgroup did not significantly differ from the main sample in antecedent variables.

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