Archival Report

Hunger Does Not Motivate Reward in Women Remitted from Anorexia Nervosa

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ABSTRACT

BACKGROUND: Hunger enhances sensitivity to reward, yet individuals with anorexia nervosa (AN) are not motivated to eat when starved. This study investigated brain response to rewards during hunger and satiated states to examine whether diminished response to reward could underlie food restriction in AN.

METHODS: Using a delay discounting monetary decision task known to discriminate brain regions contributing to processing of immediate rewards and cognitive control important for decision making regarding future rewards, we compared 23 women remitted from AN (RAN group; to reduce the confounding effects of starvation) with 17 healthy comparison women (CW group). Monetary rewards were used because the rewarding value of food may be confounded by anxiety in AN.

RESULTS: Interactions of Group (RAN, CW) × Visit (hunger, satiety) revealed that, for the CW group, hunger significantly increased activation in reward salience circuitry (ventral striatum, dorsal caudate, anterior cingulate cortex) during processing of immediate reward, whereas satiety increased activation in cognitive control circuitry (ventrolateral prefrontal cortex, insula) during decision making. In contrast, brain response in reward and cognitive neurocircuitry did not differ during hunger and satiety in the RAN group. A main effect of group revealed elevated response in the middle frontal gyrus for the RAN group compared with the CW group.

CONCLUSIONS: Women remitted from AN failed to increase activation of reward valuation circuitry when hungry and showed elevated response in cognitive control circuitry independent of metabolic state. Decreased sensitivity to the motivational drive of hunger may explain the ability of individuals with AN to restrict food when emaciated. Difficulties in valuating emotional salience may contribute to inabilities to appreciate the risks inherent in this disorder.

Keywords: Anorexia nervosa, Decision making, Delay discounting, Eating disorders, Functional MRI, Reward processing

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Anorexia nervosa (AN) is characterized by restricted eating, severe emaciation, and disturbed body image (1). Individuals with AN can severely restrict their caloric intake for years. In contrast, most people have difficulty adhering to a diet, with a high rate of recidivism after losing weight. How are individuals with AN able to ignore signals regarding hunger that otherwise motivate eating, even when severely emaciated?

One clue may be the tendency for individuals with AN to be anhedonic, finding little in life that is rewarding aside from the pursuit of weight loss. Individuals with AN are often temperamentally inhibited, constrained, and overconcerned with consequences (2). Such behaviors suggest that disturbances of reward or pleasure (3,4), coupled with alterations in neurocircuitry supporting inhibition and cognitive control, underlie behavior in individuals with AN (2,5,6), such as a propensity to override signals regarding hunger and energy deficits. For example, adolescents who are ill with AN (4) and adults with remitted AN (3) failed to differentiate monetary wins and losses

in ventral striatal regions, suggesting an impaired ability to identify the emotional significance of salient stimuli. This finding is consistent with studies showing limbic regions are underactive for motivational behavior in individuals who are ill with AN (6).

Delay discounting tasks are a common behavioral metric for examining decision making in relation to rewarding stimuli because they assess the degree to which participants suppress the desire for smaller-sooner rewards to obtain larger rewards at a later time. Behavioral studies of delay discounting have shown that both adults who are ill with AN and individuals with obsessive-compulsive disorder (7) have an enhanced ability to delay reward compared with healthy peers (8), whereas increased discounting is demonstrated in most disorders (e.g., substance abuse, attention-deficit/hyperactivity disorder, obesity).

Functional neuroimaging studies of delay discounting (9) have identified several brain systems involved in emotional

and cognitive valuation of a range of salient stimuli, including food, money, and drugs (10,11). The ventral striatum, rostral (i.e., ventromedial prefrontal cortex) and dorsal anterior cingulate cortex (ACC), caudate nucleus, and posterior cingulate cortex (PCC) are associated with reward valuation, especially for more immediate rewards (9,12,13). Another network that includes the dorsolateral prefrontal cortex (DLPFC; including the middle frontal gyrus [MFG]), ventrolateral prefrontal cortex (VLPFC), insula, and posterior parietal cortex is associated with cognitive control and is consistently engaged in delay discounting tasks, with less dependence on whether rewards are immediate or not (9,12,13).

The present study is the first to investigate delay discounting neural processing in individuals remitted from AN. Because the response to food in individuals with AN may be confounded by poorly understood factors such as anxiety, obsessions, or body image distortions, we reasoned that response to money might be a better test of response to salient rewarding stimuli. We examined only adults who were remitted from AN to avoid the confounding effects of malnutrition and because studies (2) show traits contributing to disordered eating (e.g., anxiety, harm avoidance) persist after recovery.

Hunger and satiety may influence behavioral choice by manipulating the appetitiveness of food and monetary cues in healthy participants. Imaging studies (14,15) suggest that hunger increases the motivational aspects of stimuli by activating regions associated with reward or reducing top-down inhibitory control. In contrast, satiety may reduce the rewarding value of stimuli, perhaps through decreased responsiveness of limbic circuitry or greater cognitive control. Hunger in healthy participants increases rates of delay discounting (16); reduces risk aversion (17); and can lead to overvaluation of unhealthy, higher calorie foods (18). In animals, food deprivation enhances sensitivity to drugs of abuse (19,20), suggesting hunger enhances preference for more immediate rewards.

The effects of fasting on frontostriatally mediated neural substrates of decision making have not been assessed in individuals with AN or healthy volunteers. To examine whether diminished response to reward could underlie food restriction in AN, this study used functional magnetic resonance imaging (MRI) to investigate brain activation during delay discounting in healthy women and adults remitted from AN when hungry and satiated. The purpose of the present study was to 1) elucidate the modulation of activation in regions involved in delay discounting by hunger and satiety and 2) determine whether healthy women and adults remitted from AN differ in their response to hunger and satiety during delay discounting. We hypothesized an interaction between group and metabolic state whereby adults remitted from AN would show reduced response to immediate reward when hungry in regions associated with reward valuation and increased response to decision making independent of hunger state in regions associated with cognitive control. Revealing brain reward mechanisms in adults remitted from AN will advance understanding of the neurobiology underlying the puzzling symptoms of AN and help guide development of disease-specific treatment strategies.

METHODS AND MATERIALS

Subjects

Subjects were 23 women remitted from AN (RAN group; 16 restricting subtype, 7 restricting-purging subtype), with remittance defined (3) as maintaining a weight >85% of average body weight; regular menstrual cycles; and no binge eating, purging, or restrictive eating patterns for at least 1 year before the study. These subjects were compared with 17 age-matched and weight-matched healthy comparison women (CW group) (Table 1). The RAN participants were recruited from a larger eating disorder study at the University of California, San Diego, and the CW participants were recruited from the community through local advertisements. Any previous lifetime DSM-IV Axis I diagnosis was determined (Table 1); no subject had a current DSM-IV diagnosis or history of alcohol or drug abuse or dependence 3 months before the study, medical or neurologic concerns, or conditions that were contraindications to MRI. None of the participants took psychotropic medication within 3 months before the study. The study was conducted according to the institutional review board regulations of the University of California, San Diego. Written informed consent was obtained from all subjects following a complete description of the study.

Experimental Design

Participants performed a delay discounting task (Figure S1 in Supplement 1) (9) during functional MRI on one of two scanners on two visits 24 hours apart. For the hungry state, participants fasted for 16 hours before the scan session. During the satiated state, participants consumed a personalized, standardized breakfast (determined by the individual's body mass index and containing 30% of overall daily caloric needs or approximately 450 kcal, with a macronutrient distribution of 53% carbohydrates, 32% fat, and 15% protein) 2 hours before the 9 AM scan session. Subjects were housed and meals were provided by the University of California, San Diego, Clinical & Translational Research Institute to ensure 100% compliance with this diet. The order of visits was randomized across participants and performed in the early follicular phase.

Delay Discounting Task

Two functional runs of 488 sec each were performed during each visit. For each 15-sec trial, participants were presented with two choices on either side of the screen; each choice included a monetary amount and a time delay for receiving this amount (Figure S1 in Supplement 1). The first two trials within each run were fixed to allow participants to acclimate to the task. The first trial required participants to choose between the same dollar amount available at two different delays (i.e., $27.10 available in 1 week vs. $27.10 available in 1 month) and two dollar amounts in which the smaller earlier amount was <1% of the delayed value (i.e., $0.16 today vs. $34.04 in 6 weeks). The remaining 30 trials within each run were randomly ordered. The following parameters were used: the delay to the early reward, d, was selected from the set (today, 2 weeks, 4 weeks). The delay between the late reward, d', and the early reward (i.e., $d' - d$) was selected from the set (2 weeks, 4 weeks), provided that the late reward occurred no

more than 6 weeks from the time of the study (i.e., trials with the early choice at 4 weeks and with a 4-week delay for the later choice were excluded). The percent difference in amount between the two rewards (i.e., ($R' − $R)/$R) was selected from the set (3%, 5%, 10%, 15%, 25%, 35%). Consistent with McClure *et al.* (9), at the end of the experiment, one completed trial was chosen at random, and the participant received the selected reward at the specified temporal delay.

Delay Discounting Task Performance

To determine whether choice behavior differed between the two groups, a Group × Visit × Percent Monetary Difference linear mixed effects (LME) analysis was computed using the nlme package in R (http://www.r-project.org (R Core Team, R Foundation for Statistical Computing, Vienna, Austria)). To examine group differences in response time secondary to choice difficulty, data were submitted to a Group × Visit × Difficulty (hard, easy) LME analysis.

MRI Protocol

Functional images were acquired axially using T2*-weighted echo planar imaging with an eight-channel head coil. Imaging data were collected on one of two scanners: a 3-Tesla Signa HDx (GE Medical Systems, Milwaukee, Wisconsin) (repetition time [TR] = 2000 msec, echo time [TE] = 30 msec, flip angle = 80°, matrix size = 64 × 64, array spatial sensitivity encoding technique factor = 2, 40 2.6-mm ascending interleaved slices with a .4-mm gap, 244 volumes) and a 3-Telsa GE Discovery MR750 (GE Medical Systems) (TR = 2000 msec, TE = 30 msec, flip angle = 80°, matrix size = 64 × 64, array spatial sensitivity encoding technique factor = 2, 40 3.0-mm ascending interleaved

slices, 244 volumes). The first four volumes of each run were discarded to discount T1 saturation. Echo planar imaging–based field maps were acquired to correct for susceptibility-induced geometric distortions. High-resolution T1-weighted fast spoiled gradient-recalled echo anatomic images (Signa HDx, TR = 7.7 msec, TE = 2.98 msec, flip angle = 8°, matrix size = 192 × 256, 172 1-mm slices; MR750, TR = 8.1 msec, TE = 3.17 msec, flip angle = 8°, matrix size = 256 × 256, 172 1-mm slices) were obtained in the sagittal plane for subsequent spatial normalization and activation localization. Multisite imaging studies suggest that interparticipant variance far outweighs site or magnet variance. To control for potential differences resulting from magnet hardware, groups were balanced across magnets (Table 1), each participant was scanned on the same scanner for both visits, and subject was nested within scanner and treated as a random effect in subsequent analyses.

MRI Statistical Analysis

Functional images were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (National Institutes of Health, Bethesda, Maryland), and group analyses were performed in R. Echo planar images were motion-corrected and aligned to high-resolution anatomic images with align_epi_anat.py in AFNI. Outliers were generated using AFNI 3dToutcount. Volumes with >10% of the voxels marked as outliers were censored from subsequent analyses. Approximately 2.3% of all volumes were censored overall (for all subjects, mean = 11.0 volumes; SD = 4.5; range = 1–25). Registration to the Montreal Neurological Institute 152 atlas was performed using the Non-linear Image Registration Tool FNIRT, part of the FMRIB Software Library (http://fsl.fmrib.ox.

Table 1. Participant Demographics and Characteristics

Characteristic	CW (*n* = 17)		RAN (*n* = 23)		*t* or χ^2 Value	*df*	*p* Value	Cohen's *d*
Scanner					.00	1.00		
Signa Excite	10		14					
MR 750	7		9					
Demographics								
Age	25.3 ± 1.4	[20.6–40.9]	27.7 ± 1.6	[19.1–45.7]	−1.2	38.0	.3	−.4
BMI	22.6 ± .7	[18.5–29.5]	21.6 ± .3	[18.9–24.2]	1.4	24.6	.2	.5
Education (years)	15.6 ± .3	[13–19]	16.8 ± .7	[13–27]	−1.6	29.3	.1	−.5
WASI IQ estimate	112.1± 3.0	[89–136]	112.7±2.9	[85–133]	−.2	35.9	.9	−.1
Estradiol (pg/mL)[a]	15.3 ± 3.1	[1.0–37.0]	19.5 ± 3.3	[1.0–45.0]	−.9	35.4	.4	−.3
Lifetime Diagnoses (No.)								
MDD	0		17		18.9	1	<.001	
Any anxiety disorder[b]	0		8		5.4	1	.02	
OCD	0		4		1.6	1	.20	
Past drug/alcohol abuse/dependence[a,c]	0		3		.9	1	.4	
Alcohol (%)[a]	0		7.9		.9	1	.4	
Cannabis (%)[a]	0		2.6		.0	1	1.0	

Entries are of the form mean ± SEM [minimum–maximum]. Statistical comparisons were via either Welsh *t* tests or χ^2 test for equality of proportions.

BMI, body mass index; WASI, Wechsler Abbreviated Scale of Intelligence; CW, healthy comparison women; MDD, major depressive disorder; OCD, obsessive-compulsive disorder; RAN, women remitted from anorexia nervosa.

[a]One member of CW group and one member of RAN group did not complete this assessment.

[b]Defined as having had at least one prior episode of panic disorder, phobia, posttraumatic stress disorder, generalized anxiety disorder, or any anxiety disorder not otherwise specified.

[c]Defined as any history of abuse or dependence per DSM-IV criteria.

Table 2. Analysis of Variance Results Within Regions of Interest Demonstrating a Main Effect of Group, a Main Effect of Visit, and an Interaction of Group with Visit for the Valuation and Cognition Circuitry

| | | | | | Peak MNI Coordinates | | | | | Post Hoc Comparisons | | |
Region	L/R	BA	Volume (μL)	Minimum cluster size (μL)	x	y	z	Peak F	Cohen's d	Contrast	z	p
							Valuation Circuitry (Beta Regressor)					
Group (RAN vs. CW)												
Anterior cingulate	L	33/24	1080	240	−12	30	18	13.3	1.2	NS		
	R	33/24	376	240	16	18	28	6.7	0.8	NS		
Posterior cingulate	L	23	296	226	−8	−26	32	9.0	1.0	NS		
	R	31	880	218	14	−24	34	9.2	1.0	NS		
Visit (hungry vs. satiated)												
None												
Group × Visit												
Ventral striatum	L		576	128	−6	12	−4	9.4	1.0	Satiated: RAN > CW	2.2	.1
	R		1136	128	16	22	−8	8.1	.9	CW: hungry > satiated	2.7	.04
										Satiated: RAN > CW	2.8	.03
Dorsal anterior caudate	L		3192	168	−18	22	8	15.5	1.3	CW: hungry > satiated	2.4	.08
										Satiated: RAN > CW	2.7	.03
	R		4096	168	16	14	6	16.2	1.3	CW: hungry > satiated	2.8	.02
										Satiated: RAN > CW	3.2	.008
Anterior cingulate	L	32/24	1832	240	−6	36	−4	9.7	1.0	CW: hungry > satiated	2.4	.07
										Satiated: RAN > CW	3.1	.01
		33/24	1800		−8	18	22	11.0	1.1	CW: hungry > satiated	2.8	.02
										Satiated: RAN > CW	3.3	.01
		24	984		−2	0	46	7.1	.8	CW: hungry > satiated	2.8	.03
										Satiated: RAN > CW	3.0	.01
	R	33/24/32	6408	240	10	14	28	18.7	1.4	CW: hungry > satiated	3.4	.003
										Satiated: RAN > CW	3.8	<.001
Posterior cingulate	L	31	2112	226	−6	−32	34	7.6	.9	NS		
	R	31/23/24	4296	218	4	−38	30	8.8	1.0	NS		
							Cognitive Circuitry (Delta Regressor)					
Group (RAN vs. CW)												
Middle frontal gyrus	L	8	1144	304	−38	30	30	10.6	1.0	RAN > CW	2.8	.005
		6	528		−48	8	40	7.1	1.0	NS		
		6	376		−38	20	54	13.1	1.2	NS		
	R	6/8	2040	304	34	22	60	11.4	1.1	RAN > CW	2.9	.004
		6	384		50	8	42	8.7	0.9	NS		
Visit (hungry vs. satiated)												
Middle frontal gyrus	L	6/8	4920	304	−32	12	42	15.3	1.3	Satiated > hungry	2.9	.004
	R	8	312	304	38	24	34	7.4	.9	NS		

Table 2. Continued

					Peak MNI Coordinates					Post Hoc Comparisons		
Region	L/R	BA	Volume (µL)	Minimum cluster size (µL)	x	y	z	Peak F	Cohen's d	Contrast	z	p
Insula	L	13	568	224	−37	2	2	13.2	1.2	Satiated > hungry	3.6	<.001
		13	384		−26	20	−4	8.1	.9	Satiated > hungry	2.7	.008
		13	248		−32	−16	0	9.1	1.0	Satiated > hungry	2.9	.004
Ventrolateral prefrontal cortex	L	44/45	3000	240	−54	18	14	14.0	1.2	Satiated > hungry	2.8	.005
	R	45	240	224	56	26	20	7.6	.9	NS		
Group × Visit												
Middle frontal gyrus	L	6	600	304	−30	8	62	11.1	1.1	CW: hungry > satiated	2.6	.04
										Satiated: RAN > CW	2.7	.03
Insula	L	13	264	224	−40	−2	8	9.5	1.0	CW: satiated > hungry	3.6	.002
	R	13	456	224	40	10	−4	8.5	.9	CW: satiated > hungry	3.1	.009
		13	320		34	8	8	10.0	1.0	NS		
Ventrolateral prefrontal cortex	R	45/47	264	224	38	26	−6	8.7	.9	CW: satiated > hungry	2.9	.02
Superior parietal cortex	L		544	256	−22	−50	38	13.0	1.2	NS		
	R		408	248	22	−54	48	9.0	1.0	NS		

Coordinates are presented in RAI format. Small volume correction was determined with Monte Carlo simulations (via Analysis of Functional Neuroimages 3dClustSim) to guard against false-positive results. Post hoc analyses were conducted using glht from the multcomp package in R to calculate general linear hypotheses using Tukey's all-pair comparisons.

BA, Brodmann area; CW, healthy comparison women; L, left; MNI, Montreal Neurological Institute; NS, not significant; R, right; RAI, right anterior inferior; RAN, women remitted from anorexia nervosa.

ac.uk/fsl/; FMRIB Analysis Group, University of Oxford, Oxford, United Kingdom). The modeled hemodynamic responses were subsequently scaled so that beta weights would be equivalent to percent signal change. Data were spatially blurred with a 4.2-mm full-width at half maximum spatial filter.

Statistical analyses were performed based on the approach in McClure *et al.* (9) using two separate general linear models, with individual events (i.e., onset of each choice trial) modeled using the AFNI SPMG3 function, which convolves the hemodynamic response with a gamma variate basis function. To model reward valuation response (e.g., incentive of immediate rewards or impatience), the first general linear model (i.e., beta regressor) included only decision trials in which the early reward option was available immediately (i.e., "Today"). To model cognitive control response (e.g., deliberate decision making or patience), a second general linear model (i.e., delta regressor) included all decision trials. Six motion parameters (three rotations and three translations) were used as nuisance regressors to account for motion artifact.

Regions of interest (ROIs) were based on prior findings (9,12,13). The ROIs associated with valuation included the ventral striatum, dorsal anterior caudate, rostral (also known as ventromedial prefrontal cortex) and dorsal ACC, and PCC. The ROIs associated with cognitive control included the superior posterior parietal cortex, MFG (including the DLPFC and premotor cortex), insula, and VLPFC (see Supplement 1 for details).

We employed a Group (RAN, CW) × Visit (hungry, satiated) LME analysis in R for the valuation and cognitive models separately within their respective ROIs. Each ROI was treated as a search region. Subjects were nested within scanner and treated as random effects, with Group and Visit as fixed effects. Small volume correction was determined with Monte Carlo simulations (via AFNI 3dClustSim) to guard against false-positive results. Minimum cluster sizes required to achieve an a posteriori ROI-wise probability of $p < .05$, with an a priori voxel-wise probability of $p < .05$ are listed in Table 2. Post hoc analyses were conducted using glht from the multcomp package in R to calculate general linear hypotheses using Tukey's all-pair comparisons (21). Within the RAN group, exploratory logistic regressions using the mean percent signal change within each significant cluster resulting from the Group × Visit LME analysis and presence/absence of a lifetime history of major depressive disorder or anxiety disorder were performed separately for each visit to determine whether past psychiatric morbidity influenced current results.

RESULTS

Demographics and Clinical Assessments

Individuals within the RAN and CW groups were of similar age, body mass index, education, intelligence, and history of alcohol or drug use (Table 1). Consistent with previous findings (2), the RAN group had a significantly higher frequency of lifetime major depressive disorder or anxiety disorder.

Behavioral Analysis

Assessments Before and After Scanning. Participants reported significantly greater hunger during the hungry condition relative to the satiated condition (Figure 1 and Table S1 in Supplement 1).
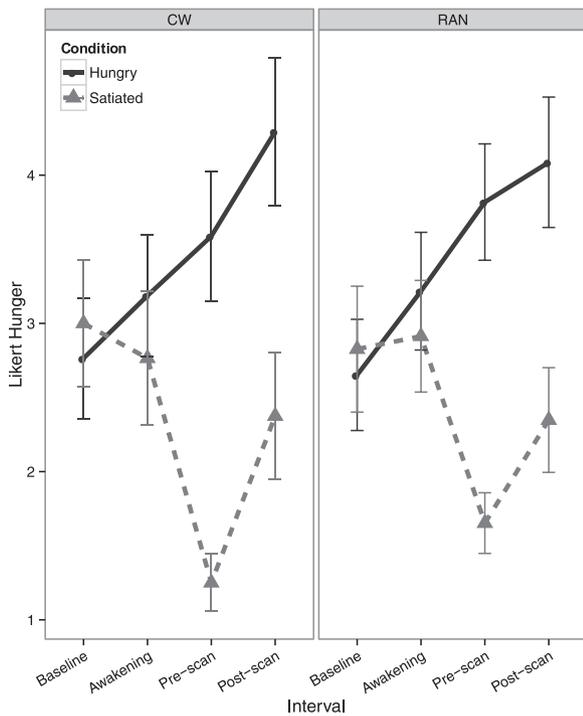
Figure 1. Line graphs reflecting self-report Likert visual analog scale values. Line graph of self-report measures of hunger before and after scanning shows a main effect of Visit [$F_{1,111} = 123.2$, $p < .001$, $d = 3.6$] and of Interval [$F_{1,111} = 12.7$, $p \leq .001$, $d = 1.1$] resulting from a Group (RAN, CW) $\times$ Visit (hungry, satiated) $\times$ Interval period (prescan, postscan) linear mixed effects. Participants reported greater hunger during the hungry condition relative to the satiated condition ($z = 6.0$, $p < .001$); participants also tended to be more hungry at the postscan interval relative to the prescan interval ($z = 1.8$, $p = .08$). Error bars represent the standard error. CW, healthy comparison women; RAN, women remitted from anorexia nervosa.

Delay Discounting Task Performance. Participants were significantly less likely to choose the early option for choices with larger differences in the size of the monetary outcomes (Figure 2A). No significant group differences were found in choice behavior. The CW group responded significantly more slowly when satiated than when hungry, indicating greater deliberation to make a choice (Figure 2B). Response time in the RAN group when satiated was similar to the CW group but was not significantly faster when hungry.

ROI Analyses

Valuation Circuitry. For the valuation circuitry (e.g., modeled brain response for choices including an immediate reward), we found a significant interaction of Group with Visit within the bilateral ventral striatum, dorsal anterior caudate, rostral and dorsal aspects of the ACC, and PCC (Table 2 and Figure 3A). Post hoc analyses revealed that for all but the left ventral striatum, the CW group activated significantly more to immediate reward when hungry relative to when satiated, and the CW response was less than the RAN response when satiated in all ROIs. The RAN response did not differ significantly between hunger and satiety (all $p > .14$), suggesting that these brain areas are less sensitive to metabolic state
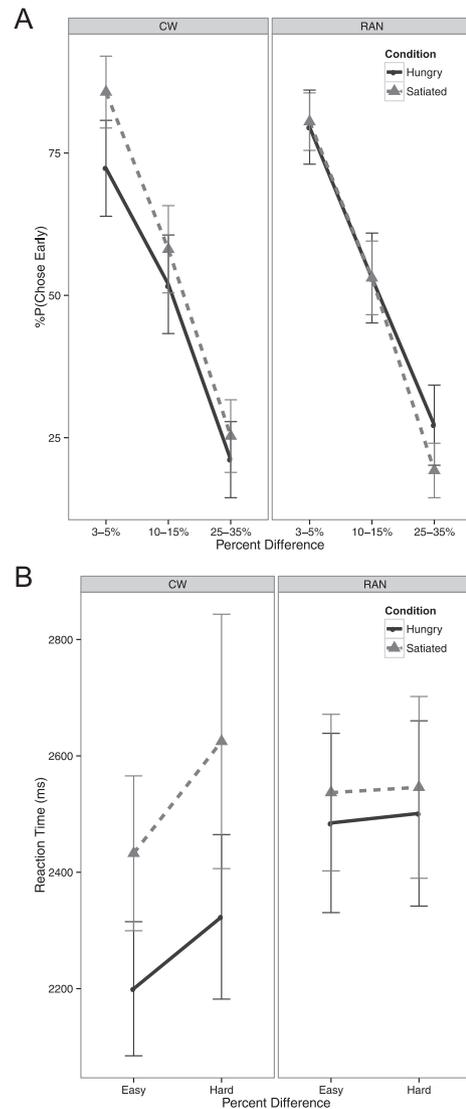
Figure 2. Plots showing group differences in behavioral choice and their modulation by satiety. Hard choices were defined as choices in which the probability of choosing the smaller-sooner reward was approximately 50% and corresponded to difference in dollar amounts of 10%–15%; all other choices were defined as easy. **(A)** We examined the probability of choosing the early reward with respect to the percent difference in amount between the early and later choices. Participants showed a main effect of percent difference [$F_{2,190} = 173.0$, $p < .001$, $d = 4.2$], such that participants were less likely to choose the early option as the percent monetary difference between choices increased (from 3%–5% to 10%–15%, $z = 3.1$, $p = .006$; from 3%–5% to 25%–35%, $z = 7.8$, $p < .001$; from 10%–15% to 25%–35%, $z = 4.7$, $p < .001$). There was also a significant interaction of Group with Visit [$F_{1,190} = 4.2$, $p = .04$, $d = .7$], but the post hoc analyses were not significant (all $p > .6$). **(B)** For reaction time, there was a main effect of Visit [$F_{1,114} = 5.1$, $p = .03$, $d = .7$], with participants showing a tendency for faster response times when hungry than when satiated ($z = 1.7$, $p = .09$). There was also a trend for an interaction of Group with Visit [$F_{1,114} = 3.0$, $p = .09$, $d = .6$]. Post hoc analyses found that this trend was due to CW having a faster response time when hungry ($z = 2.8$, $p = .02$); RAN did not show this effect. CW, healthy comparison women; RAN, women remitted from anorexia nervosa.

A   VALUATION CIRCUITRY

B   COGNITIVE CIRCUITRY
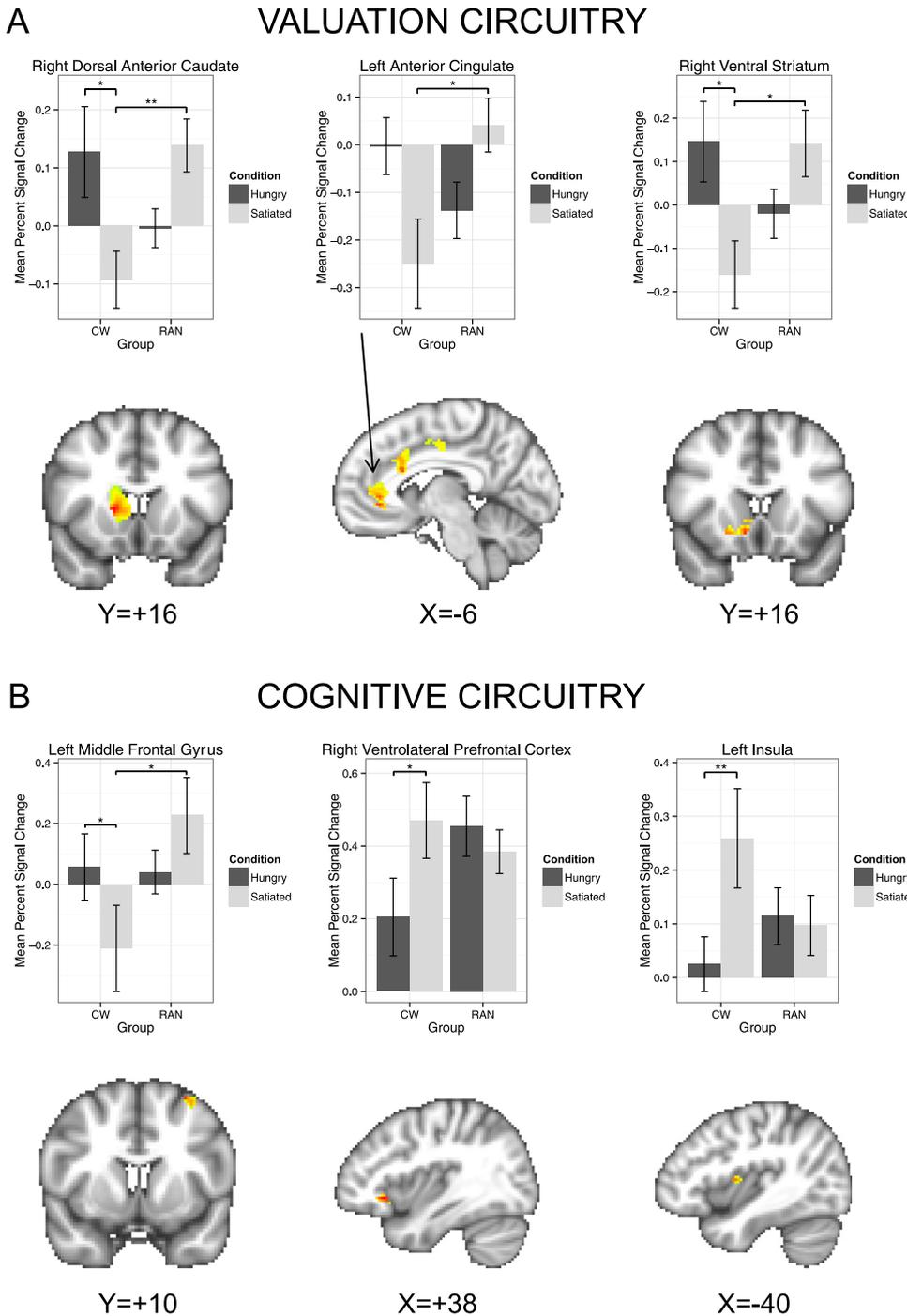
Figure 3. Plots demonstrating a significant Group × Visit interaction within representative regions of interest. **(A)** Valuation-related regions of interest for the beta ("Today") regressor. Left: Within the right dorsal anterior caudate, CW had an elevated response when hungry relative to when satiated ($z = 2.8$, $p = .02$); when satiated, RAN had a greater response relative to CW ($z = 3.2$, $p = .008$). Middle: Within the rostral zone of the left anterior cingulate, CW had an elevated response when hungry relative to when satiated ($z = 2.4$, $p = .07$); when satiated, RAN had a greater response relative to CW ($z = 3.3$, $p = .01$). Right: Within the right ventral striatum, CW had a greater response when hungry than when satiated ($z = 2.7$, $p = .04$); when satiated, RAN had a greater response than CW ($z = 2.8$, $p = .03$). **(B)** Cognitive-related regions of interest for the delta ("All Decisions") regressor. Left: Within the left middle frontal gyrus, CW responded more strongly when hungry than when satiated ($z = 2.6$, $p = .04$); when satiated, RAN responded more robustly CW ($z = 2.7$, $p = .03$). Middle: Within the right ventrolateral prefrontal cortex, CW responded more strongly when satiated than when hungry ($z = 2.9$, $p = .02$). Right: Within the left insula, CW responded more strongly when satiated than when hungry ($z = 3.6$, $p = .002$). Error bars represent the standard error for each group. *$p < .05$; **$p < .01$. CW, healthy comparison women; RAN, women remitted from anorexia nervosa.

when determining the value of rewarding stimuli. Main effects of Group and Visit did not reach statistical significance in any ROI based on post hoc analysis.

Cognitive Circuitry. Satiety differentially modulated cognitive control response by group during intertemporal choice across all trials. We found a significant interaction of Group with Visit for the left MFG, bilateral insula, right VLPFC, and

bilateral superior parietal cortex (Table 2 and Figure 3B). Post hoc analyses revealed that within the bilateral insula and right VLPFC, the CW group responded significantly more strongly when satiated relative to when hungry, suggesting greater cognitive control when sated. Within the left MFG, the significant interaction was associated both with stronger response for the CW group when hungry relative to when satiated and with stronger response for the RAN group than
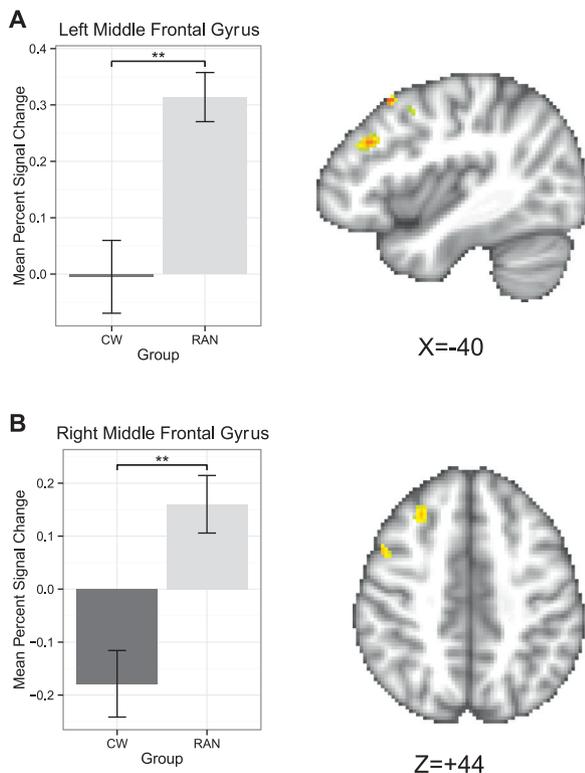
Figure 4. Regions of interest associated with cognition showing a main effect of Group for the delta regressor. **(A)** Within the left middle frontal gyrus, RAN responded more robustly than CW ($z = 2.8$, $p = .005$). **(B)** Similarly, RAN responded more robustly than CW within the right middle frontal gyrus ($z = 2.9$, $p = .004$). Error bars represent the standard error for each group. **$p < .01$. CW, healthy comparison women; RAN, women remitted from anorexia nervosa.

the CW group when satiated. Post hoc analyses for the parietal cortex ROI were not significant. Several clusters within the MFG demonstrated a significant main effect of Group (Figure 4); the RAN group responded more strongly than the CW group, suggesting elevated cognitive control in the RAN group regardless of satiety or hunger. Finally, a main effect of Visit was detected within the bilateral MFG, the left insula, and the bilateral VLPFC (Figure 5) secondary to a greater response to decision trials when satiated relative to when hungry.

Relationship Between Blood Oxygen Level–Dependent Response and Psychiatric History. Logistic regressions between blood oxygen level–dependent response during delayed discounting and presence of a lifetime diagnosis of either major depressive disorder or an anxiety disorder did not survive correction for multiple comparisons.

DISCUSSION

Metabolic state had a differential effect on brain response to delay discounting in the CW group compared with the RAN group. For the CW group, hunger increased brain response in reward salience circuitry, whereas satiety increased response in circuitry responsible for cognitive control during decision making. This finding is consistent with behavioral studies

showing hunger enhances preference for immediate reward and reduces risk-averse behavior (17). In contrast, hunger and satiety in the RAN group did not result in significant changes in valuation or cognitive neural circuitry, revealing insensitivity to metabolic state during delay discounting. This finding
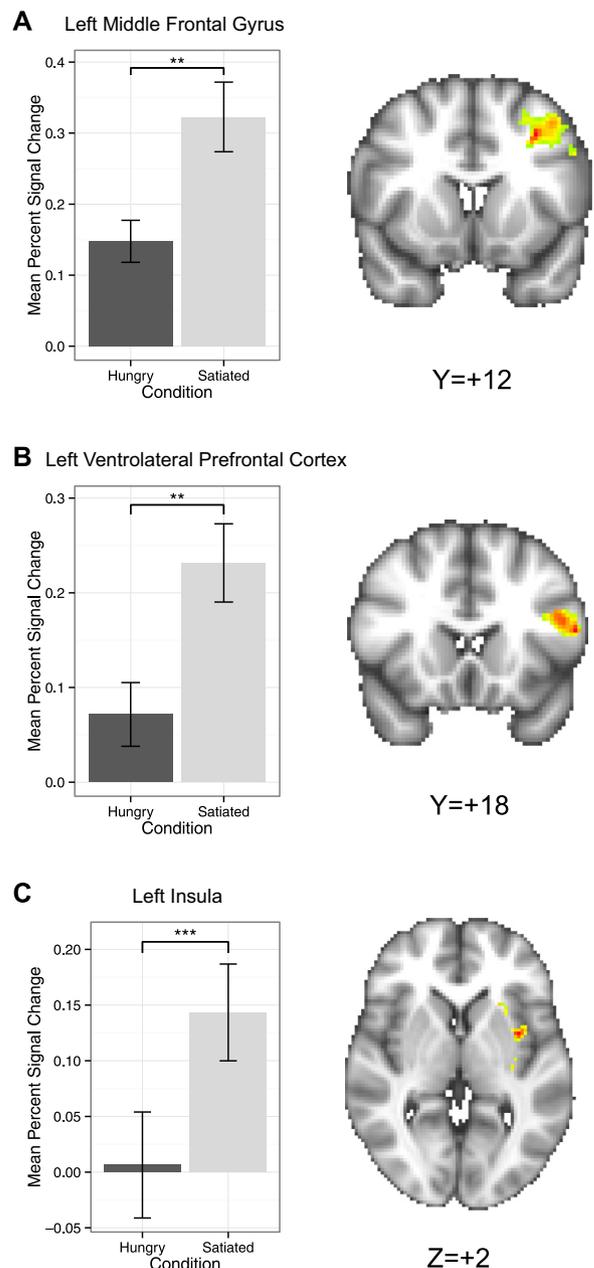
Figure 5. Regions of interest associated with cognition showing a main effect of Visit for the delta regressor. **(A)** Within the left middle frontal gyrus, there was a significantly greater response when satiated than when hungry ($z = 2.9$, $p = .004$). **(B)** Within the left ventrolateral prefrontal cortex, there was a greater response when participants were satiated than when hungry ($z = 2.8$, $p = .005$). **(C)** Similarly, participants exhibited a greater response within the left insula when satiated than when hungry ($z = 3.6$, $p < .001$). Error bars represent the standard error for each group. **$p < .01$; ***$p < .001$.

suggests that individuals remitted from AN are less influenced by motivation of hunger when making decisions about salient stimuli.

Valuation Circuitry

Increased activation in valuation-related brain regions in the CW group when hungry suggests that metabolic state influences decision making by making immediate rewards more appetitive. The CW subjects were quicker to make a choice (Figure 2B) when hungry, suggesting that they engaged in less deliberation when making decisions. Limbic and paralimbic regions such as the ventral striatum, anterior caudate, rostral ACC, and PCC have been associated with the preferential valuation of immediate outcomes in delay discounting (9,12) specifically related to signaling reward expectancy for monetary, social, or taste rewards (22,23); conflict monitoring; and encoding valence (24,25).

Neuroimaging studies that manipulate satiety have demonstrated hunger-enhanced responses to appetitive tastes or food pictures in several limbic regions, including the orbitofrontal cortex and insula (26,27). People naturally favor larger over smaller rewards and rewards received sooner rather than later (28). This is the first imaging study to show that hunger can also elevate the valuation response to financial cues, further demonstrating that metabolic state plays an important role in the modulation of the brain's response to reward. The powerful effect of hunger on neural circuits may have important implications for treatment of substance abuse or obesity. People with these disorders, which may be related to enhanced reward response or reduced cognitive control (29), may be particularly susceptible to hungry states.

The lack of difference between brain responses in valuation or cognitive regions in RAN subjects when hungry versus satiated suggests a failure to integrate homeostatic state into decision making. The finding of altered response to salient stimuli in RAN subjects is consistent with other studies that have not controlled for hunger and satiety but that show limbic regions do not differentiate between positive and negative monetary outcomes in individuals remitted from AN (3) and are underactive for motivational behavior in individuals who are ill with AN (6,30). Altered reward activation in individuals remitted from AN also occurs in response to tastes of palatable foods (31). The lack of susceptibility to hunger-driven reward seeking behavior raises the possibility that this pathophysiology may play a critical role in successful food restriction in AN, in that hunger does not make salient stimuli more appetitive in individuals with AN.

How does metabolic state drive reward? There is evidence that peptides involved in energy balance, such as leptin, insulin, orexin, ghrelin, and peptide YY, also provide signals to reward processes, in the service of modulating feeding in response to changes in energy states (29). For example, ghrelin has orexigenic effects (32), and ghrelin levels increase before meals and during fasting to prompt food seeking. Ghrelin also alters the function of areas involved in reward and incentive motivation (e.g., ventral striatum) and decision making (e.g., prefrontal cortex), suggesting a role in food reward. Women ill with AN as well as weight-restored women with a history of AN failed to show the expected association

between ghrelin levels and blood oxygen level–dependent response to visual food cues in limbic regions (e.g., amygdala, hippocampus, insula, and orbitofrontal cortex) (33). Aberrant peptide function provides a possible pathway that may mediate the relationship between hunger and diminished reward response in individuals with AN. In addition, several neurotransmitters, including dopamine (DA), cannabinoids, opioids, and serotonin, have been implicated in the rewarding effects of food (29). Adults remitted from AN have altered DA and serotonin activity, raising the possibility that monoamine dysregulation contributes to a diminished response to reward (34). For example, individuals with remitted AN show altered ventral striatal function that is consistent with diminished endogenous DA activity (35,36). Whether the abnormal mechanism is peptide-based or located in reward processes related to DA or serotonin systems, or both, remains to be determined. This study defines a paradigm that can be used to discriminate and test altered reward response to fasting in individuals with AN, both to systematically dissect contributing neurotransmitter, peptide, and neural circuitry mechanisms and to identify and test new drugs that might enhance reward response to fasting in individuals with AN.

Cognitive Circuitry

The CW group showed the opposite pattern within cortical areas responsible for cognitive control and decision making; these subjects had greater brain responses in the MFG, VLPFC, and insula when satiated compared with when hungry. The DLPFC subregion of the MFG and the VLPFC are often associated with cognitive control, including numeric computation, future planning, and inhibition (37), and the insula is involved in the perception of time (38) and codes the selection of options for immediate versus delayed gratification (39).

The RAN group did not show different brain responses during decision making when hungry versus satiated. Instead, the RAN subjects exhibited elevated brain response compared with CW subjects independent of hunger state in regions of the MFG including the DLPFC and premotor cortex. This insensitivity to hunger is also reflected in their response time: the RAN subjects, in contrast to the CW subjects, showed similar response times regardless of decision difficulty or hunger.

Functional MRI studies in individuals with remitted AN demonstrate elevated frontoparietal activation relative to healthy comparison subjects (3,6), suggesting a more strategic approach during task performance. Elevated DLPFC activation has been observed in individuals with remitted AN relative to healthy subjects in response to aversive tastes (40), and elevated resting state connectivity has been shown between the DLPFC and precuneus in individuals with remitted AN relative to healthy subjects (41). Behavioral studies point to impaired decision making (42), reflecting cognitive inflexibility. Our findings provide further support for enhanced cognitive control in individuals with remitted AN that is insensitive to hunger. Enhanced inhibition, self-control, or insensitivity to interoceptive signals such as hunger in reward circuits may facilitate persistent food restriction. Healthy subjects and individuals with remitted AN may use different strategies to evaluate choice, with individuals with remitted AN relying on

cognitive evaluation to compensate for impaired reward processing.

Limitations

In contrast to prior work (8), we did not show behavioral choice differences in discounting between groups, although recent findings suggest discounting rate may normalize with weight restoration (43). Because performance differences between groups can obscure whether differences in brain activation reflect biological differences or individual differences in ability, designs that equate performance are often preferable (44). The similar performance between the RAN and CW groups strengthens conclusions regarding group differences in brain systems involved during delay discounting.

We studied individuals remitted from AN to avoid confounding effects of malnutrition. The premorbid occurrence of similar temperament traits, such as altered response to reward and risk avoidance, supports the notion that these findings in the RAN group reflect neurobiological underpinnings of heritable traits that contribute to the anorectic phenotype and a vulnerability for pathologic eating that persists even after nutrition and weight normalize. Alternatively, more recent studies in animals raise the question of whether extremes of food ingestion produce chronic effects on the reward system (45). Given the frequency of dieting and weight loss in our culture, if extreme dieting produced powerful brain changes, the incidence of AN would be much higher, or weight loss in obesity would be much easier. Lastly, response to reward was higher for the RAN group than the CW group when satiated, raising the possibility that satiety is associated with abnormal motivation in individuals remitted from AN.

Clinical Implications

A lack of understanding of AN pathophysiology has hindered development of effective treatments. For example, individuals with AN tend to lack motivation to engage in treatment (46) or balance appropriately the risk of emaciation versus the benefits of a healthy weight. The present study shows that, consistent with the literature (3,4), individuals remitted from AN may have difficulty in valuating everyday choices because of altered brain response, recognition, or coding of reward. Limbic and cognitive circuits interact to code stimulus-reward value, maintain representations of predicted future reward and future behavioral choice, and play a role in integrating and evaluating reward prediction to guide decisions. These data support the possibility that individuals with AN have an inherent altered ability to identify the emotional significance of stimuli, which may translate to an inability to make appropriate decisions to engage in treatment or appreciate the consequences of their behaviors. This study examined response to monetary choice and raises the question of whether the failure of the RAN subjects to value monetary reward appropriately generalizes to valuation of food when hungry. As shown in the CW subjects, hunger enhances neural mechanisms that heighten the valuation of salient stimuli. Holsen et al. (33) investigated the effects of hunger and satiety on response to images of food and found hypoactivation in food motivation regions involved in the assessment of the reward value of food in ill and remitted AN subjects. Together,

data support the likelihood that individuals with AN fail to increase valuation of salient stimuli when hungry and overly rely on cognitive appraisal, explaining their ability to restrict food even though emaciated and their lack of motivation to seek treatment.

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