Effect of Adolescent Bariatric Surgery on the Brain and Cognition: A Pilot Study

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Objective: Neurocognitive deficits in pediatric obesity relate to poor developmental outcomes. We sought preliminary evidence for changes in brain and cognitive functioning relevant to obesogenic behavior following vertical sleeve gastrectomy (VSG) in adolescents relative to wait-listed (WL) and healthy controls (HC).

Methods: Thirty-six adolescents underwent fMRI twice 4 months apart, during executive, reward, and episodic memory encoding, in addition to behavioral testing for reward-related decision making.

Results: VSG adolescents lost weight, while WL gained weight and HC did not change between time points. Gains in executive and reward-related performance were larger in VSG than control groups. Group × Time interaction ($P < 0.05$ corrected) in left prefrontal cortex during N-back showed greater presurgical activation and postsurgical reduction comparable to HC levels but increased in WL between time points. Similarly, left striatal parametric response to reward value reduced after surgery to HC levels; WL did not change. Memory-related medial temporal activation did not change in any group.

Conclusions: Results provide pilot evidence for functional brain changes induced by VSG in adolescents with severe obesity. Weight loss and gain were paralleled by reduced and increased prefrontal activation, respectively, suggesting neural plasticity related to metabolic change.

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Introduction

Severe obesity, defined as BMI 120% above the 95th percentile cutoff for obesity, is prevalent in 8% of adolescents (1) and confers elevated risk for serious medical comorbidities during adolescence (2) and later in adulthood (3). Additional risks for adverse developmental outcomes are posed by poor neurocognitive functioning (4), particularly self-regulatory processes important not only for psychosocial health (5) and academic performance (6) but also for controlling obesogenic behaviors (e.g., food and activity choices) that promote and maintain obesity (7,8). Bariatric surgery is one treatment option (9), with evidence of success for weight loss and improved metabolic health (10,11). Whether it improves neurocognitive functioning in adolescents, however, is not known. Adolescence is a critical period for maturation of risk/reward-related regulatory function (12), and severe obesity during this period puts youth at far greater risk for poor developmental outcomes. If bariatric surgery improves neurocognitive functioning, it has the potential to reverse the course of maladaptive development in youth with severe obesity.

Studies with adults support neurocognitive changes within a year following weight loss intervention including bariatric surgery (13). Cognitive processing pertinent to obesity includes executive function, the ability to constrain behavior toward goals mediated by prefrontal-parietal cortices, reward-related function mediated by striatum, and episodic memory mediated by medial temporal lobes (MTLs). Together, these processes enable self-control and learning, which guide decision-making about food and activity (7). Meta-analyses of adult studies support improved cognitive function following weight loss intervention (14) and bariatric surgery (13) for executive and memory functioning. Furthermore, adults reported less food motivation (15,16) and showed activation reductions in reward regions and increases in executive regions in response to food more than nonfood images following bariatric surgery (16). Other evidence suggests that structural (17) and functional (18,19) network properties of the brain resembled healthy adults after surgery. These neurocognitive improvements may hold the key to sustained healthy behaviors for controlling weight gain.

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We conducted a pilot study to evaluate the effect of bariatric surgery on executive, reward, and episodic memory functioning and underlying neural substrates in prefrontal-parietal, striatal, and MTL regions, respectively, using functional magnetic resonance imaging (fMRI) in adolescents with severe obesity compared with two age-matched control groups: adolescents with severe obesity wait-listed for surgery (WL) and those with healthy weight (HC). The HC group allows estimation of improvement due to effects of repeated testing and familiarity with MRI.

**Methods**

**Participants**

Thirty-six participants aged 14 to 21 years either had healthy weight (HC; \( n = 12 \); BMI (kg/m\(^2\)); mean [M] = 21.6, SD = 2.6), were scheduled for vertical sleeve gastrectomy (VSG) as part of clinical standard of care at enrollment (\( n = 10 \); BMI: M = 47.2, SD = 7.0), or were awaiting VSG because of insurance delays or personal choice (WL; \( n = 14 \); BMI: M = 45.3, SD = 8.2) at Children’s National Health System. HC were recruited from the Washington, DC, area. Informed consent and assent were acquired according to guidelines of the Institutional Review Boards of Georgetown University and Children’s National Health System. Groups did not differ on age, IQ, gender, ethnicity, racial composition, and socioeconomic status (measured with family income and maternal education). As expected, BMI was lower in HC than the two groups with obesity, which did not differ from each other (Table 1).

All participants completed two testing sessions 2.5 to 7 months apart, with average interval matched across groups (HC = 4.6 [3-7], VSG = 4.5 [3-7], WL = 3.8 [2-5]). Surgery participants’ first session (Time 1) was 1 to 4 weeks before VSG, and the second session (Time 2) was 3 to 4 months after VSG. Only youth with BMI below 50 were able to fit in the MRI bore. Including those with acceptable head motion in at least one task, final samples with two fMRI sessions were: VSG: \( n = 6 \); WL: \( n = 9 \); HC: \( n = 12 \). Successful behavioral data were acquired from participants unable to fit in the MRI, yielding larger behavioral than fMRI samples. Thus, sample sizes are listed for each result.

Participants with obesity met standard criteria for VSG, listed in Supporting Information. Criteria met by all participants included full-scale IQ ≥ 74 and no past or current diagnosis of type 2 diabetes, psychiatric or neurological disorder, and/or prescription of psychotropic medication.

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**Table 1** Demographic characteristics

| Healthy control, mean (SD) | VSG, mean (SD) | Wait list, mean (SD) | One-way ANOVA | P |
|---------------------------|---------------|---------------------|--------------|---|
| BMI baselinea | 21.57 (2.59) | 47.18 (6.98) | 45.32 (8.19) | 57.53 | 0.78 | <0.001 |
| Age (y) | 16.51 (1.27) | 17.00 (1.37) | 16.42 (1.33) | 0.613 | 0.04 | 0.548 |
| IQ | 97.75 (5.53) | 92.20 (19.04) | 97.71 (11.45) | 0.518 | 0.03 | 0.601 |
| Maternal education (y) | 14.83 (2.62) | 13.30 (4.81) | 13.92 (4.86) | 0.373 | 0.02 | 0.692 |

| Gender, n | | | | Pᵇ |
| Male | 6 | 4 | 4 | 0.534 |
| Female | 6 | 6 | 10 | |

| Handedness, n | | | | 0.402 |
| Right | 11 | 10 | 11 | 0.418 |
| Left | 2 | 0 | 3 | |

| Ethnicity, n | | | | 0.294 |
| Hispanic/Latino | 1 | 2 | 4 | |
| Not Hispanic/Latino | 11 | 6 | 10 | |
| Not reported | 0 | 2 | 0 | |

| Race, n | | | | 0.384 |
| Black/African American | 6 | 5 | 5 | |
| White | 4 | 3 | 3 | |
| Other/mixed | 2 | 0 | 5 | |
| Not reported | 0 | 2 | 1 | |

| SES, n | | | | 0.384 |
| >$80,000 | 4 | 2 | 6 | |
| $50,000-$80,000 | 3 | 1 | 4 | |
| <$50,000 | 5 | 7 | 4 | |

ᵃHealthy control vs. VSG and healthy control vs. wait list, \( P < 0.05 \)
ᵇP value derived from Fisher exact or \( \chi^2 \) test.

SES, socioeconomic status; VSG, vertical sleeve gastrectomy

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We conducted a pilot study to evaluate the effect of bariatric surgery on executive, reward, and episodic memory functioning and underlying neural substrates in prefrontal-parietal, striatal, and MTL regions, respectively, using functional magnetic resonance imaging (fMRI) in adolescents with severe obesity compared with two age-matched control groups: adolescents with severe obesity wait-listed for surgery (WL) and those with healthy weight (HC). The HC group allows estimation of improvement due to effects of repeated testing and familiarity with MRI.
Measures and procedure
The fMRI protocol comprised tasks probing executive, reward, and memory function administered in E-Prime (20) via a magnet-compatible projector through a mirror mounted on the head coil. Participants practiced each task outside the scanner. Tasks were presented in a fixed order across subjects. Two versions of each task were created from the same stimulus set and randomly assigned and counterbalanced across sessions. A reward-related decision-making task was administered on a laptop outside the MRI scanner. Tasks are described briefly here with more design details found in the Supporting Information.

Episodic memory. During fMRI, participants classified 46 color scenes as indoor/outdoor. Outside the scanner, participants encoded an additional 46 new scenes, which were included as distractors to increase interference on the recognition memory test, during which participants indicated whether 184 serially presented scenes (46 in scanner, 46 outside scanner, 96 foils) were “new” (i.e., not previously seen) or “old” (i.e., previously seen during either encoding). For fMRI analysis, activation during encoding was compared between in-scanner scenes that were remembered (correct “old”) relative to those that were forgotten (encoded scenes rated as “new”).

Executive function. The verbal N-back task with three load blocks (1-back, 2-back, 3-back) was used to probe activation during dynamic working memory, a component process of executive function. Participants viewed consonant letters and were instructed to press a right-hand button when the current letter matched the letter presented at trials ago, with higher reflecting higher load.

Reward function. The commonly used monetary incentive delay (MID) task (21) probed activation during anticipation of monetary reward. Each trial presented a cue signaling gain/loss and points at stake followed by the target, which participants were instructed to respond to as fast as possible (target timing parameters were calibrated to ensure 66% success rate). Points gained/lost and the current total number of points were presented after each trial. Participants were informed at the outset that points earned could be exchanged for a monetary reward; unbeknownst to participants, all received a $5 gift card. Because the fMRI task evokes evaluation of reward in the brain but does not provide a measure of performance related to reward, a decision-making task, the balloon analog risk-taking (BART) task (22), was administered outside the scanner. A Bayesian model was applied to performance to derive parameters related to response consistency and reward sensitivity (see Supporting Information) (23).

fMRI acquisition and analyses
Imaging was performed on a 3T Trio scanner (Siemens, Erlangen, Germany). A high-resolution T1-weighted structural scan (MPRAGE) was acquired lasting 7.23 minutes with the following parameters: TR/TE = 2,300/2.94 ms, TI = 900 ms, 90-degree flip angle, 1 slab, 160 sagittal slices with a 1.0-mm thickness, FOV = 256 × 256 × 256 mm³, resulting in an effective resolution of 1.03 mm isotropic voxels. Functional MRI used a T2*-sensitive gradient echo pulse sequence with the following parameters: TR/TE = 2,000/30 ms, 90-degree flip angle, 43 interleaved slices (width = 2.5 mm, gap width = 0.5 mm, effective width = 3 mm) ascending in the transverse plane, FOV = 192 × 192 mm². Slice acquisition was angled in the plane of the hippocampus to optimize MTL signal and parallel to orbitofrontal cortex for N-back and MID to minimize susceptibility artifacts. Head movement was minimized with padding between the head and coil.

Functional images were analyzed using SPM12 (Wellcome Department of Cognitive Neurology, London, UK). The first four TRs were discarded for analysis for signal stabilization. Images were corrected for motion as recommended by Wilke (24), slice-time corrected, coregistered to each participant’s MPRAGE, and smoothed with an 8-mm FWHM Gaussian kernel. fMRI responses were modeled using a canonical hemodynamic response function, which was convolved with trial/block onset vectors specific to each task. For each subject, a general linear model for each functional task modeled the following contrasts of interest: episodic memory: encoded scenes that were subsequently remembered > forgotten; executive function: 2-Back > 1-Back (the 3-back blocks were not included because of below-chance mean accuracy); reward: gain cues parametrically modeled according to point value (0, 0.5, 1, and 5 points). Additionally, each model included seven motion regressors of no interest (six realignment parameters derived estimate of effect of head motion on signal (24), and one de-weighted volumes with greater than 1.5-mm scan-to-scan [STS] motion). Participants with more than 10% of volumes with half a voxel (1.5 mm) or higher STS motion were excluded from analyses. Resulting contrast maps were normalized into Montreal Neurological Institute (MNI) standard stereotaxic space by applying the deformation field derived from participants’ MPRAGE.

Group × Time interactions for each task, controlling for mean STS, were examined using separate mixed-effects analysis of variance (ANOVA) models for VSG versus HC and VSG versus WL using GLM Flex Fast2 (http://mrtools.mgh.harvard.edu/). Controlling for age did not impact results (Supporting Information Table S1). These models were constrained by anatomical masks encompassing regions derived from meta-analyses targeting MTL (episodic memory) (25), frontoparietal (N-back) (26-28), and thalamo- striatal (MID) (29) regions for hypothesis testing (see Supporting Information for details). Multiple comparisons were controlled at $P < 0.05$ by using Monte Carlo simulation using 3dClusTsim (2-sided, nearest neighbor 2) (30) and Tukey-corrected pair-wise post hoc tests of significant interactions. As the size of the anatomical masks differed for each task, the cluster threshold satisfying the corrected threshold differed across tasks and is listed in Results. Because 12 HC participants were scanned twice successfully, 6 were randomly selected to match the smaller sample size of the VSG group for Group × Time analysis. The same participants (n = 6/group) with acceptable head motion were included across all three fMRI tasks by using list-wise deletion. Only Group × Time interaction results at the corrected threshold are presented in the main text, but for an exploratory picture of time comparisons within each group, we have presented Time 1 versus Time 2 paired t tests at an uncorrected threshold in Supporting Information Tables S3-S5.

Behavioral analyses
Time differences were assessed with paired t tests for all performance measures, while the nonparametric BART decision-making parameters were assessed with paired Wilcoxon rank sum tests; effect sizes, r, and P values are listed in the tables.
Results

Head motion

Group × Time ANOVA did not show a significant effect of Time, Group, or interaction for STS motion during any task (see full report in Supporting Information Table S1).

| Table 2: Effect of time on recognition memory for encoded scenes during fMRI for VSG, wait list, and healthy control groups |
|-----------------|-----------------|-----------------|------------------|-----------------|-----------------|
|                  | Time 1,          | Time 2,          | Time 1 vs. Time 2,| d              | P              |
|                  | mean (SD)        | mean (SD)        | Mean diff (95% CI)|                |                |
| **Episodic memory** |                 |                 |                   |                |                |
| Corrected accuracy (%) |                 |                 |                   |                |                |
| VSG               | 56.9 (22.9)      | 55.8 (23.4)      | 1.1 (–27.8 to 30.0)| 0.04           | 0.927          |
| Wait list         | 51.9 (21.2)      | 45.9 (23.8)      | 6.0 (–3. to 15.1)| 0.51           | 0.162          |
| Healthy control   | 54.7 (14.9)      | 44.9 (13.6)      | 9.8 (2.1 to 17.4)| 0.81           | 0.017          |

*Note:* Values are mean (standard deviation). P values from paired t test. 

**Weight change**

Change in weight was significant for youth with obesity, who lost 9.06 BMI units after VSG (t[9] = 12.96, d = 4.10, P < 0.001), and in WL participants, who gained 1.27 BMI units (t[13] = –3.33, d = 0.89, P = 0.005). HC participants gained 0.56 BMI units.

| Table 3: Effect of time on accuracy and speed during the N-back task for VSG, wait list, and healthy control groups |
|--------------|-----------------|-----------------|------------------|-----------------|-----------------|
|              | Time 1,          | Time 2,          | Time 1 vs. Time 2,| d              | P              |
|              | mean (SD)        | mean (SD)        | Mean diff (95% CI)|                |                |
| **1-back accuracy, %** |                 |                 |                   |                |                |
| VSG           | 96.6 (8.9)       | 97.6 (3.6)       | –1.0 (–9.8 to 7.7)| 0.10           | 0.786          |
| Wait list     | 93.2 (12.3)      | 95.6 (8.0)       | –2.4 (–8.6 to 3.8)| 0.26           | 0.414          |
| Healthy control| 97.8 (4.4)      | 97.9 (5.2)       | –0.8 (–4.3 to 2.6)| 0.17           | 0.601          |
| **2-back accuracy, %** |                 |                 |                   |                |                |
| VSG           | 87.9 (15.3)      | 92.2 (11.7)      | –4.3 (–13.4 to 4.7)| 0.40           | 0.299          |
| Wait list     | 92.0 (8.5)       | 95.2 (10.7)      | –3.2 (–11.4 to 4.9)| 0.27           | 0.400          |
| Healthy control| 96.0 (7.0)      | 96.3 (6.0)       | –0.3 (–6.4 to 5.8)| 0.04           | 0.909          |
| **3-back accuracy, %** |                 |                 |                   |                |                |
| VSG           | 75.3 (17.4)      | 79.7 (15.8)      | –4.3 (–17.8 to 9.2)| 0.26           | 0.474          |
| Wait list     | 81.5 (10.2)      | 83.8 (16.0)      | –2.3 (–13.1 to 8.5)| 0.17           | 0.643          |
| Healthy control| 90.1 (13.6)      | 89.9 (7.9)       | 0.2 (–6.3 to 6.8)| 0.02           | 0.939          |
| **1-back reaction time, ms** |                 |                 |                   |                |                |
| VSG           | 692 (218)        | 664 (361)        | 28 (–288 to 345)| 0.08           | 0.838          |
| Wait list     | 654 (191)        | 650 (260)        | 4 (–126 to 134)| 0.02           | 0.946          |
| Healthy control| 552 (111)       | 505 (64)         | 47 (–31 to 125)| 0.43           | 0.204          |
| **2-back reaction time, ms** |                 |                 |                   |                |                |
| VSG           | 750 (286)        | 692 (331)        | 58 (–175 to 291)| 0.21           | 0.574          |
| Wait list     | 631 (228)        | 643 (374)        | –12 (–224 to 201)| 0.04           | 0.908          |
| Healthy control| 547 (180)       | 495 (149)        | 52 (–119 to 223)| 0.21           | 0.507          |
| **3-back reaction time, ms** |                 |                 |                   |                |                |
| VSG           | 734.1 (386.2)    | 700.7 (280.0)    | 33.4 (–202.4 to 269.5)| 0.10           | 0.748          |
| Wait list     | 736.9 (324.2)    | 731.5 (300.1)    | 5.4 (–146.1 to 156.9)| 0.02           | 0.938          |
| Healthy control| 670.5 (237.7)   | 640.3 (297.5)    | 30.1 (–198.3 to 258.5)| 0.11           | 0.772          |

*Note:* Values are mean (standard deviation). P values from paired t test. 

VSG, vertical sleeve gastrectomy.
TABLE 4 Peak activations from clusters showing Group × Time interaction: N-back task indexing executive function and reward anticipation during the monetary incentive delay task, VSG vs. healthy controls and VSG vs. wait-list controls

| Region (BA)                        | H      | Volumea | Fb      | x     | y     | z     |
|-----------------------------------|--------|---------|---------|-------|-------|-------|
| **Executive function: 2-back > 1-back** |        |         |         |       |       |       |
| VSG vs. healthy control           |        |         |         |       |       |       |
| Anterior insula (13)              | L      | 275     | 25.21   | −37   | −2    | 6     |
| Superior frontal gyrus (6)        | L      | 277     | 22.73   | −20   | 14    | 38    |
| Inferior triangularis (9, 44)     | R      | 322     | 22.79   | 46    | 16    | 18    |
| Inferior parietal lobe (40)       | R      | 424     | 28.93   | 62    | −26   | 34    |
| **Reward anticipation: parametric response to reward value** |        |         |         |       |       |       |
| VSG vs. healthy control           |        |         |         |       |       |       |
| Putamen                           | R      | 125     | 17.40   | 20    | 10    | −4    |
| Caudate                           | L      | 119     | 77.34   | −6    | 4     | −4    |
| Thalamus                          | R/L    | 165     | 29.78   | 4     | −20   | 12    |

*Volume measured in mm³.

bF-value derived from the Group × Time interaction term.

BA, Broadmann’s area; H, hemisphere; VSG, vertical sleeve gastrectomy.

between Time 1 and Time 2, which was not statistically significant (t(11) = −2.08, d = 0.60, P = 0.062).

Episodic memory. Twenty-seven participants had complete behavioral data for the subsequent memory paradigm at both time points (VSG = 6; HC = 12; WL = 9). Corrected accuracy (percent remembered − % false alarms) did not significantly differ between time points in the VSG and WL groups but was significantly lower at Time 2 than Time 1 in the HC group (Table 2). In the MTL, comparison did not show any clusters with significant Group × Time interactions (F = 0.02, k = 88) for VSG versus HC or VSG versus WL groups. Within-group comparison at uncorrected threshold showed that MTL activation in HC and WL reduced at Time 2 relative to Time 1 but did not change in the VSG group (Supporting Information Figure S1 and Table S3).

Executive function. Twenty-nine participants had behavioral data at both time points for the N-Back task (VSG = 8; HC = 10; WL = 11). While nonsignificant, effect sizes for improvement in balanced accuracy (percent correct mean target and nontarget responses) were larger for high (2-back) than low (1-Back) or very high (3-Back) loads across all groups, with the VSG group showing the largest effect size, suggesting VSG-related effects above and beyond practice or familiarity effects (Table 3). Reaction time showed no significant time-related differences and generally small magnitudes of change in any group (Table 3).

Because of poor accuracy during 3-back load (20% of sample with obesity showed <50% correct hits), only 1- and 2-back loads were analyzed for fMRI. Comparison of the VSG group with HC showed a significant Group × Time interaction in the left anterior insula/inferior frontal gyrus (F = 0.02, k = 242; Table 4; Figure 1A), where load-related activation (2-back > 1-back) reduced from Time 1 to Time 2 in the VSG group and was greater than HC at Time 1 but not at Time 2. Thus, after weight loss due to VSG, participants showed a more similar pattern of activation to healthy peers than before surgery.

Comparison of the VSG group with WL revealed Group × Time interaction in several frontoparietal clusters (Table 4; Figure 1A), which showed that the WL but not VSG group significantly increased load-related activation from Time 1 to Time 2. These clusters included left superior frontal gyrus (WL: F_{TukeyCorrected} = 0.09) and right inferior parietal lobule (WL: F_{TukeyCorrected} = 0.050). The VSG group significantly reduced activation from Time 1 to Time 2 in the right inferior parietal lobule (VSG: F_{TukeyCorrected} = 0.045). Further, activation was significantly greater for WL relative to VSG participants at Time 2, but not Time 1, in the left superior frontal gyrus (F_{TukeyCorrected} = 0.008) and right inferior parietal lobule (F_{TukeyCorrected} = 0.026). Lastly, although there was a significant interaction in a cluster that extended to the inferior triangularis, post hoc tests revealed no significant pair-wise difference. Together, this pattern of results suggests that weight loss was associated with reductions in activation, whereas weight gain was associated with increase in activation in frontoparietal regions associated with executive function.

Reward function. A total of 25 participants (VSG = 6; HC = 12; WL = 7) had behavioral data at both sessions during the MID task. Surgery participants showed significantly faster response speed and marginal improvement in total points on the MID between time points; no differences were observed in the control groups (Table 5).

Group × Time interaction was observed in the left ventral caudate and thalamus (P < 0.02, k = 99; Table 4; Figure 1B), such that response to reward value decreased from Time 1 to Time 2 (left caudate: F_{TukeyCorrected} = 0.017; thalamus: F_{TukeyCorrected} < 0.001; right putamen: F_{TukeyCorrected} = 0.080) in the VSG group. It was significantly higher than HC participants at Time 1 (caudate: F_{TukeyCorrected} = 0.01; thalamus: F_{TukeyCorrected} = 0.005) but not at Time 2 (caudate: F_{TukeyCorrected} = 0.892; putamen: F_{TukeyCorrected} = 0.431). VSG had less activation in thalamus at Time 2 than HC (F_{TukeyCorrected} = 0.021). These results indicate that weight loss due to VSG normalized sensitivity to value of anticipated reward in the ventral striatum, a region related to reward evaluation (29) and magnitude (21). No regions showed significant Group × Time interaction for VSG versus WL participants.

Thirty-four participants completed the BART task assessing reward-related decision-making at both time points (VSG = 9; HC = 12; WL = 13). While not significant, it is notable that both VSG and HC participants’ performance suggested gains (decreased total points and number balloons popped at Time 2 than Time 1), whereas WL participants showed the opposite pattern (Table 5). To examine decision-making processes, a decision-making model (23) was used to estimate two parameters of interest: response consistency (β), which is the extent to which a participants’ responses match prior responses with lower values, indicating more variable behavior; and reward sensitivity (γt), which is sensitivity to potential gains. Although all groups showed increases in response consistency at Time 2, suggesting less erratic reward-related responding, the VSG group showed the largest effect, which was statistically significant. In contrast, while the VSG and HC groups showed only small effects of time on reward sensitivity, the WL group showed a very large effect, with greater reward sensitivity at Time 2 than Time 1 (Table 5). Together with the
behavioral outcomes, these results suggest that after weight loss due to VSG, participants adopted a more consistent, less reward-driven strategy at Time 2, while after weight gain, the WL group’s performance suggested greater reward sensitivity at Time 2.

**Discussion**

Results of our pilot study suggest normalization of prefrontal-parietal and striatal engagement associated with executive function...
and reward anticipation, respectively, 3 to 4 months following VSG relative to repeated testing at the same time interval in two age-matched control groups: wait-listed surgery candidates with severe obesity and healthy controls. Surgery participants lost significant weight and showed reduction in cortico-striatal activation, whereas wait-listed participants gained weight during the 4-month interval and increased prefrontal-parietal activation during that period. MTL regions associated with episodic memory did not reveal significant time-related change. Improvement of a larger magnitude was observed for the surgery group for high-load executive performance, statistically significant for speed, and some parameters of reward-related decision-making relative to that in the control groups. These results must be considered preliminary until their stability is established with replication in larger samples. They are useful for estimating effects sizes and generating hypotheses to guide future work.

Our pilot results must be viewed in the context of the following factors. First, the small sample sizes illustrate the challenges of conducting successful fMRI in a well-controlled, within-subjects design with two control groups in a 1-year period. Youth with BMI > 50 could not fit in the Trio scanner bore. Furthermore, compliance with restricting head motion was more difficult in youth with obesity.

### TABLE 5 Effect of time on performance during the monetary incentive delay and balloon analog risk-taking tasks for VSG, wait-list, and healthy control groups

|                          | Time 1, mean (SD) | Time 2, mean (SD) | Time 1 vs. Time 2 |
|--------------------------|-------------------|-------------------|------------------|
| **Monetary incentive delay task** |                   |                   |                  |
| Total points             |                   |                   |                  |
| VSG                      | 13.0 (4.2)        | 18.3 (3.1)        | −5.3 (−11.5 to 1.0) | 0.88 | 0.084*† |
| Wait list                | 14.3 (8.0)        | 14.6 (7.6)        | −0.3 (−2.8 to 2.2) | 0.10 | 0.777 |
| Healthy control          | 15.1 (5.1)        | 12.7 (5.7)        | 2.4 (−6.6 to 11.4) | 0.28 | 0.521 |
| Reaction time, ms        |                   |                   |                  |
| VSG                      | 199.9 (20.1)      | 180.0 (13.1)      | 19.9 (5.2 to 34.6) | 1.42 | 0.018* |
| Wait list                | 190.7 (22.7)      | 180.6 (29.1)      | 10.1 (−15.9 to 36.2) | 0.32 | 0.389 |
| Healthy control          | 175.3 (28.2)      | 168.6 (18.6)      | 6.6 (−6.0 to 19.3) | 0.55 | 0.237 |
| **Balloon analog risk-taking task** |                   |                   |                  |
| Total points             |                   |                   |                  |
| VSG                      | 6,483 (2,093)     | 5,216 (2,829)     | 1,266 (−1,237 to 3,771) | 0.51 | 0.298 |
| Wait list                | 6,655 (1,737)     | 7,015 (1,999)     | −360 (−1,573 to 853) | 0.24 | 0.544 |
| Healthy control          | 6,199 (2,322)     | 5,801 (1,953)     | 398 (−1,421 to 2,218) | 0.19 | 0.654 |
| Adjusted number of pumps |                   |                   |                  |
| VSG                      | 30.64 (11.47)     | 24.83 (16.74)     | 5.81 (−8.68 to 20.31) | 0.41 | 0.404 |
| Wait list                | 36.37 (18.18)     | 40.94 (13.87)     | −4.28 (−17.41 to 8.86) | 0.26 | 0.507 |
| Healthy control          | 31.34 (14.49)     | 28.00 (15.85)     | 3.38 (−9.48 to 16.24) | 0.22 | 0.591 |
| Balloons popped          |                   |                   |                  |
| VSG                      | 8.22 (2.68)       | 6.89 (3.79)       | 1.33 (−1.98 to 4.64) | 0.41 | 0.403 |
| Wait list                | 9.15 (5.96)       | 11.77 (3.81)      | −2.62 (−6.70 to 1.47) | 0.52 | 0.197 |
| Healthy control          | 8.92 (3.42)       | 6.92 (0.48)       | 2.00 (−1.53 to 5.53) | 0.48 | 0.251 |
| Medicine (IQR)           |                   |                   |                  |
| VSG                      | 0.09 (0.12)       | 0.12 (0.16)       | 0.06 (−0.36 to 0.00) | 0.55 | 0.055† |
| Wait list                | 0.09 (0.07)       | 0.10 (0.06)       | 0.01 (−0.04 to 0.034) | 0.09 | 0.735 |
| Healthy control          | 0.14 (0.08)       | 0.14 (0.17)       | 0.01 (−0.06 to 0.13) | 0.06 | 0.850 |
| Reward sensitivity: γ    |                   |                   |                  |
| VSG                      | 0.43 (0.68)       | 0.49 (0.63)       | 0.003 (−0.21 to 0.34) | 0.00 | 1.00 |
| Wait list                | 0.69 (0.66)       | 0.92 (0.61)       | −0.21 (−0.45 to 0.04) | 0.42 | 0.127 |
| Healthy control          | 0.57 (0.31)       | 0.40 (0.94)       | 0.06 (−0.28 to 0.26) | 0.16 | 0.622 |

*Cohen’s d.
†P value from paired t test.
‡Difference in location from Wilcoxon rank sum Z.

d derived from Wilcoxon rank sum Z.

*Wilcoxon rank sum test.

*P < 0.01.
†P < 0.05.

VSG, vertical sleeve gastrectomy.
Furthermore, follow-up and compliance with multiple testing visits that were months apart was also more challenging for youth with obesity. Together, these limitations reduced the final sample providing two fMRI sessions with high-quality data for participants with obesity to half of that for healthy controls. Thus, physical discomfort and challenges to compliance with testing requirements are higher in youth with obesity and must be factored into estimation of sample sizes for future studies. While this limited recruitment, evidence of neurocognitive changes for those in the lower BMI range of eligibility for bariatric surgery (35/40-50) bolsters its potential for intervention and reversing maladaptive developmental outcomes. Potential for neural plasticity may be higher in those with relatively better metabolic health compared with those with more severe obesity and/or medical comorbidities. Second, small sample sizes limit statistical power, and therefore, our results must be interpreted with caution. Despite slightly larger behavioral samples, neural activation was more sensitive to weight loss/gain-related changes than behavioral performance, which reached statistical significance in the surgery group only for response speed and the BART decision parameter. However, fMRI results in small sizes may be unstable; therefore, replication in larger samples is necessary. Thus, our results must be considered as preliminary and suggestive of surgery-related changes in brain function beyond those observed upon repeated testing.

Weight gain/loss-related neural changes were observed for executive and reward functioning but not for episodic memory. The N-back task, a common fMRI probe for a key component process of executive function in both adult and pediatric fMRI studies, yielded time-related activation changes in frontal-parietal regions that suggest an association between weight and neural inefficiency. Greater activation prior to weight loss and its reduction after weight loss in the surgery group to the same level as the healthy-weight controls suggest a more efficient neural response to task demand, as performance accuracy and speed improved, albeit not significantly. This pattern of activation change was paralleled in the wait-listed surgery candidates with widespread increased activation after weight gain during the 4-month interval. Their performance did not change, and therefore, the more widespread recruitment suggests a more inefficient neural response to task demands resulting. Striatal response to reward value also showed reduced engagement following surgery, suggesting that weight loss-related neural efficiency generalized across brain regions in the small set of surgery candidates included in this study. Whether this pattern of results is generalizable remains to be tested with better-powered studies in the future.

Further work is needed to probe the basis of these activation reductions and explore whether they are driven by changes in vasculature or insulin receptor activity associated with metabolic changes induced by weight loss following bariatric surgery. Association with insulin activity is suggested by hypothalamic activation reduction following glucose ingestion in humans (31), which is attenuated in obese rats (32). Our small sample sizes preclude examination of correlation of activation changes with insulin parameter changes but could be examined in future work as a first step to hypothesis generation about the metabolic basis of activation change in obesity. Activation in MTL during memory encoding and recognition memory was not sensitive to surgery. Perhaps neural plasticity in this region takes longer, beyond the 3- to 4-month postsurgery interval. Alternatively, our fMRI encoding probe may not have been optimal in detecting changes, and future studies should examine memory retrieval after longer delays.

Executive and reward-related functioning is central to behaviors such as food and activity choices, which promote and maintain obesity (7). Our fMRI probes did not use food-related stimuli, and, thus, the extent to which the observed neurocognitive changes may impact food-related decisions remains to be tested. Upon replication, these results point to the potential of surgical intervention for altering domain-general regulatory and motivational processes. Whether those changes support improvement in adaptive function and psychosocial health remains to be investigated in future work.

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