



## Neural activation during anticipated peer evaluation and laboratory meal intake in overweight girls with and without loss of control eating<sup>☆,☆☆</sup>



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### ABSTRACT

The interpersonal model of loss of control (LOC) eating proposes that socially distressing situations lead to anxious states that trigger excessive food consumption. Self-reports support these links, but the neurobiological underpinnings of these relationships remain unclear. We therefore examined brain regions associated with anxiety in relation to LOC eating and energy intake in the laboratory. Twenty-two overweight and obese (BMIz:  $1.9 \pm 0.4$ ) adolescent ( $15.8 \pm 1.6$  y) girls with LOC eating (LOC+,  $n = 10$ ) and without LOC eating (LOC-,  $n = 12$ ) underwent functional magnetic resonance imaging (fMRI) during a simulated peer interaction chatroom paradigm. Immediately after the fMRI scan, girls consumed lunch ad libitum from a 10,934-kcal laboratory buffet meal with the instruction to “let yourself go and eat as much as you want.” Pre-specified hypotheses regarding activation of five regions of interest were tested. Analysis of fMRI data revealed a significant group by peer feedback interaction in the ventromedial prefrontal cortex (vmPFC), such that LOC+ had less activity following peer rejection (vs. acceptance), while LOC- had increased activity ( $p < .005$ ). Moreover, functional coupling between vmPFC and striatum for peer rejection (vs. acceptance) interacted with LOC status: coupling was positive for LOC+, but negative in LOC- ( $p < .005$ ). Activity of fusiform face area (FFA) during negative peer feedback from high-value peers also interacted with LOC status ( $p < .005$ ). A positive association between FFA activation and intake during the meal was observed among only those with LOC eating. In conclusion, overweight and obese girls with LOC eating may be distinguished by a failure to engage regions of prefrontal cortex implicated in emotion regulation in response to social distress. The relationship between FFA activation and food intake supports the notion that heightened sensitivity to incoming interpersonal cues and perturbations in socio-emotional neural circuits may lead to overeating in order to cope with negative affect elicited by social discomfort in susceptible youth.

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### Introduction

Pediatric loss of control (LOC) eating, the subjective experience of being unable to control what or how much one eats, has been shown

to predict excessive weight gain (Tanofsky-Kraff et al., 2009a; Sonnevile et al., 2013a), exacerbated disordered eating (Tanofsky-Kraff et al., 2011; Hilbert et al., 2013), anxiety and depression (Sonneville et al., 2013a; Tanofsky-Kraff et al., 2011; Field et al., 2012; Skinner et al., 2012), and metabolic dysfunction (Tanofsky-Kraff et al., 2012). LOC eating often emerges during adolescence (Neumark-Sztainer et al., 2011; Stice et al., 2009) and is more commonly reported by girls (vs. boys) and overweight (vs. non-overweight) youth (Shomaker et al., 2010a). Among overweight and obese girls, LOC eating has clear consequence for food intake: those with reported LOC, compared to those without LOC, consume more energy at laboratory meals when instructed to “binge” versus when told to “eat normally” (Tanofsky-Kraff et al., 2009b). Despite these data, only ~50% of youth with LOC eating before age 13 years go

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on to experience persistent and exacerbated LOC eating patterns during middle to late adolescence and beyond (Tanofsky-Kraff et al., 2011; Hilbert et al., 2013; Goldschmidt et al., 2014). To improve the identification of high-risk youth with LOC eating and refine intervention targets, research is needed to elucidate the neural mechanisms that may contribute to exacerbated disordered eating and obesity.

Psychosocial correlates may inform the underlying neuropathology that promotes LOC eating. Specifically, LOC eating is associated with poor social functioning (Czaja et al., 2011; Elliott et al., 2010; Hartmann et al., 2012; Hilbert et al., 2010) and adverse mood states such as anxiety (Tanofsky-Kraff et al., 2005; Morgan et al., 2002). Interpersonal theory offers one mechanism by which LOC eating may lead to excess weight gain and binge eating-type disorders (Tanofsky-Kraff et al., 2007a). The interpersonal model proposes that hyperphagia associated with LOC episodes may reflect a response to negative affective states induced by interpersonal conflicts (Tanofsky-Kraff et al., 2007a). Our data from retrospective self-reports (Elliott et al., 2010) and ecological momentary assessment in the natural environment (Ranzenhofer et al., 2014) generally support this theoretical model in youth.

A corollary of the interpersonal model is that susceptibility for both interpersonal problems and LOC episodes result from altered neural engagement in anxiety-sensitive brain regions during social, emotional, and consummatory processes. Indeed, among youth with LOC eating, social problems are commonly reported (Czaja et al., 2011; Elliott et al., 2010; Hartmann et al., 2012; Hilbert et al., 2010) and may be a particularly potent non-homeostatic modulator of excess food consumption. Although its causes are likely multifactorial, LOC eating may occur in a subset of youth with altered brain function also linked to poor regulation during social conflicts. While brain regions such as the hypothalamus regulate normative homeostatic feeding, neural circuits implicated in tracking the emotional salience of stimuli and the complex processing of affect also impact food intake. For instance, negative affect has been associated with increased responsiveness in the striatum and amygdala, brain regions implicated in the reward and threat-based processing, during the anticipated consumption of palatable food (Bohon and Stice, 2012; Rudenga et al., 2013; Bohon et al., 2009), whereas engagement of lateral and medial aspects of prefrontal cortex (PFC), brain regions implicated in inhibitory control, have been shown to dampen craving and palatable food intake (Volkow et al., 2011). The effect of interpersonal distress on this circuit may override homeostatic regulators of intake, and thereby explain the strong connections between negative affective states and non-homeostatic feeding (Dallman, 2010). Therefore, a potential neural diathesis for LOC eating may be promoted by aberrant patterns of brain activation during episodes of social distress (Sabatini et al., 2007).

Given the robust link between LOC eating and anxiety (Tanofsky-Kraff et al., 2005; Morgan et al., 2002), research on the neurobiological mechanisms underlying adolescent mood and anxiety disorders may inform the neural underpinnings of LOC eating. Research in mood-disordered youth has identified aberrant activity within corticolimbic and striatal circuits in response to social provocation (Guyer et al., 2008; Lau et al., 2012; Masten et al., 2011; Roberson-Nay et al., 2006; Telzer et al., 2008; Monk et al., 2006, 2008; Killgore and Yurgelun-Todd, 2005; Lee et al., 2014). Together, brain structures within these circuits modulate adolescents' reactions to social interchanges and play an important role in regulating the attention, emotion, and behavioral responses evoked by potentially distressing social situations. Interestingly, there is a substantial overlap between corticolimbic and striatal brain structures implicated in mood disorders and those with aberrant neural engagement to food cues among obese individuals or those with disordered eating (Bohon and Stice, 2012; Bohon et al., 2009; Yokum et al., 2011; Stice et al., 2008, 2010; Coletta et al., 2009; Burger and Stice, 2011, 2013; Bohon, 2014; Batterink et al., 2010; Jastreboff et al., 2013; Connolly et al., 2013). Moreover, youth with LOC eating consistently report greater symptoms of anxiety and depression compared to those without LOC (Tanofsky-Kraff et al., 2011; Sonnevile et al., 2013b; Goossens et al., 2009). Therefore, LOC eating may result

from altered neural engagement common to both socio-emotional and consummatory processes.

To assess the neural underpinnings of LOC eating using an interpersonal model framework more directly, we studied blood oxygen level-dependent (BOLD) responses in the brain using functional magnetic resonance imaging (fMRI) in overweight and obese adolescent girls with and without LOC eating during a simulated peer interaction chatroom paradigm (Guyer et al., 2008, 2009). This paradigm has previously been used to identify dysregulated engagement of brain regions subserved by corticolimbic and striatal circuits among adolescents with and at risk for social anxiety (Guyer et al., 2008, 2014a; Lau et al., 2012; Jarcho et al., under review). Regions that differ between healthy or low-risk and anxious or high-risk youth in this paradigm include the ventrolateral prefrontal cortex (vlPFC) and ventromedial regions of the prefrontal cortex (vmPFC), as well as the fusiform face area (FFA), amygdala (AMY), and striatum. Engagement of these regions, as well as functional connectivity between vlPFC and AMY and between vmPFC and striatum, likely interact to integrate attention, emotion, and corresponding behavioral responses to social situations (Forbes and Grafman, 2010; Nelson et al., 2005; Lieberman, 2007). Immediately following the chatroom paradigm, girls consumed lunch at a laboratory test meal designed to model a LOC episode. Consistent with the interpersonal model (Tanofsky-Kraff et al., 2007a), we hypothesized that compared to girls without LOC, girls with LOC eating would display a differential pattern of brain activation during peer feedback that reflects susceptibility to social rejection. Furthermore, we expected that brain activation patterns during peer feedback would relate to subsequent eating behavior in the post scan test meal.

## Materials and methods

### Participants

Participants were recruited via flyers for a study examining eating behaviors in adolescents (ClinicalTrials.gov ID: NCT00631644). Potential participants were eligible if they were right-handed, female, overweight (body mass index, BMI,  $\geq$  85th percentile standards for U.S. girls (Kuczmarski et al., 2000)), between 13 and 17 years of age, had good general health (other than overweight or obesity) as indicated by medical history and physical examination, absence of urine glucose excretion, and normal serum electrolytes, hepatic, and thyroid function. Exclusion criteria were chronic illnesses, pregnancy, ongoing weight-loss treatment, use of medications likely to affect energy intake or brain function, or a full-syndrome DSM-5 psychiatric condition, other than binge eating disorder. Participants were also excluded due to a history of significant neurological injury or insult, or the presence of dental braces, or other metal in or on their body that would preclude safe and successful MRI scanning. Girls provided written assent and parents/guardians gave written consent. The study was approved by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Institutional Review Board.

### Procedure

Participants completed outpatient appointments on two separate days at the NIH Clinical Research Center. Following an overnight fast, participants were screened for eligibility at an initial visit that included a medical history and a physical examination performed by an endocrinologist or nurse practitioner. Height was measured three times to the nearest millimeter by a stadiometer (Holtain, Crymmych, Wales) calibrated before each participant's measurement. Fasting weight was measured to the nearest 0.1 kg with a calibrated digital scale (Scale-Tronix, Wheaton, IL). Height and weight were used to compute BMI (kg/m<sup>2</sup>) (Sonneville et al., 2013a). BMI standard deviation (BMIz) scores for sex and age were calculated according to the Centers for Disease Control and Prevention 2000 standards (Kuczmarski et al., 2000). The Eating

Disorder Examination version 14 OD/C.2 (Fairburn and Cooper, 1993) was administered to assess presence of LOC eating. LOC eating was defined as a subjective experience of lack of control during reported consumption of ambiguously and/or unambiguously large amounts of food. The Eating Disorder Examination has demonstrated excellent inter-rater reliability and discriminant validity for assessing LOC episodes in adolescents (Glasofer et al., 2007). Participants who reported one or more LOC episode in the month prior to assessment were included in the LOC group (LOC+); all others were included in the non-LOC (LOC-) group.

**Chatroom task**

Participants completed the well-established and reliable chatroom task (see work from Guyer and colleagues for detailed methods (Guyer et al., 2008; Lau et al., 2012; Guyer et al., 2009; Guyer et al., 2014a; Jarcho et al., under review; Guyer et al., 2014b; Guyer et al., 2012)), which is implemented across two laboratory visits. This task was designed to assess brain function during an evocative social context in which adolescents receive positive or negative feedback from high- or low-value peers (see Fig. 1). The chatroom task procedures involve the following.

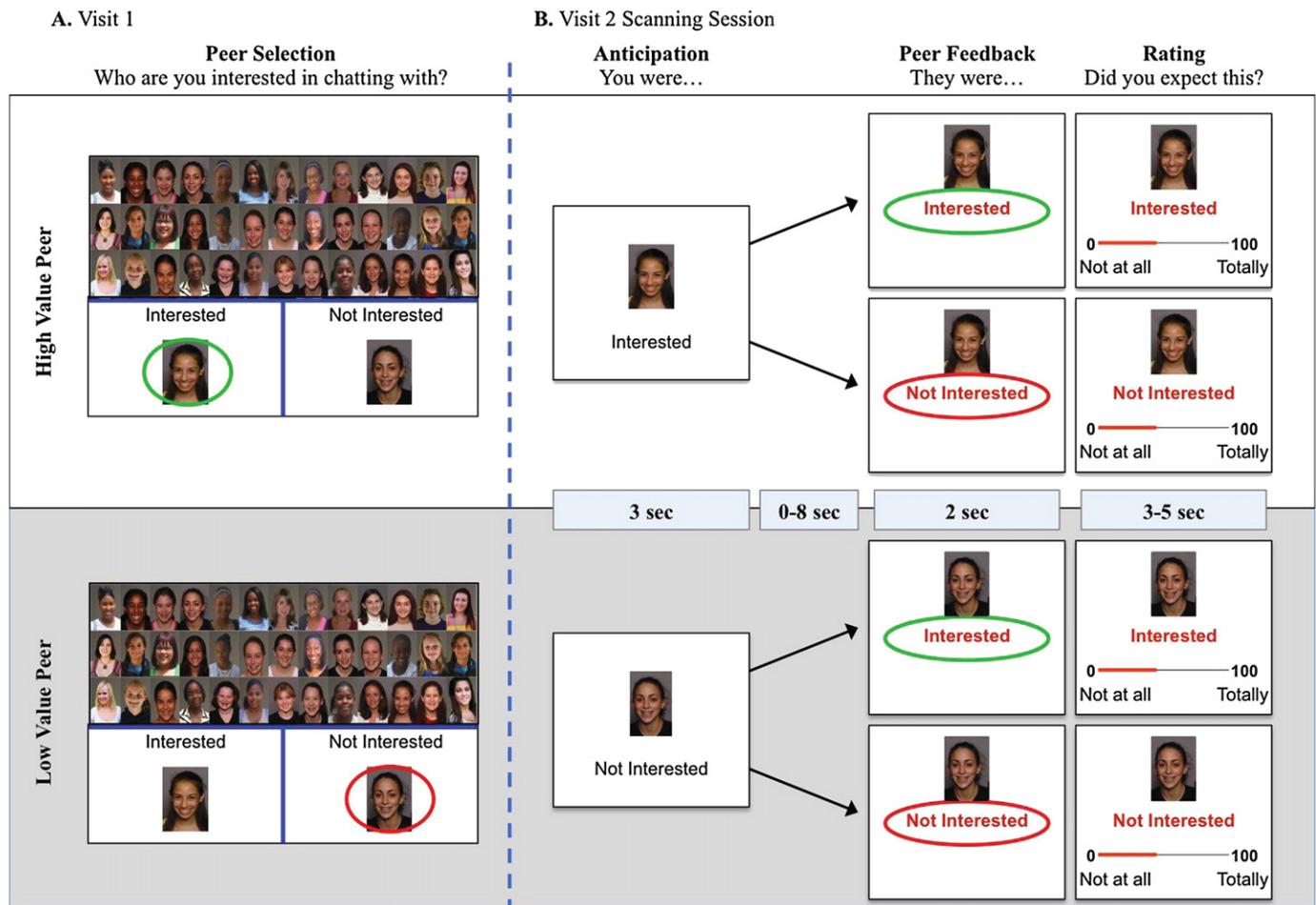
**Peer evaluation**

After completing screening procedures at their initial outpatient visit, girls were told that they would participate in an online chat session

with a peer at their next visit. To prepare for this visit, they were shown 60 photographs of female peers (ages 9–17 years) and were asked to categorize peers as 1) high-value: peers with whom they were interested in chatting; and 2) low-value: peers with whom they were not interested in chatting. Participants were then photographed and told that the 60 purported peers they had just categorized would be shown their picture. Participants were led to believe that purported peers would learn if they had been categorized as high- or low-value before making the same categorization choice for the participant.

**Social feedback from peers during fMRI scanning**

Following an overnight fast, participants reported to the NIH Clinical Center at 9:30 am for a second outpatient visit to undergo fMRI scanning and other study procedures. Girls consumed no food or drink except water after 10:00 pm on the night before the visit. Two tasks were completed in the scanner. In each task, participants were shown photographs of the previously rated peers. During the first task, participants were asked to guess how interested each peer was in chatting with them. During the second task, participants were reminded that peers were of high- or low-value. Then, they received purported feedback from the high- and low-value peers: the words *Interested* or *Not Interested* appeared beneath each photograph. Participants were told that the words indicated how each peer had categorized them. Participants were then asked to indicate how much they expected the feedback they received (0 = not at all; to 100 = totally expected). The two tasks were completed during separate functional runs of fMRI scanning.



**Fig. 1.** Depiction of the chatroom paradigm. A. Participants are asked to categorize peers as 1) high-value: peers with whom they were interested in chatting; and 2) low-value: peers with whom they were not interested in chatting. B. During the fMRI scan, participants learn if their peers are or are not interested in them.

The interpersonal model of LOC eating implicates stress elicited by a failure to cope with negative interactions in response to social feedback (Tanofsky-Kraff et al., 2007a). Therefore, brain-based analyses were restricted to data collected during the peer feedback task, obtained in the second functional run.

#### fMRI data acquisition

Data were acquired on a Siemens MAGNETOM Verio 3 T. During receipt of social feedback (functional run 2), 367 functional image volumes were acquired with a T2\* echo-planar sequence (34 oblique slices with 2.6 mm thickness; repetition time/echo time (TR/TE) = 2300/25 ms, flip = 90°; field of view (FOV) = 240 mm, matrix = 64 × 64). To facilitate anatomical localization and co-registration of functional data, a high resolution structural scan was also acquired (sagittal plane) with a T1-weighted magnetization-prepared spoiled gradient-recalled echo sequence (1 mm resolution; echo time/inversion time (TE/TI) = min full/725 ms, flip = 6°; FOV = 220 mm, matrix = 256 × 256).

#### Laboratory test meal

Immediately following the fMRI scan, a laboratory test meal was administered in a room located in the same building. Each participant was served a large food array (10,934 kcal), varied in macronutrients (54% carbohydrate, 12% protein, 33% fat) and comprised foods that most children like (Shomaker et al., 2010b). Participants received a tape-recorded instruction to “Let yourself go and eat as much as you want” to model a LOC eating episode (Tanofsky-Kraff et al., 2009b). Immediately before, and again, after each test meal, participants completed the psychometrically sound, State Form of the State-Trait Anxiety Inventory for Children (Spielberger, 1983) which measures anxiety “right now, at this very moment.” The amounts of each food and beverage consumed from the meal were measured by using the differences in weight (g) of each item before and after the meal. Energy (kcal) intakes were calculated with data from the U.S. Department of Agriculture National Nutrient Database for Standard Reference (Agricultural Research Service, Beltsville, MD) and food manufacturer nutrient information obtained from food labels. Following the test meal, participants were fully debriefed with regard to the deception involved in the chatroom task.

#### Data analysis

All non-fMRI data analyses were performed with IBM SPSS Statistics (Version 20.0). Data were screened for normality. There were no influential outliers. BMIz was considered in analyses, but since it did not contribute to any model and the results were the same with or without its inclusion (as might be anticipated for studies enrolling only overweight

and obese participants), BMIz was removed as a regressor. Self-reported expectation of social feedback during the scanning session was assessed with a repeated measures analysis of variance (ANOVA) with one between-subject factor of group (LOC+, LOC−) and two within-subject factors of peer value (high/low) and peer feedback (positive/negative).

#### General image processing

All fMRI data analyses were conducted with Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) and co-registered to the high resolution structural scan. Data were corrected for slice timing, smoothed (6 mm full width at half maximum), spatially normalized to standard Talairach space, and resampled, resulting in 2.5 mm (Tanofsky-Kraff et al., 2011) voxels. Temporally adjacent TRs with a Euclidean Norm motion derivative > 1 mm were censored and omitted from analyses. Complete data from two additional participants were excluded from analyses due to motion-related artifacts that substantially diminish quality of echoplanar images (≥25% censored TRs).

#### Individual-level fMRI analyses

Separate regressors were created for each type of social feedback event. Events were classified by two criteria: peer value (high/low) and feedback (positive/negative). Thus, four task-specific regressors were modeled: 1) positive feedback from high-value peers; 2) positive feedback from low-value peers; 3) negative feedback from high-value peers; and 4) negative feedback from low-value peers.

Task-specific regressors were convolved with a  $\gamma$ -variate basis function approximating the BOLD response (Cohen, 1997). Additional regressors modeled motion residuals and baseline drift. This analysis produced a  $\beta$ -coefficient and associated t-statistic for each regressor at each voxel. Percent signal-change maps were generated by dividing signal intensity at each voxel by the mean voxel intensity, and multiplying by 100.

#### Group-level fMRI analyses

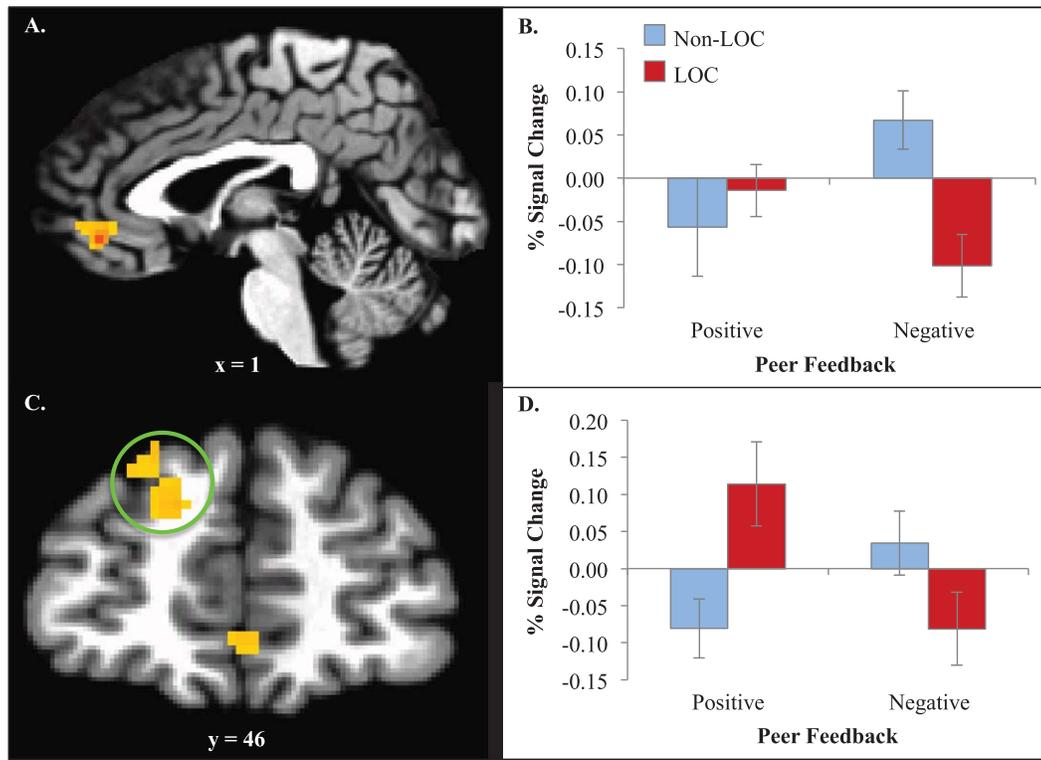
Whole-brain, group-level analyses assessing the effects of LOC status on hemodynamic response during social feedback were conducted using 3dMVM, an AFNI-based multivariate modeling program (Chen et al., 2014; <http://afni.nimh.nih.gov/sscc/gangc/MVM.html>). This analysis consisted of a repeated measure ANOVA with one between-subject factor of group (LOC+/LOC−), two within-subject factors of peer value (high/low) and peer feedback (positive/negative), and one continuous regressor of total energy intake (mean-centered) during the post scan test meal.

Five a priori regions of interest (ROIs) were considered: vIPFC, vmPFC, fusiform gyrus (which includes FFA), AMY, and striatum. These ROIs were chosen based on prior studies, including those that use the chatroom task, which show that responses in these regions

**Table 1**  
Participant characteristics.

	Loss of control (n = 10)	No loss of control (n = 12)	p-Value
Age, y, M ± SD	15.4 ± 1.7	16.1 ± 1.4	.30
Race, %	30.0% Non-Hispanic White 60.0% Non-Hispanic Black 10.0% Other	50% Non-Hispanic White 33.4% Non-Hispanic Black 16.6% Other	.37
BMI <sup>a</sup> , kg/m (Sonnevile et al., 2013a), M ± SD	33.5 ± 9.2	32.4 ± 5.1	.76
BMIz, M ± SD	1.9 ± .5	1.9 ± .3	.98
BMI percentile, M ± SD	95.1 ± 3.7	96.1 ± 3.7	.51
Pre-meal state anxiety, M ± SD	3.9 ± 6.1	1.0 ± 1.0	.11
Intake (kilocalories), M ± SD	1641.40 ± 695.09	1322.03 ± 358.95	.18
Post-meal state anxiety, M ± SD	3.4 ± 2.3	1.0 ± 1.0	.006

<sup>a</sup> BMI = body mass index.



**Fig. 2.** Significant clusters for the interaction between group and feedback type. A. Ventromedial prefrontal cortex (1, 43, -5;  $k_e = 41$ ,  $F = 35.51$ ). B. Decomposition showed that both groups responded similarly to positive feedback ( $t(20) = -.63$ ,  $p = ns$ ), but negative feedback elicited diminished engagement in LOC+ and heightened engagement for LOC- ( $t(20) = 3.40$ ,  $p < .005$ ). C. Dorsolateral prefrontal cortex (-14, 51, 40,  $k_e = 61$ ,  $F = 15.71$ ). D. Decomposition showed that while LOC- responded similarly to positive and negative feedback ( $t(10) = -1.74$ ,  $p = ns$ ), LOC+ had heightened activity to positive, relative to negative feedback ( $t(9) = 5.34$ ,  $p < .001$ ).

discriminate between high- and low-value peers and/or positive and negative social feedback (Guyer et al., 2008, 2014a; Lau et al., 2012; Jarcho et al., under review), and were defined anatomically. The vIPFC (762 voxels) is comprised of aspects of inferior frontal gyrus and middle frontal gyrus inferior to  $z = 1$ . The vmPFC (1146 voxels) is comprised of aspects of superior frontal gyrus, medial frontal gyrus, peri- and subgenual anterior cingulate cortex inferior to  $z = 8$  ( genu of cingulate). The fusiform gyrus (700 voxels; which includes FFA), AMY (69 voxels) and striatum (688 voxels; dorsal and ventral aspects of the putamen, caudate, and nucleus accumbens) were defined using masks from the Talairach–Tournoux Atlas.

ROI analyses were thresholded by an overall significance level (false detection probability) based on 10,000 Monte Carlo simulations (AFNI, AlphaSim), using a mean estimated spatial correlation of  $8.51 \times 8.71 \times 7.69$  mm FWHM, in the respective x, y, and z dimensions. Monte Carlo simulations were performed for each ROI to determine the cluster-size needed to achieve a voxel-specific threshold of  $p < .005$ , with an overall family-wise error rate of  $\alpha < .05$ . After correcting for the small volume of each ROI, simulations determined the minimum number of contiguous voxels, activated at the  $p < .005$  level, needed to identify significant activity in vIPFC ( $k_e = 14$  voxels), vmPFC ( $k_e = 18$  voxels), fusiform gyrus ( $k_e = 11$  voxels), AMY ( $k_e = 2$  voxels), and striatum ( $k_e = 12$ ; voxels). Activation clusters of interest were extracted and plotted to facilitate interpretation. Exploratory whole-brain analyses for regions not included in ROIs were set at a significance threshold of  $p < .005$ , with a cluster extent threshold of  $k_e > 20$ , and are reported for completeness. Task-based main effect and interactions for peer value and feedback are also reported for completeness using the same threshold as exploratory whole brain analyses (Table 4).

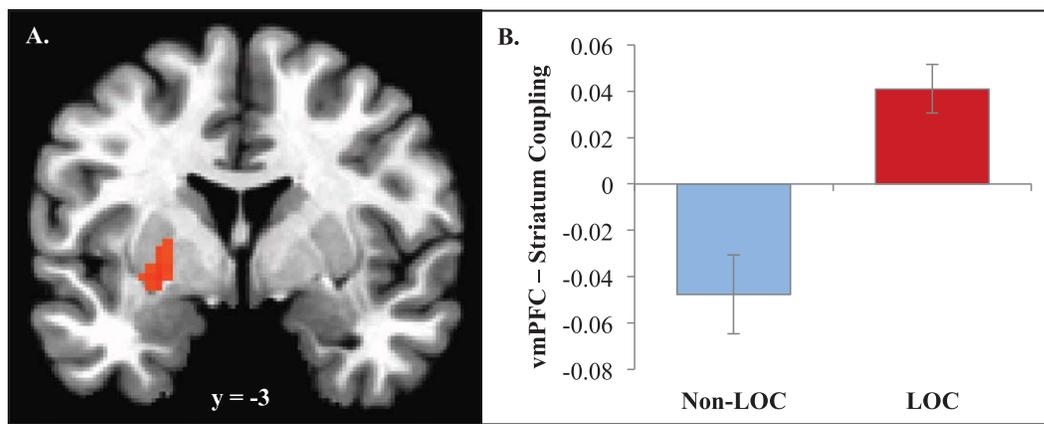
**Functional connectivity analyses**

There are widespread functional connections between prefrontal cortex and subcortical regions such as AMY and striatum. Strength of this coupling has been implicated in the capacity to regulate affect

**Table 2**  
Group-level activation clusters from exploratory whole brain analyses.

	MNI coordinates			Cluster size	F
	x	y	z	Voxels	
Group × peer value × peer feedback	-	-	-	-	-
Group × peer value					
Postcentral gyrus	57	-21	20	302	31.90
Precentral gyrus	46	-13	38	39	15.86
Insula	-57	-16	36	178	36.21
	-36	4	10	26	14.95
	-31	14	5	33	20.13
Anterior cingulate	-4	15	38	30	14.36
Inferior frontal gyrus	-36	30	0	22	14.92
Group × peer feedback					
Superior frontal gyrus	-14	51	40	61	15.71
Group					
Precentral gyrus	49	-14	31	119	41.56
	-46	-16	38	32	27.34
Temporo-parietal junction	24	-73	39	21	24.87

Whole brain analysis,  $p < .005$ , cluster size  $> 20$ . Activation clusters reflect group (LOC+/LOC-), peer value (high/low), peer feedback (positive/negative) interactions or main effects.



**Fig. 3.** Psychophysiological interaction analysis. A. Ventromedial prefrontal cortex (vmPFC) showed functional connectivity with striatum (putamen;  $-24, -4, -5$ ;  $ke = 35$ ) that varied by peer feedback and group. B. Negative, relative to positive, feedback resulted in negative vmPFC-striatal coupling in LOC- ( $t(11) = -2.79, p < .05$ ), but positive coupling in LOC+ ( $t(9) = 4.92, p < .005$ ).

(reviewed by Ochsner (Ochsner et al., 2012)), and is often disrupted in at risk and patient populations (Guyer et al., 2008; Hardee et al., 2013; Furman et al., 2011; Prater et al., 2013). Thus, exploratory functional connectivity analyses were conducted for regions of prefrontal cortex (seeds) that showed group differences in primary ROI analyses. Psychophysiological interaction (PPI) analyses were therefore performed to determine whether activation in vmPFC during negative, relative to positive feedback, covaried with activation in AMY or striatum to a different extent across groups.

For each participant, mean-adjusted eigenvariate time series data were extracted from the activation cluster in vmPFC that emerged from group-by-social feedback analyses. Time series data were deconvolved with the hemodynamic response function before a PPI term was generated for positive vs. negative social feedback. A random-effects model was calculated to identify group differences in any region showing vmPFC coupling that differed for positive, as compared with negative, social feedback. A significance threshold of  $p < .005$  and cluster extent of 20 was applied to whole-brain functional connectivity analyses.

## Results

Data are reported from 22 girls who completed the chatroom task and test meal, 10 of whom reported at least one episode of LOC eating in the past month (LOC+). Based upon LOC status, girls did not differ in age, race, BMI metrics, or post-scan/pre-meal state anxiety (Table 1).

### Manipulation check

Behavioral responses in the scanner replicated prior findings (Guyer et al., 2008, 2014a), such that there was a significant interaction between peer value  $\times$  peer feedback on participants' report of "expectation" of displayed responses,  $F(1, 21) = 18.77, p < .001$ . Regardless of LOC status, participants reported having expected positive feedback from high-value ( $M = 59.55, SD = 15.29$ ) relative to low-value peers ( $M = 41.46, SD = 16.73, p < .01$ ); and negative feedback from low-value ( $M = 61.50, SD = 11.53$ ) relative to high-value peers ( $M = 44.56, SD = 13.46; p < .001$ ). There was no main or interaction effect on self-report for LOC, nor did reported expectations relate to total energy intake across participants, or within LOC+ or LOC- groups when considered separately (all  $ps$  ns).

### Group-level fMRI analyses

#### LOC and brain response

ROI analyses revealed a significant cluster within the vmPFC for the interaction between group (LOC+ versus LOC-) and feedback type ( $x,$

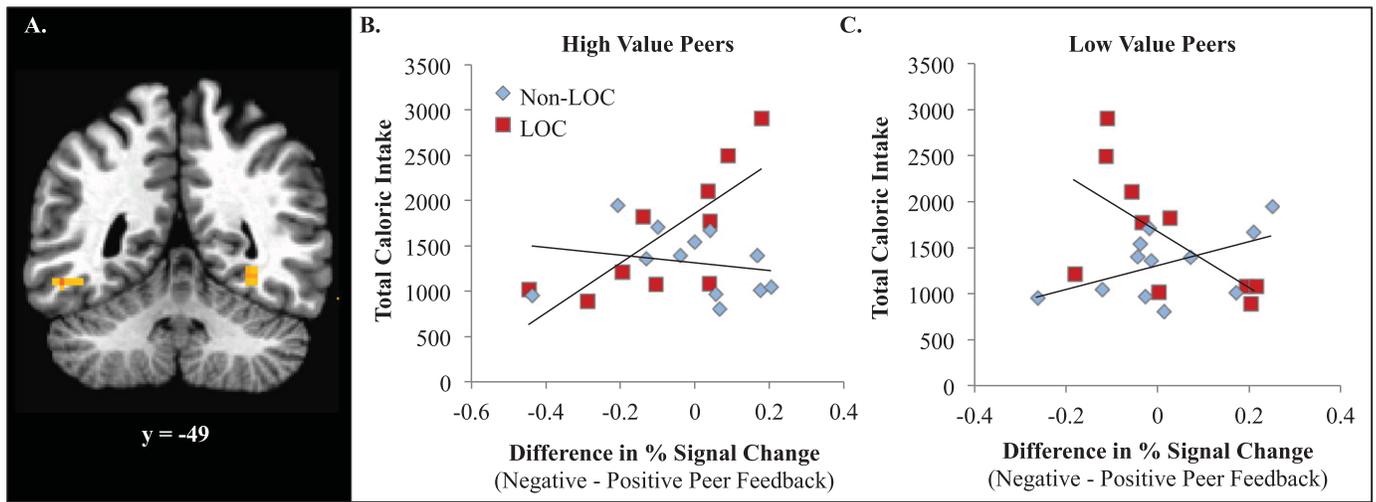
$y, z =$  co-ordinates reported in Montreal Neurological Institute standardized space:  $1, 43, -5$ ;  $ke = 41, F = 35.51$ ). Decomposition of this interaction revealed that while both groups responded similarly to positive feedback ( $t(20) = -.63, p = ns$ ), negative feedback elicited diminished engagement in LOC+, but heightened engagement for LOC- participants ( $t(20) = 3.40, p < .005$ ; Figs. 2A–B). Exploratory whole brain analyses revealed a significant cluster for the same interaction within dorsolateral PFC (dlPFC;  $x, y, z = -14, 51, 40, F = 15.71$ ). Decomposition of this interaction revealed that while LOC- responded similarly to positive and negative feedback ( $t(10) = -1.74, p = ns$ ), LOC+ had heightened activity to positive, relative to negative, feedback ( $t(9) = 5.34, p < .001$ ; Figs. 2C–D). No other main or interaction effect on brain function for group was found in other ROIs. See Table 2 for additional group-level activation clusters from exploratory whole brain analyses.

### Functional connectivity analyses

PPI analysis revealed that functional connectivity between the vmPFC seed and striatum (putamen;  $x, y, z = -24, -4, -5$ ;  $ke = 35$ ) varied as a function of peer feedback and group (see Fig. 3). Negative, relative to positive, feedback resulted in negative vmPFC-striatal coupling in LOC- ( $t(11) = -2.79, p < .05$ ), but positive coupling in LOC+ ( $t(9) = 4.92, p < .005$ ). Group differences in functional connectivity were also observed in inferior parietal lobule ( $x, y, z = -46, -68, 38$ ;  $ke = 77$ ), but were not interrogated further due to lack of a priori hypotheses about this region.

### Relation of neural activation to "LOC" meal energy intake

Two activation clusters in the fusiform gyrus varied by both group and energy intake. Four-way interactions (group  $\times$  peer feedback  $\times$  peer value  $\times$  energy intake) were observed in bilateral FFA (Right:  $x, y, z = 31, -47, -13$ ;  $ke = 13; F = 19.22$ ; Left:  $x, y, z = -49, -50, -16$ ;  $ke = 15; F = 24.93$ ; Fig. 4). These interactions were primarily driven by group differences during feedback from high-value peers (Fisher's  $r$ -to- $z$ 's: Right =  $-2.40; p < .05$ ; Left =  $-2.22; p < .05$ ). For LOC+, greater FFA activity during negative, relative to positive, feedback from high-value peers was positively associated with overall energy intake during the subsequent test meal ( $r$ 's: Right =  $.76, p = .01$ ; Left =  $.48, p = ns$ ). In contrast, for LOC-, FFA activity during peer feedback did not relate to subsequent energy intake ( $r$ 's: Right =  $.27, p = ns$ ; Left =  $-.54, p = ns$ ). Group differences were not observed in this region during feedback from low-value peers (Fisher's  $r$ -to- $z$ 's: Right =  $1.40; p = ns$ ; Left =  $.27, p = ns$ ).



**Fig. 4.** Significant clusters for the interaction between group, feedback type, peer value, and energy intake. A. Four-way interactions emerged in bilateral fusiform face area (FFA; Right:  $x, y, z = 31, -47, -13$ ;  $k_e = 13$ ;  $F = 19.22$ ; Left:  $x, y, z = -49, -50, -16$ ;  $k_e = 15$ ;  $F = 24.93$ ). B. For LOC+, greater right FFA activity during negative, relative to positive feedback, from high-value peers was positively associated with greater energy intake during the subsequent test meal ( $r = .76, p = .01$ ). For LOC-, right FFA activity during peer feedback did not relate to subsequent energy intake ( $r = .27, p = ns$ ). C. Significant group differences were not observed in FFA during feedback from low-value peers.

A three-way interaction (group  $\times$  peer value  $\times$  energy intake) was found in the AMY ( $-21, -5, -23$ ;  $k_e = 7$ ;  $F = 12.25$ ). However, because this interaction did not relate to peer response, the primary experimental condition of interest, it was not further interrogated. See Table 3 for complete group-level activation clusters from exploratory whole brain analyses.

**Discussion**

This study examined potential differences in neural response to peer feedback in girls with and without LOC eating. We found that brain activity during a paradigm known to differentially engage circuitry implicated in social anxiety, differed between girls with and without LOC, and was linked to subsequent food intake. Whereas overweight and obese girls with LOC had diminished vmPFC activation following peer

rejection (vs. acceptance), those without LOC had heightened vmPFC activation. Functional connectivity between vmPFC and striatum also varied based upon reported LOC eating. Further, after receiving negative feedback from high-value peers, greater FFA activation was associated with more subsequent energy intake in girls with reported LOC eating, but did not relate to energy intake in those without LOC. Taken together, these preliminary findings support the hypothesis that dysregulated brain response to social evaluation may be linked to overeating in overweight and obese adolescent girls with LOC eating.

Girls with LOC eating exhibited reduced vmPFC engagement in response to peer rejection. The vmPFC has been implicated in numerous aspects of socio-emotional processing, including interpreting social intentions, self-reflection, and affect modulation (Frith and Frith, 2012; Etkin et al., 2011; Amodio and Frith, 2006; Flagan and Beer, 2013). In a social context, healthy individuals generally have heightened engagement of vmPFC following exclusion (Sebastian et al., 2011; Moor et al., 2012; Bolling et al., 2011) and social evaluative threat (Somerville et al., 2013; Hughes and Beer, 2013). It has been suggested that heightened engagement of vmPFC in this context may, in fact, facilitate the regulation of negative affect typically generated by interpersonal distress (Etkin et al., 2011; Flagan and Beer, 2013; Hughes and Beer, 2013). Thus, among the girls in our sample with LOC eating, diminished engagement of vmPFC during negative peer feedback may reflect a failure to engage regulatory mechanisms following peer rejection. This response possibly accounts for data indicating poor social functioning in youth with LOC eating (Czaja et al., 2011; Elliott et al., 2010; Hartmann et al., 2012; Hilbert et al., 2010). Hypoactivity in vmPFC among girls with reported LOC eating may therefore relate to deficits in adjusting and responding to social evaluative outcomes or to emotion regulation more generally. Diminished engagement of the vmPFC may be experienced as alexithymia or the inability to identify or express affect and avoidance in coping with conflicts or articulating emotions (Sifneos, 1996). Similar cognitive-emotional deficits have been reported by youth with LOC eating during LOC eating episodes (Tanofsky-Kraff et al., 2007b; Wolkoff et al., 2011). These data can be interpreted within a Research Domain Criteria framework (Sanislow et al., 2010). Girls with LOC eating may have a compromised ability to down-regulate uncomfortable affective states that are a reflection of deficits in negative valence constructs (Tanofsky-Kraff et al., 2013). In response, such youth may seek external means of comfort, including engaging in excessive food consumption, consistent with problems in the positive valence domain.

**Table 3**  
Group-level activation clusters that predict subsequent caloric intake from whole brain analysis.

	MNI coordinates			Cluster size Voxels	F
	x	y	z		
<i>Group <math>\times</math> peer value <math>\times</math> peer feedback <math>\times</math> caloric intake</i>					
Middle temporal gyrus	57	-63	9	29	16.61
<i>Group <math>\times</math> peer value <math>\times</math> caloric intake</i>					
Hippocampus	-21	-13	-26	34	17.18
Parahippocampal gyrus	-34	-24	-14	30	23.64
Precuneus	24	-70	41	22	16.10
Posterior cingulate	-6	-51	15	60	29.02
	-4	-47	35	42	17.99
Parahippocampal gyrus	-34	-24	-24	30	23.64
	-21	-13	-26	25	17.18
Middle temporal gyrus	-52	-42	-7	25	21.33
Middle occipital gyrus	-49	-71	-11	33	19.83
<i>Group <math>\times</math> peer feedback <math>\times</math> caloric intake</i>					
Temporal pole	60	1	1	33	18.77
<i>Group <math>\times</math> caloric intake</i>					
Cuneus	-6	-82	19	75	26.15
Middle temporal gyrus	-39	-67	19	37	23.52
Precentral gyrus	-36	-22	54	23	27.38

Activation clusters reflect group (LOC+/LOC-), peer value (high/low), peer feedback (positive/negative), caloric intake (continuous measure of total intake at test meal) interactions. Whole brain analysis,  $p < .005$ , cluster size  $> 20$ .

Although dorsolateral prefrontal cortex (dlPFC) was not an a priori ROI in this study, it is a brain region that supports regulatory control, and has been linked to eating-related regulatory control among dieters (Hare et al., 2009; Weygandt et al., 2013). Our exploratory whole brain analyses found that activity in the superior frontal gyrus, a region of dlPFC commonly implicated in emotion regulation (Dorfel et al., 2014; Frank et al., 2014; Otto et al., 2014), varied as a function of LOC group and valence of social feedback. Specifically, girls with LOC eating had heightened activity in dlPFC during receipt of positive, relative to negative peer feedback; those without LOC did not differentiate between positive and negative feedback. This suggests that unlike dieters, girls with LOC have diminished regulatory control for eating, but like dieters, may engage heightened regulatory processes in contexts distinct from eating. The results may be interpreted as developmental differences in youth with LOC eating who have yet to develop overly restrictive dietary patterns (Tanofsky-Kraff et al., 2005) reported by adults with binge eating (Spurrell et al., 1997; Abbott et al., 1998). Our results also suggest that enhanced emotion regulation in girls with LOC may dampen the potential benefit of positive social feedback, while diminished emotion regulation may increase their susceptibility to the deleterious consequences of negative social feedback. Further work is needed to specifically relate affective response to peer feedback with brain function in adolescent girls with LOC, as well as those with and without restricted eating.

Group differences were also identified in exploratory analyses of functional coupling between PFC and the striatum during peer feedback. Engagement of vmPFC was associated with down-regulated striatal activity in those without LOC, but up-regulated activity in girls with LOC eating. Although evidence from both animal and human studies has linked striatal activity with appetitive behaviors including food consumption (Volkow et al., 2011; Schultz, 2000), recent work suggests that the striatum may play a more general role in tracking the affective salience of stimuli (Metereau and Dreher, 2013; Shohamy, 2011). Up-regulated striatal activity suggests that social feedback carries a heightened salience among girls with LOC eating. The striatum may also shape motivated behavior to obtain or avoid outcomes while influencing learning and habit formation (Yin et al., 2009; O'Doherty, 2004; Cavanagh et al., 2011). Indeed, dysregulated vmPFC-striatal connectivity during peer feedback in the chatroom task contributes to biases in social learning among anxious adolescents (Jarcho et al., under review). Perturbations in corticostriatal circuitry also have been found among individuals with binge-type eating disorders during stimulus-outcome learning paradigms (Balodis et al., 2013; Celone et al., 2011; Frank et al., 2011). Thus, the dysregulated ability to exert executive control over subcortical structures may relate to both aversive and appetitive behaviors. While the precise implications of dysregulated vmPFC-striatal connectivity clearly requires further investigation, the current results suggest one neural mechanism by which poor social functioning may directly relate to LOC eating behavior.

We also found that in girls with LOC eating, brain activity patterns were linked to subsequent energy intake. Specifically, greater engagement of FFA to negative, relative to positive, feedback from high-value peers was linked to higher energy intake for girls with LOC eating, but did not relate to energy intake in those without LOC. This finding parallels previously reported data of heightened FFA engagement following peer rejection among adolescents at risk for social anxiety (Guyer et al., 2014a). The FFA demonstrates a specific and selective pattern of engagement to faces and is thought to reflect highly enriched perceptual processing (Kanwisher et al., 1997; Haxby et al., 2001). The FFA also receives “back projections” from brain regions implicated in affective processing, which are thought to bias responding towards emotionally salient or arousing facial expressions (Miyahara et al., 2013; Furl et al., 2013; Lee et al., 2014). Thus, among the girls in our sample with LOC eating, heightened engagement of FFA may reflect a bias towards processing negative feedback from high-value peers. This bias, which emerged during only the most threatening of social encounters

(negative feedback from high-value peers), also was positively associated with consumption during the test meal in those with LOC eating. However, heightened FFA is also observed in response to food cues or palatable food intake among obese and/or food-deprived individuals (Siep et al., 2009; Kroemer et al., 2013a,b; Stice et al., 2013). Thus, it is somewhat difficult to determine whether caloric consumption in those with LOC is specifically related to heightened activity in FFA elicited by highly salient social cues, highly salient food cues encountered at the test buffet, or some combination thereof. For example, heightened engagement of FFA may be an index of poor affect regulation processes, which fail to buffer girls with LOC during negative social encounters. Failure to engage affect regulation processes may promote subsequent self-soothing via dysregulated eating that is potentiated by the elevated salience of food. Further complicating interpretation of these findings is the use of face-based stimuli, which are known to engage FFA (Kanwisher et al., 1997; Haxby et al., 2001). Further investigation is required to isolate the specific mechanisms that mediate the relationship between FFA and energy consumption in girls with LOC eating.

Contrary to our hypothesis, we found no relationship between AMY activation and LOC eating status or energy intake. Although youth with anxiety disorders have demonstrated AMY hyperactivation in social evaluation paradigms (Guyer et al., 2008, 2014a; Lau et al., 2012; Jarcho et al., under review), some data indicate that individuals with binge-type eating disorders exhibit AMY hypoactivation when presented with socially threatening stimuli relative to healthy controls (Ashworth et al., 2011; Miyake et al., 2010; Pringle et al., 2011). Such hypo-responsivity has been interpreted as emotional blunting, which is consistent with frequent reports of alexithymia among adolescent girls with LOC eating (Berger et al., 2014). Therefore, a lack of elevated AMY activity during the chatroom paradigm may be the result of emotional blunting among girls with LOC eating. It is also possible that the negative social feedback provided in the chatroom paradigm was insufficiently evocative to elicit a strong AMY response. Youth with LOC eating often report weight-related teasing from peers and family members (Hartmann et al., 2012; Libbey et al., 2008; Neumark-Sztainer et al., 2007), and therefore, receiving feedback that unknown peers were not interested in chatting with them for a study may have seemed relatively mild compared to the social ostracism they habitually experience. Alternatively, since all participants were overweight and obese, and thus more likely to experience higher rates of bullying and lower social support than their average-weight peers (Hayden-Wade et al., 2005), all of the girls may have found the chatroom paradigm anxiety-provoking regardless of LOC eating status. Future studies would benefit from inclusion of an average-weight comparison group and participants with full-threshold eating disorder psychopathology to evaluate these hypotheses.

Despite differences in brain activity, LOC did not relate to behavioral differences in self-reported expectation of peer feedback. While potentially puzzling, several factors may help explain this apparent discrepancy. First, it is important to underscore the fact that social interactions have complex temporal dynamics. For example, different psychological processes and corresponding neural circuits may be engaged when determining whether a peer is a desirable partner for a social interaction, subsequent anticipation and receipt of social evaluation from that peer, and finally reflecting upon the extent to which this feedback was expected. The chatroom paradigm was specifically designed to disentangle the neural circuits engaged during each step of this temporally dynamic process. Individuals with LOC eating commonly report that their eating behavior is elicited by social conflict or rejection (Czaja et al., 2011; Elliott et al., 2010; Hartmann et al., 2012; Hilbert et al., 2010). The present study focused on isolating group differences in brain activity specifically engaged by social rejection, relative to acceptance; brain activity engaged while reflecting on expected feedback was not modeled. However, unlike fMRI studies that measure brain function during passive viewing of stimuli and are unable to determine whether stimuli capture the attention of participants, obtaining these behavioral data provide greater confidence that participants were, indeed, engaged in the task at hand.

Given the proposed role of social rejection in LOC eating, one limitation of the present design is that participants were not asked to rate their emotional response to peer feedback. Group differences may have emerged had such a measure had been implemented. However, the relationship between affect elicited by specific experiences of rejection and subsequent caloric intake in LOC eating in the laboratory are not well documented in youth. Indeed, brain-based data often map on to the expression of clinically relevant behavior more closely than self-report (Berkman and Falk, 2013; McClure et al., 2007; Pine, 2007). Thus, group differences in the neural circuits engaged by social feedback, and their relation to subsequent caloric intake, may give us greater insight into the mechanisms that support LOC eating than self-reported alone. Moreover, self-report measures tend to poorly predict long-term expression of childhood disorders (Pine, 2007). Despite their relatively high incidence rates in childhood and adolescence, both social anxiety (Beesdo et al., 2009; Pine et al., 1998) and LOC eating (Tanofsky-Kraff et al., 2011; Hilbert and Brauhardt, 2014) often remit as youth transition to adulthood. Isolating neural signatures in adolescents more likely to sustain disorders into adulthood would help clinicians distinguish patients at greatest need for interventions, from those most likely to remit without such interventions (Pine, 2007; Bress et al., 2013; Matthews et al., 2006).

Strengths of the current study involve the use of interview assessment to determine LOC eating status, measurement of actual energy intake in the laboratory, and a racially diverse sample. This study also fills a needed knowledge gap in the field since socio-emotional processes have rarely been studied in adolescents with disordered eating. However, the sample size was relatively small. As a result, findings should be considered preliminary and require replication. Nevertheless, we applied stringent voxel and clusterwise False Discovery Rate correction and used theory to drive our analyses. This ensures that, despite the small sample size, future brain-based studies testing interpersonal theory are guided only by findings with appropriate statistical corrections.

Another limitation is that ROIs were defined anatomically, rather than with a functional localizer. A functional localizer approach defines ROIs using brain regions that respond differently to task-based factors, and then quantifies group differences in brain function within these regions. As described in Table 4, numerous brain regions differentially responded to task-based factors in the present study. However, they did not consistently overlap with brain regions where group differences in task-based responses emerged. This inconsistency may relate to the fact that, unlike traditional social evaluation paradigms designed to elicit stress via objectively threatening contexts (Cavanagh and Allen, 2008), the chatroom paradigm relies on more subtle meta-cognitive

factors to elicit stress. For example, instead of receiving overt and ongoing negative social feedback based on real-time performance, participants receive one-time positive or negative social feedback, purportedly generated by a peer at a prior visit. This feedback can, in turn, be interpreted in light of the peer's value to the participant, and beliefs about what motivated each peer to provide positive or negative feedback. Group differences in brain function may therefore correspond with regions directly related to task-based factors, or be more indicative of the meta-cognitive processes engaged by task-based factors.

Additionally, participants' weight history was not assessed. Although youth with LOC eating rarely report a history of weight control efforts or weight loss (Tanofsky-Kraff et al., 2005), the adult literature suggests differential neural responses between current and historical dieters and thus may be an important area for future exploration in pediatric samples (Ely et al., 2014). The lack of a measure of trait anxiety in the current study also precluded our ability to determine whether findings persisted above and beyond this potential confound. However, it is notable that youth with and without LOC eating did not differ in their level of state anxiety immediately following the chatroom task.

## Conclusions

In conclusion, our findings support the hypothesis that social-emotional neurobiological mechanisms may promote overeating in youth with LOC eating. Consistent with interpersonal theory, findings also suggest that the failure to engage prefrontal regulatory regions when receiving negative social feedback may lead to poor emotion regulation. In adolescent girls with LOC eating, biases towards heightened processing during stressful negative social interactions may promote subsequent overeating as an alternative means to more healthy or non-food-related strategies for coping with socially threatening interactions. Moreover, the present findings lay the foundation for future work aimed at distinguishing neural circuits in youth with LOC eating at greatest risk for sustained symptoms in adulthood, and thus at greatest need for early intervention.

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**Table 4**

Task effects from exploratory whole brain analyses.

	MNI coordinates			Cluster size Voxels	F
	x	y	z		
<i>Peer value × peer feedback</i>					
Fusiform gyrus	41	−41	−19	158	24.90
Middle temporal gyrus	−52	−55	−14	57	23.47
Ventral striatum extending to amygdala	−16	4	−7	42	18.98
Thalamus	−11	−27	8	26	16.34
Precuneus	31	−80	33	21	13.43
<i>Peer value</i>					
Parahippocampal gyrus	14	−35	−3	243	34.12
Precuneus	−16	−91	40	58	27.18
Dorsal anterior cingulate	−1	18	35	57	17.99
Inferior parietal lobule	−46	−36	31	50	51.38
Middle temporal gyrus	−34	−77	22	43	25.90
Superior temporal gyrus	52	9	2	26	19.08
<i>Peer feedback</i>					
Uncus extending to amygdala	21	8	−34	24	26.43

Activation clusters reflect peer value (high/low), peer feedback (positive/negative) interactions or main effects. Whole brain analysis,  $p < .005$ , cluster size  $> 20$ .

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