Published in final edited form as:

Neuroimage. 2011 June 1; 56(3): . doi:10.1016/j.neuroimage.2011.03.026.

An fMRI investigation of the fronto-striatal learning system in women who exhibit eating disorder behaviors

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Abstract

In the present study, we sought to examine whether the fronto-striatal learning system, which has been implicated in bulimia nervosa, would demonstrate altered BOLD activity during probabilistic category learning in women who met subthreshold criteria for bulimia nervosa (Sub-BN). Sub-BN, which falls within the clinical category of Eating Disorder Not Otherwise Specified (EDNOS), is comprised of individuals who demonstrate recurrent binge eating, efforts to minimize their caloric intake and caloric retention, and elevated levels of concern about shape, weight, and/or eating, but just fail to meet the diagnostic threshold for bulimia nervosa (BN). fMRI data were collected from eighteen women with subthreshold-BN (Sub-BN) and nineteen healthy control women group-matched for age, education and body mass index (MC) during the weather prediction task. Sub-BN participants demonstrated increased caudate nucleus and dorsolateral prefrontal cortex (DLPFC) activation during the learning of probabilistic categories. Though the two subject groups did not differ in behavioral performance, over the course of learning, Sub-BN participants showed a dynamic pattern of brain activity differences when compared to matched control participants. Regions implicated in episodic memory, including the medial temporal lobe (MTL), retrosplenial cortex, middle frontal gyrus, and anterior and posterior cingulate cortex showed decreased activity in the Sub-BN participants compared to MCs during early learning which was followed by increased involvement of the DLPFC during later learning. These findings demonstrate that women with Sub-BN demonstrate differences in fronto-striatal learning system activity, as well as a distinct functional pattern between fronto-striatal and MTL learning systems during the course of implicit probabilistic category learning.

Keywords

Eating disorders; fMRI; Fronto-striatal system; Weather prediction task; Bulimia nervosa; Memory system interactions

Introduction

At any given time, 10% or more of late adolescent and adult women report symptoms of eating disorders at a level that is associated with significant distress and impairment (Hudson et al., 2007). A recent review has suggested that 50%–75% of treatment-seeking individuals fit within the category Eating Disorder Not Otherwise Specified (EDNOS)

(Fairburn and Bohn, 2005). Within the EDNOS category, several subgroups have been identified. Examples of these subgroups include: subthreshold cases of individuals who just fail to meet the diagnostic thresholds for anorexia nervosa or bulimia nervosa (AN or BN), individuals who have a mixture of features of both AN and BN, and individuals who experience repeated episodes of binge eating without extreme weight control measures (termed binge eating disorder). Individuals with EDNOS show elevated levels of concern about shape, weight, and/or eating which are psychological symptoms of eating disorders that precipitate, accompany, and maintain behavioral symptoms (Byrne and McLean, 2002, Fairburn, 2008 and Hartmann et al., 2009). The positive presence of psychological symptoms is currently required for all EDNOS diagnoses (excluding variants of AN without over-concern with shape or weight) including subthreshold bulimia nervosa, and the level of psychological symptoms is considered one indicator of eating disorder severity (Byrne and McLean, 2002 and Hartmann et al., 2009). While the EDNOS category is widely used by clinicians, very little research has been carried out to characterize these individuals diagnostically, behaviorally, and neurobiologically (Rockert et al., 2007). The current experiment was conducted to evaluate individuals with subthreshold bulimia nervosa (Sub-BN) using functional imaging methods.

The fronto-striatal system plays an important role in controlling goal-directed thoughts and behaviors, including response inhibition, reward processing, and stimulus-response learning (Alexander et al., 1990 and Knowlton et al., 1996; see Miller and Cohen, 2001 for review). Changes in fronto-striatal circuitry during self-regulatory control and reward processing have been reported in individuals with BN (Marsh et al., 2009a), as well as in individuals recovered from AN and BN (Wagner et al., 2007 and Wagner et al., 2009). Specifically, Marsh et al. (2009a) showed BOLD signal hypoactivation in multiple regions of the frontal-striatal regions among individuals with BN during a task requiring motivated regulatory control and inhibition of automatic responses while Wagner et al., 2007 and Wagner et al., 2009 found that women who had recovered from BN and AN showed hypoactivation in the anterior ventral striatum in response to correct answers in a guessing-game task. In the present study, we predicted that individuals with Sub-BN, who endorse the same psychological symptoms as BN, but do not endorse a diagnostic level of behavioral symptoms, would demonstrate BOLD activity changes in the fronto-striatal system during probabilistic category learning.

Probabilistic category learning, in particular the weather prediction task (WPT), is a task that has been commonly used to assess fronto-striatal system function in healthy individuals (Aron et al., 2006, Foerde et al., 2006, Knowlton et al., 1994, Poldrack et al., 1999, Poldrack et al., 2001 and Poldrack and Rodriguez, 2004), and individuals with neurological (Moody et al., 2004 and Shohamy et al., 2004) and psychological disorders (Weickert et al., 2009). The pathway within the fronto-striatal system implicated in implicit incremental or stimulus-response learning includes the dorsolateral prefrontal cortex (DLPFC) and the dorsal striatum (Alexander et al., 1990), and is often referred to as the implicit or procedural memory system (Knowlton et al., 1996 and Packard and McGaugh, 1996). While the fronto-striatal system is integral to the process of probabilistic category learning (Knowlton et al., 1996), the system's interactions with the medial temporal lobe (MTL) mediated memory system (Squire et al., 1993) are also well characterized as being essential in implicit incremental learning (Poldrack et al., 1999, Poldrack et al., 2001 and Poldrack and Packard, 2003). These reports suggest parallel activation and suppression of distinct regions during category learning, including the caudate nucleus and dorsolateral prefrontal cortex of the fronto-striatal system and the hippocampal formation within the MTL (Poldrack et al., 2001). Therefore, by utilizing the WPT, we were able to examine patterns of fronto-striatal fMRI activity in Sub-BN, along with the well-characterized interactions with the MTL memory system during probabilistic category learning. Based on previous reports, which

propose an under-utilization of the fronto-striatal regions in AN (Steinglass and Walsh, 2006) and BN (Marsh et al., 2009b), we hypothesized that Sub-BN participants would demonstrate decreased fronto-striatal activity and increased involvement of the MTL during the WPT. We also hypothesized we would see differences across time in the recruitment of fronto-striatal and MTL memory systems between Sub-BN participants and healthy control women.

Methods

Participants and clinical assessments

This study was approved by the Boston University Charles River Campus Institutional Review Board as well as the Partners Healthcare Human Research Committee. Participants were recruited from the greater Boston area and responded to public recruitment materials. Written informed consent was obtained from all participants prior to enrollment. Eighteen women with clinically significant symptoms of subthreshold bulimia nervosa (Sub-BN) and nineteen control women (MC) who were group-matched for age, years of education and body mass index (BMI) participated (Table 1). All participants were assessed using the Structured Clinical Interview for DSM-IV (SCID) (First et al., 2002) and the Eating Disorder Examination (EDE) (Fairburn et al., 1993). The EDE provides positive diagnosis of an eating disorder on the basis of the behavioral symptoms of objective binge eating disorder and compensatory behaviors, as well as the attempted restraint of caloric intake, and over-concern with shape and weight. The EDE provides two cognitive subscales (over-concern with shape and with weight) and a restraint subscale reflecting efforts to restrict or restrain eating. The global EDE score is the mean of these three subscales, and has been widely used as a sensitive measure of the severity of eating disorder psychological symptoms (Cooper et al., 1989 and Fairburn and Cooper, 1993). Participants were excluded on the basis of any previous or current neurological or medical disease, learning disabilities, or substance abuse, and all MC participants were free of any current DSM-IV-TR Axis 1 psychiatric disorder and of the use of psychoactive medication.

The criteria for an eating disorder diagnosis of Sub-BN requires the positive presence of over-concern with weight or shape; recurrent binge-eating episodes (including loss of control over eating, resulting in the consumption of an objectively or subjectively large amount of food); and recurrent compensatory behaviors (i.e., purging by vomiting or laxative/diuretic use, severe caloric restriction, or driven exercise), at a frequency that falls short (1 binge per week on average for three months) of that required to diagnose full BN (2 binges per week on average for three months). The diagnostic criteria for full-threshold bulimia nervosa specify that you must have an average of 2 objectively large binges per week on average for three months. Our Sub-BN participants did not meet this frequency criteria for objective binge episodes, and therefore do not meet the full-criteria for BN. However, when subjective binge episodes are included, our sample included participants who did have more than 2 combined subjective and objective binge episodes on average per week. Sub-BN participants were not excluded for previous or current mood and anxiety disorders because these conditions are often comorbid with eating disorders (Godart et al., 2007), but were excluded for current treatment with psychoactive medication. Participants with a history of significantly low body weight (< 85% ideal body weight) or past or current diagnosis of anorexia nervosa were also excluded.

Severity of eating disorder (ED) symptoms was measured using subscale scores from the Eating Disorder Exam/Examination (EDE) and was corroborated by scores on self-report questionnaires [Eating Attitudes Test (EAT-26) (Garner et al., 1982), Eating Disorder Inventory (EDI-2) (Garner, 1991)]. All participants also completed the Beck Depression Inventory (BDI-II) (Beck, 1997). A brief neuropsychological test battery was also conducted

to ensure accurate cognitive characterization of the two groups. The focus of the neuropsychological testing was to assess fronto-striatal function on tasks of executive function [Wisconsin card sorting test, Go/No-Go, Trail Making Tests A and B, Stroop color-word test, Wechsler Adult Intelligence Scale (WAIS)-III letter-number sequencing], as well as control for normal explicit learning and memory function (Rey auditory verbal learning test), attention and concentration (WAIS-III Digit span) and general cognitive ability (American National Adult Reading Test, WAIS-III matrix reasoning).

Weather prediction task (WPT)

Fig. 1 illustrates the WPT probabilistic category learning paradigm. In the WPT, participants gradually learn cue-outcome associations based on feedback which is probabilistically determined. The task design and timings utilized in the current task were based on studies from Poldrack et al., 2001 and Foerde et al., 2008. Before entering the scanner, participants were instructed to try and learn which cards predicted sunshine and which predicted rain, and then practiced 17 weather prediction and perceptual-motor baseline trials on novel stimuli not seen during the actual scanning run. During the prediction blocks, subjects were asked to decide which of two outcomes (rainy or sunny weather) would occur on the basis of a set of one, two, or three cues (out of four possible cues). The stimuli consisted of four tarot cards, each with different shapes (circle, square, triangle, diamond). Each of the four cues was independently associated to an outcome with a fixed probability, and the two outcomes (rain or sunshine) occurred equally as often. The probabilities for each cue combination followed those used by Knowlton et al. (1994) (For full probability structure, see Supplemental Table 1). The actual weather outcome and response feedback was given after each prediction was made (correct: green check marks; incorrect: red X's). During the perceptual-motor baseline task, participants were instructed to respond each time a set of three baseline cards was presented on the screen (Poldrack et al., 2001). All stimuli presented in prediction and perceptual-motor baseline blocks were presented for 3000 ms, and feedback was displayed for 1000 ms. Prediction blocks lasted for a total of 76.5 s (17 trials) or 72 s (16 trials) and the perceptual-motor blocks lasted for a total of 76.5 s (17 trials). Prediction and perceptual-motor blocks were counterbalanced across the entire study.

Accuracy of behavioral performance on individual trials was defined as a response that predicts the outcome most strongly associated with the set of cards presented, instead of the individual trial feedback. In this way, accuracy represents the ability to average the strength of each cue over a number of trials.

WPT post-scan tests

Following scanning, participants were given a single cue estimation and a cue selection test to assess knowledge acquired about the relationship between the four cues and the weather outcome (Gluck et al., 2002). Subjects were first shown each of the four cue cards one at a time and asked to choose one of four possible percentage outcomes: 20%, 40%, 60%, and 80%. Participants were then shown all four cues and asked, "What if you knew it was going to be rainy and one card was showing, which card would it be?" The same question was also asked for the sunny weather outcome.

Neuroimaging

Scanning took place at the Martinos Center for Biomedical Imaging on a 3-Tesla Siemens MAGNETOM TrioTim MRI system using a whole-head 12-channel coil. High-resolution T1-weighted (MP-RAGE) structural scans were acquired for anatomical localization (GRAPPA; TR = 2,530 ms; TE = 3.44 ms; flip angle = 7°; slices = 176; field of view = 256; resolution = 1 mm × 1 mm × 1 mm). Acquisition of the functional images employed an echoplanar T2*-weighted gradient echo sequence (32 axial slices aligned along the anterior

and posterior commissure line, slice thickness = 4.5 mm, TR = 2000 ms, TE = 30 ms, flip angle = 90°, 64 × 64, 4.5 mm³ voxels).

WPT behavioral data analysis

Percentage correct and reaction times were defined as the dependent measures of learning in the WPT. Both percentage correct and reaction times were aggregated in quartiles representing 50 WPT trials in order to better assess the temporal pattern of learning (Fera et al., 2005). Mixed factor repeated measures ANOVAs with within participant factors of quartile, as well as percentage correct or reaction times and a between-participant factor of group were implemented. The main effect of quartile for both percentage correct and reaction time were examined to determine learning of cue-outcome contingencies throughout the experiment.

We used independent sample t-tests of the percentage correct of post-scan estimation of single cue outcomes for both rain and sunshine to assess between-group differences in the outcome associations learned in the WPT. For the cue selection post-scan tests, group differences in flexible identification of the single cue most highly associated with both the rain and sunshine outcomes were assessed using independent 2 × 2 (MC/Sub-BN, correct/incorrect) X2 analyses.

fMRI preprocessing and modeling

fMRI data were preprocessed using Statistical Parametric Mapping software (SPM8; Wellcome Department of Cognitive Neurology, London, UK) under the assumption of the general linear model. fMRI images were reoriented so the origin (i.e., coordinate xyz = [0 0 0]) was at the anterior commissure. Images were realigned with respect to the first scan in the fMRI time-series using INRIAlign (Freire et al., 2002), a motion correction algorithm unbiased by local BOLD signal changes. The high-resolution structural images were then coregistered to the mean fMRI image created during the motion correction step and segmented into white and gray matter images. Normalization of structural and fMRI images into standard Montreal Neurologic Institute (MNI) space was performed using the Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolbox included with SPM8 and resampled to 2 mm isotropic voxels. The normalized structural images of all 37 participants were averaged after normalization for displaying overlays of functional results. All functional images were spatially smoothed using a 6 mm full-width at half-maximum Gaussian filter.

Design matrices for the WPT were modeled using a boxcar function convolved with the canonical hemodynamic response function. Several sources of variance were controlled for by regression of nuisance variables by following the procedure described in Buckner et al. (2009). These nuisance variables included: six parameter rigid body head motion (obtained from motion correction), the BOLD signal averaged over the whole-brain [correlates with respiration-induced fMRI signal fluctuations (Birn et al., 2006 and Wise et al., 2004)], the BOLD signal averaged over regions centered bilaterally in the lateral ventricles, and bilateral regions centered in the deep cerebral white matter. Temporally shifted versions of these waveforms were also removed by inclusion of the first temporal derivatives in the linear model. To assess category learning related BOLD activation, linear contrasts of the prediction blocks relative to perceptual-motor baseline blocks were created at the individual participant level. To better evaluate the temporal dynamics of learning-related BOLD changes, the prediction blocks were aggregated into quartiles of 50 trials.

Within- and between-group patterns of category learning related BOLD activity

A region of interest (ROI) based SPM full factorial ANOVA with factors of group, condition, and quartile was conducted to assess group level differences in category learning related BOLD activity (prediction > perceptual-motor baseline). Individual participant weather prediction vs. perceptual-motor baseline contrasts were used as the condition factors in order to account for within-participant variance. The main effect of condition examined differential category learning related BOLD activity across participants within our ROIs. Regional differences in category learning related BOLD activity between the Sub-BN and MC participants were examined by the interaction between group and condition within our ROIs and regional differences in category learning related BOLD activity that varied across time were examined by the interaction between group, condition and quartile. Caudate, putamen, hippocampus, parahippocampal gyrus, anterior cingulate, precuneus and prefrontal cortex (including dorsolateral and ventrolateral prefrontal cortex and middle frontal gyrus) served as anatomical ROIs and were derived as masks from the AAL ROI library; a standard set of anatomical definitions defined by hand on a single brain which matched the MNI/ICBM templates (Tzourio-Mazoyer et al., 2002).

Post-hoc ROI-based one-sample and two-sample t-tests, as well as percent BOLD signal change extractions using peaks of regional activation identified within the group level main effect and interaction contrasts of the omnibus ANOVA were employed to determine the directionality of within-group fMRI activity (activation vs. deactivation), as well as between-group fMRI activity differences (increases vs. decreases). Percent BOLD signal change was extracted from each individual participant utilizing the MarsBar region of interest toolbox for SPM8 (Brett et al., 2002). For anatomical ROIs with more than one significant peak, only the most significant peak (Z-score) was subjected to post-hoc analyses. All peaks were surrounded by spheres of 5 mm. Only non-zero voxels within the anatomical mask and sphere for each participant were examined. Additional post-hoc ANOVAs were performed in PASW 18 (SPSS, Inc., Chicago IL.).

On all factorial ANOVA and one-sample t-test statistical parametric maps (SPMs), an individual voxel threshold of $p = 0.01$ was used which was corrected for multiple comparisons at the cluster level of $p = 0.05$ using 57 contiguous resampled voxels. The cluster extent threshold was obtained by simulating whole-brain fMRI activation using custom software written in MATLAB (Slotnick et al., 2003). By modeling the functional image matrix ($64 \times 64 \times 32$ voxels), assuming a type I error voxel activation probability of 0.01, and smoothing the activation map by convolution with a 3-dimensional 6-mm FWHM Gaussian kernel, the size of each contiguous cluster of voxels was determined using Monte Carlo statistics. The probability of each cluster size was determined by 10,000 simulations and the cluster extent that yielded $p < 0.05$ was selected for use for the voxel extent thresholding. All between-group SPMs were corrected at an individual voxel threshold of $p = 0.05$ corrected for multiple comparisons at the cluster level of $p = 0.05$ using 103 contiguous resampled voxels.

Correlations of category learning related BOLD activity and level of depression

To determine if a relationship existed between depression and the brain regions identified in the main effect of category learning and group $\times$ category learning analyses, correlations with BDI-II score and percent signal change were run for each brain region identified in Table 2 across all participants ($n = 37$). Category learning fMRI activity was calculated by taking the difference between prediction and perceptual-motor baseline percent BOLD signal change extractions. Correlations were corrected for multiple comparisons (Bonferroni).

Results

Participant characterization

Data are reported from eighteen women with clinically significant symptoms of subthreshold bulimia nervosa (Sub-BN) and nineteen control women (MC) who were group-matched for age, years of education, and BMI (see Table 1). Self-reported history of eating disorder symptoms ranged from 1 to 8 years (mean = 4.1 ± 2.0 years).

Eating disorder symptoms were comparable in severity to those observed among other eating-disorder samples. For each of the 3 months prior to study participation, Sub-BN participants reported $7.73 (\pm 7.72)$ objective and $4.75 (\pm 5.53)$ subjective binge episodes, $8.41 (\pm 6.37)$ purging episodes, and $12.33 (\pm 11.20)$ non-purging compensatory behaviors on average per month (assessed as 28 days on the Eating Disorder Examination). Non-purging compensatory behaviors included extreme restriction (< 1200 calories per day), driven exercise, and diet pill use. Average EDE subscale scores for the Sub-BN participants (see Table 1) did not significantly differ ($p > 0.1$ in all cases) from the published normative data for bulimia nervosa (based on comparison to norms published in Fairburn and Cooper, 1993). All Sub-BN participants reported stable and consistent menstrual cycles for each of the 3 months prior to the study. Sub-BN participants scored significantly higher than MC participants on the BDI-II (Beck, 1997) [$t(34) = -6.648, p < 0.0001$; see Table 1].

There were no significant group differences on any cognitive functions assessed by the neuropsychological test battery (see Supplemental Table 2).

WPT behavioral performance

The mixed factor repeated measures ANOVA of accuracy scores revealed a main effect of quartile [$F(3,102) = 5.360, p < 0.002$], which demonstrated a significant linear trend [$F(1,35) = 6.669, p < 0.014$], suggesting improved performance in both groups across quartiles during the WPT. A mixed factor repeated measures ANOVA of reaction times revealed a main effect of quartile [$F(3,102) = 15.734, p < 0.0001$] which also demonstrated a significant linear trend over quartile [$F(1,35) = 23.402, p < 0.0001$] (Fig. 2).

Post-scan tests

Results from the single-cue estimation test revealed that the information learned during the WPT did not differ between Sub-BN and MC participants. Across both Sub-BN and MC groups, the ability to select the cue cards most highly associated with rain and sunshine outcomes did not differ between groups for both outcomes. In addition, the number of participants within each group who correctly predicted both outcomes did not differ between groups.

ROI-based SPM factorial ANOVA

The ROI-based SPM factorial ANOVA revealed regional main effects of category learning related BOLD activity (prediction $>$ perceptual-motor baseline), group $\times$ category learning related BOLD interactions, and group $\times$ category learning $\times$ quartile interactions. In addition, no regional main effect of group was identified suggesting that over time, within-participant category learning related BOLD activity did not consistently differ within our ROIs.

Main effect of category learning

Consistent with previous studies (Fera et al., 2005, Poldrack et al., 1999, Poldrack et al., 2001 and Weickert et al., 2009), the spatial distribution of the BOLD signal involved the

bilateral caudate nucleus, left hippocampus, bilateral dorsolateral prefrontal cortex [DLPFC; Brodmann's area (BA) 9 and 46], and middle frontal gyrus (BA 8 and 10), anterior and posterior cingulate cortex (BA 32 and 30) and precuneus (BA 7) (Fig. 3; Table 2). Post-hoc one-sample t-tests confirm the participation of these regions within each group (Fig 4a) (Supplemental Table 3) and reveal that both groups demonstrated increased category learning related BOLD activity within bilateral caudate nucleus and putamen, hippocampus, anterior cingulate cortex (BA 32), dorsolateral PFC (BA 9 and 46) and precuneus (BA 7). Increases in category learning related suppression of BOLD signal were found in both Sub-BN and MC groups in bilateral MFG (BA 8 and 10) and left posterior cingulate cortex (Supplemental Table 3). These results confirm the presence of category learning related BOLD signal within a priori regions of interest across groups that are consistent with previous reports of category learning related patterns of BOLD signal activation and suppression (Poldrack et al., 1999 and Poldrack et al., 2001).

Group × category learning interactions

The ROI-based SPM full factorial ANOVA also identified a significant group × category learning related interaction spanning bilateral DLPFC and VLPFC (BA 9 and 44, respectively) and anterior cingulate cortex (BA 32), as well as right MFG (BA 6), and left precuneus (BA 7) (Fig. 3b) (Table 2). Post-hoc two-sample t-tests revealed that collapsed across quartiles, the Sub-BN participants demonstrated greater increases in category learning related BOLD activity in the right caudate nucleus [Z score = 3.68; k = 126; peak = 14 0 14], bilateral DLPFC (BA 9 and 46) [right: Z score = 3.45; k = 822; peak = 34 32 22 and Z score = 2.58; k = 136; peak = 44 34 6; left: Z score = 3.40; k = 814; peak = -30 28 42], right precuneus [Z score = 3.33; k = 1070; peak = 4 -40 58], right anterior cingulate cortex [Z score = 2.66; k = 579; peak = 6 40 24], and left putamen [Z score = 2.40; k = 155; peak = -32 0 4] compared to MC participants (Fig. 4b). The MC participants did not demonstrate any significant areas of increased category learning related BOLD activity collapsed across quartiles.

Percent BOLD signal change extractions revealed that the Sub-BN participants show greater increases in category learning related BOLD activity in right caudate nucleus and bilateral DLPFC (BA 9 and 46) compared to the MC group (Fig. 4b). While the Sub-BN participants activated the left DLPFC, MC participants demonstrated inhibition of BOLD activity in this region (Fig. 4b). Sub-BN participants also demonstrated greater category learning related BOLD activity in the right anterior cingulate cortex, represented as decreased suppression of BOLD activity, or less net suppression (Devor et al., 2007 and Shmuel et al., 2006) during category learning compared to the perceptual-motor baseline (Fig. 4b). MC participants demonstrated greater inhibition of category learning related BOLD activity in the right precuneus suggesting greater suppression of this region during category learning (prediction > perceptual-motor baseline) in MCs (Fig. 4b). These results demonstrate greater category learning related BOLD activity in the caudate nucleus and DLPFC, in addition to reduced suppression of anterior cingulate cortex and precuneus category learning related BOLD activity in Sub-BN participants compared to the MC group.

Group × category learning × quartile interactions

The ROI-based SPM full factorial ANOVA also identified a significant group × category learning × quartile interaction within the left posterior cingulate, hippocampus, MFG (BA 10), and anterior cingulate cortex (BA 24) (Fig. 3c) (Table 2), suggesting that category learning related BOLD signal changes over time differ between groups in these regions. Post-hoc two sample t-tests demonstrate that over time, the MC participants show greater early (quartiles 1 and 2) category learning related BOLD signal contributions within bilateral hippocampus, bilateral anterior cingulate cortex, left MFG (BA 10), left

retrosplenial cortex, and right precuneus (BA 7) (Fig. 5a) (Table 3). Sub-BN participants demonstrate greater late category learning related BOLD signal contributions within the right VLPFC (area 45), bilateral DLPFC (BA 9), bilateral anterior cingulate (BA 32), and bilateral precuneus (BA 7) (Fig. 5a) (Table 3). These results suggest disparate patterns of regional cortical and hippocampal utilization between Sub-BN and MC participants. MC participants demonstrate increased regional cortical and hippocampal BOLD signal contributions early in category learning (prediction > perceptual-motor baseline) while Sub-BN participants demonstrate increased cortical BOLD signal contributions later in category learning.

Percent BOLD signal change extractions from the left posterior cingulate cortex (BA 23), hippocampus, MFG (BA 10), and anterior cingulate cortex (BA 24) identified in the group $\times$ category learning $\times$ quartile interaction were subsequently entered into an additional post-hoc ANOVA, with factors of region, quartile and group, to determine the pattern of the category learning related BOLD signal over time. A significant group $\times$ quartile interaction was revealed [$F(3,105) = 7.805$; $p = 0.0001$], but no group $\times$ quartile $\times$ region interaction was found suggesting the pattern of category learning between groups was similar across ROIs. Fig. 5b shows that while the MC participants demonstrated a linear decrease in category learning related BOLD signal contribution from the left posterior cingulate, hippocampus, MFG, and anterior cingulate cortex, the Sub-BN participants demonstrated a different pattern with later increases in category learning related BOLD signal within these ROIs.

Correlations of category learning related activity and level of depression

Across both MC and Sub-BN participants, correlation analyses between category learning related percent BOLD signal change extractions and level of depression, measured with the BDI-II, revealed no significant correlations when corrected for multiple comparisons. Prior to correction for multiple comparisons, the left precuneus [peak = $-0 -40 58$; $r(35) = 0.394$; p (uncorrected) = 0.016] was the only region that demonstrated a significant correlation with level of depression.

Discussion

Despite performing similarly during probabilistic category learning, women with subthreshold bulimia nervosa (Sub-BN) generated overall increases in BOLD signal activity in regions of the fronto-striatal learning system compared to healthy control women (MC). The Sub-BN participants demonstrated increased overall category learning related activity in the right caudate nucleus and bilateral dorsolateral prefrontal cortex (DLPFC) and decreased suppression of the category learning related BOLD signal in the anterior cingulate cortex. The direction of the BOLD signal changes within the fronto-striatal system differs from our initial hypothesis, which was based on an earlier neuroimaging study of individuals with BN (Marsh et al., 2009b). The Marsh et al. study demonstrated hypoactivity of the fronto-striatal system in individuals with BN during a self-regulatory control task (Marsh et al., 2009b). The pattern of hypoactivity observed in BN participants from Marsh et al. (2009b) was interpreted specifically in light of findings indicating that individuals with BN are impulsive. In contrast, our results demonstrate hyperactivity of the fronto-striatal system during an implicit learning task. Our findings suggest a different but not contradictory pattern. While both studies suggest inefficiency of the fronto-striatal system in individuals with BN, it may be that different task demands will result in different patterns of hypo or hyperactivity within the system. A similar difference has been noted using the weather prediction and serial reaction time tasks in healthy individuals (Poldrack et al., 2001 and Schendan et al., 2003).

It is also important to point out that these changes in BOLD signal in the Sub-BN participants occurred in the absence of a difference in behavioral performance between groups. In neuroimaging studies of patient groups, hyperactivation in the absence of behavioral differences has been conceptualized in the fMRI literature to reflect changes related to brain compensation or brain efficiency (which includes both cognitive and pathological determinants of efficiency), although these two mechanisms are not mutually exclusive (Tinaz et al., 2008). Distinction between the two concepts is drawn by the nature of the regional involvement, in that, compensatory brain processing would be reflected by activity in areas not normally found to be task-related (Rauch et al., 2007), and less efficient brain processing would be reflected by hyperactivation within the normal task-related network (Tinaz et al., 2008). In our Sub-BN subjects, hyperactivation within the fronto-striatal network may reflect that this system is working inefficiently, a finding that is consistent with other studies of BN (Marsh et al., 2009b and Wagner et al., 2009).

Differences in temporal patterns of BOLD activity between the fronto-striatal and the medial temporal lobe (MTL) memory systems were also found. Sub-BN participants demonstrated increased suppression during early category learning (prediction > perceptual-motor baseline) in regions that comprise the MTL memory system, including the hippocampus, retrosplenial cortex, and middle frontal gyrus (BA 10), in addition to increased late contributions to category learning in the anterior cingulate, precuneus (BA 7), ventrolateral prefrontal cortex (VLPFC; BA 45), and DLPFC (BA 9). Probabilistic category learning initially requires the involvement of flexible and fast learning dependent on the MTL memory system, which then, after sufficient learning has taken place, transfers to the striatal-mediated implicit memory system (Packard and McGaugh, 1996, Poldrack et al., 2001 and Yin and Knowlton, 2006). Consistent with category learning research in healthy young adults (Poldrack et al., 1999 and Poldrack et al., 2001), the control (MC) participants demonstrated this pattern, represented by initial decreased suppression in the hippocampus, retrosplenial cortex, middle frontal gyrus, and anterior and posterior cingulate, which was gradually more suppressed over the course of learning. Sub-BN participants, however, demonstrated initial increases in MTL memory system suppression which were gradually less suppressed over time and overall increases in right caudate and bilateral DLPFC. These findings suggest a distinct pattern of MTL and fronto-striatal memory system utilization; such that Sub-BN participants appear to preferentially engage the fronto-striatal system during implicit probabilistic category learning.

In addition to their eating disorder symptoms, the Sub-BN participants in our study also demonstrated significantly elevated levels of depression compared to MC participants. Both lifetime and current prevalence of mood disorders is common in eating disorders, and lifetime prevalence estimates range from 30% to 50% in community samples of BN and subthreshold or partial syndrome BN (Godart et al., 2007). By correlating level of depression with our ROI data, we demonstrated that level of depression did not influence our fronto-striatal and MTL findings. Interestingly, prior to correcting for multiple comparisons, the left precuneus demonstrated a significant positive correlation with level of depression, a region of the posterior medial cortex that has been implicated in depression and associated with difficulty disengaging from self-reflection (Johnson et al., 2009). It should also be noted that stage of menstrual cycle and feeding status prior to fMRI scanning were not controlled; therefore, future studies are needed to delineate the contribution of potential caloric deprivation, which can lead to metabolic, neuroendocrine and volumetric differences, to these findings.

Conclusions

The current results demonstrate changes in the processing efficiency of the fronto-striatal system in women with Sub-BN. The results further our understanding of subthreshold bulimia nervosa by demonstrating that individuals with Sub-BN display distinct patterns of functional activity in the fronto-striatal system during probabilistic category learning in the absence of differences in behavioral performance. The reduced efficiency of the fronto-striatal system may also contribute to the presence of psychological symptoms of eating disorders (elevated levels of concern about shape, weight, and/or eating) that precipitate, accompany, and maintain behavioral symptoms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

This research was supported by the Boston University Department of Psychology, and National Center for Research Resources (P41RR14075). We thank Dr. Russell Poldrack and Dr. Karin Foerde for providing their weather prediction task experimental design, as well as Jessica Saurman for her help with participant recruitment. We also thank Mary Foley, Larry White, and the Martinos Center staff for assistance with magnetic resonance imaging data collection.

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Research Highlights

- fMRI study of fronto-striatal learning system in eating disorder behaviors.
- Participants characterized as subthreshold bulimia (Sub-BN) category of EDNOS.
- Sub-BNs did not vary behaviorally from controls on probabilistic category learning.
- Sub- BNs showed increases in caudate nucleus and dorsolateral prefrontal cortex.
- Sub-BNs showed distinct temporal pattern of fronto-striatal and MTL systems.

Fig. 1.

Schematic representation of the weather prediction task experimental paradigm. The left panels represent prediction trials while the right panels represent perceptual-motor trials. Participants completed two runs of six weather prediction blocks (prediction; 100 trials per run) and three perceptual-motor baseline blocks (perceptual-motor; 51 trials per run), for a total of 200 prediction trials and 102 perceptual-motor trials. Cue cards were presented for a total of 3000 ms. There were four possible cue-outcome association strengths: 75%, 57%, 43%, or 25%. Feedback was presented for 1000 ms. Participants were made aware of their progress by showing them their scores during the rest period following weather prediction blocks. The score was initially set at 600 and increased by one unit for each correct response and decreased by one unit for each incorrect response.

Fig. 2. WPT behavioral performance. (a) A trend ($p = 0.089$) toward between-group differences in accuracy may suggest a potential delay in habit acquisition in subthreshold bulimia nervosa (Sub-BN) participants compared to healthy control women (MC) which occurs in quartile 3. (b) Reaction time performance measures revealed no between-group differences. Main effect of quartile for reaction time demonstrated a significant linear trend.

Fig. 3. ROI-based SPM factorial ANOVA. SPMs demonstrate significant differences in category learning related BOLD activity (prediction > perceptual-motor baseline) across groups in anatomical regions of interest. Slices are overlaid on the group-averaged anatomical map. (a) Regions demonstrating significant category learning related BOLD activity in both subthreshold bulimia nervosa (Sub-BN) and matched healthy control (MC) groups. (b) Regions demonstrating significant category learning related BOLD activity by group interactions. (c) Left posterior cingulate, MTL, MFG (BA 10), and anterior cingulate cortex (BA 24) demonstrate significant category learning related BOLD activity by group by quartile interactions. All SPMs corrected for multiple comparisons to $p < 0.05$.

Fig. 4.

Post-hoc contrasts for main effect of category learning related BOLD activity and category learning related BOLD activity $\times$ group interaction. Slices are overlaid on the group-averaged anatomical map. (a) Regions showing significantly different category learning related BOLD activity across all participants when compared to the control task. Regions where category learning related BOLD activity showed greater BOLD signal compared to the control task in both groups are shown in red while regions in blue show greater decreases in fMRI BOLD signal during category learning (prediction > perceptual-motor baseline) compared to the control task. (b) Regions where Sub-BN participants demonstrate greater category learning related BOLD activity. Bar graphs represent percent signal change and are included to demonstrate directionality of fMRI activity differences. Sub-BN participants revealed greater category learning related BOLD activity in the caudate nucleus, bilateral dorsolateral PFC and anterior cingulate cortex. Additionally, Sub-BN participants showed category learning related specific reductions in fMRI BOLD signal in precuneus when compared to MC participants.

Fig. 5.

Group $\times$ category learning $\times$ quartile interactions. (a) Post-hoc random effects two sample t-tests demonstrate significant fMRI BOLD category learning related activity within anatomical regions of interest within each quartile. Slices are overlaid on the group-averaged anatomical map. ROIs where women with subthreshold bulimia nervosa (Sub-BN) demonstrated greater category learning related BOLD activity compared to healthy control women (MC) over time is represented by the red color scale (Sub-BN increased activity) and ROIs where the MC group demonstrated greater category learning related BOLD activity compared to the Sub-BN group over time is represented by the blue color scale (Sub-BN decreased activity). (b) Line graph illustrates significant group $\times$ quartile interaction revealed by post-hoc repeated measures ANOVA utilizing percent signal change extractions from regions demonstrating significant group $\times$ category learning $\times$ quartile effects. While MC participants demonstrate a linear decrease in category learning related BOLD activity within the left posterior cingulate cortex, MTL, middle frontal gyrus (BA 10), and anterior cingulate cortex (BA 24), the Sub-BN participants demonstrate a dysregulated pattern with late increases in category learning related BOLD activity.

Table 1

Demographic and clinical data

	MC (n = 19)		Sub-BN (n = 18)		p-value	Cohen's d
	Mean	SD	Mean	SD		
Age	20.42	1.95	20.67	2.10	0.712 *	-0.12
Education	14.74	1.66	14.26	1.70	0.353 *	0.29
BMI	22.47	2.71	22.98	2.12	0.531 *	-0.21
BDI-II	3.42	3.00	18.33	9.10	<0.0001	-2.20
EDE-restraint	0.21	0.57	3.19	1.18	<0.0001	-3.22
EDE-eating concern	0.01	0.05	2.47	1.01	<0.0001	-3.44
EDE-weight concern	0.20	0.29	3.50	1.36	<0.0001	-3.36
EDE-shape concern	0.39	0.45	3.82	1.21	<0.0001	-3.76
EDI-drive for thinness	0.68	1.70	15.04	4.34	<0.0001	-4.36
EDI-2 bulimia	0.00	0.00	9.17	5.46	<0.0001	-2.38
EDI-2 body dissatisfaction	3.05	5.19	14.72	6.50	<0.0001	-1.98
EDI-2 ineffectiveness	0.58	1.26	8.61	7.00	0.003	-1.60
EDI-2 interpersonal distrust	0.79	1.18	4.78	4.67	0.034	-1.17
EDI-2 interoceptive awareness	2.05	0.52	9.28	5.79	0.001	-1.76
EDI-2 perfectionism	5.05	3.71	9.17	3.92	0.034	-1.10
EDI-2 maturity fears	3.74	2.21	5.44	3.62	1.00	-0.60
EAT26 total	1.26	1.50	28.72	13.38	<0.0001	-2.88
EAT26 dieting	0.68	1.10	20.33	7.42	<0.0001	-3.70
EAT26 bulimia and food prep	0.58	1.10	7.61	5.03	0.0003	-1.93
EAT26 oral control	1.32	2.40	1.50	2.50	1.00	-0.07

* p-values not corrected for multiple comparisons.

Table 2

Results from ROI-based SPM factorial ANOVA

Main effect of category learning activations			
Brain region	x y z (MNI) coordinates	Z-score	k
R dorsolateral PFC (BA 46)	44 32 26	>8	1547
R precuneus (BA 7)	20 -64 42	>8	883
L dorsolateral PFC (BA 9)	-44 14 28	>8	1453
L posterior cingulate (BA 30)	-8 -54 12	>8	1128
L middle frontal gyrus (BA 10)	-4 54 -2	>8	283
L middle frontal gyrus (BA 8)	-22 26 44	>8	198
L caudate nucleus (body)	-14 2 14	>8	354
R caudate nucleus (body)	16 0 16	>8	306
L anterior cingulate (BA 32)	-6 30 30	>8	262
L hippocampus	-30 -32 -12	>8	166
R middle frontal gyrus (BA 10)	32 50 4	7.75	223
Group × category learning interaction activations			
Brain region	x y z (MNI) coordinates	Z-score	k
R dorsolateral PFC (BA 9)	34 38 32	4.87	1110
L ventrolateral PFC (BA 44)	-44 14 30	4.33	1132
L precuneus (BA 7)	-0 -40 58	4.22	1100
R middle frontal gyrus (BA 6)	30 8 56	3.76	213
L anterior cingulate (BA 32)	-10 32 24	3.22	185
R anterior cingulate (BA 32)	10 42 22	3.12	233
Group × category learning × quartile interaction activations			
Brain region	x y z (MNI) coordinates	Z-score	k
L posterior cingulate (BA 23)	-6 -58 14	4.96	2332
L hippocampus	-18 -32 -10	4.24	119
L middle frontal gyrus (BA 10)	-26 40 30	4.23	534
L anterior cingulate (BA 24)	-2 38 8	3.52	250

R, right; L, left; BA, Brodmann area; PFC, prefrontal cortex.

k = number of voxels in the cluster.

Table 3

Between group differences

Group × category learning × quartile activations			
MC>Sub-BN			
Brain region	x y z (MNI) coordinates	Z-score	k
<i>Quartile 1</i>			
R hippocampus	20 -26 -12	3.71	190
L hippocampus	-18 -32 -10	3.86	156
L post cingulate (BA 29)	-10 -50 8	3.31	849
L ant cingulate (BA 32)	-0 50 2	2.93	186
L middle frontal gyrus (BA 10)	-32 34 14	2.77	346
<i>Quartile 2</i>			
R hippocampus	22 -42 0	3.85	440
R precuneus (BA 7)	18 -76 48	2.66	144
L retrosplenial cortex	-22 -52 4	4.52	357
R ant cingulate	16 50 14	2.95	180
R middle frontal gyrus (BA 10)	32 50 4	7.75	223
Sub-BN>MC			
Brain region	x y z (MNI) coordinates	Z-score	k
<i>Quartile 2</i>			
R VLPFC (BA 45)	44 32 6	3.28	130
L ant cingulate (BA 32)	-12 34 28	3.26	113
R precuneus	6 -54 48	2.77	260
<i>Quartile 3</i>			
R precuneus (BA 7)	14 -48 56	2.80	190
<i>Quartile 4</i>			
R dorsolateral PFC (BA 9)	44 26 30	2.73	369
L dorsolateral PFC (BA 9)	-28 30 40	3.19	423
R ant cingulate (BA 32)	6 40 22	3.08	403
L precuneus (BA 7)	0 -50 56	3.79	1878

R, right; L, left; BA, Brodmann area; PFC, prefrontal cortex.

k = number of voxels in the cluster.