Altered Temporal Difference Learning in Bulimia Nervosa

Guido K.W. Frank, Jeremy R. Reynolds, Megan E. Shott, and Randall C. O'Reilly

Background: The neurobiology of bulimia nervosa (BN) is poorly understood. Recent animal literature suggests that binge eating is associated with altered brain dopamine (DA) reward function. In this study, we wanted to investigate DA-related brain reward learning in BN.

Methods: Ill BN ($n = 20$, age: mean = 25.2, SD = 5.3 years) and healthy control women (CW) ($n = 23$, age: mean = 27.2, SD = 6.4 years) underwent functional magnetic resonance brain imaging together with application of a DA-related reward learning paradigm, the temporal difference (TD) model. That task involves association learning between conditioned visual and unconditioned taste stimuli, as well as unexpected violation of those learned associations. Study participants also completed the Sensitivity to Reward and Punishment Questionnaire.

Results: Bulimia nervosa individuals showed reduced brain response compared with CW for unexpected receipt and omission of taste stimuli, as well as reduced brain regression response to the TD computer model generated reward values, in insula, ventral putamen, amygdala, and orbitofrontal cortex. Those results were qualitatively similar in BN individuals who were nondepressed and unmedicated. Binge/purge frequency in BN inversely predicted reduced TD model response. Bulimia nervosa individuals showed significantly higher Sensitivity to Reward and Punishment compared with CW.

Conclusions: This is the first study that relates reduced brain DA responses in BN to the altered learning of associations between arbitrary visual stimuli and taste rewards. This attenuated response is related to frequency of binge/purge episodes in BN. The brain DA neurotransmitter system could be an important treatment target for BN.

Key Words: Bulimia nervosa, computational, dopamine, imaging, reward, temporal difference model

Bulimia nervosa (BN) is a severe eating disorder associated with episodic binge eating followed by extreme behaviors to avoid weight gain, such as self-induced vomiting, use of laxatives, or excessive exercise (1). Individuals with BN present with fear of gaining weight, as well as food and body weight-related preoccupations, but are at normal or often high-normal weight. The pathophysiology of BN is largely unknown.

Only a few functional brain imaging studies have investigated the neurobiology of BN. One group (2) found that BN subjects demonstrated increased activity in the anterior cingulate cortex and insula in response to food images, possibly representing the increased emotional salience associated with the images. A second study explored body image perception in a small BN sample ($n = 9$) (3); BN individuals demonstrated a reduced response in the lateral fusiform gyrus when presented with line drawings of body shapes and such reduced responses were thought to reflect an aversion-driven restraint in brain response. A few neurotransmitter-receptor studies have been done in BN. One study reported reduced binding of [^{123}I]beta-CIT, a radiotracer that binds to brain serotonin (5-HT) and dopamine (DA) transporter receptors (4). Reduced [^{123}I]beta-CIT binding in BN could be related to altered serotonin (5-HT) (5) or DA (6,7) brain activity during the ill state. Another study found increased 5-HT type 1A receptor binding in ill BN subjects (8), most prominently in prefrontal, cingulate, and a parietal cortex area. This increased binding could reflect upregulated receptor activity associated with the decrease in central 5-HT function in BN (5).

The compulsive nature of binge episodes and comorbidity with substance use disorders (9) suggested that BN could, at least in part, share vulnerabilities and pathophysiology with substance use disorders. Substance use disorders are largely associated with abnormalities in the neural systems associated with processing salient stimuli and regulating the desire and ingestion of rewarding stimuli such as drugs or food (i.e., the reward system). The neurotransmitter system that has received the most attention in that respect is DA, partially because it is well characterized (10,11). Dopamine regulates the motivational aspects of the reward pathway (12) and seems to adjust to repetitive substance use with gradual desensitization and chronic dysphoria outside of times of acute use (13). Substance use disorders commonly are associated with lower DA D2/3 receptor availability (14), which has implications on reinforcement learning, reward processing, and eventually action selection (15). While DA dysfunction is commonly associated with substance abuse, there are also animal models linking the pathophysiology of binge eating to DA abnormalities. Those studies suggest withdrawal and tolerance development in the context of binge eating (16,17), as well as DA D2 receptor reductions (18). While the animal models suggest a link between DA and BN, DA research in BN has been sparse, but there appear to be reduced DA metabolites in cerebrospinal fluid (6,7) and reduced DA transporter availability in BN (4).

In this study, we used event-related functional magnetic resonance imaging (fMRI) to investigate DA-related responding in a classical conditioning paradigm (19–21). Before learning, the DA system produces a phasic response to the (unexpected) unconditioned reward stimulus (US). After learning that the US is predictably preceded by a conditioned stimulus (CS), DA response transfers in time, such that it follows the CS but no longer the US. Further,

From the Department of Psychiatry (GKWF, MES), University of Colorado Denver, The Children's Hospital, Aurora; Department of Neuroscience (GKWF), University of Colorado Denver, Anschutz Medical Campus, Aurora; Department of Psychology (JRR), University of Denver, Denver; and Department of Psychology and Neuroscience (RCO), University of Colorado Boulder, Boulder, Colorado.

Address correspondence to Guido K.W. Frank, M.D., University of Colorado Denver, Departments of Psychiatry and Neuroscience, The Children's Hospital, 13123 East 16th Avenue, Aurora, CO 80045; E-mail: Guido.Frank@ucdenver.edu.

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after such training, if the CS is followed by an omission of the US, a reduction in DA firing occurs at the time of the expected US. Thus, brain DA response parallels the difference between the amount of reward observed and that predicted, i.e., a reward prediction error. This type of prediction error and learning process can be characterized by a temporal difference (TD) algorithm (11). This algorithm has been explored empirically in both rodent models (21) and event-related human neuroimaging paradigms (20) and is widely thought to be a reasonable description of the learning process. The primary brain areas demonstrating responses that parallel signals produced by a TD model are the ventral striatum and midbrain (21), although the amygdala (22) and insula are also intimately involved in reward processing (23). Our goal was to test whether we would find diminished DA-related taste reward processing across a large brain network that would distinguish BN from control women (CW) individuals.

Methods and Materials

Study Participants

Forty-one female study participants participated in this study (Table 1), 20 individuals with purging type BN and 23 healthy CW, matched for age and level of education. Bulimia nervosa individuals were recruited from the Eating Disorder Center Denver. No BN subject approached for this study declined study participation. Bulimia nervosa individuals showed typical behaviors on mood and personality measures and showed significantly greater sensitivity to punishment and sensitivity to reward (Sensitivity to Punishment and Sensitivity to Reward Questionnaire [SPSRQ]) compared with CW (Table 1). Bulimia nervosa fulfilled all diagnostic criteria for the disorder up to 1 week before the study. Study participants had no electrolyte or other laboratory abnormalities. Among BN individuals, three had a major depressive disorder (MDD) but no other comorbidity, two had MDD and social phobia, one had MDD and social phobia and generalized anxiety disorder, two had MDD and posttraumatic stress disorder, two had MDD and generalized anxiety disorder, and two had social phobia without MDD. No BN subject had a substance use disorder. The study was approved by the Colorado Multiple Review Board and all subjects signed informed consent.

Assessment Procedures

Psychiatric diagnoses, including BN, or absence of any psychiatric disorders in CW were established by the Structured Clinical Interview for DSM-IV diagnoses (24) applied by a doctoral level interviewer. All participants completed the Eating Disorder Inventory-3 (25,26), Sensitivity to Punishment and Sensitivity to Reward Questionnaire (27), Beck's Depression Inventory (28), and Cloninger's Temperament and Character Inventory (29).

Study subjects met with the principal investigator to ensure diagnosis and underwent a blinded taste test, where subjects were presented with a tray of randomly assorted small cups with six sucrose (Mallinckrodt Chemicals, Phillipsburg, New Jersey) solutions (0%-distilled water, 2%, 4%, 8%, 16%, and 1 mol/L), as well as artificial saliva (25 mmol/L potassium chloride, 2 mmol/L sodium bicarbonate) (20). Study participants rated the solutions blindly for sweetness and pleasantness. This was to test taste sensitivity across groups. Taste test and brain imaging were conducted in all study participants during the first 10 days of the menstrual cycle to keep hormonal variation low (30).

Brain Imaging Procedures

On the study day, participants ate breakfast between 7:00 AM and 8:00 AM, BN individuals according to their meal plan; CW had breakfast matched in quality and calories to the average meal plan breakfast (Table 1.). Bulimia nervosa individuals' meal plan was adjusted so that their morning snack after the study was less study sucrose solution calories, to not add anxiety. Functional magnetic resonance imaging was performed between 8:00 AM and 9:00 AM. Brain images were acquired on a GE Signa 3T scanner (General Electric, Waukesha, Wisconsin). T2* weighted echo planar imaging for blood oxygenation level-dependent (BOLD) functional activity was performed, with 3.4 × 3.4 × 2.6 mm voxel size, 1.4 mm gap, repetition time = 2100 miliseconds, echo time = 30 milliseconds, flip angle 70°, 30 slices. We also acquired structural images (T1 spoiled

Table 1. Demographic Variables of Study Participants

	CW (n = 23)		BN (n = 20)			
	Mean	SD	Mean	SD	U	p
Age (years)	27.2	6.4	25.2	5.3	190.5	ns
Illness Duration (months)	—	—	74.2	63.7	—	—
Weekly Binge/Purge Episodes	—	—	23.5	16.9	—	—
Body Mass Index (kg/m^2)	21.5	1.2	22.6	5.7	201.0	ns
Novelty Seeking (TCI)	17.9	6.1	22.1	6.7	142.0	.032
Harm Avoidance (TCI)	10.7	6.6	23.0	5.8	50.5	<.001
Depression (BDI)	1.0	1.0	24.5	11.3	.0	<.001
Drive for Thinness (EDI-3)	2.7	3.5	23.1	4.5	1.0	<.001
Bulimia (EDI-3)	.8	1.2	22.7	5.3	.0	<.001
Body Dissatisfaction (EDI-3)	4.4	4.3	30.7	8.0	4.0	<.001
Sensitivity to Reward (SPSRQ)	8.7	3.8	12.3	4.5	122.0	.008
Sensitivity to Punishment (SPSRQ)	7.6	5.0	16.1	4.8	56.0	<.001
Pleasantness 1 mol/L Sucrose	4.8	2.2	5.5	2.9	196.5	ns
Sweetness 1 mol/L Sucrose	8.3	.8	8.7	.6	180.0	ns
Breakfast Calories	511.2	81.3	473.2	95.3	188.5	ns

BDI, Beck's Depression Inventory; BN, bulimia nervosa; CW, control women; EDI-3, Eating Disorder Inventory-3; ns, nonsignificant; SPSRQ, Sensitivity to Punishment and Sensitivity to Reward Questionnaire; SD, standard deviation; TCI, Cloninger's Temperament and Character Inventory; U, Mann-Whitney *U* test.