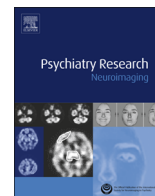




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## Altered brain response to reward and punishment in adolescents with Anorexia nervosa



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### ABSTRACT

Adults recovered from Anorexia nervosa (AN) have altered reward modulation within striatal limbic regions associated with the emotional significance of stimuli, and executive regions concerned with planning and consequences. We hypothesized that adolescents with AN would show similar disturbed reward modulation within the striatum and the anterior cingulate cortex, a region connected to the striatum and involved in reward-guided action selection. Using functional magnetic resonance imaging, twenty-two adolescent females (10 restricting-type AN, 12 healthy volunteers) performed a monetary guessing task. Time series data associated with monetary wins and losses within striatal and cingulate regions of interest were subjected to a linear mixed effects analysis. All participants responded more strongly to wins versus losses in limbic and anterior executive striatal territories. However, AN participants exhibited an exaggerated response to losses compared to wins in posterior executive and sensorimotor striatal regions, suggesting altered function in circuitry responsible for coding the affective context of stimuli and action selection based upon these valuations. As AN individuals are particularly sensitive to criticism, failure, and making mistakes, these findings may reflect the neural processes responsible for a bias in those with AN to exaggerate negative consequences.

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### 1. Introduction

Anorexia nervosa (AN) typically has an onset during adolescence in females and is characterized by emaciation, an intense fear of gaining weight despite being underweight, and disturbed body image (American Psychiatric Association, 2000). Genetic heritability accounts for ~50–80% of the risk of developing AN and contributes to the neurobiological factors underlying this illness (Kaye et al., 2009). There are few effective treatments that reverse core symptoms. Consequently, AN often has a chronic and relapsing course, with the highest death rate of any psychiatric illness.

Individuals with restricting-type AN tend to refuse food, are anhedonic, and find little in life that is rewarding aside from the pursuit of weight loss. Such behaviors have raised the possibility

that there are intrinsic disturbances of reward or pleasure (Wagner et al., 2007), perhaps related to altered striatal dopamine function (Frank and Kaye, 2005). The role of dopamine in reward processing is well established (Schultz, 2006). Human neuroimaging studies show that a highly interconnected network of brain areas, including the dopaminergic midbrain and striatum as well as cortical regions such as the frontal lobes and amygdala, are involved in reward processing of both primary (i.e., pleasurable tastes) and secondary (i.e., money) reinforcers (O'Doherty, 2004). Through a feed-forward series of nonreciprocal connections, dopamine-mediated information progresses from the limbic (ventral) to executive (dorsal central) to sensorimotor areas of the striatum (Martinez et al., 2003). The ventral limbic neural circuit, which includes, among other regions, the anterior ventral striatum and ventral anterior cingulate cortex (ACC), is necessary for identifying rewarding and emotionally significant stimuli and for generating affective responses to these stimuli (Phillips et al., 2003). A dorsal executive function neural circuit, which includes the dorsal caudate and dorsal ACC, is thought to modulate selective

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attention, planning, and effortful regulation of affective states. The *sensorimotor circuit* includes the posterior putamen and motor cingulate; this circuit is involved with movement and stimulus-response habits (Yin and Knowlton, 2006). Together, these circuits code stimulus-reward value, maintain representations of predicted future reward and future behavioral choice, and transform decisions into motor output, thereby integrating and evaluating reward prediction to guide decisions. Striatal dysfunction may contribute to many behaviors seen in AN, including altered reward and affect, decision-making, executive control, and decreased food ingestion (Kaye et al., 2009).

Prior studies by our group have shown that adults recovered from AN (Wagner et al., 2007) exhibit a failure to differentiate feedback valence in ventral striatal regions and an exaggerated response to both reward and punishment in dorsal executive regions in a simple monetary choice feedback task (Delgado et al., 2000) relative to healthy comparison women. Findings in recovered adult AN may be confounded by years of malnutrition or treatment; alternatively, they may be traits of the disorder. The current study investigated AN when ill during adolescence. A replication of altered striatal response to reward and punishment in ill adolescent AN using the same monetary choice task previously employed in recovered adult AN (Wagner et al., 2007) would provide support for the notion that altered limbic and executive striatal processes may be trait related.

Recent studies have shown that adults with AN have structural (Friederich et al., 2012) and functional (Zastrow et al., 2009) alterations within the cingulate, a region that is strongly interconnected with the striatum (Haber and Knutson, 2010) and may be subdivided based upon its response to feedback valence (Liu et al., 2011). Notably, Delgado et al. (2005) reported rostral ACC response in healthy volunteers to a probabilistic cue period as well as to feedback in a variant of the task presented herein. As voxelwise analyses of the monetary choice task have also reported anterior cingulate activation (Delgado et al., 2000; May et al., 2004; Wagner et al., 2007), we have included this area as a region of interest.

## 2. Methods

### 2.1. Participants

Twelve adolescent females aged 12–18 and meeting DSM-IV criteria for a diagnosis of restricting-type AN within six months of study participation and experiencing their first anorectic episode were recruited from local eating disorder (ED) treatment programs. Twelve age-matched healthy comparison adolescent (CA) females were recruited through local advertisements. Axis I diagnoses were made by clinicians with expertise in ED in children and adolescents; assessments included the Mini International Neuropsychiatric Interview for Children and Adolescents (MINI-KID) (Sheehan et al., 2010) and a modified Module H (ED diagnosis) from the Structural Clinical Interview for DSM-IV Axis I Disorders (First et al., 1996) that included additional questions to further define ED characteristics. Exclusion criteria for all participants included: past history of alcohol or drug abuse or dependence three months prior to study; medical or neurologic concerns; and any condition contraindicative to MRI. Two participants with AN were on low-dose psychotropic medication (olanzapine). The CA and their first-degree relatives had no history of an ED. The study was conducted according to the Institutional Review Board regulations of the University of California, San Diego. Participants under the age of 18 gave written informed assent, and their parents gave written informed consent; participants aged 18 gave written informed consent. Participants completed other diagnostic and clinical assessments (Beck Depression Inventory [BDI], Temperament Character Inventory [TCI], State-Trait Anxiety Inventory [STAI], Yale-Brown Cornell Eating Disorder Scale) described elsewhere (Wagner et al., 2006), as well as the Similarities and Matrix Reasoning subtests of the Wechsler Abbreviated Scale of Intelligence (Wechsler, 1999) and the Reading subtest of the Wide Range Achievement Test Revision 4 (Wilkinson and Robertson, 2006). Participants completed the Wisconsin Card Sorting Test (WCST) (Heaton, 2005) at a separate session occurring, on average, 27 days (range: 1–102 days) prior to the imaging session. At the end of imaging procedures, one adolescent with AN was excluded due to equipment failure, and a second participant with AN was excluded due to motion artifact. Between group comparisons of assessment scores were performed using Student's *t*-tests and

assumed unequal variance. Effect sizes were computed as the standardized mean difference using Hedges' *g* so as to account for bias caused by small sample size (Hedges, 1985).

### 2.2. Experimental design

Participants performed a monetary guessing task during fMRI (Delgado et al., 2000; Wagner et al., 2007). The participant was instructed to guess whether the hidden number was less than or greater than 5. The card had an unknown value ranging from 1 to 9, with the number 5 excluded. The participant won \$2.00 for each correct guess, lost \$1.00 for each incorrect guess, and lost \$0.50 if she failed to make a guess in the allotted time period. At the trial onset, a question mark appeared inside the card for 1 s as a cue that the participant should make a guess. Following this, the hidden number was displayed for 500 ms, followed by a colored arrow for 500 ms, indicating a win (green up arrow), a loss (red down arrow), or a failure to respond (yellow down arrow). All visual information occurred during the first 2 s of each trial followed by an intertrial interval of 12 s. Participants were instructed that the computer selected numbers randomly, and that there was no way to know what number would be revealed. In reality, the paradigm randomly preselected a trial as a win or loss, and presented to the participant a number that was congruent with the outcome. A total of four blocks, each containing 26 trials (13 wins, 13 losses), was presented. Participants were compensated \$25 upon completing the task.

### 2.3. MRI

Imaging data were collected with a 3T Signa Excite scanner (GE Medical Systems). fMRI was performed with gradient-recalled echoplanar imaging (TR=2000 ms, TE=30 ms, flip angle=80°, 64 × 64 matrix, ASSET factor=2, 40 2.6-mm ascending interleaved axial slices with a 0.4-mm gap, 186 volumes) (Kwong et al., 1992; Ogawa et al., 1992). The first four volumes of each run were discarded so as to discount T1 saturation. EPI-based field maps were acquired for correcting susceptibility-induced geometric distortions. A high resolution T1-weighted image (SPGR, TI=600 ms, TE=min full, flip angle=8°, 256 × 192 matrix, 170 1.2 mm contiguous slices) was obtained for subsequent spatial normalization.

### 2.4. Definition of anatomical regions of interest

#### 2.4.1. Striatal regions of interest (ROIs)

Striatal ROIs were defined a priori based on known functional distinctions (Martinez et al., 2003). For the limbic circuit, the nucleus accumbens represented the 'classic' limbic striatum, although the 'limbic' striatum extends beyond this region (Haber and Knutson, 2010). The executive (AKA cognitive) regions included the putamen anterior to the anterior commissure and both the anterior and posterior caudate nucleus, divided at the anterior commissure. The sensorimotor circuit included the putamen posterior to the anterior commissure. Consistent with Martinez (Martinez et al., 2003), some subtle anatomical distinctions within the striatum were neglected; for example, while the caudate is considered largely executive, a small dorsolateral portion is a part of the sensorimotor circuit. The putamen has a small dorsolateral part rostral to the anterior commissure that is sensorimotor, whereas a ventromedial part of the putamen caudal to the anterior commissure is both executive and limbic. Given the resolution of BOLD fMRI images and the standard application of spatial smoothing, these ROIs were meant to serve as probabilistic functional distinctions rather than absolute representations of functional striatal subdivisions.

#### 2.4.2. Cingulate ROIs

The anterior cingulate was based on the Harvard-Oxford atlas and was further divided into three subregions (Yucel et al., 2003). The rostral anterior cingulate, known to project to the limbic striatum (Haber and Knutson, 2010), was distinguished from the cognitive zone of the dorsal anterior cingulate by drawing a 45° line from the anterior commissure. The cognitive zone of the dorsal anterior cingulate, which projects to executive striatal and prefrontal regions, was defined from this line to a line vertical to the anterior commissure. Finally, the motor zone of the dorsal anterior cingulate, which projects to the sensorimotor cortical areas as well as the putamen, was defined as the remaining portion of the original anterior cingulate mask.

### 2.5. Statistical analysis

Functional images were preprocessed and analyzed using Analysis of Functional NeuroImages (AFNI) software (Cox, 1996) and R statistical packages (<http://www.r-project.org>). EPI images were motion-corrected and aligned to high-resolution anatomical images. Time points with isolated head movements not corrected by coregistration were censored from the statistical analysis. Statistical analyses were performed using a general linear model (GLM), with individual events modeled using AFNI's TENT function. The TENT function is a piecewise linear

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