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Evidence of prefrontal hyperactivation to food-cue reversal learning in adolescents with anorexia nervosa

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ABSTRACT

Food avoidance in anorexia nervosa (AN) has been hypothesized to occur as a result of deficits in reversal learning and altered neuronal processing of food—cue relationships. Extant findings suggest that those with AN may rely on heightened recruitment of prefrontal regions during initial formation of food—cue learning and difficulty extinguishing these relationships may result from elevated insula activity. We tested this hypothesis by comparing behavioral and neuronal responses to food—cue acquisition and reversal between adolescents with AN and healthy controls. Compared to controls, acquisition of a food—cue association and its reversal were associated with elevated prefrontal activation in adolescents with AN. There were no significant differences between groups in insula activation and no behavioral differences in the ability to acquire or reverse the food—cue association. The results suggest that adolescents with AN recruit prefrontal regulatory networks to acquire and alter expectancies to food. This pattern of top-down prefrontal control suggests that clinical interventions that target changes in food—cue relationships and rely on cognitive control may be less effective. Interventions that alter behavior without reliance on this top-down control may have advantages with this population.

1. Introduction

1.1. Anorexia nervosa

Anorexia nervosa (AN) is a serious psychiatric disorder characterized by the relentless pursuit of thinness with an intense fear of weight gain despite significantly low body weight (Walsh, 2013). The disorder is associated with high rates of morbidity and mortality (Arcelus, Mitchell, Wales, & Nielsen, 2011; Fichter & Quadflieg, 1999; Sullivan, 1995) and long-term outcomes for patients diagnosed with AN are concerning. A six-fold increased mortality rate has been observed among individuals with AN in comparison to the general population, and mortality rates remain high 20 years or more after initial hospitalization (Papadopoulos, Ekbom, Brandt, & Ekselius, 2009). Less than half of patients experience a full recovery, approximately one-third improve somewhat, and another 20% demonstrate a chronic course after a 4–10 year follow-up period (Steinhausen, 2002). Pinpointing the neurophysiologic factors that contribute to clinically significant food avoidance has heuristic value for understanding the pathophysiology of AN and offers the potential to identify new targets for intervention. In particular, food-cue learning is the development (or reversal) of food expectancies (or its absence) with a neutral cue such as a social environment, person, or object. Difficulty reversing aversive food expectancies is thought to motivate food avoidance in AN.

The neuronal basis of AN is likely multifactorial. Predominant models suggest that disturbances in dopaminergic and serotonergic signaling affect temperamental disposition to favor harm avoidance, anxiety, and perfectionism (Kaye et al., 2013). An imbalance in these systems alters the motivational salience for feeding, with evidence that patients with AN do not respond appropriately to hunger signals, in part, because of altered coding of gustatory signals and emotion processing in the insula (Nunn, Frampton, Fuglset, Torzsok-Sonnevend, & Lask, 2011). This failure to adapt to feeding signals, including hunger/satiety, persists into recovery and includes failure to activate hedonic neurocircuits in a food deprived state and favors cognitive control (vlPFC, insula) in the context of reward valuation (Wierenga et al.,

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2015). When extended to food choice, patients with AN demonstrate greater engagement of the dorsal loop between cortex and striatum (Foerde, Steinglass, Shohamy, & Walsh, 2015)—a finding suggestive of altered cognitive control over preference for less palatable food. Part of the complexity of these models are their potential contributions to a range of avoidance phenomena including sensitivity to and avoidance of punishment/error, low cognitive flexibility, and alterations in emotional processing (Frank, 2015).

1.2. Neuronal basis of food-cue learning in anorexia nervosa

Numerous reports of blunted neural responses to the sight and taste of food in ventral striatum, amygdala, and anterior insula among women with AN have been purported to reflect the altered valuation of food rewards (Holsen et al., 2012; Oberndorfer et al., 2013; Wagner et al., 2008) and reduce the effects of existing treatments targeting weight increase through changes in food choice. However, this hypoactivation may signal a broader disturbance involving limbic mechanisms that underlie the acquisition and modification of food-cue relationships (Sehlmeyer et al., 2009). The anterior insula receives extensive visceral sensory input (Augustine, 1996), is the primary gustatory cortex encoding taste (Small, 2010), and mediates the experience of disgust (Gu, Hof, Friston, & Fan, 2013; Klucken et al., 2012). Anterior insula projects to numerous nuclei of the amygdala, including the basolateral nucleus (Augustine, 1996), which encodes neural representations of rewarding and aversive unconditioned stimuli essential for the expression of conditioned responses (Gore et al., 2015). The interaction of the two regions tracks the relationship between visceral stimuli and neutral cues (Denny et al., 2014). In turn, separate populations of neurons in ventromedial prefrontal cortex (vmPFC) respond preferentially to conditioned stimuli associated with rewarding and aversive outcomes (Morrison & Salzman, 2011) and together encode expected outcomes associated with predictive cues (Schoenbaum, Roesch, Stalnaker, & Takahashi, 2011). The association of food and eating with an aversive state that elicits disgust (e.g., feeling fat) may hijack these limbic mechanisms for stimulus-response learning.

Functional interaction of amygdala and ventral striatum contribute to the acquisition of cued-safety that accompanies aversive learning and motivates behavioral avoidance. The ventral striatum encodes neural representations of reinforcement prediction error (Li, Schiller, Schoenbaum, Phelps, & Daw, 2011), signaling the cued-absence of aversive stimuli, and promoting a shift to avoidance of the aversive stimuli (i.e., food cues; Boeke, Moscarello, LeDoux, Phelps, & Hartley, 2017). Feelings of disgust may increase the salience of avoidance behaviors by enhancing the striatal reward prediction signal and accelerating the rate of cued-safety acquisition in the amygdala (Watanabe, Sakagami, & Haruno, 2013). The interaction of the amygdala and striatum is dynamic—as reinforcers are repeated and prediction accuracy improves, activation decreases in the ventral striatum (Burger & Stice, 2013). Among AN patients, passive viewing of novel food stimuli yields reliable activation of the amygdala, insula, and anterior cingulate cortex (ACC; Joos et al., 2011)—suggesting processing of food stimuli engages the saliency network. Successful reversal of aversive conditioning entails activation of regulatory mechanisms in dorsolateral prefrontal cortex (dlPFC), which strengthens the top-down control of vmPFC, and effectively attenuates associative processing in the insula and amygdala (Schiller, Levy, Niv, LeDoux, & Phelps, 2008; Zhang, Mendelsohn, Manson, Schiller, & Levy, 2015). The failure to reverse the aversive associations that underlie food avoidance may be related to impairments in prefrontal inhibitory control functions reported in patients with AN (Hildebrandt, Grotzinger, & Schulz, 2016).

Aversive-disgust conditioning presents an eminently testable model of food avoidance in AN that can account for the motivational salience of cued-safety (i.e., absence of food) and the resistance of these aversive food-cue associations to reversal (Hildebrandt et al., 2015). This model, and related hypotheses, does not contradict other models of the neurobiology of AN. Rather, this model is orthogonal and complimentary because other models of impaired reward or habit learning do not preclude concurrent difficulties in reversal of food-cue relationships or the contribution of disgust in this complex phenomenon. We used functional magnetic resonance imaging (fMRI) together with a food-based reversal learning paradigm to test limbic-prefrontal mechanisms that underlie aversive conditioning in young women with AN. Hypotheses were based on prior research that used the reversal learning paradigm to study fear conditioning (Schiller et al., 2008; Zhang et al., 2015). Compared to matched healthy controls, adults with AN were predicted to show 1) enhanced insula and prefrontal cortex activation while rapidly acquiring the food-cue association and 2) reduced prefrontal activation accompanied by difficulty reversing the learned association.

2. Methods

2.1. Participants

Participants were recruited from individuals seeking treatment at the Mount Sinai Eating and Weight Disorders Program. Exclusion criteria included current psychotropic medication, and current substance abuse as evidenced by diagnostic interview, active suicidality, brain trauma or disease via chart review and coordination with primary care provider. Healthy controls were recruited from local street fairs, word of mouth, and posting of flyers on community boards. They were excluded if they met criteria for any Axis I psychiatric disorder according to the *Diagnostic and Statistical Manual of Mental Disorder*, *Fourth Edition* (DSM-IV-TR; American Psychiatric Association, 2000) and age appropriate diagnostic instruments were used for participants over 18 (i.e., Structured Clinical Interview *for DSM-IV-TR* (SCID-I; First, Spitzer, Gibbon, & Williams, 2002) and adolescents (i.e., Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997). Participants with AN were enrolled if they met *DSM-IV-TR* criteria for AN, or a sub-threshold variant of the disorder (i.e., met for all but one criteria). Adolescent (age ≤ 18) AN and sub-threshold participants were either currently a BMI-for-age percentile equal to or below 5%, or had lost greater than 20% of their body weight within the last year. Adult AN and subthreshold AN participants were either currently less than 85% of their ideal body weight, or had lost greater than 20% of their body weight within the last year. If the latter criterion was met for adolescents or adults, participants were included only if they met for all of the other primary criteria. The full sample of clinial participants reported onset of the disorder within the past year.

2.2. Appetitive reversal learning task

The appetitive reversal learning task was compiled and run using *E*-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA). The paradigm measures the ability to acquire and modify cue-reward associations specific to food, and has been validated in several clinical populations, including obese women (Zhang, Manson, Schiller, & Levy, 2014). The task was presented in a single run that lasted 16.25 min and consisted of discrete acquisition and reversal phases that each contained 40 trials. As shown in Fig. 1, red and blue playing cards served as the conditioned stimuli and food cue was represented by an image of chocolate candies (i.e., M&M'S®). Participants were told they would receive the candies earned as rewards upon completion of the task. During the acquisition phase, one conditioned stimulus (e.g., red card) was paired with the food cue on 8 of 24 (33%) trials (CS+), while the other conditioned stimulus (e.g., blue card) was paired with a blank image on all 16 trials (CS−). The reward contingencies were covertly switched during the ensuing reversal phase, such that the previously unreinforced stimulus (i.e., blue card) was now paired with the food cue on 8 of 24 (33%) trials (new CS+) and the previously rewarded

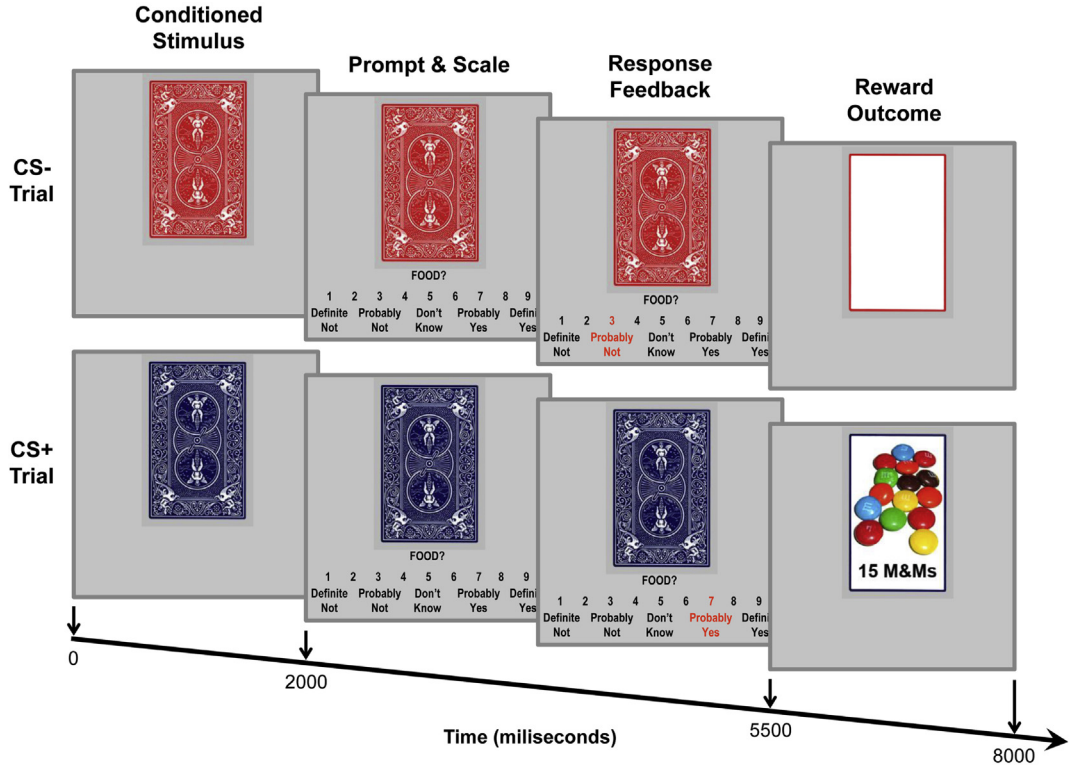

Fig. 1. Schematic illustration of single CS+ and CS− trials of the appetitive reversal learning task. Both trials started with the conditioned stimulus presented at fixation for 2000 ms before participants were prompted to rate their expectation of receiving a reward on a scale that was displayed below the stimulus for 3500 ms. Responses were highlighted in the scale to provide feedback, and failure to respond within 3000 ms prompted the warning "No response" to be displayed for the remaining 500 ms. The reward outcome was then presented at fixation for 2500 ms, in the form of an image of candies (i.e., M&M'S®) for 33% of CS + trials and a blank image for all other CS+ and CS− trials. The designation of red and blue cards as CS+ and CS− was counterbalanced across participants and the reward contingencies were covertly switched during the ensuing reversal phase. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

stimulus (i.e., red card) was now paired with a blank image on all 16 trials (new CS−). The designation of red and blue cards as CS+ and CS− was counterbalanced across participants.

The CS+ and CS− trials differed only in stimulus color and reward outcome. The trials all started with the conditioned stimulus presented at fixation for 5500 ms; after a 2000 ms delay, the prompt "Food?" and a rating scale that ranged from one to nine were displayed below the stimulus for 3500 ms. Participants were instructed to rate their expectation of receiving a food cue using fiber optic button response units in both hands, and their responses were highlighted in the scale to provide feedback. If participants did not respond within 3000 ms, the prompt and scale were replaced by the warning "No response" for the remaining 500 ms. The reward outcome was then presented at fixation for 2500 ms, in the form of an image of candies for 33% of CS + trials and a blank image for all other CS+ and CS− trials. The total duration of each trial was 8 s and the inter-trial interval was jittered from two to 8 s. The order of trials was pseudorandomized to ensure that CS+ was rewarded within the first three trials of both the acquisition and reversal phases. We modeled expectancy in linear mixed effects model, with trial type (CS + vs. CS−), trial phase (Acquisition vs. Reversal), and their interaction as within subjects effects and group (AN vs HC) as a between subjects effect.

2.3. Image acquisition

Participants were scanned using either a 3.0T Siemens Allegra or Skyra (Siemens, Erlangen, Germany) head-dedicated MRI scanner. Gradient-echo echo-planar imaging was used to obtain functional T2*-weighted images depicting the blood oxygenation level-dependent (BOLD) signal in a single run of 390 vol on the Allegra (repetition time [TR] = 2500 ms, echo time [TE] = 27 ms, flip angle = 82°, field of view [FOV] = 240 mm^2, matrix = 64 × 64, slice thickness = 4 mm contiguous, 40 slices) or Skyra (TR = 2500 ms, TE = 30 ms, flip angle = 90°, FOV = 230 mm^2, matrix = 76 × 76, slice thickness = 3 mm contiguous, 42 slices) scanner. A high-resolution T2-weighted anatomical image was acquired at the same slice locations with a turbo spin-echo pulse sequence (Allegra: TR = 4000 ms, TE = 99 ms, flip angle = 170°, matrix = 512 × 336; Skyra: TR = 4250 ms, TE = 89 ms, flip angle = 139°, matrix = 384 × 384). Images were acquired in the axial plane with slices positioned parallel to the anterior commissure – posterior commissure line.

2.4. Image preprocessing

Image preprocessing was conducted with the use of SPM12 software (Wellcome Trust Centre for Neuroimaging, London, United Kingdom; http://www.fil.ion.ucl.ac.uk/spm/), which was implemented on a MatLab platform (Version R2016a; MathWorks, 2016). The functional scans were sinc-interpolated in time to correct for the staggered acquisition of slices during echo-planar imaging and were then realigned to the first volume as correction for interscan movements by means of a rigid body transformation with three rotation and three translation parameters. The functional scans were then co-registered to the high-resolution T2-weighted image and spatially normalized to a standard template (Montreal Neurologic Institute [MNI] template, Montreal, Quebec, Canada), with normalization parameters estimated from the T2-weighted image. The functional images were resampled through a bilinear transformation, resulting in a voxel size of 2 mm × 2 mm × 2 mm. Finally, the functional images were spatially smoothed with a 8-mm full-width at half-maximum Gaussian kernel.

2.5. First-level (individual) modeling

First-level analyses of the neural effects of reversal learning were conducted individually for each participant using SPM12 software. The CS+ and CS− trials were modeled as delayed boxcar functions that corresponded to 8 s epochs time-locked to stimulus onset and encompassing the scale, feedback, and outcome trial components. The trials were modeled separately in the acquisition and reversal phases. Food stimuli were modeled as events with stick functions time-locked to the onset of the reward image across the acquisition and reversal phases. Participant-specific general linear models (GLM) were conducted to fit beta weights to 5 regressors representing expected neural responses to 2 trial types (CS+, CS−) × 2 phases (acquisition, reversal), as well as to food stimuli irrespective of phase, all convolved with the default SPM12 hemodynamic response function (Friston et al., 1998). The neural effects of interest, namely stimulus-reward associative learning, reversal of learned stimulus-reward associations, and exposure to food stimuli were tested by applying appropriate contrasts to the beta weights for CS + trials during acquisition, new CS− trials during reversal, and the food cues event, respectively, resulting in three contrast maps for each participant.

2.6. Second-level (group) analyses

The three contrast images for each participant were entered into second-level group analyses conducted with separate random-effects GLM that included scanner (Allegra vs. Skyra) as a binary covariate. One- and two-sample *t*-tests were used to analyze within-group and between-group effects in the contrasts of interest, respectively. The height (intensity) threshold for each activated voxel was set at an uncorrected *p*-value of 0.01 and the resultant voxel-wise statistical maps were thresholded for significance using a cluster-size algorithm that protects against false-positive results in spatially extended continuous data (Hayasaka, Phan, Liberzon, Worsley, & Nichols, 2004). A previous Monte Carlo simulation of the brain volume used in the current study established that a cluster extent of 25 contiguous resampled voxels (2 mm^3) was necessary to correct for multiple voxel comparisons at $p < 0.05$ (Schulz, Bedard, Czarnecki, & Fan, 2011).

3. Results

3.1. Behavioral results

Fig. 2 summarizes differences in group expectancy ratings by trial type and phase. Results of the mixed-effects model indicated significant within-subject effects of trial type ($\beta = 1.17$, $SE = 0.33$, $p < 0.001$), trial phase ($\beta = 2.08$, $SE = 0.38$, $p < 0.001$) and their interaction ($\beta = -2.43$, $SE = 0.55$, $p < 0.001$). These results indicated that subjects discriminated between CS+ and CS−, were able to change expectancy ratings after covert switching, and that these changes reflected a reversal of these expectancies with reduced expectancy for original CS + after reversal (no longer reinforced) and increased expectancy for original CS− (intermittently reinforced) after covert switching. The between-subject effect of group on expectancy was not significant for random slope ($\beta = 0.04$, $SE = 0.14$, $p = .78$) or intercept ($\beta = -0.09$, $SE = 0.34$, $p = .80$).

3.2. Neuroimaging results

3.2.1. Stimulus-food cue associative learning

Adolescents with AN and healthy controls demonstrated similar patterns of frontoparietal activation for the acquisition of stimulus-food cue associations (i.e., CS + trials), including partially overlapping regions of anterior insula, supplementary motor area, and postcentral gyrus. The anterior insula activation was bilateral and extended to large areas of adjacent frontal operculum in controls, but was limited to the

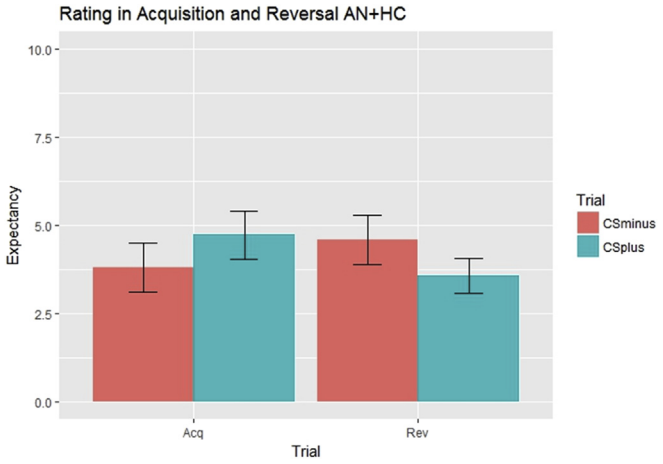

Fig. 2. Regions of significantly greater activation for the acquisition and reversal of learned cue-food stimulus associations in female adolescents with AN compared to healthy females. Adolescents with AN showed enhanced activation in dorsolateral prefrontal cortex (DLPFC) and bilateral inferior frontal gyrus for the conditioned stimulus paired with food stimulus (CS+) in the acquisition phase and with a blank image (new CS−) in the reversal phase, following the covert switch in reward contingencies. Figures are thresholded at $p < 0.01$ (corrected for multiple comparisons with a cluster threshold > 25 voxels). Numbers at bottom indicate *z* coordinates in the Montreal Neurological Institute brain template space.

Table 1
Regional activation for the acquisition of cue-food stimulus associations in 15 adolescent females with anorexia nervosa and 14 healthy adolescent controls.

Brain Region	Side	BA	MNI Coordinates			# Voxels	*t*
			x	y	z		
Anorexia nervosa							
Anterior insula	L	13	−36	18	6	543	5.37
DLPFC	L	9/46	−42	32	26	87	4.47
Middle frontal gyrus	R	9	54	10	42	1269	5.42
Inferior frontal gyrus (orbital)	L	47	54	16	−2	442	5.57
Supplementary motor area	L	6	−2	8	54	836	11.05
Precentral gyrus	R	6	32	−18	72	540	5.89
Postcentral gyrus	L	1	−60	−20	24	117	4.41
Postcentral gyrus	R	1	64	−16	28	49	3.58
Fusiform gyrus	L	19	−42	−66	−12	14,086	10.44
Controls							
Anterior insula	L	13	−42	14	4	80	4.21
Anterior insula	R	13	42	18	0	38	3.13
Frontal operculum	R	44	46	10	32	1326	5.72
Frontal operculum	L	44	−40	6	30	638	3.62
Supplementary motor area	R	6	4	6	62	1454	9.57
Postcentral gyrus	R	1	60	−16	24	56	3.63
Intraparietal sucal area	L	7	−20	−64	46	19,161	12.20
Thalamus	L	–	−16	−30	−2	145	5.03
Anorexia nervosa > Controls							
DLPFC	R	46	50	40	10	103	3.27
DLPFC	L	46	−48	38	24	33	3.04
Inferior frontal gyrus (orbital)	L	47	−38	32	−14	173	4.36
Inferior occipital gyrus	L	18	−24	−90	−10	27	3.66

BA = Brodmann Area; DLPFC = dorsolateral prefrontal cortex; MNI = Montreal Neurological Institute. The *x, y,* and *z* coordinates and the *p* statistic refer to the peak voxel of activation within each cluster. Statistical significance was set at a height threshold of $p < 0.01$ and a cluster threshold of 25 voxels, which corrected for multiple voxel comparisons at $p < 0.05$.

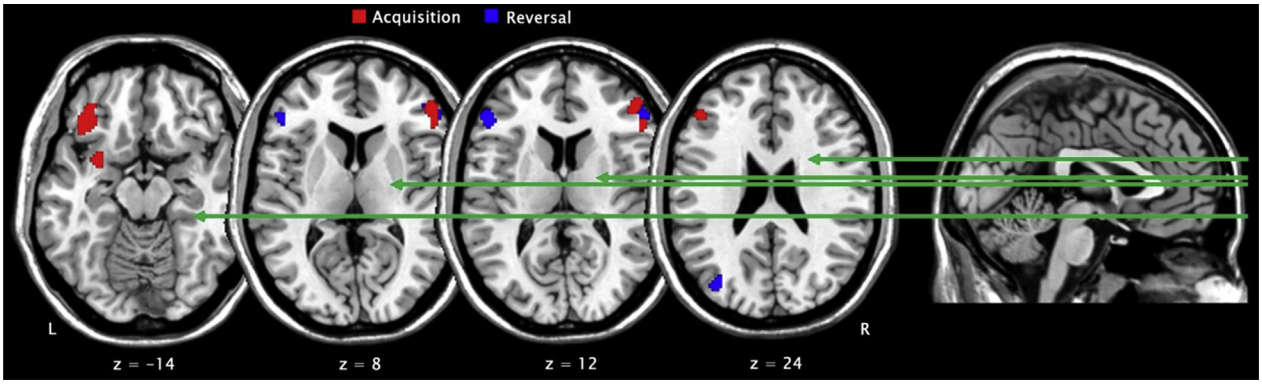

Fig. 3. Mean expectancy ratings and standard errors for the acquisition and reversal of CS+ and CS− in female adolescents with anorexia nervosa (AN) compared to healthy control (HC) females. The CS+ and CS− significantly differed in acquisition and reversal, but there were no group differences in expectancy ratings.

left hemisphere and associated with more widespread prefrontal activation in adolescents with AN. Regional activations for the acquisition of stimulus-food cue associations are listed in Table 1. Direct comparison of the groups confirmed that adolescents with AN showed enhanced activation for associative learning in bilateral dlPFC, the orbital aspect of left inferior frontal gyrus (IFG), and left inferior occipital gyrus compared to controls ($p < 0.01$, corrected with a cluster threshold > 25 voxels). An illustration of these group differences in activation is presented in Fig. 3. There were no regions of significantly greater activation for controls than adolescents with AN.

3.2.2. Reversal of learned stimulus-reward associations

The modification of the learned cue-reward coupling (i.e., new CS− trials) in the reversal phase was associated with activation in right IFG pars orbitalis, right supplementary motor area, and left middle occipital gyrus in both adolescents with AN and healthy controls. Healthy controls activated left anterior insula for the reversal of the cue-reward associations; the closest comparable activation in adolescents with AN was found in a more anterior and lateral region of left frontal operculum. The two groups also activated different motor, parietal, and subcortical regions in the reversal phase. Regional activations for the reversal of learned stimulus-food cue associations are presented in Table 2. Direct comparison of the two groups revealed significantly greater activation in left ventrolateral (vlPFC), right dlPFC, left IFG, and left middle occipital gyrus in adolescents with AN compared to healthy controls ($p < 0.01$, corrected with a cluster threshold > 25 voxels). The between-group differences in activation during the reversal phase are depicted in Fig. 3. There were no regions in which activation was significantly greater for controls than adolescents with AN.

3.2.3. Exposure to food cues

Food cues stimulated widespread activation in inferior and middle frontal gyri, anterior and posterior cingulate cortices, bilateral parietal and temporal regions, and left caudate nucleus in adolescents with AN. Healthy controls demonstrated a more limited pattern of activation in right anterior insula, VLPFC, supplementary motor area, and temporal cortex, as well as left middle occipital gyrus. However, direct comparisons found no significant group differences in activation for food cue. Regional responses to food cue are listed in Appendix A, Table A1.

Table 2
Regional activation for the reversal of learned cue-food stimuli associations in 15 adolescent females with anorexia nervosa and 14 healthy adolescent controls.

Brain Region	Side	BA	MNI Coordinates			# Voxels	*t*
			x	y	z		
Anorexia nervosa							
Inferior frontal gyrus (orbital)	R	47	38	22	0	29	3.51
Frontal operculum	L	44	−58	14	30	177	4.11
Supplementary motor area	R	6	2	6	54	56	4.46
Primary motor cortex	R	4	30	−20	74	53	3.41
Postcentral gyrus	R	2	46	−30	58	117	3.81
Post central gyrus	L	2	−58	−20	26	27	3.29
Middle occipital gyrus	L	18	−32	−88	8	10,147	9.99
Controls							
Anterior insula	L	13	−40	−4	16	675	5.54
Inferior frontal gyrus (orbital)	R	47	32	22	0	155	3.53
Supplementary motor area	R	6	2	6	58	740	12.69
Premotor cortex	L	6	−40	−4	60	234	5.76
Posterior cingulate cortex	R	23	6	−30	30	126	4.34
Middle occipital gyrus	L	18	−30	−90	14	19242	16.7
Thalamus	R	–	14	−16	8	440	7.93
Thalamus	L	–	−18	−28	0	363	5.11
Controls > Anorexia nervosa							
VLPFC	L	10	−32	58	−2	47	3.62
DLPFC	R	46	52	40	8	94	4.41
Inferior frontal gyrus	L	45	−50	34	10	74	2.86
Middle occipital gyrus	L	19	−36	−78	28	70	3.63

BA = Brodmann Area; DLPFC = dorsolateral prefrontal cortex; MNI = Montreal Neurological Institute; VLPFC = ventrolateral prefrontal cortex. The *x, y,* and *z* coordinates and the *p* statistic refer to the peak voxel of activation within each cluster. Statistical significance was set at a height threshold of $p < 0.01$ and a cluster threshold of 25 voxels, which corrected for multiple voxel comparisons at $p < 0.05$.

4. Discussion

4.1. Key findings

In sum, our study demonstrates: (a) successful acquisition and reversal of food-cue and food-absence relationships occurred in both groups, (b) these behaviors were associated with greater activation of dlPFC and the orbital aspect IFG during acquisition of the food-cue relationship in the AN group, (c) greater vlPFC, dlPFC and more superolateral IFG activation was observed during reversal of the food-cue relationship in the AN group, and (d) no significant group differences in brain activation were found during presentation of the food-cue.

4.2. Implications of prefrontal hyperactivation in AN

Adults with AN showed enhanced dlPFC activation during the acquisition and reversal of cue-reward associations, which in the context of expectancy ratings comparable to controls and the absence of limbic anomalies, suggests an increased reliance on higher-order prefrontal

regulatory mechanisms during associative learning. The magnitude of dlPFC activation tracks competition between response options (i.e., two CS trials) during associative learning, with activation increasing as response conflict increases (e.g., similar reward values for CS trials, reversal of reward contingencies), and decreasing as conflict is reduced (e.g., larger reward value for CS + than CS−), regardless of behavioral performance or task difficulty (Mitchell et al., 2009). In turn, dlPFC exerts control of task-essential sensorimotor effectors to flexibly adapt goal-directed behavior to the context (Mitchell, Rhodes, Pine, & Blair, 2008), by amplifying cortical representations of appropriate actions (Egner & Hirsch, 2005; Hester, D'Esposito, Cole, & Garavan, 2007). Thus, our findings of enhanced dlPFC activation suggests that adults with AN recruited prefrontal regulatory mechanisms to overcome conflict between CS+ and CS− trials during both the acquisition and extinction of the differential associations with food cues. A similar pattern for dorsal control is evident in food choice among patients with AN (Foerde et al., 2015). The limited neural responses to food cues suggests that the failure to experience the images of food as emotionally salient contributed to conflict between CS trials (Monteleone et al., 2017). Based on our prior work (Hildebrandt et al., 2015), emotional salience (e.g., disgust), or the emotional relevance of the cue, may be a particularly important factor in demonstrating impairment in reversal learning among participants with AN. Similar functional impairments in dlPFC for reversal learning have been linked to behavioral inflexibility in alcohol dependence (Beylergil et al., 2017), obsessive-compulsive disorder, and major depression (Remijnse et al., 2009).

The distinct regional localization of IFG abnormalities for the acquisition and reversal of cue-reward associations offer clues about the underlying impairments in adults with AN. Adults with AN showed enhanced activation for acquisition of cue-reward relationships in orbital aspects of IFG that integrate object-related visual input from infratemporal cortex and affective input from the amygdala to assign behavioral significance to cues (Sakagami & Pan, 2007). This orbital region of IFG contains separate populations of neurons that respond to cues signaling action execution and inhibition (Sakagami et al., 2001), and has been implicated in modulating stimulus-response maps during probabilistic learning (Greening, Finger, & Mitchell, 2011). Thus, the enhanced activation in this region in adults with AN may represent greater cognitive effort to differentiate the behavioral significance of the two CS trials during acquisition, possibly to compensate for the food-cue lacking emotional salience. In contrast, adolescents with AN demonstrated increased activation in the more superolateral pars triangularis of IFG for the extinction of the previous cue-food stimuli association following contingency reversal. The pars triangularis is purported to be a neural effector for both goal-directed hand actions (Iacoboni & Wilson, 2006) and the inhibition of such actions (Garavan, Hester, Murphy, Fassbender, & Kelly, 2006; Xue, Aron, & Poldrack, 2008). Thus, increased activation in this region following contingency reversal may reflect either greater effort to inhibit the previous cue-food stimuli coupling or interference from this coupling. Recent findings in recovered patients with AN suggest that enhanced prefrontal activation for reversal learning represents a trait-like impairment in cognitive control (Ritschel et al., 2017) that exists as part of larger set of impaired decision making that favors a rigid or perseverative set of behavioral responses, particularly in the context of ambiguity or risk (Brown et al., 2017; Guillaume et al., 2015; Tenconi et al., 2016).

4.3. Implications for food-cue learning in AN

There was no evidence of anterior insula or amygdala abnormalities for probabilistic or reversal learning in adults with AN. Both patients with AN and healthy controls activated anterior insula for the acquisition of the CS+ and demonstrated similar learning rates in the current study. Similar probabilistic reversal learning across groups is consistent with another behavioral study of reversal to probabilistic associations in patients with AN (Adoue et al., 2015). However, others have found impaired reversal learning (Lao-Kaim et al., 2015; Sato et al., 2013). The inconsistent findings across studies may relate to differences in methodology (e.g., type of reinforcement), weight status (e.g., low-weight vs. weight restored), and developmental stage, with group differences particularly notable in adolescents (Westwood, Stahl, Mandy, & Tchanturia, 2016). Our prior work found the emotional salience or relevance of the food-cues to be a particularly important factor in whether patients with AN demonstrate impairments in the reversal of probabilistic food-cue relationships (Hildebrandt et al., 2015). Patients with AN and recovered AN consistently show enhanced limbic responses to rewarding taste stimuli (e.g., sucrose, chocolate taste, etc.; Cowdrey, Park, Harmer, & McCabe, 2011; Monteleone et al., 2017; Oberndorfer et al., 2013).

Our study is the first investigation of food-cue reversal learning in AN patients which differs from previous studies in two important ways. First, the present study utilized a less salient associative learning paradigm (i.e., food stimuli and CS+ were only paired on 30% of trials), which resulted in both groups demonstrating the ability to discriminate food-cue (CS+) and food-absence (CS−), but did not yield measurable differences in the experience of food-reward. The pattern of activation during the task suggested greater activation in prefrontal regions implicated in flexible learning, particularly reversal learning to aversive stimuli (Schiller et al., 2008) by those with AN. The greater activation of prefrontal regions involved in inhibitory control (e.g, IFG) and rule governed responding (vlPFC, dlPFC (Everling & DeSouza, 2005); are consistent with a greater cognitive, “top-down,” activity involved in acquisition of food-cue associability and its reversal, suggesting that even when an intermittently rewarded food-cue is present, those with AN experience a greater degree of prefrontal activation during both acquisition and reversal. It is possible that food-cue reversal engages prefrontal and parietal regulatory systems to manage the potential threat associated with uncertain stimulus frequency. The dlPFC is particularly important for tasks that involve flexible learning to salient rewarding and aversive stimuli and is also implicated in reversal difficulties among addictive and compulsive disorders (Apergis-Schoute et al., 2017; Beylergil et al., 2017). Secondly, the nature of our task involves analyzing the brain's response to the CS + as opposed to the food-reward per se. Thus, our focus is on the brain's response to an associated cue (i.e., colored square) rather than the target food stimulus itself (M&M) and offers a model of an environment where food avoidance persists from a generalized set of cues that signal safety and threat to the target stimulus—when the target stimulus is difficult to predict.

Alternative models for food avoidance in AN suggest that food-reinforcement learning (as opposed to reversal) is associated with corticolimbic hyperactivation resulting from sensitivity within dopaminergic neurocircuitry (Frank, 2015) and explains the mesolimbic hyperactivation found in both reward prediction error and punishment (Bernardoni et al., 2018; DeGuzman, Shott, Yang, Riederer, & Frank, 2017). This pattern of CNS sensitivity to salient threat/reward stimuli extends to the sensory processing of interoceptive signals for a range of peripheral organs including heart and stomach (Kerr et al., 2016). Consequently, the interoceptive processing of threats, rewards, and prediction errors may elicit heightened cognitive control in AN patients. In these reinforcement learning models, frontoparietal control is an adaptation to an elevated sensitivity to punishment and reward that favors behavioral adaptation in the context of prediction error (as opposed to natural reinforcement). This pattern of behavioral adaptation is also evident with neutral cues. Using a non-food based stimuli, Giesler et al. (2017) found that adolescents with AN demonstrated greater dACC activation during trials where patients adapted their behavioral response—suggesting that error detection may be the driving component in motivating new behavioral choices. In the context of AN, choosing a high calorie food may elicit an error signal (violating the expected rule that these foods make you fat or cause visceral discomfort) and promote behavioral adaptation in the form of safety (e.g., compensatory restriction or activity, avoidance of cue that signals

possibility of choosing high calorie food). As high calorie food remains aversive and in violation of expected rule/generates aversive interoceptive signal (e.g., disgust), learning would only adapt in the direction of avoidance.

4.4. Study limitations

The results of this study must be considered in the context of several possible methodological limitations. First, the analyses of group differences in activation for the acquisition and reversal of cue-reward associations would have benefitted from a larger sample size. The relatively small sample size may have limited the power to detect more subtle effects in limbic regions, but does not detract from our findings of significant group differences in prefrontal cortex activation. Second, the blocked-design analysis of the CS trials as 8-s epochs that encompassed the cue, scale, feedback, and outcome trial components may have masked more subtle effects in limbic regions. Thus, our findings must therefore be considered preliminary until replicated in larger samples using food stimuli with more emotional salience to patients with AN. In addition, a non-food paradigm or contrast between low and high salience foods was not included, and differences for food specific stimuli could not be compared in this study. Others have relied on these types of comparisons to demonstrate alterations in processing of food stimuli in patients with AN (e.g., Scaife, Godier, Reinecke, Harmer, & Park, 2016). Lastly, our population was early in their development of AN (< 1 year) and treatment seeking. It is possible that greater evidence of behavioral and brain disturbances would emerge after a longer duration of illness as has been noted in chronic adult samples (Fladung, Schulze, Scholl, Bauer, & Gron, 2013).

4.5. Conclusions and future considerations

The clinical implications of our findings are consistent with other research indicating that cognitive overcontrol contributes to difficulties in making lasting behavioral changes in eating among those who suffer from AN. Given the known chronicity of this condition, identifying novel treatment options is particularly important, and changing behavior in the context of the overcontrol observed in this study suggests two potential areas for future development. The first is to investigate conditioning models that can alter the valence of a cue independent of the cortical influence. Capitalizing on the nature of evaluative conditioning may offer one potential method to achieve this shift in cue valence (Schweckendiek et al., 2013). For example, associating eating with positive stimuli may produce a change in liking that could be enhanced over time. A second option could be to reduce attention and limbic response to food safety cues via target of attentional and mesolimbic responsivity, as with obesity (Stice, Yokum, Veling, Kemps, & Lawrence, 2017), where a response and attention training intervention could affect responsivity to food cues and body weight. Applications of findngs from this study and similar studies may help to improve behavior therapy models that rely on relevant assumptions about learning to make changes.

Conflicts of interest

The authors have no conflicts of interest to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brat.2018.08.006.

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