Psychiatry Research: Neuroimaging 288 (2019) 76–84

Contents lists available at ScienceDirect

Psychiatry Research: Neuroimaging

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

Neural correlates of taste reward value across eating disorders

Aviva K. Olsavsky[a], Megan E. Shott[a], Marisa C. DeGuzman[a,b], Guido K.W. Frank[a,b,*]

[a] Department of Psychiatry, University of Colorado Anschutz Medical Campus, School of Medicine, Aurora, Colorado, USA
[b] Department of Neuroscience, University of Colorado Anschutz Medical Campus, School of Medicine, Aurora, ColoradoO, USA

ARTICLE INFO

Keywords:
Brain imaging
Eating disorders
Value
Temporal difference

ABSTRACT

Individuals with eating disorders (ED) make extreme food choices, raising the possibility of altered food-value computation. We utilized an associative taste reward learning paradigm to test whether value signaling differs between participants with EDs vs. healthy controls (HC). We followed up on previous work examining prediction error (PE) signaling, which is a brain response to violation of a learned reward contingency. Expected value (EV) signal is a trial-by-trial assessment of reward significance accounting for error signaling, reward-likelihood, and learning rate. Adult female participants (N = 111) performed a temporal difference (TD) fMRI taste task, which is a specific type of associative reward learning paradigm, to determine EV signal: Anorexia Nervosa-ill (N = 28), Anorexia Nervosa-recovered (N = 20), Bulimia Nervosa (BN) (N = 20), and HC (N = 43). Anatomical region-of-interest (ROI) analyses were performed utilizing EV regressors derived via algorithm, with ROIs based on prior EV analyses: orbitofrontal cortex, anterior cingulate (ACC), amygdala, and striatum. EV signal was elevated in the bilateral ACC in AN-ill vs. HC and BN. Intolerance of uncertainty negatively correlated with EV in AN-ill. BMI and EV were negatively-correlated across groups. Altered ACC EV computation in response to food stimuli could contribute to food restriction in AN-ill.

1. Introduction

Neural circuitry underlying food approach and avoidance behaviors is complex, with multiple elements: energy-homeostasis, higher-order sensory, cognitive, emotional, and reward circuitry (Chen et al., 2016). Previous work has examined the interplay of neural and neuroendocrine mechanisms in healthy humans (Rolls, 2015). Like other decision-making processes (Ernst and Paulus, 2005; Rangel et al., 2008), food approach-avoidance is driven by assigning value to stimuli, suggesting that value computation influences pathological eating behaviors.

Prior neuroimaging work suggests that response to reward cues/receipt differs between eating disorder patient groups (ED) (Frank, 2013; Kaye et al., 2013; O'Hara et al., 2015). Findings regarding response to food reward delivery are variable, with one study demonstrating higher activity in women recovering from Anorexia Nervosa (AN-rec) vs. healthy controls (HC) to chocolate taste in reward-related (ventral striatum, putamen) and sensory (posterior cingulate) areas (Cowdrey et al., 2011). Another study suggested decreased insula response to sweet taste stimuli in AN-rec, while women recovering from Bulimia Nervosa (BN) had increased response (Oberndorfer et al., 2013). A third study revealed lower activation in BN vs. HC to receipt of milkshake stimulus in prefrontal cortex, insula, and thalamus (Bohon and Stice, 2011). Further, investigations have revealed differences in the balance between activation in areas typically associated with reward receipt and those associated with cognitive control in AN-ill and AN-rec (Ehrlich et al., 2015; Geisler et al., 2017). Finally, one study in patients with Binge-Eating Disorder found alterations in insula and ventrolateral prefrontal cortex activation associated with reward-related decision-making deficits (Reiter et al., 2017). Overall, teasing apart reward anticipation, learning, and value computation across diagnoses remains an important research focus in ED, given implications of these processes for instantiating and perpetuating pathological eating behaviors.

As a tool for more precisely differentiating subprocesses underlying reward learning, the temporal difference (TD) model, previously characterized in animal models (Amiez, 2006; Fiorillo et al., 2003; Schultz et al., 1997; Schultz et al., 2000; Tobler et al., 2005) and humans (O'Doherty et al., 2003; Seymour et al., 2004), provides one method to examine reward value and error signaling. Based on the Rescorla Wagner model of reinforcement learning (Rescorla, 1972), TD tasks (Figure S1) teach a reward contingency through associative learning (e.g.—fractal image with taste stimulus), and subsequently violate the contingency in a percentage of trials. Two neural signals are elicited: prediction error (PE) signal, which is generated when the reward

* Corresponding author at: Departments of Psychiatry and Neuroscience Director, Developmental Brain Research Program University of Colorado Anschutz Medical Campus; Children's Hospital Colorado, Gary Pavilion A036/B-130; 13123 East 16th Avenue, Aurora, Colorado 80045, USA.
E-mail address: Guido.Frank@ucdenver.edu (G.K.W. Frank).

https://doi.org/10.1016/j.pscychresns.2018.08.010
Received 26 January 2018; Received in revised form 14 August 2018; Accepted 15 August 2018
Available online 18 August 2018
0925-4927/ © 2018 Elsevier B.V. All rights reserved.

contingency is violated (e.g.—expecting sugar solution, but instead receiving nothing), and expected value (EV) signal, which is a cumulative function of reward significance upon reward receipt, calculated using PE, probability of reward receipt, learning rate, and discount factor to account for effect of immediate vs. delayed rewards (Schultz, 2015; Schultz et al., 2000).

In animal and human studies, while PE is subserved by dopaminergic reward circuitry and insula (O'Doherty et al., 2003; Schultz, 1998), EV is associated with similar regions to PE (ventral striatum and amygdala), in addition to orbitofrontal cortex (OFC) and ACC (Daw et al., 2006; Knutson et al., 2005; O'Doherty, 2004; Rolls et al., 2008; Tremblay and Schultz, 1999). Comparatively speaking, OFC has more evidence compared to ACC in value signaling given multiple meta-analyses demonstrating effects in ventromedial prefrontal cortex (Bartra et al., 2013; Clithero and Rangel, 2014). However, there has been considerable work supporting a distinct role for ACC compared to OFC in value-based decision-making, with implications for foraging behaviors, value computation (historical versus current), balancing costs with value, and the role of effortful control in reward processes (Kennerley et al., 2011; Kolling et al., 2012; Rushworth and Behrens, 2008; Shenhav et al., 2013). For instance, one, study in AN revealed increased activation in dACC associated with adaptation to negative feedback during a reversal learning task and suggested a relationship with difficulty tolerating uncertainty (Geisler et al., 2017). Differences across EDs in personality traits may be relevant to this distinction in role of ACC in value computation, given increased anxiety-related traits in AN (Frank et al., 2012b; Guarda et al., 2015; Sternheim et al., 2015). In particular, intolerance of uncertainty has been associated with differences in ACC activation during decision-making in adolescents with anxiety disorders (Krain et al., 2008), and is noted to be elevated in AN and BN (Frank et al., 2012b). The connection between the role of ACC in value computation and decision-making and the way that the brain deals with uncertainty is potentially relevant to these personality findings in AN.

This study follows up on previous examinations of PE signal in participants with ED and HC across a range of BMIs. In prior studies of adult patients with ED using the TD model, AN-ill exhibited higher PE signal vs. HC and participants with obesity in anterior insula, ventral striatum, and orbitofrontal cortex (Frank et al., 2012a). Furthermore, a second study revealed that AN-rec had elevated insula activation to unexpected reward omission vs. HC (Frank et al., 2016). A third study revealed that BN had decreased PE signal vs. HC in insula, putamen, amygdala and OFC (Frank et al., 2011). Results in AN adolescents are mixed, with one study finding that higher PE signal in caudate was associated with lower weight gain in AN during treatment, suggesting that PE may be a marker of severity (DeGuzman et al., 2017), while another study found no differences in PE or EV signaling in patients in AN vs. HC, although AN-ill had increased ACC signal following negative feedback (Geisler et al., 2017). Another study in an adolescent-young adult AN population found increased learning rate following punishment, associated with greater posterior medial PFC activation during a similar reversal learning task (Bernardoni et al., 2018).

Based on prior work, we hypothesized that AN would exhibit a distinct pattern of EV signal vs. other groups. Specifically focusing on BN, we wondered if EV signal would differentiate AN and BN—groups with overlapping anxious traits but contrasting behaviors. Given data suggesting that AN and BN have opposite reward-related activity to reward receipt, we hypothesized that AN would have higher value signal in areas associated with EV signaling vs. BN and hypothesized that this between-group difference might be correlated with subtle differences in anxious traits. As such, we performed exploratory analyses of personality measures to examine if differences in anxiety-related scales between groups might relate to imaging analyses. Finally, we were interested in whether differences noted in AN-ill might normalize in patients following recovery.

2. Methods

2.1. Study participants

We studied adult female participants (total $N = 111$; mean age = 26; range = 18–45 years): restricting type Anorexia Nervosa, AN-ill ($N = 28$) and AN-rec ($N = 20$); BN ($N = 20$); and healthy controls (HC) ($N = 43$). Data from participants with ED utilizing the same associative taste reward task were previously reported on regarding PE signaling (AN-ill = 19; AN-rec = 20; BN = 17), but approximately half of the HC participants are not previously published on (20 out of 43 HC participants) and EV has not been reported in any participants (Frank et al., 2011; Frank et al., 2012a; Frank et al., 2016). Furthermore, previously-reported studies (Frank et al., 2011; Frank et al., 2012a; Frank et al., 2016) have not examined PE signal across all groups, which is an exploratory aim of this study. Research was performed at University of Colorado-Denver and approved by Colorado Multiple Institutional Review Board. Participants provided written informed consent and were categorized diagnostically utilizing the Structured Clinical Interview for DSM-IV Axis I Disorders (First MB, 2000). HC participants did not meet criteria for any DSM-IV diagnoses. AN and BN participants were admitted to a specialized ED treatment program, were studied during the first 1–2 weeks of treatment, and laboratory tests upon admission (complete blood count, complete metabolic panel, pregnancy test) were unremarkable or negative. All AN-ill and AN-rec participants were restricting-subtype without history of BN. AN-rec were defined as having a history of restricting-type AN but having had normal weight for height, menstrual cycle, exercise, and food intake for at least 1 year. Exclusion criteria included neurological disorders, psychotic disorders, IQ < 70, major medical illness (i.e.—Diabetes Mellitus, chronic kidney disease), and recent alcohol/drug use. Mood and anxiety disorders were included given high ED comorbidity.

2.2. Procedures

2.2.1. Study questionnaires

All participants completed Intolerance of Uncertainty Scale (IUS) (Buhr and Dugas, 2002), Sensitivity to Reward (SR subscale) and Punishment (SP subscale) Questionnaire (O'Connor R, 2004), ED Inventory-3 (EDI-3, Drive for Thinness (DT) subscale) (Garner, 2004), the Spielberger Trait and State Anxiety (Spielberger C.D., 1970), Beck Depression Inventory (Beck AT, 1961), and the Temperament and Character Inventory (Harm Avoidance (HA) subscale) (Cloninger, 1994). Age difference between groups was tested with one-way ANOVA and *post hoc* comparisons (Bonferroni-corrected). Between-group differences for categorical variables (mood or anxiety disorders, treatment with antidepressant or antipsychotic medications) were assessed with chi-squared tests.

2.2.2. TD model task

The TD task is adapted for human subjects (O'Doherty et al., 2003). Each trial begins with presentation of one of three fractal visual stimuli (2sec), followed by one of three taste stimuli (via customized programmable-syringe pump) (J-Kem Scientific, St. Louis, MO): (1) pleasant 1M sucrose solution—100 trials (CS+); (2) no solution—100 trials (CS−); (3) artificial saliva 80 trials—(Francis et al., 1999; Frank et al., 2003), which is included to provide a rinse between sucrose solution trials to minimize habituation, and which was not modeled in the EV regressor given this role, leaving 200 total trials for modeling EV regressor. During taste stimulus, fixation cross is presented (4 s). The first 10 CS+ stimuli are presented with subsequent reward (sugar solution). For 20/90 remaining trials, when the fractal stimulus associated previously with sugar solution is seen, the sugar solution is not delivered. Likewise, for 20 trials in which a fractal stimulus not associated with sugar solution is seen, sugar solution is unexpectedly delivered. All trials other than the first 10 CS+ trials were randomized. Boxcar

function had onset at beginning of each trial with fractal image and included the entire trial. The experimental paradigm lasts approximately 28.5 minutes. Visual and taste stimuli delivery was triggered using E-Prime (Psychology Software Tools, Pittsburgh, PA). See Supplementary Data for details of neurocomputational modeling.

2.2.3. Functional MRI methodology

Participants ate breakfast (7–8 AM) before fMRI (ED participants according to their meal plans, with control meal matched to typical meal plans. Participants were scanned afterwards using GE Signa 3T MRI scanner. T2* weighted echo-planar images for BOLD (blood oxygen-level dependent) signal were acquired: voxel size = 3.4 × 3.4 × 2.6 mm;1.4 mm gap;TR = 2100 ms; TE = 30 ms;flip angle = 70 degrees;30 slices. Structural images (T1 SPGR) were acquired for coregistration with functional images.

2.3. Analyses

2.3.1. Image preprocessing

Images were preprocessed and analyzed using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12 with Marsbar (Brett, 2002) and Anatomy Toolboxes (Eickhoff et al., 2005) MATLAB and Statistics Toolbox Release 2009b, The MathWorks, Inc., Natick, Massachusetts, United States). We utilized the unified segmentation algorithm from the SPM12 package. Slice-timing correction was applied followed by realignment to first volume and normalized to MNI template, and subsequently smoothed with 6-mm FWHM Gaussian kernel. Images were inspected individually during preprocessing to ensure adequate brain coverage and to examine results of alignment. Imaging data was collected on 124 participants (AN-ill N = 30, AN-rec N = 24, HC N = 47, BN N = 23) and 13 were excluded due to motion or image artifacts. There was no between-group difference in number of participants excluded for either excessive motion (>3 mm maximum displacement from the first volume) or image artifacts (AN-ill N = 2, AN-rec N = 4, HC N = 4, BN N = 3). We utilized two *post hoc* repeated measures ANOVAs (translational and rotational analyzed separately) to assess between-group differences in motion parameters (Table S2).

2.3.2. Single-subject analyses

Modeling single-subject parameter estimates was performed with boxcar function utilizing general linear model with temporal and dispersion derivatives, but not autoregression given issues with this procedure. Low-frequency BOLD-signal fluctuations were removed with 128 s high-pass filter. Single-subject models included 6 motion regressors as well as expected value regressor which was calculated on a trial-by-trial basis and served as a parametric modulator.

2.3.3. Anatomical region of interest analyses

Anatomical ROI analyses included bilateral ACC and OFC as well as ventral striatum and amygdala, given the role for these areas in processing EV signal. As addressed in the introduction, we chose *a priori* anatomical regions of interest based on literature regarding the TD model and reward decision-making literature more broadly. EV signal is associated with some similar regions to PE, as well as distinct regions (Daw et al., 2006; Knutson et al., 2005; O'Doherty, 2004; Rolls et al., 2008; Schultz et al., 2000). ROIs were derived from an automated anatomical labeling atlas (Tzourio-Mazoyer et al., 2002). Anatomical ROI analyses were chosen as opposed to primarily whole-brain analyses in order to be more conservative given recent issues raised with cluster-thresholding in the literature (Eklund et al., 2016). We Bonferroni-corrected our p-value ($p < 0.00625$) based on number of tests (8 total, independently testing left and right). Average ROI signal was extracted from SPM and analyzed utilizing a univariate general linear model in SPSS for each of the following areas separately: amygdala, ventral striatum, orbitofrontal cortex, anterior cingulate cortex (left and right for each ROI). GLM includes covariate (age at scan) and cofactors (presence/absence of mood diagnosis, anxiety diagnosis, antipsychotic treatment, and antidepressant treatment), given between-group differences in these variables. *Post hoc* comparisons (Bonferroni-corrected) decomposed significant effects. We performed regression diagnostics and sensitivity analyses as well as bootstrapping (1000 samples, 95% confidence intervals). (Supplementary Materials, Table S2)

2.3.4. Regression analyses

Given between-group differences in behavioral scales and age, Pearson correlation analyses examined EV signal relationship across and within groups in significant anatomical ROI areas: age, BMI, the IUS, SR, SP, HA, and EDI-3 DT. FDR-correction was performed for multiple tests separately for correlations across within group (Benjamini and Hochberg, 1995). *P*-values are reported in regression scatterplots and are starred if they survived correction for multiple tests. To ascertain whether EV signal was driven by sweetness or pleasantness ratings of sucrose solution, we performed *post hoc* regression analyses with EV signal.

2.3.5. Exploratory whole-brain analyses

EV whole-brain between-group analysis was performed utilizing thresholding according to random field theory, which provides some correction for multiple comparisons (Brett, 2004; Worsley et al., 2004). We acknowledge the recent controversy regarding thresholding methods and thus emphasize that these are necessarily exploratory analyses (Eklund et al., 2016; Flandin and Friston, 2017). Despite PE results being published previously in a portion of the sample, we chose to perform an exploratory whole-brain analysis regarding PE signal across the 4 groups to obtain the benefit of examining a more parsimonious model with additional HC participants included, for which we used similar thresholding. Within-group whole-brain analyses of EV and PE were performed to examine main effects of calculated regressors utilizing consistent thresholding parameters ($p < 0.001$ voxel-wise, uncorrected, k > 100 extent threshold). Cluster extent threshold was arrived at utilizing similar parameters to the threshold determined by random field theory in the primary whole-brain group analyses.

3. Results

3.1. Participant characteristics

As expected with heterogeneity across EDs in illness course, comorbidity, and presentation, there were between-group differences in demographic variables (Table 1). Age differed between groups ($p < 0.01$) with AN-ill younger than AN-rec. BMI differed between groups ($p < 0.01$), with AN-ill having lower BMI than all other groups and no other group differences. There were consistent between-group differences in psychological scales (Table 1) driven by AN-ill and BN having higher scores in anxiety-related scales vs. other groups. There were no differences in pre-scanning calories ($p > 0.05$). There were no between-group effects in either translational or rotational motion parameters ($p > 0.05$) (Table S2).

3.2. Anatomical ROI analyses

Left and right anterior cingulate anatomical ROIs (BA 24/32) revealed a between-group difference in EV signal without effects of age, diagnosis or medication [Left ACC: $F_{3,102} = 6.34$, $p < 0.01$, $\eta_p^2 = 0.157$. Right ACC: $F_{3,102} = 5.51$, $p < 0.01$, $\eta_p^2 = 0.139$] (Fig. 1A/B). The difference was driven by AN-ill > HC and AN-ill > BN ($ps < 0.05$). Identical models were constructed for bilateral orbitofrontal cortex, amygdala, and ventral striatum with no significant

Table 1
Demographics table.

	AN-ill	AN-rec	HC	BN	*p*-value
Sample (*N*)	28	20	43	20	–
Age mean (years) (SD)	22.9 (5.0)	30.0 (8.0)	26.4 (5.4)	25.3 (4.6)	$p < 0.01$[a]
Range	18–37	19–45	19–43	20–37	
BMI mean (kg/m[b]) (SD)	16.1 (1.0)	20.7 (2.0)	21.6 (1.5)	23.0 (5.7)	$p < 0.01$[b]
Range	14–18	18–28	18–26	18–41	
IUS mean (SD)	88 (16)	56 (17)	52 (13)	87 (19)	$p < 0.01$[c]
Range	57–120	37–104	32–82	38–107	
Sensitivity—reward mean (SD)	7 (4)	6 (3)	5 (3)	8 (4)	$p < 0.01$[d]
Range	2–14	2–13	1–15	2–13	
Sensitivity—punishment mean (SD)	13 (4)	7 (4)	5 (3)	13 (4)	$p < 0.01$[e]
Range	4–18	2–17	1–14	1–17	
Harm avoidance mean (SD)	24 (6)	16 (7)	11 (5)	23 (6)	$p < 0.01$[f]
Range	12–34	4–27	2–22	8–31	
Drive for thinness (EDI-3) mean (SD)	19 (6)	9 (6)	3 (4)	23 (5)	$p < 0.01$[g]
Range	7–28	0–23	0–15	12–28	
Spielberger trait anxiety mean (SD)	55 (11)	35 (14)	28 (6)	60 (10)	$p < 0.01$[h]
Range	35–80	22–60	20–48	41–70	
Spielberger state anxiety mean (SD)	53 (11)	33 (12)	27 (6)	51 (14)	$p < 0.01$[i]
Range	31–76	20–63	20–42	22–75	
Beck depression inventory mean (SD)	26 (11)	4 (4)	2 (2)	23 (11)	$p < 0.01$[j]
Range	9–48	0–12	0–6	6–42	
Binge/purge frequency (per week)[k]	N/A	N/A	N/A	24	N/A
	–	–	–	2–70	
Mood diagnosis (*N*)	15	4	–	11	$p < 0.01$
% of Group	54%	20%	0%	55%	
Anxiety diagnosis (*N*)	15	5	–	14	$p < 0.01$
% of Group	54%	25%	0%	70%	
Antidepressant treatment (*N*)	14	4	–	13	$p < 0.01$
% of Group	50%	20%	0%	65%	
Antipsychotic treatment (*N*)	3	–	–	3	$p < 0.05$
% of Group	11%	0%	0%	15%	

Abbreviations: Anorexia Nervosa-ill (AN-ill), Anorexia Nervosa-recovered (AN-rec), Healthy Control (HC), Bulimia Nervosa (BN), BMI (Body Mass Index), EDI-3 (Eating Disorder Inventory-3)

[a] Age *post hocs*: AN-ill < AN-rec, $p < 0.01$; all other differences not significant.
[b] BMI *post hocs*: AN-ill < all other groups all *ps* < 0.001; all other differences not significant.
[c] IUS *post hocs*: AN-ill and BN both > all other groups, all *ps* < 0.001. AN-ill vs. BN, $p > 0.05$.
[d] Sensitivity to reward *post hocs*: AN-ill > HC and BN > HC, *ps* < 0.05; all other differences not significant.
[e] Sensitivity to punishment *post hocs*: AN-ill > AN-rec, AN-ill > HC, BN > AN-rec, BN > HC, all *ps* < 0.001; no other significant differences.
[f] Harm avoidance *post hocs*: AN-ill > AN-rec, AN-ill > HC, all *ps* < 0.001; BN > AN-rec, BN > HC, all *ps* < 0.001; AN-rec > HC, $p < 0.05$.
[g] Drive for thinness (EDI-3) *post hocs*: AN-ill > AN-rec, AN-ill > HC, AN-rec > HC, BN > AN-rec, BN > HC, all *ps* < 0.001.
[h] Spielberger trait anxiety *post hocs*: AN-ill > AN-rec and HC, BN > AN-rec and HC, all *ps* < 0.001; AN-rec > HC, $p < 0.05$.
[i] Spielberger state anxiety *post hocs*: AN-ill > AN-rec and HC, BN > AN-rec and HC, all *ps* < 0.001.
[j] Beck depression inventory *post hocs*: AN-ill > AN-rec and HC, BN > AN-rec and HC, all *ps* < 0.001.
[k] Binge/purge frequency missing for 4 BN participants.

differences (all *ps* > 0.05). GLM models of left and right ACC were inspected to assess effects of influential points on results. *Post hoc* analyses with removal of influential points were performed, as well as bootstrapping (1000 samples, 95% confidence intervals), and the analyses retained significance. (Supplementary Materials, Table S2).

3.3. Regression analyses

There was no correlation of age with EV ($p > 0.05$) across or within-groups. BMI across groups was negatively correlated with EV in left ACC anatomical ROI, $r = -0.36$, $p < 0.001$, $N = 111$, surviving FDR-correction for multiple tests. BMI across groups was negatively correlated with EV in right anatomical ACC ROI, $r = -0.34$, $p < 0.001$, $N = 111$, surviving FDR-correction (Fig. 2A). There was no significant correlation of BMI within groups in left or right ACC. To assist with interpretation of the BMI finding, we performed a *post hoc* analysis collapsed across groups with normal-high normal BMI vs. low BMI and repeated correlation analyses within and across groups. BMI negative correlation with EV signal was significant in the normal-high normal BMI group in left ACC ($r = -0.23$, $p < 0.05$) and trend-level in right ACC ($r -0.21$, $p = 0.054$). There was not a significant correlation in either right or left ACC in AN-ill. (Fig. 2B) There was no correlation of IUS with value signal across groups in left or right ACC (all *ps* > 0.05). However, within the AN-ill group, there was a negative correlation of left ACC anatomical ROI EV signal with IUS, with lower EV associated with higher IUS, $r = -0.61$, $p < 0.005$, $N = 28$ (Fig. 3A). Results survived FDR-correction for multiple tests within groups. There was a similar relationship in right ACC anatomical ROI between EV and IUS ($r = -0.53$, $p < 0.005$, $N = 28$) (Fig. 3B), though this result did not survive FDR-correction. To assist with interpretation of IUS correlation with EV signal, we performed *post hoc* correlations between IUS and anxiety-related measures including STAI-trait and state questionnaires as well as measures of eating disorder severity (EDI3-DT) to see if IUS was a proxy for anxiety-related phenomena. There was no correlation within AN-ill between STAI State or Trait scores with IUS or EV signal in bilateral ACC (*ps* > 0.05). There was no correlation between EDI3 and ACC EV signal, but there was a positive correlation between IUS and EDI3-DT ($r = 0.39$, $N = 28$, $p < 0.05$). There was no correlation between EV signal and subjective sweetness or pleasantness ratings by participants of the 1M sucrose solution in *post hoc* regression analyses, either between or within groups (all *ps* > 0.05). There was no correlation in ACC of EV signal within or between groups with Sensitivity to Reward or Punishment, Harm Avoidance, or EDI-3 Drive for Thinness subscale (*ps* > 0.05).

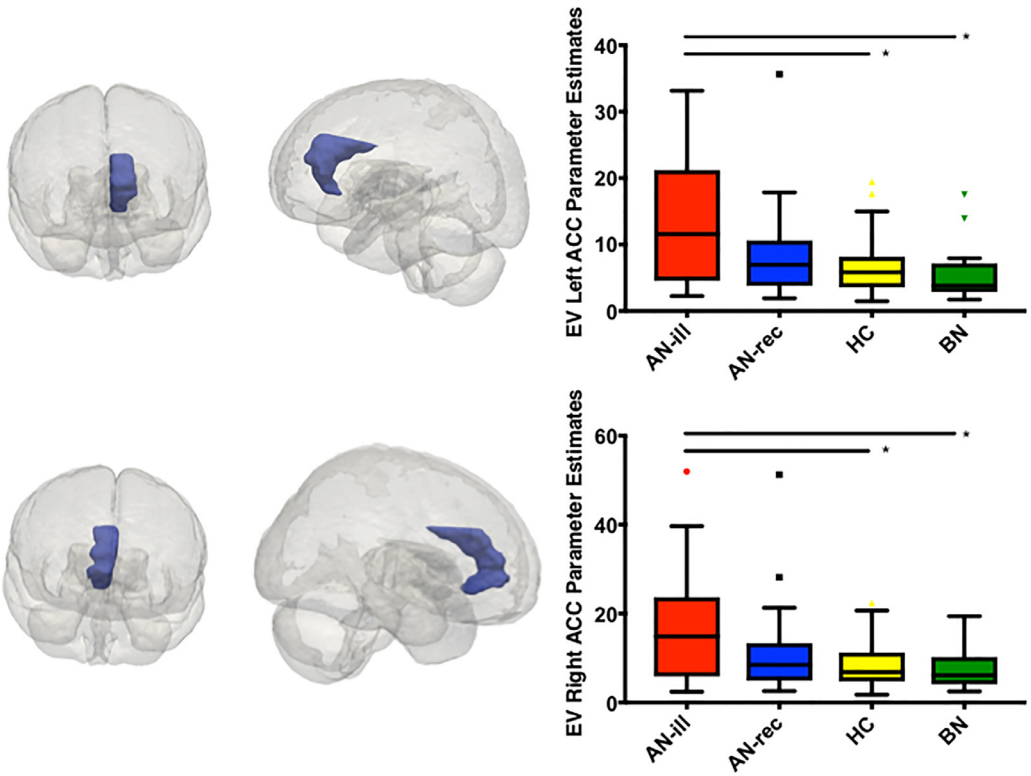

Fig. 1. (A). Left anterior cingulate anatomical ROI, $F_{3,102} = 6.34$, $p < 0.01$, $\eta_p^2 = 0.157$; *post hoc* tests: AN-ill > HC, AN-ill > BN, *ps* < 0.01, all other *ps* > 0.05. (B). Right anterior cingulate anatomical ROI, $F_{3,102} = 5.51$, $p < 0.01$, $\eta_p^2 = 0.139$; *post hoc* tests: AN-ill > HC, AN-ill > BN *ps* < 0.05, all other *ps* > 0.05.

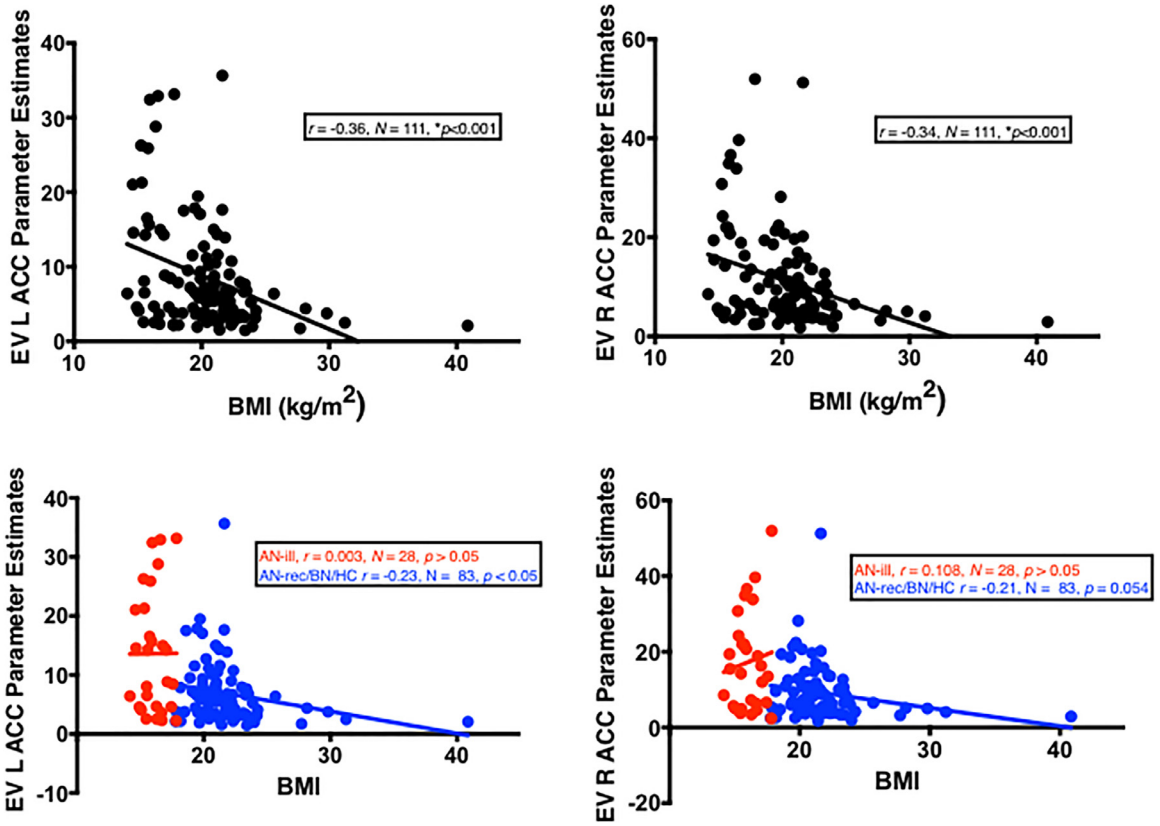

Fig. 2. (A). Bilateral anterior cingulate anatomical ROI correlation with Body Mass Index (BMI) across all groups. *Correlation survives FDR-correction for across-group tests. (B). Bilateral anterior cingulate anatomical ROI correlation with Body Mass Index (BMI) with AN-ill (red) and AN-rec, HC, and BN (blue). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

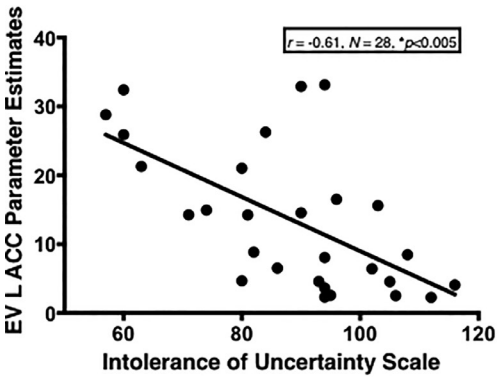

Fig. 3. (A). Left anterior cingulate anatomical ROI correlation with Intolerance of Uncertainty Scale (IUS) in Anorexia Nervosa-ill group only. *Correlation survives FDR-correction for within-group tests. (B). Right anterior cingulate anatomical ROI correlation with Intolerance of Uncertainty Scale (IUS) in Anorexia Nervosa-ill group only.

3.4. Exploratory whole-brain analyses

Whole-brain analyses within groups ($p_{FWE} < 0.05$, $k > 0$) to examine the main effect of EV signal within HC revealed activation in frontal and temporal areas as well as in anterior and posterior cingulate, insula, caudate, and visual areas (Figure S3). We have outlined the larger clusters of activation associated with EV for each group ($k > 100$) in Table S1A-D. Additionally, we have included within-group SPM maps ($p_{FWE} < 0.05$, $k > 0$) for the PE signal (Figure S4), which included more basal ganglia and less cortical activation. EV and PE signal findings were somewhat distinct maps, though there was some overlap.

In the EV whole-brain analysis we found a between-group effect in left ACC ([−4 44 2], $p_{uncorr} < 0.001$, $k = 269$, $F_{3,102} = 12.88$, $Z = 4.97$), driven by AN-ill having higher EV signal vs. other groups (all $ps < 0.005$). There were no effects of any confounders included in the model (mood or anxiety diagnosis, antipsychotic or antidepressant treatment, age at scan) (Fig. 4A). We found a between-group difference in right supramarginal gyrus ([50 −30 32], $p_{uncorr} < 0.001$, $k = 100$, $F_{3,102} = 11.30$, $Z = 4.63$), likewise driven by AN-ill having higher signal vs. other groups (all $ps < 0.05$, some of which did not survive bootstrapping) (Fig. 4B, Table S2). For this cluster, the model revealed in addition to main effect of group, a main effect of antidepressant use, associated with lower EV signal ($p < 0.005$) and a main effect of antipsychotic medication, associated with increased EV signal ($p < 0.05$). Briefly, the whole-brain analysis of PE signal we found a main effect of group in right middle temporal gyrus that survived random field theory thresholding ([48 2 −20], $p_{uncorr} < 0.001$, $k = 18$, $F_{3,102} = 10.93$, $Z = 4.54$), driven by AN-ill having higher PE signal than all other groups (all $ps < 0.005$). However, there were also main effects of having a diagnosis of any anxiety disorder, which was associated with higher PE signal ($p < 0.01$) and age ($p < 0.05$). Please see Figure S5A/B for the detailed results of PE between-group whole-brain analysis.

4. Discussion

This study indicates that AN-ill exhibit elevated expected value response in bilateral ACC in the context of an associative learning reward

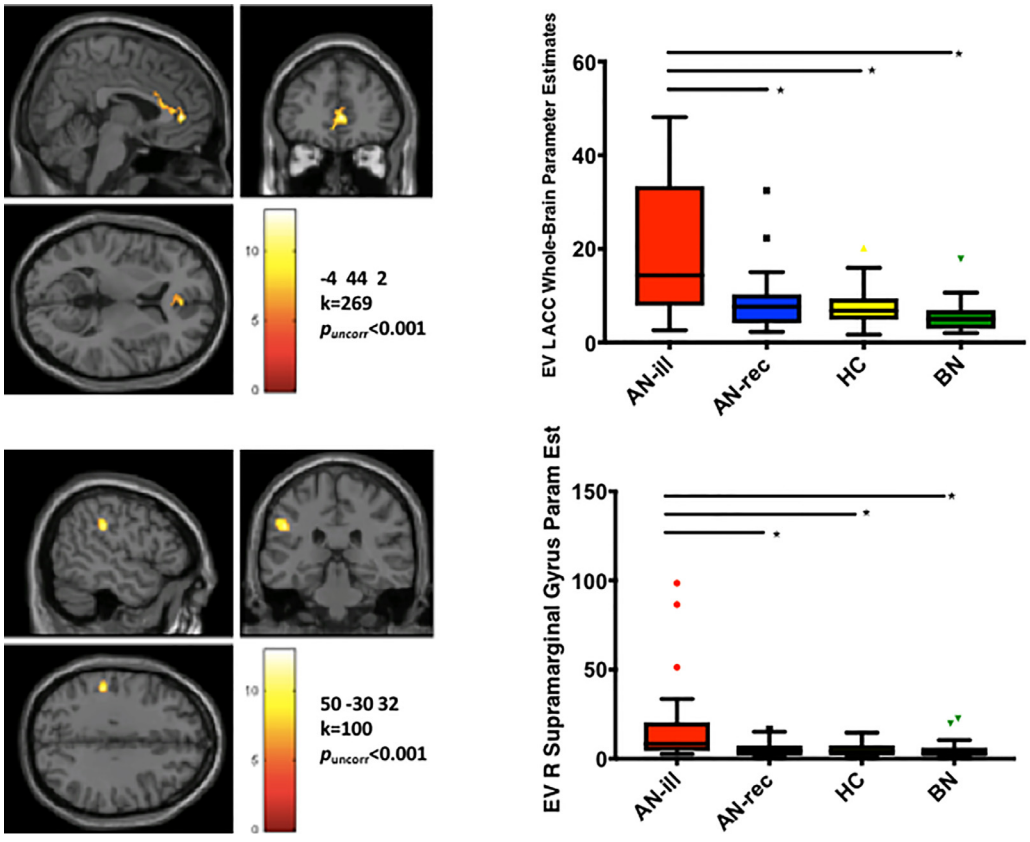

Fig. 4. (A). Exploratory whole-brain analysis for Expected Value signal, left anterior cingulate cortex cluster, MNI coordinates [−4 44 2], Group Effect - $F_{3,102} = 12.88$, $Z = 4.97$, $p_{uncorr} < 0.001$, $k = 269$. (B). Exploratory whole-brain analysis for Expected Value signal, right supramarginal gyrus cluster, MNI coordinates [50 −30 32], $F_{3,102} = 11.30$, $Z = 4.63$, $p_{uncorr} < 0.001$, $k = 100$.

task. EV signal in ACC was negatively-correlated with BMI across groups, such that participants with lower BMI had higher EV signal, an effect that did not appear to be driven by the low-BMI AN-ill group. Whether taste stimuli inversely drive reward signal processing or whether there is another mechanism moderated by BMI is unclear. Furthermore, there was an inverse relationship between ACC EV signal and intolerance of uncertainty (IUS) in AN-ill. Interestingly, between-group differences in EV signal were largely driven by AN-ill being different from HC and BN. However, there were no observed differences between AN-rec and other groups, though this result is limited by the small sample size. Interestingly, we did not observe a between-group difference in OFC, ventral striatum, or amygdala, other areas involved in EV signaling. Whole-brain analyses revealed a distinct pattern of neural regions for EV vs. PE, and within-group maps suggested that groups may exhibit different patterns, with AN-ill having greater EV signal compared to others, which is consistent with previous PE findings (Frank et al., 2011; Frank et al., 2012a; Frank et al., 2016).

There are multiple models positing how AN may differ from other groups in reward processing. One model suggests that taste and other food reward-related stimuli assume an aversive interpretation in AN, and that with greater illness, individuals experience more reward from food restriction behaviors and less reward from typically-rewarding taste stimuli (Keating, 2010; O'Hara et al., 2015). Another line of research has suggested that premorbid anxiety-related traits in AN may be exacerbated by neuroendocrine changes correlated with illness state (Guarda et al., 2015; Kaye et al., 2009). The role of habit-formation is also discussed in the literature (Walsh, 2013). However, habit relates more to the process by which ED behaviors like food restriction become entrained in the brain and evolve into pathology. Furthermore, there is likely a distinction between association learning which is the type employed in this task vs. habit formation (Rangel et al., 2008).

Another line of work connects anxiety-related processes with reward processing in ED, particularly, in AN. First, there is literature demonstrating higher prevalence of anxiety-related personality traits like harm avoidance and intolerance of uncertainty and increased anxiety comorbidity in AN, and to a lesser degree in BN (Atiye et al., 2015; Fassino et al., 2002; Kaye et al., 2004). Second, there is work suggesting activation of cognitive control or conflict-oriented circuitry during reward processing in patients with ED (Brooks et al., 2011; Uher et al., 2003; Uher et al., 2004), which raises the question of whether reward paradigms may elicit distinct higher order cognitive processes in patient populations, thus enabling them to experience a greater sense of control during tasks (Keating, 2010; Shenhav et al., 2013). This notion would also connect to the difficulty tolerating uncertainty seen in certain populations with ED (Frank et al., 2012b). Lastly, abnormalities in discrimination between reward and punishment in AN have been demonstrated, suggesting dysfunctional feedback-processing during reward learning (Bischoff-Grethe et al., 2013; Wagner et al., 2007), a deficit which may be shared by AN and BN (Wagner et al., 2010).

Increased conflict-detection during reward processing, specifically associated with value computation, may be one explanation for increased bilateral ACC activation in AN-ill vs. other groups. It has been previously suggested that not all activation labeled as reward value in studies ends up being reward value, and that there is variability based on task structure and other factors (O'Doherty, 2014). Thus, caution must be employed in interpreting this finding as there is always a concern for reverse inference when implying that a particular finding represents a given cognitive process (Wager et al., 2016). The task utilized in this study was adapted from a well-validated paradigm adapted for human subjects, based on animal electrophysiological studies (O'Doherty et al., 2003), which provides support for the fact that reward learning processes are indeed interrogated by the task. Furthermore, it is interesting that in the between-group EV analysis the only area that exhibited a clear difference between groups was the ACC, despite the fact that other ROIs have more of a basis in the literature with respect to EV (O'Doherty, 2004). This discrepancy begs the question of whether there may indeed be other non-reward related processes at work during the task, particularly in AN-ill. As noted previously, other types of tasks including a monetary reward task suggested differences in frontal areas in both AN-ill and AN-rec, suggestive of greater self-monitoring behavior during reward tasks (Ehrlich et al., 2015; Geisler et al., 2017), which is inconsistent with our not finding a difference between AN-rec vs. other groups, likely due to power and task-related differences. Another piece of preliminary evidence for a relationship between potential conflict in the context of reward valuation may be the IUS finding in AN-ill. Originally there was a question of whether anxiety-related traits might influence value computation. In one sense IUS is an anxiety-related trait and has been shown to perturb decision-making processes in people who struggle with anxiety (Krain et al., 2008). On the other hand, trait and state anxiety were unrelated to either IUS or the imaging finding in AN-ill. Another reason for caution in interpretation is the absence of a behavioral response which might be evaluated with respect to value and included in calculation of the EV regressor. This is an important limitation of the study. However, the broad activation of frontal areas shown in the SPM main effect maps suggest that the task may evoke motor planning or other active responses, more in AN-ill vs. other groups. Lastly, the ACC is also involved in cognitive control and thus the signal that is elevated in AN-ill may indeed be evidence of effortful control during this task due to discomfort elicited by taste stimuli (Botvinick, 2007; Shenhav et al., 2013).

By contrast with the AN-ill finding, it is more difficult to interpret the BN lack of activation. Overall, examining the within-group main effect SPM maps, BN do seem to have a much lower level of activation vs. other groups across the brain. However, this difference does not rise to the level of significance. One could ask the question of whether EV signal differences between AN-ill and BN are similar to the prior finding that with respect to PE signal, AN-ill had higher signal while participants with obesity had decreased signal, with HC in the middle (Frank et al., 2012a). There may be differences in brain function associated with increased caloric consumption whereby BN and people with obesity are less sensitive to taste stimuli. Another possible explanation for the BN finding may be that if ACC activation in this case represents conflict-detection, BN may be different secondary to differences in emotion regulation between the groups or we might speculate that conflict-detection may be particularly elevated in AN-ill.

4.1. Limitations

Across the populations our study, there is heterogeneity in age, comorbidity, BMI, and medication use. We attempted to account for these differences by including cofactors and covariates in the model. However, with increased number of cofactors or covariates, the sensitivity to detect subtle differences declines. Another limitation is the moderate number of participants in each group. Further, our whole-brain analyses require replication given concerns for false positives (David et al., 2013). Regression analyses were based on traits often increased in AN and should thus be thought of as preliminary. There is also a limitation regarding EV computation in the absence of behavioral responses related to decision-making in this passive reward learning task, which may also contribute to model fit being less accurate compared to tasks where there is a behavioral outcome that can be measured and included in the analyses. Thus, when regressors are modeled, they are modeled based on task parameters, and one can investigate via analysis of main effects whether imaging data fits with the regressor, but one cannot test whether the model fits participant responses. Lastly, the study was performed in females to minimize gender-related variance, and thus may not apply to males.

4.2. Future Directions

The study of reward processing across the spectrum of eating behaviors is important to further our understanding of how food rewards are processed in the brain and for targeting pathological mechanisms in patients with EDs. Our results suggest that AN-ill EV computation may differ from that of the other populations we studied. In addition, higher-order cognitive processes such as conflict-detection, may be activated in certain populations in the context of a reward task. However, it would be important to perform further studies to replicate these findings and to better characterize the intersection between conflict processing and reward in AN-ill. One approach might be to employ tasks that integrate choices in the context of reward tasks, thus enabling one to differentiate more explicitly between high- and low-conflict reward processing. It would also be important to more explicitly examine the differences between specific groups, such as AN-rec, as our current finding may indeed be related more to illness state than to the risk factors for eating pathology.

In summary, this is a transdiagnostic study examining expected value computation in participants with ED and healthy comparisons. Overall, the most prominent findings include AN-ill having higher EV signal in bilateral ACC, which in turn correlate with their intolerance of uncertainty, such that the higher the intolerance, the lower the expected value signal. Future work might include deeper phenotyping of anxiety-related traits and use of latent variable modeling to focus on specific traits that might become targets for treatment.

Funding and Disclosure

All authors report no biomedical financial interests or potential conflicts of interest.

This work was supported by the following NIMH grants: T32 MH015442 (AKO) (Developmental Psychobiology Research Group Program); K23 MH080135, R01 MH096777 and MH103436 (GKWF). MD was supported by NIH grant T32 HD041697 (University of Colorado Neuroscience Program).

Acknowledgments

We would like to thank all of the individuals who participated in this study.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.pscychresns.2018.08.010.

References

Amiez, C., Joseph, J.P., Procyk, E., 2006. Reward encoding in the monkey anterior cingulate cortex. Cereb. Cortex 16, 1040–1055.
Atiye, M., Miettunen, J., Raevuori-Helkamaa, A., 2015. A meta-analysis of temperament in eating disorders. Eur. Eat. Disord. Rev. 23, 89–99.
Bartra, O., McGuire, J.T., Kable, J.W., 2013. The valuation system: a coordinate-based meta-analysis of BOLD fMRI experiments examining neural correlates of subjective value. Neuroimage 76, 412–427.
Beck, AT, W.M., MendelsonM, Mock, J, Erbaugh, J., 1961. An inventory for measuring depression. Arch. Gen. Psychiatry 4, 53–63.
Benjamini, Y., Hochberg, Y., 1995. Controlling the false discovery rate—a practical and powerful approach to multiple testing. J Roy. Stat. Soc. B Met. 57, 289–300.
Bernardoni, F., Geisler, D., King, J.A., Javadi, A.H., Ritschel, F., Murr, J., Reiter, A.M.F., Rossner, V., Smolka, M.N., Kiebel, S., Ehrlich, S., 2018. Altered medial frontal feedback learning signals in anorexia nervosa. Biol. Psychiatry 83, 235–243.
Bischoff-Grethe, A., McCurdy, D., Grenesko-Stevens, E., Irvine, L.E., Wagner, A., Yau, W.Y., Fennema-Notestine, C., Wierenga, C.E., Fudge, J.L., Delgado, M.R., Kaye, W.H., 2013. Altered brain response to reward and punishment in adolescents with anorexia nervosa. Psychiatry Res. 214, 331–340.
Bohon, C., Stice, E., 2011. Reward abnormalities among women with full and subthreshold bulimia nervosa: a functional magnetic resonance imaging study. Int. J. Eat. Disord. 44, 585–595.
Botvinick, M.M., 2007. Conflict monitoring and decision making: Reconciling two perspectives on anterior cingulate function. Cogn. Affect Behav. Neurosci. 7, 356–366.
Brett, M., Anton, J., Valabregue, R., Poline, J., 2002. Region of interest analysis using an SPM toolbox,. In: 8th International Conference on Functional Mapping of the Human Brain, Sendai, Japan, NeuroImage.
Brett, M., Penny, W., Kiebel, S., 2004. Introduction to random field theory. In: Frackowiak, R.S.J. (Ed.), Human Brain Function, 2nd ed. Elsevier Academic Press, Amsterdam; Boston, pp. 867–880.
Brooks, S.J., O'Daly, O.G., Uher, R., Friederich, H.C., Giampietro, V., Brammer, M., Williams, S.C., Schioth, H.B., Treasure, J., Campbell, I.C., 2011. Differential neural responses to food images in women with bulimia versus anorexia nervosa. Plos One 6, e22259.
Buhr, K., Dugas, M.J., 2002. The Intolerance of Uncertainty Scale: psychometric properties of the English version. Behav. Res. Ther. 40, 931–945.
Chen, J., Papies, E.K., Barsalou, L.W., 2016. A core eating network and its modulations underlie diverse eating phenomena. Brain Cogn. 110, 20–42.
Clithero, J.A., Rangel, A., 2014. Informatic parcellation of the network involved in the computation of subjective value. Soc. Cogn. Affect. Neurosci. 9, 1289–1302.
Cloninger, C.R., 1994. The temperament and character inventory (TCI): a guide to its development and use. Center for Psychobiology of Personality, 1st ed. Washington University, St. Louis, Mo.
Cowdrey, F.A., Park, R.J., Harmer, C.J., McCabe, C., 2011. Increased neural processing of rewarding and aversive food stimuli in recovered anorexia nervosa. Biol. Psychiatry 70, 736–743.
David, S.P., Ware, J.J., Chu, I.M., Loftus, P.D., Fusar-Poli, P., Radua, J., Munafo, M.R., Ioannidis, J.P., 2013. Potential reporting bias in fMRI studies of the brain. Plos One 8, e70104.
Daw, N.D., O'Doherty, J.P., Dayan, P., Seymour, B., Dolan, R.J., 2006. Cortical substrates for exploratory decisions in humans. Nature 441, 876–879.
DeGuzman, M., Shott, M.E., Yang, T.T., Riederer, J., Frank, G.K.W., 2017. Association of elevated reward prediction error response with weight gain in adolescent anorexia nervosa. Am. J. Psychiatry 174, 557–565.
Ehrlich, S., Geisler, D., Ritschel, F., King, J.A., Seidel, M., Boehm, I., Breier, M., Clas, S., Weiss, J., Marxen, M., Smolka, M.N., Roessner, V., Kroemer, N.B., 2015. Elevated cognitive control over reward processing in recovered female patients with anorexia nervosa. J. Psychiatry Neurosci. 40, 307–315.
Eickhoff, S.B., Stephan, K.E., Mohlberg, H., Grefkes, C., Fink, G.R., Amunts, K., Zilles, K., 2005. A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data. Neuroimage 25, 1325–1335.
Eklund, A., Nichols, T.E., Knutsson, H., 2016. Cluster failure: why fMRI inferences for spatial extent have inflated false-positive rates. Proc. Natl. Acad. Sci. U S A 113, 7900–7905.
Ernst, M., Paulus, M.P., 2005. Neurobiology of decision making: a selective review from a neurocognitive and clinical perspective. Biol. Psychiatry 58, 597–604.
Fassino, S., Abbate-Daga, G., Amianto, F., Leombruni, P., Boggio, S., Rovera, G.G., 2002. Temperament and character profile of eating disorders: a controlled study with the temperament and character inventory. Int. J. Eat. Disord. 32, 412–425.
Fiorillo, C.D., Tobler, P.N., Schultz, W., 2003. Discrete coding of reward probability and uncertainty by dopamine neurons. Science 299, 1898–1902.
First, M.B., S.R., GibbonM, Williams, J.B.W., 2000. Structured Clinical Interview for DSM-IV-Text Revision Axis I Disorders Patient Edition, 4th ed. American Psychiatric Association, Washington, DC.
Flandin, G., Friston, K.J., 2017. Analysis of family-wise error rates in statistical parametric mapping using random field theory. Hum Brain Mapp. https://doi.org/10.1002/hbm.23839. [Epub ahead of print] PubMed PMID: 29091338.
Francis, S., Rolls, E.T., Bowtell, R., McGlone, F., O'Doherty, J., Browning, A., Clare, S., Smith, E., 1999. The representation of pleasant touch in the brain and its relationship with taste and olfactory areas. Neuroreport 10, 453–459.
Frank, G.K., 2013. Altered brain reward circuits in eating disorders: chicken or egg? Curr Psychiatry Rep 15, 396.
Frank, G.K., Collier, S., Shott, M.E., O'Reilly, R.C., 2016. Prediction error and somatosensory insula activation in women recovered from anorexia nervosa. J. Psychiatry Neurosci. 41, 304–311.
Frank, G.K., Kaye, W.H., Carter, C.S., Brooks, S., May, C., Fissell, K., Stenger, V.A., 2003. The evaluation of brain activity in response to taste stimuli—a pilot study and method for central taste activation as assessed by event-related fMRI. J. Neurosci. Methods 131, 99–105.
Frank, G.K., Reynolds, J.R., Shott, M.E., Jappe, L., Yang, T.T., Tregellas, J.R., O'Reilly, R.C., 2012a. Anorexia nervosa and obesity are associated with opposite brain reward response. Neuropsychopharmacology 37, 2031–2046.
Frank, G.K., Reynolds, J.R., Shott, M.E., O'Reilly, R.C., 2011. Altered temporal difference learning in bulimia nervosa. Biol. Psychiatry 70, 728–735.
Frank, G.K., Roblek, T., Shott, M.E., Jappe, L.M., Rollin, M.D., Hagman, J.O., Pryor, T., 2012b. Heightened fear of uncertainty in anorexia and bulimia nervosa. Int. J. Eat. Disord. 45, 227–232.
Garner, D., 2004. Eating Disorder Inventoryt-3 (EDIt-3). Psychological Assessment Resources, Inc., Lutz, Florida.
Geisler, D., Ritschel, F., King, J.A., Bernardoni, F., Seidel, M., Boehm, I., Runge, F., Goschke, T., Roessner, V., Smolka, M.N., Ehrlich, S., 2017. Increased anterior cingulate cortex response precedes behavioural adaptation in anorexia nervosa. Sci. Rep. 7, 42066.
Guarda, A.S., Schreyer, C.C., Boersma, G.J., Tamashiro, K.L., Moran, T.H., 2015. Anorexia nervosa as a motivated behavior: relevance of anxiety, stress, fear and learning. Physiol. Behav. 152, 466–472.
Kaye, W.H., Bulik, C.M., Thornton, L., Barbarich, N., Masters, K., 2004. Comorbidity of anxiety disorders with anorexia and bulimia nervosa. Am. J. Psychiatry 161,

2215–2221.
Kaye, W.H., Fudge, J.L., Paulus, M., 2009. New insights into symptoms and neurocircuit function of anorexia nervosa. Nat. Rev. Neurosci. 10, 573–584.
Kaye, W.H., Wierenga, C.E., Bailer, U.F., Simmons, A.N., Wagner, A., Bischoff-Grethe, A., 2013. Does a shared neurobiology for foods and drugs of abuse contribute to extremes of food ingestion in anorexia and bulimia nervosa? Biol. Psychiatry 73, 836–842.
Keating, C., 2010. Theoretical perspective on anorexia nervosa: the conflict of reward. Neurosci. Biobehav. Rev. 34, 73–79.
Kennerley, S.W., Behrens, T.E., Wallis, J.D., 2011. Double dissociation of value computations in orbitofrontal and anterior cingulate neurons. Nat. Neurosci. 14, 1581–1589.
Knutson, B., Taylor, J., Kaufman, M., Peterson, R., Glover, G., 2005. Distributed neural representation of expected value. J. Neurosci. 25, 4806–4812.
Kolling, N., Behrens, T.E., Mars, R.B., Rushworth, M.F., 2012. Neural mechanisms of foraging. Science 336, 95–98.
Krain, A.L., Gotimer, K., Hefton, S., Ernst, M., Castellanos, F.X., Pine, D.S., Milham, M.P., 2008. A functional magnetic resonance imaging investigation of uncertainty in adolescents with anxiety disorders. Biol. Psychiatry 63, 563–568.
O'Doherty, J.P., 2004. Reward representations and reward-related learning in the human brain: insights from neuroimaging. Curr. Opin. Neurobiol. 14, 769–776.
O'Doherty, J.P., 2014. The problem with value. Neurosci. Biobehav. Rev. 43, 259–268.
O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H., Dolan, R.J., 2003. Temporal difference models and reward-related learning in the human brain. Neuron 38, 329–337.
O'Hara, C.B., Campbell, I.C., Schmidt, U., 2015. A reward-centred model of anorexia nervosa: a focussed narrative review of the neurological and psychophysiological literature. Neurosci. Biobehav. Rev. 52, 131–152.
O'Connor, R, C.C., HawkL., 2004. Confirmatory factor analysis of the sensitivity to punishment and sensitivity to reward questionnaire. Pers. Indiv. Differ. 37, 985–1002.
Oberndorfer, T.A., Frank, G.K., Simmons, A.N., Wagner, A., McCurdy, D., Fudge, J.L., Yang, T.T., Paulus, M.P., Kaye, W.H., 2013. Altered insula response to sweet taste processing after recovery from anorexia and bulimia nervosa. Am. J. Psychiatry 170, 1143–1151.
Rangel, A., Camerer, C., Montague, P.R., 2008. A framework for studying the neurobiology of value-based decision making. Nat. Rev. Neurosci. 9, 545–556.
Reiter, A.M., Heinze, H.J., Schlagenhauf, F., Deserno, L., 2017. Impaired flexible reward-based decision-making in binge eating disorder: evidence from computational modeling and functional neuroimaging. Neuropsychopharmacology 42, 628–637.
Rescorla, R.A., Wagner, A.R., McMaster University Hamilton Ont., 1972. A theory of Pavlovian conditioning: variations in the effectiveness of reinforcement and non-reinforcement. In: Black, A.H., Prokasy, W.F. (Eds.), Classical Conditioning II: Current Research and Theory. Appleton-Century-Crofts, New York, pp. 64–99.
Rolls, E.T., 2015. Taste, olfactory, and food reward value processing in the brain. Prog. Neurobiol. 127–128, 64–90.
Rolls, E.T., McCabe, C., Redoute, J., 2008. Expected value, reward outcome, and temporal difference error representations in a probabilistic decision task. Cereb. Cortex 18, 652–663.
Rushworth, M.F., Behrens, T.E., 2008. Choice, uncertainty and value in prefrontal and cingulate cortex. Nat. Neurosci. 11, 389–397.
Schultz, W., 1998. Predictive reward signal of dopamine neurons. J. Neurophysiol. 80, 1–27.
Schultz, W., 2015. Neuronal reward and decision signals: from theories to data. Physiol. Rev. 95, 853–951.
Schultz, W., Dayan, P., Montague, P.R., 1997. A neural substrate of prediction and reward. Science 275, 1593–1599.
Schultz, W., Tremblay, L., Hollerman, J.R., 2000. Reward processing in primate orbitofrontal cortex and basal ganglia. Cereb. Cortex 10, 272–284.
Seymour, B., O'Doherty, J.P., Dayan, P., Koltzenburg, M., Jones, A.K., Dolan, R.J., Friston, K.J., Frackowiak, R.S., 2004. Temporal difference models describe higher-order learning in humans. Nature 429, 664–667.
Shenhav, A., Botvinick, M.M., Cohen, J.D., 2013. The expected value of control: an integrative theory of anterior cingulate cortex function. Neuron 79, 217–240.
Spielberger, C.D., G.R.L., LusheneR.E., 1970. STAI Manual for the State Trait Anxiety Inventory. Consulting Psychologists Press, Palo Alto, CA.
Sternheim, L., Startup, H., Schmidt, U., 2015. Anxiety-related processes in anorexia nervosa and their relation to eating disorder pathology, depression and anxiety. Adv. Eat. Disord. 3, 13–19.
Tobler, P.N., Fiorillo, C.D., Schultz, W., 2005. Adaptive coding of reward value by dopamine neurons. Science 307, 1642–1645.
Tremblay, L., Schultz, W., 1999. Relative reward preference in primate orbitofrontal cortex. Nature 398, 704–708.
Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., Mazoyer, B., Joliot, M., 2002. Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. Neuroimage 15, 273–289.
Uher, R., Brammer, M.J., Murphy, T., Campbell, I.C., Ng, V.W., Williams, S.C., Treasure, J., 2003. Recovery and chronicity in anorexia nervosa: brain activity associated with differential outcomes. Biol. Psychiatry 54, 934–942.
Uher, R., Murphy, T., Brammer, M.J., Dalgleish, T., Phillips, M.L., Ng, V.W., Andrew, C.M., Williams, S.C., Campbell, I.C., Treasure, J., 2004. Medial prefrontal cortex activity associated with symptom provocation in eating disorders. Am. J. Psychiatry 161, 1238–1246.
Wager, T.D., Atlas, L.Y., Botvinick, M.M., Chang, L.J., Coghill, R.C., Davis, K.D., Iannetti, G.D., Poldrack, R.A., Shackman, A.J., Yarkoni, T., 2016. Pain in the ACC. Proc. Natl. Acad. Sci. U S A 113, E2474–E2475.
Wagner, A., Aizenstein, H., Venkatraman, V.K., Bischoff-Grethe, A., Fudge, J., May, J.C., Frank, G.K., Bailer, U.F., Fischer, L., Putnam, K., Kaye, W.H., 2010. Altered striatal response to reward in bulimia nervosa after recovery. Int. J. Eat. Disord. 43, 289–294.
Wagner, A., Aizenstein, H., Venkatraman, V.K., Fudge, J., May, J.C., Mazurkewicz, L., Frank, G.K., Bailer, U.F., Fischer, L., Nguyen, V., Carter, C., Putnam, K., Kaye, W.H., 2007. Altered reward processing in women recovered from anorexia nervosa. Am. J. Psychiatry 164, 1842–1849.
Walsh, B.T., 2013. The enigmatic persistence of anorexia nervosa. Am. J. Psychiatry 170, 477–484.
Worsley, K.J., Taylor, J.E., Tomaiuolo, F., Lerch, J., 2004. Unified univariate and multivariate random field theory. Neuroimage 23 (Suppl 1), S189–S195.