Behaviour Research and Therapy 71 (2015) 131–138

Contents lists available at ScienceDirect

Behaviour Research and Therapy

journal homepage: www.elsevier.com/locate/brat

Testing the disgust conditioning theory of food-avoidance in adolescents with recent onset anorexia nervosa

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ARTICLE INFO

Article history:
Received 1 March 2015
Received in revised form
10 June 2015
Accepted 18 June 2015
Available online 20 June 2015

Keywords:
Anorexia nervosa
Reversal learning
Electromyography
Emotion
Food learning

ABSTRACT

Anorexia nervosa is characterized by chronic food avoidance that is resistant to change. Disgust conditioning offers one potential unexplored mechanism for explaining this behavioral disturbance because of its specific role in facilitating food avoidance in adaptive situations. A food based reversal learning paradigm was used to study response flexibility in 14 adolescent females with restricting subtype anorexia nervosa (AN-R) and 15 healthy control (HC) participants. Expectancy ratings were coded as a behavioral measure of flexibility and electromyography recordings from the levator labii (disgust), zygomaticus major (pleasure), and corrugator (general negative affect) provided psychophysiological measures of emotion. Response inflexibility was higher for participants with AN-R, as evidenced by lower extinction and updated expectancy ratings during reversal. EMG responses to food stimuli were predictive of both extinction and new learning. Among AN-R patients, disgust specific responses to food were associated with impaired extinction, as were elevated pleasure responses to the cued absence of food. Disgust conditioning appears to influence food learning in acutely ill patients with AN-R and may be maintained by counter-regulatory acquisition of a pleasure response to food avoidance and an aversive response to food presence. Developing strategies to target disgust may improve existing interventions for patients with AN.

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Food avoidance is a core pathological behavior of anorexia nervosa (AN) that is characterized by severe restriction in the range and amount of food consumed, which results in clinically low body weight. This behavior has adaptive significance in a number of contexts ranging from preventing food waste under the influence of environmental threat (e.g., drought) to conditioned aversion evolved to prevent ingestion of poison or other toxins (Pacheco-Lopez & Bermudez-Rattoni, 2011). In theory, food avoidance behaviors are the functional output of a classically conditioned relationship between a food/eating cue and an aversive emotional state (i.e., negative punishment). Consequently, these behaviors onset via a classically conditioned relationship between food and an internal emotional cue that occurs after ingestion of an aversive substance or food (e.g., spoiled food) or via observation of a peer experiencing an aversive reaction to a substance or food (Welzl, D'Adamo, & Lipp, 2001). Avoidance is later maintained via a negative reinforcement mechanism as the individual finds relief from anticipatory distress associated with the food/eating cue. Avoidance persists, and becomes pathological, because individuals fail to reverse the association between food/eating and the conditioned aversive emotional response, despite the increased value of food/eating that results from the starved state (Keating, 2010). This impairment in learning may reflect a pre-existing cognitive vulnerably or change in cognitive flexibility that emerges as a consequence of malnutrition.

1. Cognitive flexibility and anorexia nervosa

Cognitive flexibility is a broader construct composed of distinct capabilities including set-shifting and reversal learning. Attentional set-shifting measures the ability to shift attention from one

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http://dx.doi.org/10.1016/j.brat.2015.06.008
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stimulus feature (e.g., color) to another (e.g., shape). Conversely, reversal learning measures the ability to override previously learned contingencies between stimuli and an outcome designed to elicit a natural response. The key distinction, and why reversal learning is of particular interest in the context of pathological food avoidance, is that reversal learning, but not set-shifting, measures the ability to update responses after negative feedback (i.e., classical extinction). Accumulating data indicate that starvation leads to impairments in general cognitive flexibility. A number of case control studies report impairments among acutely ill patients with AN (Holliday, Tchanturia, Landau, Collier, & Treasure, 2005; Tchanturia et al., 2012; Tchanturia, Morris, Surguladze, & Treasure, 2002). However, the majority of these studies have utilized paradigms (e.g., the Wisconsin Card Sorting Task) that conflate set-shifting and reversal learning capabilities. Disparate neural and neurochemical correlates for reversal learning and attentional set-shifting have been identified (Fineberg et al., 2010), suggesting that general tasks that do not distinguish between these behaviors may fail to identify clinically relevant distinctions (Wildes, Forbes, & Marcus, 2014).

Impaired reversal learning may uniquely relate to food avoidance in AN, as it would limit the ability to extinguish the associations between food/eating stimuli and negative affect. Reversal learning of reward/threat associations provides a superior model for the learning demands of a complex environment where cues can rapidly shift from threatening to rewarding (Schiller, Levy, Niv, LeDoux, & Phelps, 2008; Schiller & Delgado, 2010; Li, Schiller, Schoenbaum, Phelps, & Daw, 2011; Zhang, Manson, Schiller, & Levy, 2014). Reversal learning tasks measure the ability to override previously learned stimulus-reward/threat associations. There is evidence to suggest that weight status may alter the ability to flexibly learn cue-food relationships; populations characterized by excess weight exhibited impaired reversal learning when food, but not money, was used as the reward (Zhang et al., 2014). These domain specific findings are presumably because of the enhanced rewarding value of food among obese individuals. However, it remains unclear if the same impairment exists for individuals with AN or if reversal learning rate is related to an aversive emotional response to food/eating cues (e.g., disgust, fear, anger, etc.).

2. Disgust conditioning and anorexia nervosa

Disgust conditioning offers a theoretical link between food avoidance and its resistance to extinction in AN patients. Conditioning models of food avoidance in AN have used fear conditioning as the theoretical basis for this behavior (Strober, 2004) in which those with AN learn to associate foods and food related stimuli with a fear response (Steinglass et al., 2011, 2012) and subsequently avoid eating. Indeed, AN patients evidence an increased startle eyeblink response—a psychophysiological measure of fear—when viewing food stimuli (Friederich et al., 2006). However, direct tests of the fear conditioning hypothesis are lacking. Preliminary results from clinical treatments developed using this theory yielded significant but modest behavioral change (i.e., increase in 49 kcal consumed), despite evidence that they reduce self-reported anxiety (Steinglass et al., 2014) and that pre-meal anxiety is negatively associated with caloric intake (Steinglass et al., 2010). Unlike fear, disgust has evolved specifically to help animals avoid eating (Chapman & Anderson, 2012) and is characterized by a distinct resistance to extinction (Olatunji, Forsyth, & Cherian, 2007).

Patients with AN report elevated levels of disgust sensitivity that positively correlates with eating disorder symptom severity (Aharoni & Hertz, 2012; Troop, Murphy, Bramon, & Treasure, 2000). AN patients also report higher levels of disgust than controls when viewing pictures of high calorie food (Joos et al., 2011) and report food avoidance as a primary method for coping with the feeling of disgust (Espeset, Gulliksen, Nordbo, Skarderud, & Holte, 2012). Disgust often couples with other emotions (e.g., fear, anger, etc.) and operates as a pervasive indicator of general negative affect (Fox et al., 2013), especially when the aversive stimuli involves a strong interoceptive component. Thus, disgust may contribute to food avoidance via heightened interoceptive processing of food and anticipation of food ingestion (Vicario, 2013).

3. Hypotheses

We aimed to test whether patients with AN or subthreshold variants of AN demonstrated deficits in food-cue reversal learning compared to healthy controls (HCs) and to characterize the emotional correlates of this learning process. The current reversal learning task is an interference paradigm of classical conditioning where conflicting information given in the subsequent reversal stage interferes with the initial association (Bouton, 1993; Bouton & Brooks, 1993; Schiller et al., 2008), which allows for a fine-grain analysis of the gradual change in expectancy and facial EMG responses to cues that alternate in predicting food rewards. We chose to use facial EMG to measure the emotional context to avoid confounds of alexithymia in the AN/SAN population. Specifically, we hypothesized that associative learning between a stimulus and food would be associated with higher likelihood of levator labii activation and that the frequency of this association would be predictive of impaired extinction in the reversal phase of the experiment. Consistent with the perseveration of avoidance in AN, we also hypothesized that associative learning between a stimulus and the absence of food presentation would be positively associated with zygomaticus major activation in AN/SAN patients but not HCs.

4. Method

4.1. Inclusion and exclusion criteria

Participants were recruited from a population of individuals presenting for treatment at the Mount Sinai Eating and Weight Disorders Program. General exclusion criteria included current psychotropic medication, and current substance abuse, active suicidality, brain disease, or brain trauma. Potential healthy controls 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). For participants over 18 this was determined using the Structured Clinical Interview for DSM-IV-TR (SCID-I; First, Spitzer, Gibbon, & Williams, 2002) and the Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL; Kaufman et al., 1997) for participants under 18. Participants with self-reported anorexia nervosa (AN) were enrolled if they met DSM-IV-TR criteria for AN, or a subthreshold 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 20% of their body weight within the last year. Adult AN and SAN participants were either currently less than 85% of their ideal body weight, or had lost 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 AN/SAN participants reported onset of the disorder within the past year.

4.2. Participants

The final sample ranged in age from 11 to 22 and consisted of 14

AN-Restrictors (M_{age} = 15.05, SD = 1.87) and 15 healthy controls (HC; M_{age} = 17.64, SD = 2.71). AN participants body mass index (BMI; M = 17.52, SD = 2.91) was significantly lower ($p < .001$) than HCs (M = 22.49, SD = 2.94). Twenty-six participants identified as Caucasian, one participant as Hispanic, and two participants as Asian. Of the ten postmenarcheal AN participants, seven reported a loss of menses for at least three months (i.e., amenorrhea), one reported a loss of menses for the last month only, and two reported no disruption in their menstrual cycle. The remaining four AN participants were premenarcheal. Five HC participants reported current use of oral contraceptives.

Tanner staging, designed to measure changes in external genitalia, breast development, and pubic hair growth on a 5-point ordinal scale (1 = *prepubertal*, 5 = *mature stage*) was assessed on-site by a licensed physician at the Mount Sinai Clinical Research Unit. AN (M = 3.93, SD = .83) and HC (M = 4.47, SD = .83) participants did not significantly differ on this scale ($p = .063$) suggesting group results were not merely a proxy for pubertal timing. All participants were paid for their time. The Icahn School of Medicine Institutional Review Board granted study approval, and all participants, or their parental guardians, gave consent to participate in the study.

4.3. Conditioning paradigm

The present study used a food based discrimination and reversal learning paradigm adapted from Schiller et al. (2008); see Fig. 1 for further description of the paradigm) that has been used in an obese population (Zhang et al., 2014). In the first part of the task, the unconditioned stimulus (US) is associated with stimulus A, but not stimulus B. In the second phase, the contingencies change without warning; stimulus B is paired with the US, while stimulus A is always presented alone. Stimuli A and B were two different colored (i.e., blue and purple) squares, and the unconditioned stimulus (US) was a picture of 15 chocolate candies (M&Ms). The color of stimulus A was counterbalanced across subjects.

To increase US saliency, subjects saw the actual candies and were informed they would receive any candy images seen during the task once the experiment was over. During each trial, subjects were asked to rate the degree to which they expected to see food, following presentation of a colored square, on a scale from 1 (*definitely not*) to 9 (*definitely yes*). We used a 30% reinforcement schedule, as intermittent stimulus-food pairings slow acquisition and extinction (Gottlieb, 2005), which allowed us to examine gradual learning rates.

4.4. Physiological assessments

Alexithymia is characteristic of the disease state among individuals with AN (Bourke, Taylor, Parker, & Bagby, 1992; Courty et al., 2013; Kessler, Schwarze, Filipic, Traue, & von Wietersheim, 2006) and raises questions about the validity of self-report measures of affect in this population (Lane, Sechrest, Riedel, Shapiro, & Kaszniak, 2000). Facial electromyography (EMG) offers a robust psychophysiological measure that can replace self-report emotion (Lang, Greenwald, Bradley, & Hamm, 1993), particularly among individuals with difficulty recognizing their own emotional state (Fitzgibbons & Simons, 1992; Smith, Bradley, & Lang, 2005). Disgust can be discriminated from other negative emotions by heightened activation of the levator labii muscles, which expresses when individuals engage in avoidance of interoceptive signals (Vrana, 1993). In contrast, the zygomaticus major activates when experiencing joy/pleasure, while the corrugator muscle site generally activates during a range of negative affective states (e.g., anger, sadness, etc; Witvliet & Vrana, 1995).

To prepare the skin for EMG measurements, participants' faces were abraded with an exfoliating scrub applied to a cotton pad. Circular surface EMG (Ag/AgCl) electrodes were then filled with a saline base highly conductive gel, and affixed to the skin using 4 *mm* adhesive disks. Impedance between the skin and electrode was checked with predetermined acceptable levels of <10 Ω. Recordings were obtained on the left side of the face from the zygomaticus, corrugator, and levator labii muscle regions following facial EMG placement recommendations (Fridlund & Cacioppo, 1986). Electrodes were 7.2 *mm* in total diameter, with a 4 *mm* contact area, and were placed approximately 1 cm apart. Data were collected using Biopac MP150 biopotential amplifiers at a sampling rate of 2000 Hz.

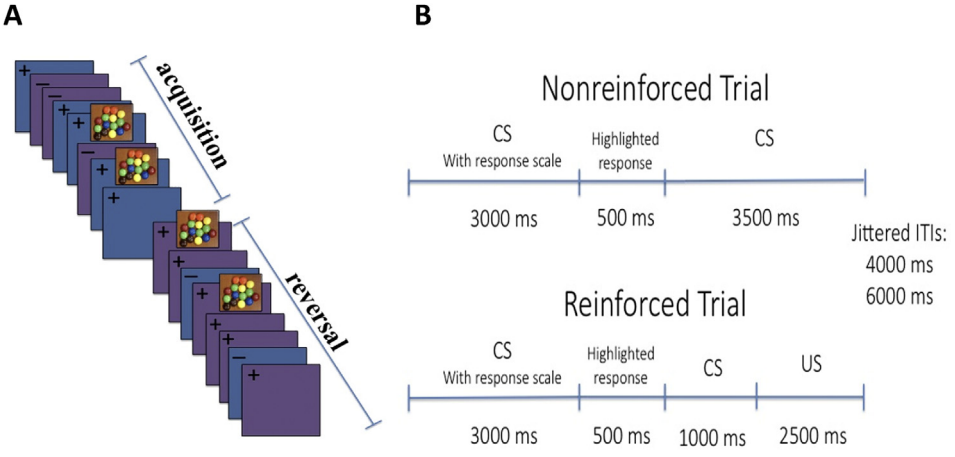

Fig. 1. (*A*) The experiment was split into two phases: acquisition and reversal. During the acquisition phase, stimulus A was intermittently paired with food (i.e., the unconditioned stimulus) while stimulus was never paired with food. The acquisition phase consisted of 14 presentations of each stimulus alone, along with 7 stimulus/food pairings. In the reversal phase, stimulus B was intermittently paired with food, while stimulus A was always presented alone. The reversal phase was marked as the first reinforced trial of stimulus B. Trial order was randomized for acquisition and reversal. The figure displays possible 8 trials at the beginning of each phase. (*B*) On all eighty trials participants first saw a stimulus and a 9-point expectancy scale for 3000 *ms*. Participants were initially instructed to use the scale to indicate the degree (1 = *definitely not*, 9 = *definitely yes*) to which they expected to see food during the trial. Participants then saw a screen for 500 *ms* that either highlighted their response if one was made in the allotted time, or displayed text reading "No Response" in red letters. On reinforced trials the stimulus was subsequently presented alone for 1000 *ms*, followed by food for 2500 *ms*. Nonreinforced trials ended with presentation of the stimulus alone for the remaining 3500 *ms*. Subjects first read on-screen instructions explaining the task, and subsequently completed four practice trials using stimuli that were unrelated in color from those presented during the actual experiment.

4.5. Behavioral analysis

Expectancy ratings were averaged across the first (i.e., early) and second (i.e., late) half of both the acquisition and reversal phase. These averages were then used to compute behavioral difference scores between early acquisition and early reversal (earlyAcq/earlyRev), late acquisition and early reversal (lateAcq/earlyRev), and late acquisition and late reversal (lateAcq/lateRev). For stimulus A, a larger positive difference score reflects higher levels of extinction. Conversely, lower negative difference scores for stimulus B are indicative of an ability to form a new association in the context of other learning, and a prior history of negative predictive value.

4.6. Physiological data pre-processing and analyses

Raw EMG signals were pre-processed using BIOPAC Systems AcqKnowledge software (Goleta, CA). The raw data were first filtered using a band pass attenuating all responses below 10 Hz and above 500 Hz. The attenuated response was then transformed into an absolute value by deriving the root mean square with a time window of 125 *ms*. Using the pre-processed values, we examined activation for the first 2.5 s at the start of trials and US presentation (see Fig. 1 for timing).

We sought to examine the possibility that during presentation of stimulus A, patients with AN would experience an elevated disgust response that would be represented by clustering of muscle activation after pairing with the US. A jump in elevated disgust activation would be consistent with a robust, early, disgust association and subsequent reduced activation in reversal would represent a compensatory mechanism consistent with attentional avoidance. In order to test the effect of heightened physiological activation on single-trial learning, we calculated the spike frequency by summing the number of physiological "spikes" for each of the muscle sites in the acquisition phase during the initial 2.5 s of originally reinforced stimulus (i.e., stimulus A) presentation. Individual spikes were coded as 0 or 1, and were defined by a threshold of >2.5 *SD*s, where *SD*s were computed within each participant and muscle site for activation in response to stimulus A in both phases. The average number of spikes was entered as a predictor of behavioral expectancy rating stimulus A difference scores for each group. We chose to focus on stimulus A difference scores as they provided a measure of behavioral extinction. We examined group as a moderator of physiology predicting behavior via comparisons of Pearson correlations using Fisher's z-test. Missing data were replaced by multiple imputation using Bayesian estimation methods available in M*plus* (Muthén & Muthén, 2011).

5. Results

5.1. Behavioral expectancy ratings

Graphs of expectancy ratings were created for each trial to determine if participants appropriately increased their expectancy rating for stimulus A (the originally reinforced stimulus pairing M&M with colored square) in acquisition and stimulus B (the originally nonreinforced stimulus, pairing nothing with alternative colored square) in reversal, and decreased their ratings for stimulus A in reversal and stimulus B in acquisition. Both AN and HC participants showed discriminative learning between M&M Cue (Stimulus A) and M&M Absence (Stimulus B) in acquisition as indicated by the gap between stimuli (Fig. 2).

Results for M&M Absence revealed significant group learning effects across the acquisition and reversal blocks (Fig. 3). There was a large negative difference for HC participants and a smaller positive difference for AN participants. Results further revealed

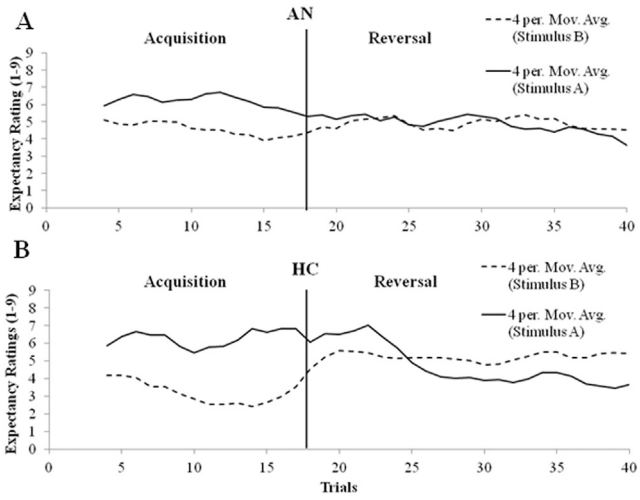

Fig. 2. Behavioral expectancy ratings by trial. Both AN (A) and HC participants (B) exhibited a clear distinction between stimuli in acquisition suggesting participants learned to discriminate between stimuli A and B.

significant group extinction effects for the M&M Cue when measured either early [lateAcq/earlyRev comparisons, $t(27) = 3.06$, $p = .005$, $d = 1.18$] or late in reversal [lateAcq/lateRev, $t(27) = 2.86$, $p = .008$, $d = 1.10$]. The differences between acquisition and reversal expectancy ratings were greatest for HC participants. There was no

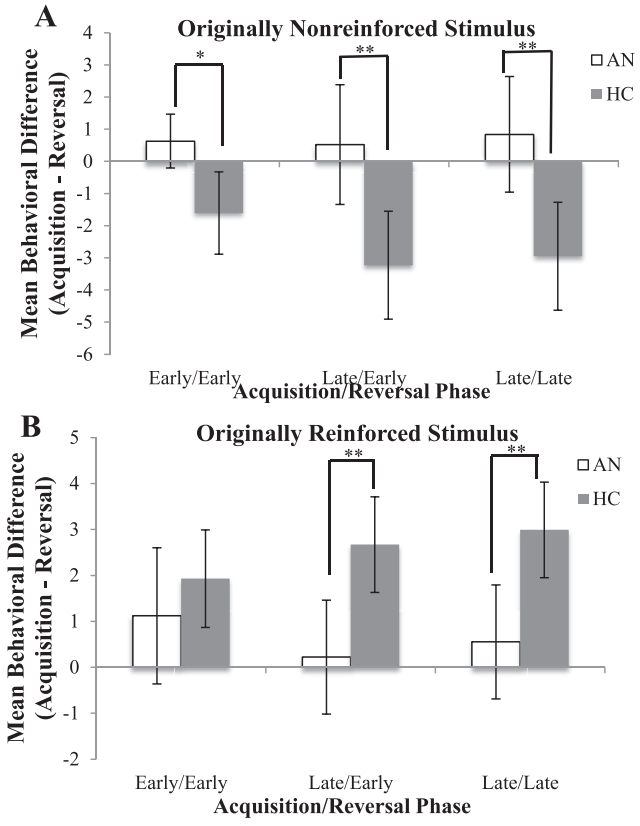

Fig. 3. Figures depict mean differences between groups in acquisition and reversal. (A) Mean differences for the originally nonreinforced stimulus (i.e., M&M Absence). AN participants were significantly worse at updating learning for the earlyAcq/earlyRev, $t(27) = 2.43$, $p < .05$, Cohen's $d = .94$; lateAcq/lateRev, $t(27) = 3.01$, $p = .006$, $d = 1.16$; and lateAcq/earlyRev comparisons, $t(27) = 3.06$, $p = .005$, $d = 1.18$. (B) Mean differences for the originally reinforced stimulus (i.e., M&M cue). Error bars indicate 95% confidence intervals. Significant difference from zero: $^{*}p < .05$, $^{**}p < .01$.

significant group effect for the earlyAcq/earlyRev difference score.

5.2. Physiological results

5.2.1. Disgust learning

We tested whether patients with AN relative to HCs experienced more frequent levator labii spikes in response to the M&M Cue during acquisition, indicative of higher levels of disgust conditioning. Indeed, controlling for corrugator spikes as a covariate, AN participants ($M = .65$, $SD = .39$) were more likely to have a distinct spike in levator labii activation, relative to HC participants ($M = .27$, $SD = .36$), $F(1, 26) = 13.44$, $p = .001$, $d = 1.36$. To test group differences in levels of associative disgust we used Fisher's z-scores to compare Pearson correlations between levator labii spikes in response to M&M Cue presentation during the acquisition phase, and M&M Cue difference scores (i.e., extinction). Comparisons revealed that the number of levator labii spikes were predictive of poor extinction in reversal for AN participants, but not HC participants (Table 1).

5.2.2. Pleasurable avoidance

We tested whether patients with AN experienced a greater clustering of zygomaticus major spikes to M&M Absence trials in acquisition, suggesting the experience of pleasure in response to the acquisition of cued-absence of food (i.e., pleasurable avoidance). AN participants ($M = .42$, $SD = .32$), relative to HC participants ($M = .33$, $SD = .26$), were more likely to react with pleasure to cued-absence of food, though the difference was non-significant when controlling for corrugator spikes, $F(1, 26) = 1.41$ $p = .246$. Table 2 summarizes findings indicating that more robust zygomaticus activation in response to M&M Absence was associated with worse extinction for M&M Cue among the AN patients, but the opposite was true for HCs where less robust activation of zygomaticus was associated with poorer extinction.

5.2.3. Covariate effects

To determine if there were important additional covariate effects on the model, we examined the influence of age, depression, IQ, menstrual status, and tanner stage on physiological and behavioral outcomes. The primary group differences in expectancy ratings for acquisition and extinction of M&M Cue survived covariate analyses. The group effect for M&M Absence earlyAcq/earlyRev expectancy difference scores was non-significant when controlling for either menstrual status or depression (Table 3). These analyses confirm that expectancy impairments in both extinction and updated learning for AN participants were not better explained by a related confound.

Table 1
Z-Scores comparing Pearson correlations between physiological spikes and behavior.

Muscle site	Originally reinforced stimulus		
	Early/Early	Late/Late	Late/Early
Levator labii			
HC	.43	.10	.19
AN	−.45	−.45	−.55
z-score	**2.26***	1.40	1.94
Corrugator			
HC	−.57	−.44	−.41
AN	−.28	−.18	−.42
z-score	.86	.70	.03
Zygomaticus			
HC	.04	−.36	−.16
AN	−.47	−.40	−.48
z-score	1.32	.11	.87

Note. Spikes were defined as activation greater than 2.5 *SDs*. *$p < .05$.

Table 2
Z-Scores comparing Pearson correlations between physiological spikes to the originally nonreinforced stimulus (M&M absence) and behavior.

Muscle site	Originally reinforced stimulus		
	Early/Early	Late/Late	Late/Early
Zygomaticus			
HC	.51	.08	.31
AN	−.38	−.24	−.23
z-score	**2.31***	.39	1.33

Note. Spikes were defined as activation greater than 2.5 *SDs*. *$p < .05$, **$p < .01$.

6. Discussion

Adolescents with recent onset AN-R demonstrated clear deficits on a food-based reversal learning task compared to HCs. As predicted, this pattern of results indicate that those with acute onset of AN have intact probabilistic learning of associations between food and neutral stimuli, but difficulty extinguishing and updating these associations. This impairment was not explained by self-reported depression, age, pubertal development, or global intelligence (see Table 3) suggesting that learning differences are evident even at the initial onset of the illness, before chronic starvation and brain development have the opportunity to contribute to this deficit. These findings are consistent with data obtained using general measures of cognitive flexibility (Lang, Stahl, Espie, Treasure, & Tchanturia, 2014), but offer evidence that this deficit extends to food-specific stimuli.

Acute bursts of levator labii muscle activity (i.e., disgust response) resulting from a pairing of a neutral stimulus and M&Ms (Figure S1), was predictive of more difficulty extinguishing the food-cue association for AN participants, but not controls, who additionally evidenced fewer levator labii spikes (Figure S2). The results of this comparison are consistent with the proposed disgust conditioning model of AN, whereby AN patients have difficulty extinguishing negative associations with food cues in the context of simultaneous cued absence of food. Most AN-R is initiated by restriction of food for the purpose of weight loss or increased fitness/health. An efficient strategy to accomplish this goal would be to assign a disgust response to high calorie/high density foods and to increase the value of situations that are free of the threat of eating. When this restriction results in an unhealthy physical or mental state, however, patients with AN likely experience difficulty updating these associations, possibly due to the unique role disgust plays in food-based associative learning.

Consistent with the switching of attentional resources from evaluation of the threatening stimuli to the safety cue characteristic of disgust conditioning (Armstrong, McClenahan, Kittle, & Olatunji, 2014; Armstrong, Olatunji, Sarawgi, & Simmons, 2010; Cisler, Olatunji, Lohr, & Williams, 2009), we found evidence that patients with AN experienced robust pleasure responses to the stimulus not associated with food during acquisition (M&M Absence; i.e., cued safety). Moreover, there was a distinct predictive value of pleasurable responses in acquisition, such that it was negatively associated with the reversal of the food-cue associations for AN participants but not HCs. We interpret this pattern to indicate that attentional, and likely motivational resources, dedicated to cued-safety interfere with extinction of the conditioned disgust response. This pattern of attentional weighting toward safety, and down-regulation of physiological activation to the cued-threat may explain why it is so difficult to extinguish negative food associations among patients with AN. It remains unclear if the pleasurable facial response identified in response to M&M Absence in the acquisition phase in this study represents a motivational state cued by direct activation (Rogan, Leon, Perez, & Kandel, 2005) or cued

Table 3
F-Values [and 95% confidence intervals] for behavioral group differences controlling for IQ, tanner stage, menstrual status, age and depression.

Covariates	Originally reinforced stimulus			Originally nonreinforced stimulus		
	Early/Early	Late/Late	Late/Early	Early/Early	Late/Late	Late/Early
IQ	2.62 [.91, 2.28]	13.18** [1.39, 3.35]	11.18** [1.29, 2.86]	5.96* [−2.96, −1.10]	12.02** [−7.52, −1.67]	11.51** [−7.24, −1.62]
Tanner Stage	1.04 [.80, 1.94]	6.59* [1.12, 2.81]	7.45* [1.13, 2.46]	5.41* [−2.76, −1.06]	8.14** [−6.31, −1.34]	8.18** [−6.19, −1.36]
Menstrual Status	1.53 [.78, 2.02]	5.40* [1.06, 2.62]	6.39* [1.09, 2.39]	**3.83 [−2.50, −.97]**	6.44* [−5.55, −1.20]	6.30* [−5.01, −1.18]
Age	1.22 [.70, 2.01]	4.51* [1.02, 2.90]	6.06* [1.09, 2.74]	5.59* [-3.15, −1.08]	6.46* [−7.01, −1.23]	5.40* [−6.17, −1.12]
Depression	2.21 [.87, 2.42]	6.22* [1.11, 3.06]	8.65** [1.21, 2.90]	**3.69 [−3.72, −1.04]**	5.92* [−6.11, −1.16]	6.43* [−6.25, −1.21]

Note. Bolded scores were previously significant. $^{*}p < .05$, $^{**}p < .01$, $^{***}p < .001$.

disinhibition (Nasser & McNally, 2013) of the appetitive system. Extending this model of pleasurable avoidance to situations where disgust represents the aversive response may help explain why it interferes with extinction of food-based associative learning.

The levator labii findings in this study are also consistent with the growing evidence of dysregulation in the anterior insula among patients with AN (Nunn, Frampton, Fuglset, Torzsok-Sonnevend, & Lask, 2011). Elevated activation of this region reliably discriminates disgust from other negative emotional states (Fusar-Poli et al., 2009) and likely weights interoceptive information in the processing of a potential threat (Klucken et al., 2012). Neuroimaging studies aimed at examining neuronal response to food stimuli in AN patients suggest a hypo-responsivity of the anterior insula to pleasurable tastes and hyper-activity to food anticipation in women recovered from AN (Oberndorfer et al., 2013a,b), possibly reflecting impaired interoceptive processing of food, indicative of disgust. Indeed, a number of neuroimaging studies have found altered processing of pleasurable and aversive stimuli in the insula of patients with AN (Frank, Kullmann, & Veit, 2013; Jappe et al., 2011; Wagner et al., 2007).

Psychophysiological measures of emotion collected during the learning task indicated that patients with AN had lower overall arousal than controls. This reduced variability in muscle activation, which is indicative of lower central nervous system arousal, may be a natural adaptive consequence of starvation (Basoglu et al., 2006) and could also lead to general deficits in emotional processing. Patients with AN demonstrated the low variability in psychophysiological activation characteristic of alexithymia (Davydov, Luminet, & Zech, 2013; Pollatos, Schubo, Herbert, Matthias, & Schandry, 2008). However, there was clear evidence of muscle spikes in both groups, which provides evidence that emotional learning did occur and was associated with behavioral responses in the expected directions for each group.

Wildes, Ringham, and Marcus (2010) theorize that emotional avoidance is fundamental to the pathology observed among patients with AN. The electrophysiological data from this study provide evidence that disgust may be uniquely avoided in the context of food-cue learning, and offer one possible explanation for why food avoidance and emotional avoidance would overlap. Rodent literature has consistently demonstrated that induction of general anxious states in conjunction with food consumption yields conditioned taste aversion (Guitton & Dudai, 2004) and that this aversion can affect social interaction (Guitton, Klin, & Dudai, 2008). The nature of disgust also makes this emotion particularly difficult to change because of its resistance to extinction (Mason & Richardson, 2010) and influence over attentional resources (Armstrong et al., 2014). This change in attention may explain why repeated 'exposures' to food in the context of meeting daily nutritional needs, or why formal exposure and response prevention (EXRP) exercises, fail to substantially change behavior.

Walsh (2013) posited that the stimulus-response learning process that occurs during initial dieting becomes habitual via a variety of factors, including the intermittent reinforcement of weight loss, the persistent effort needed for dieting success, and the catalyzing effect of stress on habit formation. Although Walsh's habit-theory of food avoidance does not exclude a role for affect, the perseverance of the food-cue associations observed in this study support the possibility that the stressful context that keys food avoidance is disgust-based among patients with AN. Because disgust-conditioning is often evaluative (i.e., assigns valence of 'good' or 'bad'), the food-response conditioning observed among patients may mimic or facilitate habit formation (i.e. behavioral response occurs without decision making processing; Dezfouli & Balleine, 2013). The evidence of pleasurable avoidance among the AN patients, however, is more consistent with pleasure derived from the cued-absence of an aversive stimulus. A pure habit model would suggest that the avoidance behaviors persist without pleasure motivating the response. Women with AN have clear deficits in processing of reward, failing to demonstrate hedonic motivation in reward learning to natural reinforcers (Oberndorfer et al., 2013a,b; Wagner et al., 2007). However, stimuli that serve to cue absence of an undesirable state (i.e., thin vs. overweight stimuli) are associated with increased hedonic salience marked by increased activation in the ventral striatum early in the disease progression (Fladung et al., 2010). These data suggest that the avoidance symptoms noted in early onset AN are more consistent with a hedonic model of pleasurable avoidance than Walsh's proposed habit model per se. It is possible, however, that the initial reinforcing properties associated with terminating anxious emotions indicative of pleasurable avoidance that transitions into habits over the course of the illness.

There were a number of limitations to the current study. We used only a single psychophysiological marker of emotion and future research will need to expand these findings to include measures of attention (e.g., eye-tracking) and autonomic arousal (e.g., pupil dilation). As starvation causes changes in central nervous system arousal (Pirke, 1996; Plata-Salaman, 2000), comparisons between healthy subjects and patients with active AN may be difficult to interpret. The current sample included only the AN-Restricting subtype, while future research should look to identify whether the reported findings also hold for the binge-eating/purging subtype. Another limitation was the use of only M&Ms as food, where prior research suggests that group differences in food preference may be contingent on the type of food (e.g., sweet vs high-fat; Simon, Bellisle, Monneuse, Samuel-Lajeunesse, & Drewnowski, 1993). The use of a food picture as the US may also have produced weaker effects, whereas immediate administration of food is likely to yield more robust findings. Finally, the difficulty in assessing self-reported emotions among those with alexithymia limits our ability to map psychophysiology to the self-reported emotional experience of participants. We did not formally measure alexithymia, so it remains unclear if this deficit in emotional labeling manifested in EMG or behavioral responses.

Evidence of disgust conditioning in AN raises some important possibilities for future research and development of clinical interventions. For instance, counterconditioning interventions have been developed to target evaluative conditioning characteristic of

disgust (de Jong, Vorage, & van den Hout, 2000; Schweckendiek et al., 2013). These data were also collected on adolescents with recent onset AN, and the behavioral responses may reflect developmental differences in emotional conditioning. For instance, fear is flexibly learned in adulthood but less so in adolescence (Andrzejewski et al., 2011; Pattwell et al., 2012). It is unclear what, if any, developmental differences in disgust conditioning may also occur during this period; however, identifying how developmental processes influence flexibility in emotional learning may help explain the persistence of AN symptoms.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brat.2015.06.008.

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