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Differential Brain Activation in Anorexia Nervosa to Fat and Thin Words During a Stroop Task

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Abstract

We measured brain activation in six anorexia nervosa patients and six healthy controls performing a novel emotional Stroop task using Fat, Thin, and Neutral words, and words made of XXXXs. Reaction times increased in the patient group in Thin and Fat conditions. In the Thin-XXXX contrast, patients showed greater activation than controls at the junction of left insula, frontal and temporal lobes and in left middle and medial frontal gyri. In the Fat-XXXX contrast, controls showed greater activation in left dorsolateral prefrontal cortex and right parietal areas. Mechanisms underlying attentional bias in anorexia nervosa likely differ under conditions of positive and negative valence. This paradigm is a promising tool to examine neural mediation of emotional response in anorexia nervosa.

Keywords

anorexia nervosa; fMRI; emotional Stroop; attentional bias; neuroimaging; psychopathology; fear of fatness; drive for thinness; dorsolateral prefrontal cortex; insula

Introduction

Anorexia nervosa is a serious behavioral disorder that carries a mortality for hospitalized patients of 5 - 18%, among the highest of psychiatric illnesses [1]. Patients experience disturbed feelings, behaviors, and thoughts, such as “morbid fear of fatness” and the “drive for thinness” [2,3]. One way to assess the influence of these phenomena on behavior is by

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measuring attentional bias, the degree to which performance on attention-requiring tasks can be degraded by stimuli whose emotional content reflects these constructs. One such task is the emotional Stroop.

Emotional Stroop tasks use emotionally salient words to interfere with performance. Such tasks have been performed in a variety of clinical populations [4-7]. In eating disorders, several studies show that negatively-valenced words (e.g., “fat”, “thighs”, “cake”) evoke response latency increases [8]. Only one study used both positively- and negatively-valenced words [10]. Further, no studies have used functional magnetic resonance imaging (fMRI) to measure attentional bias in eating disorders. We therefore sought to map neural correlates of attentional bias in patients with anorexia nervosa, employing both negatively-valenced “fat” words and positively-valenced “thin” words in separate conditions, since interference in these two conditions might arise from distinct neural mechanisms.

Methods

Participants

The current study was approved by the Institutional Review Board of the Johns Hopkins University School of Medicine. All participants provided written consent, were women ages 18-45 without history of neurological illness or traumatic brain injury, and able to undergo MRI. Patients were admitted to a specialty treatment program. All were diagnosed with anorexia nervosa (restricting or binge-purge type) using the Structured Clinical Interview for DSM-IV [11]. Healthy controls were recruited from University environs.

Clinical Measures

Height and weight were measured on the day of the scan. Participants completed the Beck Depression Inventory (BDI) [12] and Eating Attitudes Test, 26-item version (EAT-26) [13]. The BDI is a widely used, 21 item self-report instrument measuring characteristic attitudes and symptoms of depression, with good reliability and validity [14]. The EAT-26 detects eating disorders broadly [15]. Controls had to score below 15 on the EAT-26 (five points below the threshold for detection of an eating disorder [13]) and 10 on the BDI (no or minimal depression [14]) in order to be included. Statistical analyses of clinical and reaction time data were performed using the Statistical Package for the Social Sciences, version 16 (Chicago, IL).

Stroop Task

Participants underwent a brief training session outside of the scanner on a laptop computer and subsequently in the scanner prior to image acquisition. Participants were instructed to press one of four buttons on a hand-held apparatus; each button corresponded to a color, red, green, yellow, or blue. Instructions and stimuli were projected onto a viewing screen positioned at the end of the scanner bore, visible via a 45 degree mirror mounted atop the scanner head coil and presented via ePrime™ software (version 1.2; Psychology Software Tools, Inc., Pittsburgh, PA). Each trial began with the presentation of a colored stimulus word for 1.75s or until the participant responded correctly, whichever came first, followed by a central hatch mark for the time period calculated to exactly end the trial at 2s. Instructions were presented on the screen at the beginning of the experiment stating, “Match the INK to a color below.” Color swatches representing each of the four buttons remained on the screen for the duration of the experiment. A run consisted of four blocks, one for each condition (XXXX, Neutral, Fat, Thin). Each block consisted of 20 trials. Blocks in the first run were presented in the order XXXX, Neutral, Fat, Thin; blocks in runs 2 – 4 were counterbalanced to avoid order effects. Hash marks preceded each block and lasted 10s. Words for each of the conditions were: Neutral: copier, ruler, shelf, tape; Fat: huge, bacon, plump, burger; Thin: celery, gaunt, salad, thin. The experiment lasted 819s. Patients were scanned between hospital days 5 and 10 (mean day 7.8, SD 1.7).

Acquisition Sequences

Images were acquired on a 3.0T Philips MRI scanner at the F.M. Kirby Research Center for Functional Brain Imaging at the Kennedy Krieger Institute in Baltimore, MD. Functional image acquisition occurred while subjects performed the task described above. Images were obtained as follows: a sagittal localizer scan was performed to orient, for subsequent acquisition, 34 contiguous 3 mm thick transaxial slices with no gap, parallel to the intercommissural plane. After acquisition of a Magnetization Prepared RApid Gradient Echo (MPRAGE) structural image a gradient echo, echo-planar T2-weighted sequence with the following settings was used to obtain functional images: TR = 2000 ms, TE = 35 ms, flip angle = 70°, FOV = 240 mm, EPI matrix = 80×80 (reconstructed to 128×128).

Image Processing

Imaging data were analyzed using Statistical Parametric Mapping (SPM5, Wellcome Department of Imaging Neuroscience, University College, London, UK) running under MATLAB 7.0 (The Mathworks, Sherborn, MA, USA). Slice-timing correction was performed using slice 17 as the reference slice. Motion correction was performed by realigning the scans from every session to the mean image of all functional scans in the session. Linear and nonlinear normalization was performed to deform each brain into standard stereotaxic space [16], using a high resolution EPI template (Montreal Neurologic Institute, McGill University, Montreal, Canada). The normalized scans were re-sliced to isotropic voxels (2 mm³) and spatially smoothed with a full-width at half-maximum 8 mm³ Gaussian kernel. Talairach atlas labels were retrieved using the MNI Space Utility by Pakhomov [17].

Stroop Behavioral Analysis

Repeated measures ANOVAs were performed with Group (Patient and Control) as the independent variable and reaction time (RT) as the dependent variable, using a within-subject 4 × 4 × 20 design (Condition [XXXX, Neutral, Fat, Thin] × Run × Trial). In order to conduct these analyses, missing RTs were replaced with the mean from each 20-trial block for each participant. There were no differences in the fraction of RTs imputed between Groups (Patient vs. Control, 0.26 vs. 0.31%; $t(10)=-0.191$, $p=0.852$).

Functional MRI Analysis

Individual time series analyses were conducted using the General Linear Model within the framework of SPM5. The design matrix estimated activation unique to the blocks of interest (Fat and Thin words) by subtracting components that were shared with the XXXX blocks. The model was convolved with the hemodynamic response function to account for the lag between stimulation and the blood-oxygen-level-dependent (BOLD) signal and fitted to each time series. Beta coefficients were calculated for each voxel and weighted images were created and used to generate thresholded t -maps. Second order, random effects analyses of whole brain were conducted using Fat-XXXX and Thin-XXXX contrasts from each individual; these were used to investigate group differences in activation during active and baseline conditions using two-sample t -tests comparing patients to controls. Significance thresholds were set at $p=0.005$, uncorrected, for voxel-wise, and $p=0.05$, corrected, for cluster-wise tests.

Results

Six patients and 6 controls participated (see Table 1). Patients had been ill a mean of 9.7 years (range 4-18, SD 5.54 years), and five of six were diagnosed with purging type anorexia. Repeated measures ANOVA of RTs revealed significant main effects of Group (Patients vs. Controls; $F(1)=17.65$, $p=0.002$) and Condition (XXXX, Neutral, Fat, Thin; $F(1)=15.53$,

$p=0.003$), and a significant interaction of Group $\times$ Condition ($F(3,8)=5.09$, $p=0.029$). See Figure 1.

Patients were not significantly slower than controls in the XXXX condition; however, RTs increased to a greater extent for the patients than the controls in the other conditions.

We performed whole-brain, second-order, random effects modeling of the BOLD response for the between-group (patients vs. controls) Thin-XXXX and Fat-XXXX contrasts (see Table 2 and Figure 2). In the Patient-Control, Thin-XXXX contrast, there were two clusters. The first cluster contains voxels in an area at the junction of insula, frontal and temporal lobes; auditory cortex; associational areas in the insula; Wernicke's area; and an area in the posterior frontal lobe. The second cluster contains voxels in left BA 6 as well as voxels in dorsolateral prefrontal cortex, and dorsal anterior cingulate cortex. There were no significant clusters in the Control-Patient, Thin-XXXX contrast.

In the Control-Patient, Fat-XXXX contrast there were also two clusters. The first cluster lies in the left precentral, inferior and middle frontal gyri, including BA 45, 9, 8, 46, 47, and 44. The second cluster, in the right parietal lobe, lies in the superior parietal lobule, the precuneus, and the inferior parietal lobule, primarily in BA 7, with some additional activation in BA 40 and 19. There were no significant clusters showing greater activation for patients than controls in the Fat-XXXX contrast.

Discussion

The two main findings of this study are that anorexia nervosa patients demonstrate attentional bias to blocks of Fat and Thin words, and patients and controls activate distinct brain regions during performance of those blocks compared with XXXX blocks of our eating disorders emotional Stroop paradigm, depending on the valence of the stimuli in the blocks. To our knowledge, only one study by Sackville et al. [10], using an out of scanner emotional Stroop, has shown attentional bias using negatively and positively valenced words in eating disorders. Lee and Shafraan conclude that because this study showed response latency to positively and negatively valenced words, the interference mechanism must be the same [9]. We demonstrate that supposition to be false.

Instead, we show that anorexia nervosa patients in the Thin-XXXX contrast, but not in the Fat-XXXX contrast, demonstrate a cluster of increased activation at the junction of the insula, frontal, temporal and parietal lobes. The insula contains secondary gustatory areas [18] and areas implicated in interoceptive awareness, which in turn is involved in craving [19]. That this cluster also projects to language areas in the superior temporal gyrus implies a connection between language, craving, and task performance that may be specific to the use of positively-valenced Thin words in our eating disorder emotional Stroop.

Patients also exhibited increased activity in Thin versus XXXX conditions in regions previously found by Compton et al. to be activated in an emotional Stroop task in controls, including left BA 6 and 22 in the middle/medial frontal gyri [20]. Of note, the authors found these areas in primarily "negative versus neutral" tasks, but found no areas of activation for "positive versus neutral" tasks. One possible explanation for this difference is that our patients responded to thin words in an ambivalent way because they had already begun treatment when they were scanned, and thoughts and feelings underlying the drive for thinness may have been attenuated by the treatment itself.

We did not find greater amygdala activation in patients in the Fat versus XXXX conditions. Activation of the amygdala was seen by Isenberg et al. using a region of interest analysis of an emotional Stroop paradigm in controls [21] and by Treasure's group in anorexia nervosa

patients shown caloric versus non-caloric beverages [22]. It may be that region of interest analyses will be required to measure differences in activation in amygdala. Alternatively, it may be that patients who binge find fat words less threatening, and five of six of our patients had binge/purge type anorexia.

The current study also demonstrates that controls show greater activity in the Fat versus XXXX conditions in different regions also implicated in emotional Stroop tasks, namely the left dorsolateral prefrontal cortex (BA 46, 9) and middle frontal gyrus (BA 45), and right superior parietal lobule (BA 7) [20]. These regions, however, are distinct from regions activated in the patients in the Thin-XXXX contrast.

Contrary to other studies using emotional Stroop tasks, we did not find increased activation in ventral anterior cingulate cortex (ACC). We did find greater activation of dorsal ACC in patients in Thin versus XXXX conditions (BA 32). The dorsal ACC is thought to be the cognitive rather than the affective division of the ACC, e.g., color-word Stroop tasks tend to demonstrate increased activation in dorsal ACC, whereas emotional Stroop tasks tend to show increased ventral ACC activation [23]. In one study, however, patients with depression showed minimal activation of ACC during an emotional Stroop task [24]. Since our patients had significant depressive symptomatology, this may account for the minimal, dorsal ACC activation.

The main limitation of the current study is sample size. That said, the behavioral findings are robust and consistent with previous behavioral studies. The fact that we present only clusters whose activations survive a corrected, cluster-level threshold of $p = 0.05$ reduces the likelihood of making Type I error. A second limitation is that the patient group consisted of 5 patients with purging type anorexia, and only one with restricting anorexia. While this may potentially limit the generalizability of the findings, there is some evidence that cerebral blood flow does not differ between diagnostic subtypes [25]. Future work should examine the effect of treatment and diagnostic subtype, and correlate task performance and activation with measures of psychological state and trait.

Conclusion

Anorexia nervosa patients demonstrate attentional bias to Fat and Thin words, and demonstrate distinct activation of brain regions during performance of emotionally evocative blocks compared with XXXX blocks of our eating disorders emotional Stroop paradigm depending on the valence of the stimuli in the blocks. Patients exhibited greater activation in Thin versus XXXX conditions, while controls exhibited greater activation in Fat versus XXXX conditions.

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Figure 1. Repeated measures analysis for the eating disorders emotional Stroop paradigm in anorexia nervosa patients and healthy controls.

Figure 2.

Between Group Contrasts in the Eating Disorder Emotional Stroop paradigm, superimposed on a template T1-weighted image. Yellow voxels are more active in patients than controls in the Thin-XXXX contrast in two clusters, one at the junction of the left insula, frontal, temporal, and parietal lobes ($p=.012$, corrected), and one in the left superior, middle and medial frontal gyri ($p=.029$, corrected). Blue-green voxels are more active in controls than patients in the Fat-XXXX contrast in the left frontal ($p=.002$, corrected) and right parietal regions ($p=.018$, corrected).

Table 1

Demographic and Clinical Characteristics. EAT-26 = Eating Attitudes Test, 26-item version [13]; BDI=Beck Depression Inventory [12].

	Patients (n=6)	Controls (n=6)	Significance
Mean age, yrs (SD)	27 (5.0)	24 (2.3)	NS
Caucasian, n	5	5	NS
Education, yrs (SD)	15 (1.7)	17 (1.6)	NS
Mean EAT-26 score (SD)	40.8 (14.9)	1.0 (0.9)	t(10)=16.14, p<.001
Mean BDI score (SD)	22.8 (9.8)	1.2 (1.5)	t(10)=5.35, p<.001
Body Mass Index, kg/m ² (SD)	15.7 (1.5)	22.3 (1.9)	t(10)=-6.70, p<.001

Table 2

Clusters of activation for the “Patient-Control, Thin-Fat” and “Control-Patient, Thin-Fat” contrasts. MNI=Montreal Neurological Institute; BA=Brodmann Area; P_{corr} = corrected, cluster-wise p-value; P_{uncorr} = uncorrected, voxel-wise p-value; PCG = Postcentral Gyrus; PreCG = Precentral Gyrus; STG = Superior Temporal Gyrus; I = Insula; TTG = Transverse Temporal Gyrus; SFG = Superior Frontal Gyrus; MFG = Medial Frontal Gyrus; MedFG = Medial Frontal Gyrus; IFG = Inferior Frontal Gyrus; SPL = Superior Parietal Lobule; PC = Precuneus; IPL = Inferior Parietal Lobule.

Cluster							MNI Coordinates (mm)		
Region	L/R	Size	P_{corr}	T	Z	P_{uncorr}	x	y	z
Patient-Control, Thin-XXXX									
PCG, PreCG, STG, I, TTG (BA 43, 42, 13, 22, 6)	L	212	.012	5.85	3.77	.000	-52	-12	12
				5.77	3.74	.000	-46	-16	16
SFG, MFG, MedFG (BA 6, 8, 32)	L	182	.029	5.07	3.49	.000	-18	10	56
				4.54	3.27	.001	-24	14	52
				4.51	3.26	.001	-12	12	52
Control-Patient, Fat-XXXX									
IFG, MFG, PreCG (BA 45, 9, 8, 46, 47, 44)	L	326	.002	8.22	4.43	.000	-50	26	6
				4.85	3.40	.000	-52	26	14
				4.40	3.21	.001	-48	20	34
SPL, PC, IPL (BA 7, 40, 19)	R	227	.018	6.57	4.00	.000	30	-58	46
				5.88	3.78	.000	20	-58	42