

# Deficient Activity in the Neural Systems That Mediate Self-regulatory Control in Bulimia Nervosa

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**Context:** Disturbances in neural systems that mediate voluntary self-regulatory processes may contribute to bulimia nervosa (BN) by releasing feeding behaviors from regulatory control.

**Objective:** To study the functional activity in neural circuits that subserve self-regulatory control in women with BN.

**Design:** We compared functional magnetic resonance imaging blood oxygenation level–dependent responses in patients with BN with healthy controls during performance of the Simon Spatial Incompatibility task.

**Setting:** University research institute.

**Participants:** Forty women: 20 patients with BN and 20 healthy control participants.

**Main Outcome Measure:** We used general linear modeling of Simon Spatial Incompatibility task–related activations to compare groups on their patterns of brain activation associated with the successful or unsuccessful engagement of self-regulatory control.

**Results:** Patients with BN responded more impulsively and made more errors on the task than did healthy con-

trois; patients with the most severe symptoms made the most errors. During correct responding on incongruent trials, patients failed to activate frontostriatal circuits to the same degree as healthy controls in the left inferolateral prefrontal cortex (Brodmann area [BA] 45), bilateral inferior frontal gyrus (BA 44), lenticular and caudate nuclei, and anterior cingulate cortex (BA 24/32). Patients activated the dorsal anterior cingulate cortex (BA 32) more when making errors than when responding correctly. In contrast, healthy participants activated the anterior cingulate cortex more during correct than incorrect responses, and they activated the striatum more when responding incorrectly, likely reflecting an automatic response tendency that, in the absence of concomitant anterior cingulate cortex activity, produced incorrect responses.

**Conclusions:** Self-regulatory processes are impaired in women with BN, likely because of their failure to engage frontostriatal circuits appropriately. These findings enhance our understanding of the pathogenesis of BN by pointing to functional abnormalities within a neural system that subserves self-regulatory control, which may contribute to binge eating and other impulsive behaviors in women with BN.

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**B**ULIMIA NERVOSA (BN) TYPICALLY begins in adolescence or young adulthood. Primarily affecting girls and women, it is characterized by recurrent episodes of binge eating followed by self-induced vomiting or another compensatory behavior to avoid weight gain. These episodes of binge eating are associated with a severe sense of loss of control.<sup>1,2</sup> Mood disturbances and impulsive behaviors are common in individuals with BN, suggesting the presence of more pervasive difficulties in behavioral self-regulation.<sup>2</sup> Thus, dysregulated control systems may contribute to the binge eating and associated purging behaviors, perhaps by releasing feeding behav-

iors from regulatory control. Concomitant with familial and sociocultural determinants,<sup>1</sup> disturbances in these systems likely contribute to the pathogenesis of BN.

The functions of self-regulatory control rely on frontostriatal components of cortico-striato-thalamo-cortical circuits, including projections from the ventral prefrontal cortex (PFC) and anterior cingulate cortex (ACC) to the basal ganglia.<sup>3</sup> The Simon Spatial Incompatibility task<sup>4</sup> engages these functions by requiring participants to ignore a prepotent feature of a stimulus to respond to a more task-relevant one. Participants must indicate the direction that an arrow is pointing (left or right), regardless of the side of a screen on

which it appears. When the direction matches the side of the screen on which the arrow appears, participants perform the task easily, as demonstrated by their rapid responses and infrequent errors. When the direction does not match the side of the screen (eg, a leftward-pointing arrow on the right side), the task is more difficult, as indicated by slower responses and more errors. Ignoring the task-irrelevant feature on these incongruent trials requires the mobilization of attentional resources, resolution of cognitive conflict, inhibition of automatic response tendencies, and thus the engagement of voluntary self-regulatory control processes.

Healthy individuals activate large expanses of ACC, PFC, and striatum while performing the Simon Spatial Incompatibility task<sup>5-7</sup>; this is consistent with findings from studies of healthy individuals performing other tasks requiring conflict resolution and response inhibition (eg, Stroop, go/no-go, flanker, and stop tasks).<sup>7-12</sup> By comparing brain activation during successful and unsuccessful trials, these studies have additionally highlighted the differential contributions of various prefrontal regions to self-regulatory functions. Some findings suggest that the dorsal ACC preferentially mediates performance or error monitoring,<sup>7-10</sup> whereas others implicate the rostral ACC in affective responses to the commission of errors.<sup>13-15</sup>

Patients with BN perform worse than controls on various executive function tasks.<sup>16-18</sup> Findings of increased interference from disorder-salient words (eg, food- and/or body shape-related stimuli) on modified Stroop tasks<sup>19-24</sup> suggest that poor inhibitory performance in patients with BN reflects their attentional bias toward food, weight, and body shape. However, patients with BN also tend to make more inhibitory failures than controls on go/no-go tasks<sup>25</sup> and show deficits in cognitive switching,<sup>26,27</sup> which suggests that they are cognitively impulsive<sup>26,28</sup> and have more generalized deficits in response inhibition and voluntary control processes. No functional magnetic resonance imaging study to date has investigated these processes in BN with a standard task of response inhibition.

We report on an event-related functional magnetic resonance imaging study in which we used the Simon Spatial Incompatibility task to investigate differences in the neural substrates of self-regulatory control in women with and without BN. Our a priori hypothesis was that patients with BN would not engage frontostriatal regulatory circuits to the same extent as healthy comparison participants. Based on prior electrophysiological findings of reduced error monitoring in patients with anorexia nervosa,<sup>29</sup> we suspected that exploratory analyses would reveal an altered pattern of error-related brain activity in the ACC of patients relative to controls.

## METHODS

### PARTICIPANTS

Patients were recruited through the Eating Disorders Clinic at the New York State Psychiatric Institute, where they were receiving treatment. Controls were recruited through flyers posted in the local community. Patients and controls were women matched by age and body mass index. Participants with a history of neurological illness, past seizures, head trauma with loss

of consciousness, mental retardation, pervasive developmental disorder, or current Axis I disorders (other than major depression in the patients) were excluded. Controls had no lifetime Axis I disorders. The institutional review board at the New York State Psychiatric Institute approved this study and all participants gave informed consent before participating.

Formal diagnoses of BN were established through clinical interviews conducted by a board-certified psychiatrist. The presence of comorbid neuropsychiatric diagnoses were established using the Structured Clinical Interview for DSM Disorders.<sup>30</sup> Bulimic symptom severity and prior diagnoses of anorexia nervosa were assessed using the Eating Disorders Examination.<sup>31</sup> The Beck Depression Inventory II (BDI-II)<sup>32</sup> and the Hamilton Depression Scale<sup>33</sup> quantified depressive symptoms. The DuPaul-Barkley attention-deficit/hyperactivity disorder rating scale quantified symptoms of inattention and hyperactivity.<sup>34</sup> Full-scale IQs were estimated using the Wechsler Abbreviated Scale of Intelligence.<sup>35</sup>

### STIMULI

Stimuli were presented through nonmagnetic goggles (Resonance Technology Inc, Northridge, California) using E-Prime software (Psychology Software Tools Inc, Pittsburgh, Pennsylvania). A series of white arrows pointing either left or right were displayed against a black background either to the left or right of a midline crosshair. Stimuli subtended 1° vertical and 3.92° horizontal of the visual field. Stimuli were either congruent (pointing in the same direction as their position on the screen) or incongruent (pointing in the opposite direction of their position on the screen).

Participants were instructed to respond quickly to the direction of the arrows by pressing a button on a response box with their right hand, using their index finger for a left-pointing arrow and their middle finger for a right-pointing arrow. The button-press recorded responses and reaction times for each trial. Stimulus duration was 1300 milliseconds, with an interstimulus interval of 350 milliseconds. Each run contained 102 stimuli (185 seconds), with an incongruent stimulus presented pseudorandomly every 13 to 16 congruent stimuli (21.5-26.4 seconds apart). In each run, 51 arrows were left-pointing and 51 were right-pointing; 51 appeared to the left of the midline and 51 appeared to the right. Half of the incongruent stimuli required the same response as the preceding congruent stimulus. Each experiment contained 10 runs, totaling 68 incongruent and 952 congruent stimuli.

### IMAGE ACQUISITION

The functional images were obtained using a T2\*-sensitive, gradient-recalled, single-shot, echo-planar pulse sequence (repetition time=2200 milliseconds, echo time=30 milliseconds, 90° flip angle, single excitation per image, 24 × 24-cm field of view, 64 × 64 matrix, 34 slices 3.5-mm thick, no gap, covering the entire brain). We collected 80 echoplanar imaging volumes for each run.

### BEHAVIORAL ANALYSIS

Reaction times and accuracy scores were entered as dependent variables in separate repeated-measure, linear mixed models in SAS, version 9.0 (SAS Institute Inc, Cary, North Carolina) with diagnosis (BN or healthy control), age, full-scale IQ, and BDI-II scores as covariates. Stimulus type (congruent or incongruent) was the within-subject variable in each model. Group differences in performance on congruent and incongruent trials were tested by assessing the significance of the diagnosis × stimulus interaction in each model. We used an un-

**Table 1. Demographic and Clinical Characteristics of Study Participants**

Characteristic	Mean (SD)		$t_{38}$	P Value
	Patients With Bulimia Nervosa (n=20)	Controls (n=20)		
Age, y	25.7 (7.0)	26.35 (5.7)	0.32	.75
Height, cm	165.4 (8.9)	164.8 (4.8)	-0.18	.85
Weight, kg	62.0 (5.8)	59.9 (5.8)	-1.11	.27
Body mass index <sup>a</sup>	22.92 (2.3)	22.24 (2.2)	-0.96	.34
Duration of illness, y	9 (7.2)			
Education, y	15.52 (2.2)	16.4 (1.7)	1.36	.18
WASI IQ				
Full-scale	111.9 (10.9)	118.55 (13.0)	1.68	.10
Verbal	112.5 (12.4)	121.15 (11.4)	2.28	.02
Performance	109.15 (10.9)	110.75 (13.5)	0.41	.68
EDE rating, mean (SD), range				
OBEs in past 28 d	35.8 (30.7), 8-135			
Vomiting episodes in past 28 d	65.25 (75.2), 2-28			
Preoccupation with shape and weight	4.4 (2.0), 2-6			
HAM-D score	12.05 (7.9)	1.05 (1.2)	-6.09	<.001
BDI-II score	17.35 (14.5)	1.55 (2.8)	-4.75	<.001
ADHD rating scores				
Total current	14.21 (10.8)	5.6 (5.9)	-3.09	.004
Inattention	8.36 (6.7)	2.95 (3.8)	-3.09	.004
Hyperactivity	5.85 (5.3)	2.65 (2.4)	-2.42	.02
Past AN, No. (%)	6 (30)			
Taking medication, No. (%)	6 (30)			
Subclinical bulimia nervosa, No. (%) <sup>b</sup>	3 (15)			

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AN, anorexia nervosa; BDI-II, Beck Depression Inventory II; EDE, Eating Disorders Examination; HAM-D, Hamilton Depression Scale; OBE, objective bulimic episode; WASI, Wechsler Abbreviated Scale of Intelligence.

<sup>a</sup>Calculated as weight in kilograms divided by height in meters squared.

<sup>b</sup>Patients who presented with subclinical bulimia nervosa, with no binge eating (n=2) or vomiting episodes (n=1) during the 28 days prior to participation.

paired *t* test to assess group differences in interference scores (mean reaction times for incongruent–mean reaction times for congruent trials). Posterror adjustments in performance were calculated for both groups.<sup>36,37</sup> In patients, correlation analyses assessed the association of behavioral performance with the severity of symptoms.

## IMAGE ANALYSIS

Preprocessing procedures are described in Supplemental Material available at [http://childpsych.columbia.edu/brainimaging/supplementalmaterial/MarshR\\_0804.doc](http://childpsych.columbia.edu/brainimaging/supplementalmaterial/MarshR_0804.doc). First-level parametric analyses were conducted individually for each participant using a modified version of the general linear model in statistical parametric mapping 2 (SPM2) (Wellcome Department of Imaging Neuroscience, London, England). Preprocessed blood oxygenation level–dependent time series data at each voxel, concatenated from all 10 runs of the Simon Spatial Incompatibility task (800 volumes), were modeled using 3 independent functions for each run (30 independent variables in total): (1) a boxcar function representing incongruent correct trials, convolved with a canonical hemodynamic response function, (2) a boxcar function representing congruent correct trials, convolved with a hemodynamic response function, and (3) a constant, following the principles of SPM.<sup>38</sup> Euclidean normalization and orthogonalization of parametric variables (SPM2 default functions) were not performed. For each participant, least-squares regression estimated parameters for the 30 independent variables. These estimates for the 10 runs were summed to produce 2 contrast images per participant: (1) incongruent-correct vs congruent-correct, and (2) incongruent-incorrect vs incongruent-correct, which assessed brain activity during engagement of self-regulatory control and the commission of errors, respectively.

## HYPOTHESIS TESTING

We tested whether patients and controls differed in brain activity during correct responses on incongruent trials compared with correct responses on congruent trials. An analysis of covariance with interference scores as covariates identified group differences in brain activity, independent of task performance (Supplemental Material).

## RESULTS

### PARTICIPANTS

Twenty BN patients and 20 controls participated. All were right-handed. Patients included 9 inpatients who underwent testing within 1 month of admission and 8 outpatients. The remaining 4 patients were no longer receiving treatment but were still symptomatic. No one met criteria for major depression or attention-deficit/hyperactivity disorder (**Table 1**). Six patients were taking selective serotonin reuptake inhibitors. Groups did not differ in movement during the scan (Supplemental Material).

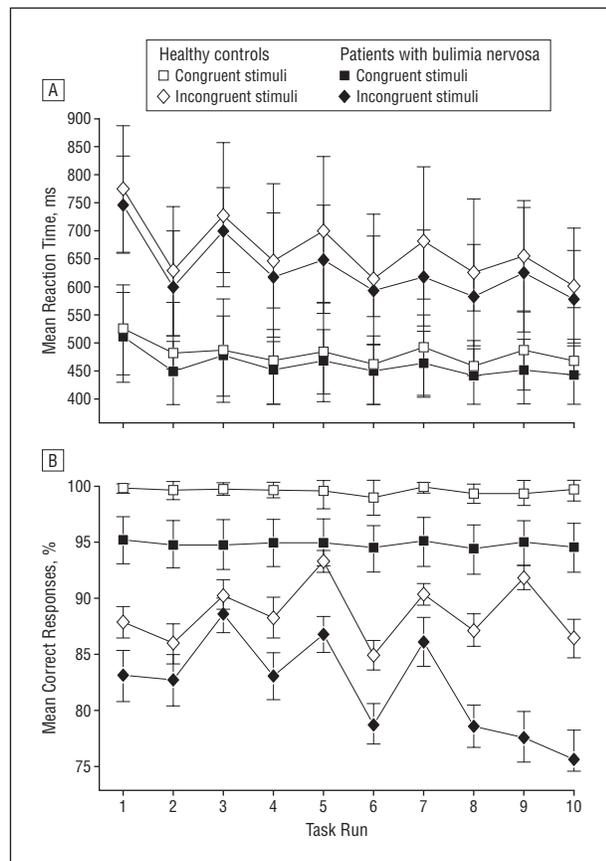
### BEHAVIORAL PERFORMANCE

There was a significant diagnosis  $\times$  stimulus type interaction ( $F_{1,38}=4.67$ ;  $P=.03$ ) that derived from faster reaction times in the patients during incongruent correct trials compared with controls ( $t_{38}=2.33$ ,  $P=.02$ ; mean [SD], 634 [8.6] vs 664 [8.6] milliseconds). Inter-

**Table 2. Group Differences on Performance Measures**

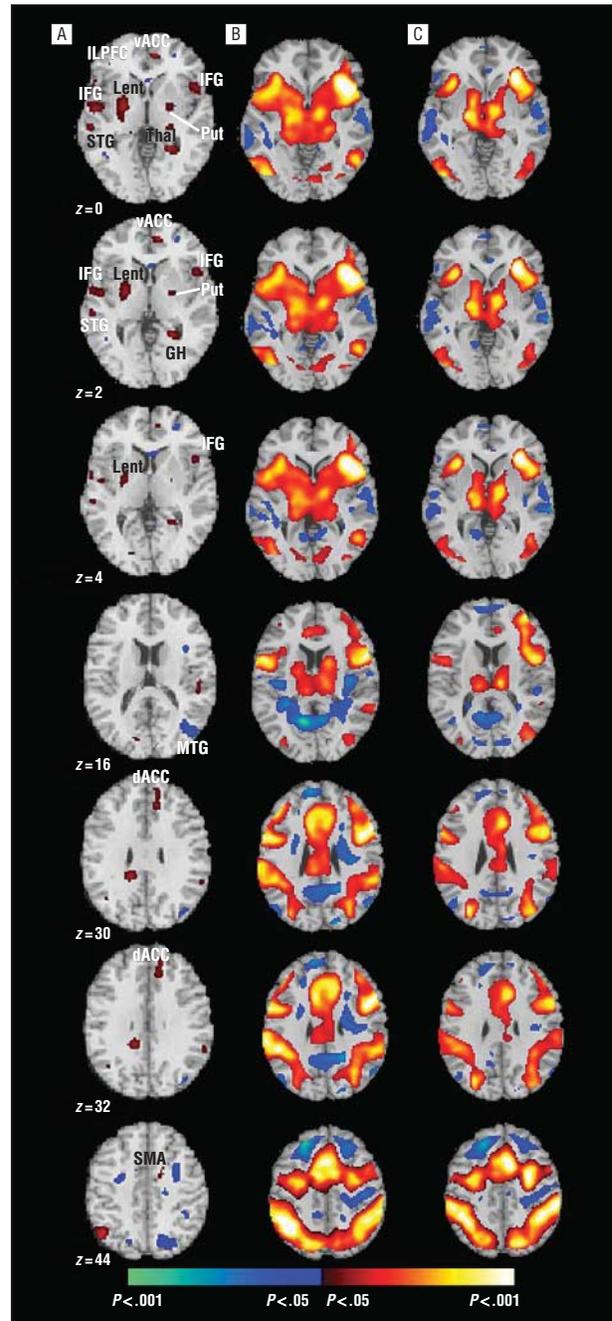
Measure	Mean (SD)		$t_{38}$	P Value
	Patients With Bulimia Nervosa	Controls		
Mean reaction time, ms				
Incongruent	634 (8.6)	664 (8.6)	2.57	.01
Congruent	462 (8.6)	480 (8.6)	1.49	.14
Interference <sup>a</sup>	172 (4.4)	185 (4.4)	2.08	.04
Errors				
Incongruent, %	10.1 (0.7)	7.4 (0.7)	-2.59	.01
Congruent, %	4.5 (0.7)	4.2 (0.7)	-0.33	.75
Effect <sup>b</sup>	5.5 (0.76)	3.2 (0.76)	2.18	.04
Posterior adjustments, ms	-40.69 (59.3)	-24.5 (79.1)	0.69 <sup>c</sup>	.49

<sup>a</sup>Interference = mean reaction time for incongruent tasks - mean reaction time for congruent tasks.  
<sup>b</sup>Error effect = errors for incongruent tasks - errors for congruent tasks.  
<sup>c</sup> $t_{18}$ .



**Figure 1.** Mean latency (A) and accuracy (B) of responses on the Simon Spatial Incompatibility task as a function of bulimia nervosa.

ference scores were significantly lower in patients owing to their faster responses on incongruent trials; they also made significantly more errors on incongruent trials (**Table 2**). Accuracy on incongruent trials decreased across runs in the patients, suggesting a diminishing reserve for inhibitory control with time



**Figure 2.** Axial slices showing group average brain activations during correct trials of the Simon Spatial Incompatibility task in healthy controls and patients with bulimia nervosa. A, Group  $\times$  stimulus (congruent vs incongruent) interactions were detected in frontostriatal regions (red). Main effects of stimulus condition (congruent vs incongruent) are shown for the healthy participants (B) and those with bulimia nervosa (C) ( $P < .05$ , cluster  $> 25$  adjacent voxels; yielding a conjoint effective,  $P < .000005^{39}$ ). The combined application of a statistical threshold and cluster filter substantially reduces the false-positive identification of activated pixels at any given threshold.<sup>40</sup> Increases in signal during correct incongruent trials relative to correct congruent trials are shown in red, and decreases are shown in blue. dACC indicates dorsal anterior cingulate cortex; GH, hippocampal gyrus; IFG, inferior frontal gyrus; ILPFC, inferolateral prefrontal cortex; Lent, lenticular nucleus; MTG, medial temporal gyrus; Put, putamen; SMA, supplementary motor area; STG, superior temporal gyrus; Thal, thalamus; vACC, ventral anterior cingulate cortex.

(**Figure 1**). Full-scale IQ, BDI-II, and attention-deficit/hyperactivity disorder rating scores did not account for significant variance in reaction times or

**Table 3. Greater Frontostriatal Activations in Controls Compared With Patients With Bulimia Nervosa During the Engagement of Self-regulatory Control**

Activated Region	Location		No. of Voxels	Peak Location			<i>t</i> Statistic	<i>P</i> Value
	Side	BA		x	y	z		
Inferolateral prefrontal cortex	L	45	112	-40	42	-6	2.55	.004
Lenticular nucleus	L	NA	917	-22	-4	-2	2.77	.008
Inferior frontal gyrus	L	44	448	-52	-6	-4	2.55	.007
	R	44	322	48	2	-6	2.68	.005
Thalamus	L/R	NA	55	24	-26	-2	2.39	.01
Anterior cingulate cortex	R	32	205	12	36	32	2.40	.01
	R	32	33	12	50	0	2.34	.01
Putamen	R	NA	151	22	-6	0	2.16	.01
Caudate nucleus	R	NA	32	20	6	16	2.14	.01

Abbreviations: BA, Brodmann area; L, left; NA, not applicable; R, right.

accuracy ( $P > .1$ ). Neither group exhibited posterror slowing; to the contrary, patients responded significantly faster on trials following incorrect (vs correct) responses to incongruent stimuli (BN, mean,  $-40.7$  [SD, 79] milliseconds, paired  $t_{18} = -2.91$ ,  $P = .01$ ). Significant inverse associations of accuracy scores on incongruent trials with Eating Disorders Examination scores (objective bulimic episodes:  $r = -0.21$ ,  $P < .001$ ; vomiting episodes:  $r = -0.26$ ;  $P < .001$ ; preoccupation with weight and body shape ratings:  $r = -0.09$ ,  $P = .003$ ) indicated that the most symptomatic patients made the most errors on trials that required volitional control. These inverse associations remained significant even when covarying for depression severity and when 4 patients with BDI-II scores greater than 29 were removed from the analyses.

#### A PRIORI HYPOTHESIS TESTING OF NEURAL ACTIVITY DURING CORRECT RESPONSES

Correct responding on incongruent trials was associated with greater activation of frontostriatal regions in controls than in patients (**Figure 2** and **Table 3**), including the left inferolateral PFC (Brodmann area [BA] 45,  $P = .004$ ) and left lenticular nucleus ( $P = .008$ ). On the right side, these regions included the ventral and dorsal ACC (BA 24/32,  $P = .01$ ), putamen ( $P = .01$ ), and caudate nucleus ( $P = .001$ ). Increased activation in controls was detected bilaterally in the inferior frontal gyrus (BA 44,  $P = .005$ ) and thalamus ( $P = .01$ ).

#### EXPLORATORY ANALYSES

##### Interference Correlates

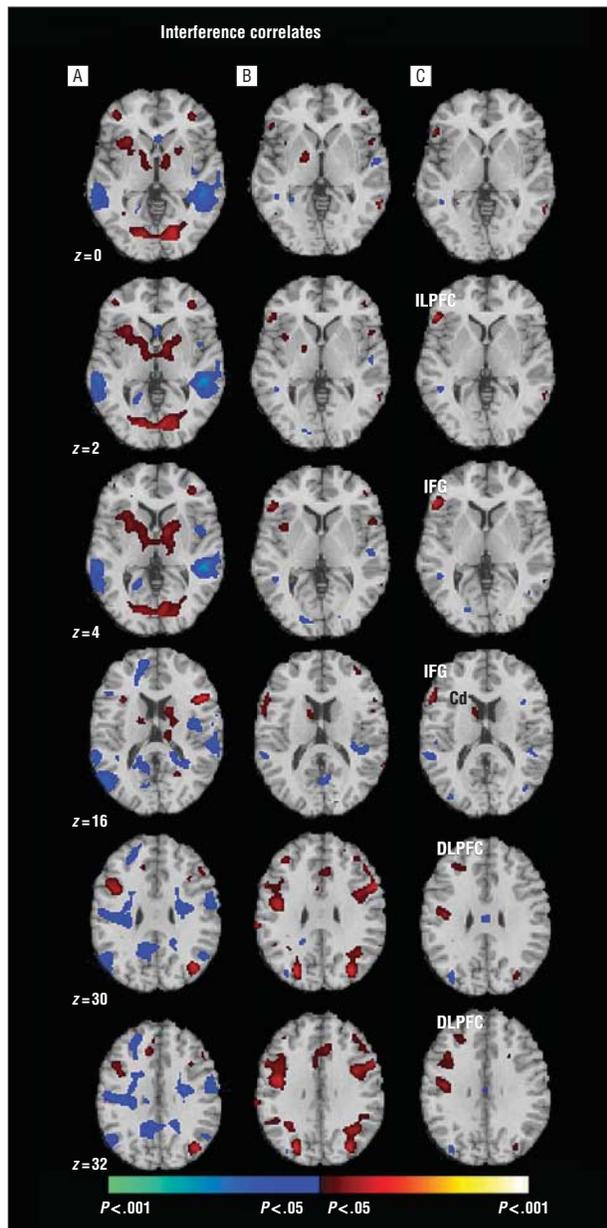
Significant interactions of diagnosis with interference scores during correct responses to conflict trials were detected in prefrontal cortices (inferolateral PFC, inferior frontal gyrus, and dorsolateral PFC) and the dorsal striatum (**Figure 3C**) deriving from stronger correlations in the patients, in whom higher interference scores accompanied greater activation of the dorsolateral PFC and parietal cortices (Figure 3B). In contrast, greater subcortical activation (dorsal striatum, lenticular nucleus, and

thalamus) and less activation of the ventral ACC and the superior temporal and posterior cingulate cortices accompanied greater interference scores in controls (Figure 3A).

##### Neural Activity During the Commission of Errors

Activity in subcortical brain areas during the commission of errors relative to correct responses on conflict trials was greater in controls than in patients, particularly in the right caudate ( $P = .01$ ) and right lenticular nucleus ( $P = .01$ ), and less in the dorsal ACC (BA 24/32) and dorsolateral PFC (BA 9/46) (**Figure 4** and **Table 4**). These findings suggest a differential role of subcortical and cortical regions in task performance in controls, with greater subcortical activity accompanying errors and greater dorsal ACC and dorsolateral PFC activity accompanying correct responses. In contrast, slightly greater dorsal ACC activity was detected in patients during errors than during correct responses (BA 24/32,  $P = .006$ ) (Figure 4C), suggesting that the neural origin of errors and the response to them likely differs between BN patients and controls.

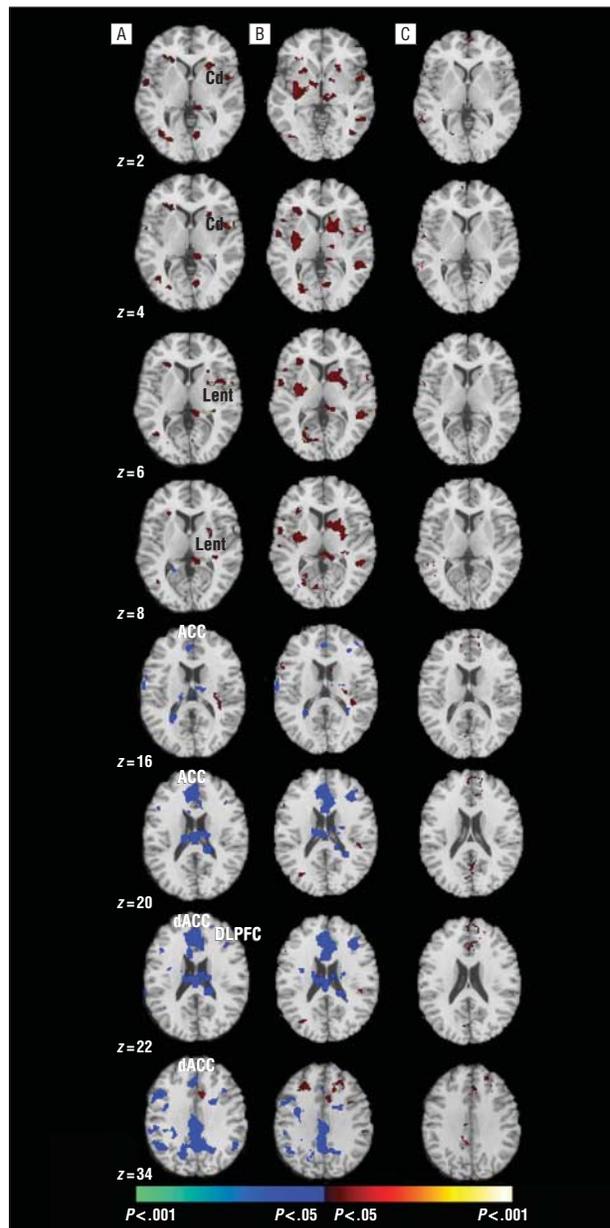
Correlations of activation during correct responses to conflict stimuli with the number of errors committed throughout the task support this interpretation. More errors were committed by the controls who activated subcortical regions (ventral striatum and lenticular nucleus) and the inferior supplementary motor area the most (**Figure 5A**). In contrast, patients who made the most errors generated the least activation of the PFC (ventral ACC and inferior frontal gyrus), insula, ventral striatum, and supplementary motor area (Figure 5B). These group differences produced diagnosis  $\times$  error interactions in frontostriatal regions (Figure 5C). Moreover, correlations of posterror adjustment scores with activation during errors indicated that less dorsal ACC activation during errors (relative to correct responses) accompanied greater posterror slowing in controls (Figure 5D). Time course analyses revealed that dorsal ACC activations following correct and incorrect responses were prolonged in controls compared with activations in patients, rising earlier and declining later (**Figure 6**).



**Figure 3.** Correlations of mean reaction times with signal change during correct conflict trials of the Simon Spatial Incompatibility task in healthy controls (A) and patients with bulimia nervosa (B). Positive correlations are in red, and inverse correlations are in blue. C, Diagnosis  $\times$  interference interactions in prefrontal regions and the caudate nucleus (Cd) stemming from the interference correlates in the patients ( $P < .05$ , cluster  $> 25$  adjacent voxels). DLPFC indicates dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; and ILPFC, inferolateral prefrontal cortex.

### Correlations With Symptom Severity

The number of objective bulimic episodes in the patient group correlated inversely with activation of the right medial prefrontal ( $P = .005$ ), temporal ( $P = .003$ ), and inferior parietal ( $P = .001$ ) cortices and the caudate nucleus ( $P = .005$ ) (Figure 7A), indicating reduced frontostriatal activation in those with the most severe symptoms. In addition, their ratings of preoccupation with body shape and weight correlated inversely with activation of the left caudate ( $P = .03$ ) and left insula ( $P = .03$ ), indicating that the most preoccupied patients engaged these areas the least (Figure 7B).



**Figure 4.** Group average brain activity during the commission of errors. A, Group  $\times$  response (incorrect vs correct) interactions were detected in frontostriatal brain areas ( $P < .05$ , cluster  $> 25$  adjacent voxels). Functional magnetic resonance imaging signal associated with incorrect vs correct responding on incongruent trials of the Simon Spatial Incompatibility task was greater in controls compared with patients with bulimia nervosa in the striatum (red). Increased activity in patients with bulimia nervosa was most prominent in the anterior cingulate cortex (ACC) (blue). Main effects of response are shown in the controls (B) and patients with bulimia nervosa (C). Increases in signal during incorrect incongruent trials relative to incorrect congruent trials are shown in red, and decreases are shown in blue. Cd indicates caudate nucleus; dACC, dorsal ACC; DLPFC, dorsolateral prefrontal cortex; and Lent, lenticular nucleus.

### Medication, IQ, and Comorbidity Effects

Comparing the group average activation map of only the patients who were not taking medications with a map of all patients suggested that medication did not contribute to our findings. Likewise, a history of anorexia nervosa, depressive or attention-deficit/hyperactivity disorder symptoms, and IQ scores were not associated with

**Table 4. Error-Related Activations in Patients With Bulimia Nervosa and Controls**

Activated Region	Location		No. of Voxels	Peak Location			<i>t</i> Statistic	<i>P</i> Value
	Side	BA		x	y	z		
More activation in controls than patients								
Putamen	L	NA	249	-12	0	-8	2.45	.009
Caudate nucleus	R	NA	151	24	18	-2	2.45	.01
Lenticular nucleus	R	NA	53	8	12	10	2.21	.01
More activation in patients than in controls								
Anterior cingulate cortex	L/R	32	1859	-4	44	18	2.62	.006
Dorsolateral prefrontal cortex	R	9/46	198	42	26	22	2.44	.01
Inferior frontal gyrus	R	47	235	40	10	-12	2.51	.008

Abbreviations: BA, Brodmann area; L, left; NA, not applicable; R, right.

group differences in brain activations (**Figure 8** and Supplemental Material).

### COMMENT

Patients with BN exhibited greater impulsivity than did control participants, responding faster and making more errors on conflict trials that required self-regulatory control to respond correctly. They responded faster on congruent trials following incorrect conflict trials, suggesting impulsive responding even immediately after having committed an error. Even when they responded correctly on conflict trials, the patients did not generate the same magnitude of neural activity as controls in the frontostriatal pathways that subserve self-regulatory control, including the left inferolateral PFC (BA 45), lenticular nucleus, inferior frontal gyrus (bilaterally) (BA 44), dorsal ACC (BA 24/32), putamen, and caudate. The less they activated these circuits, the faster they responded to conflict trials. Moreover, patients who generated less activation of frontostriatal circuits (ACC, inferior frontal gyrus, insula, and caudate) also committed more errors across all trials, whereas controls committed more errors when generating greater activity in the striatum. Likewise, when erring on conflict trials, controls displayed more activity in subcortical portions of frontostriatal circuits (left putamen, right caudate, and right lenticular nuclei) and less activation of the dorsal ACC, suggesting that their overreliance on subcortical nuclei in the absence of dorsal ACC activity was associated with more errors. In addition, greater dorsal ACC activity during correct compared with incorrect conflict trials accompanied more posterror slowing in the controls, likely reflecting enhanced conflict monitoring relative to patients.<sup>10,41-43</sup> In contrast, patients generated slightly more activity in the dorsal ACC when making errors than when responding correctly on conflict trials, suggesting enhanced error detection in the patients but limited success in monitoring performance and correcting errors.<sup>41,44,45</sup> Finally, the patients who generated less activity in frontostriatal circuits were those most severely affected with bulimic symptoms.

These group differences in performance and patterns of brain activity suggest that individuals with BN do not activate frontostriatal circuits appropriately, perhaps contributing to impulsive responses to conflict stimuli that

normally require both frontostriatal activation and the exercise of self-regulatory control to generate a correct response. We speculate that this inability to engage frontostriatal systems also contributes to their inability to regulate binge-type eating and other impulsive behaviors.

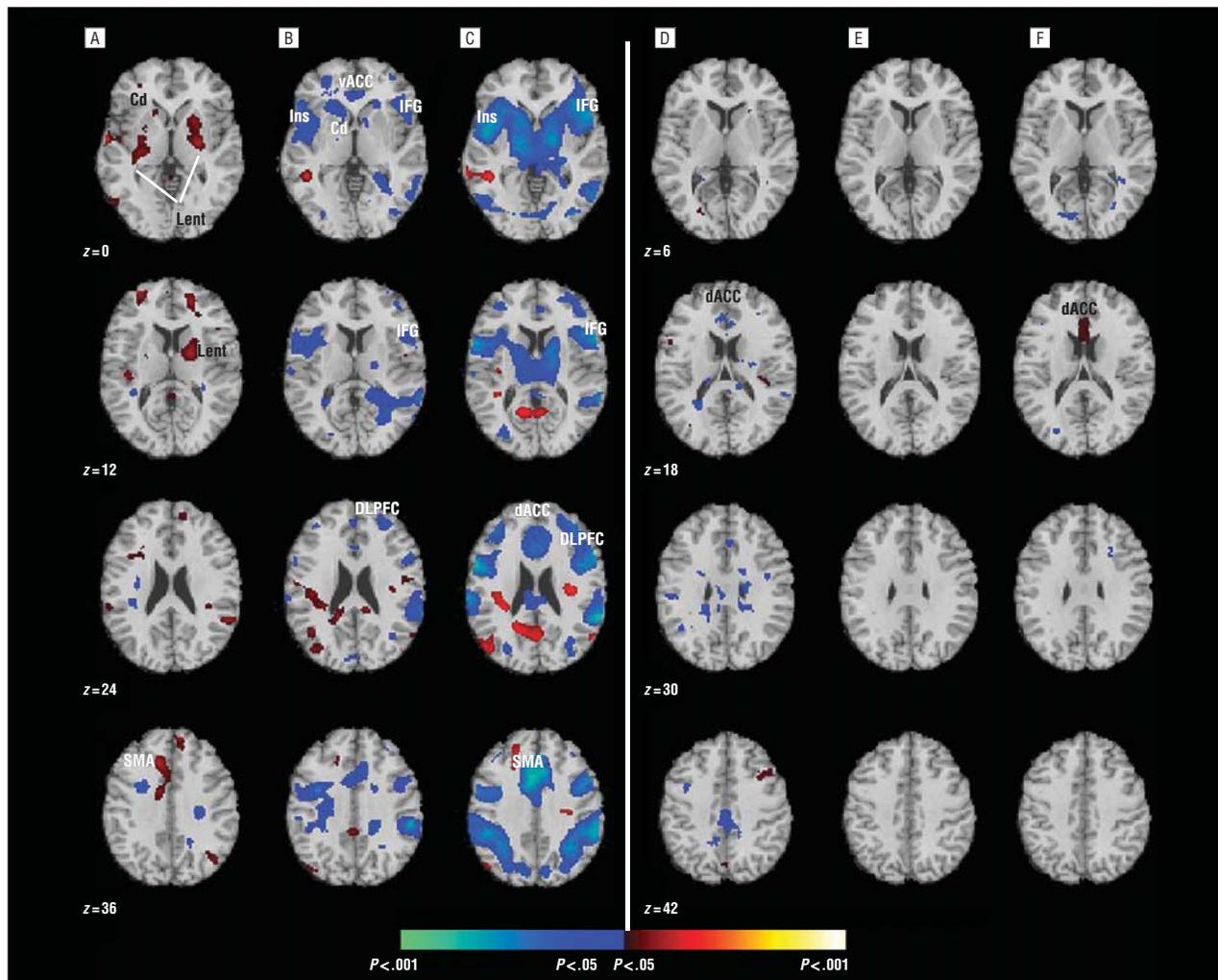
### IMPAIRED BEHAVIORAL PERFORMANCE

Impulsive responding in women with BN suggests the presence of an impaired ability to regulate responses to conflict stimuli, which is consistent with their impulsivity during binge eating while they struggle with conflicting desires to consume fattening foods and avoid weight gain. Our behavioral findings are consistent with those of impaired performance on a go/no-go task in patients with BN<sup>25</sup> and with hypothesized links of binge-eating behaviors to behavioral impulsivity.<sup>46,47</sup> Moreover, accuracy on the Simon Spatial Incompatibility task correlated inversely with BN symptom severity, indicating that those with the most severe symptoms were proportionately less able to inhibit incorrect responses on incongruent trials. Thus, patients with BN may have a more generalized difficulty regulating thought and behavior in domains other than feeding.

### DEFICIENT ACTIVITY IN NEURAL SYSTEMS THAT SUBSERVE SELF-REGULATORY CONTROL

Patients did not generate the same magnitude of activation in frontostriatal circuits as controls during correct responses on conflict trials. Previous functional magnetic resonance imaging studies reported prominent frontostriatal activity in healthy individuals during Simon conflict trials, particularly in the ACC, supplementary motor area, middle and inferior frontal cortex, dorsolateral PFC, caudate, and putamen.<sup>5-7,37</sup> Similar paradigms that measure the ability to inhibit cognitive interference or prepotent responses also generate frontostriatal activity in healthy individuals.<sup>8,11,12,48,49</sup>

Although controls activated both frontal and striatal regions more with increasing interference, patients primarily activated the dorsolateral PFC and parietal cortex more with increasing interference (Figure 3). These findings suggest that increasing activity of frontostriatal circuits in the Simon task supports the regulation of behavior in the presence of conflicting response tenden-



**Figure 5.** Correlations of activations during correct trials with the total number of errors made on the Simon Spatial Incompatibility task by healthy controls (A) and patients with bulimia nervosa (B). Positive correlations are shown in red, and inverse correlations are shown in blue. C, Diagnosis  $\times$  error interactions were detected in prefrontal and striatal regions. Correlations of activations during the commission of errors with posterror adjustment scores in the controls (D) and patients with bulimia nervosa (E). These scores were calculated as the difference of the mean reaction times on trials immediately following erroneous responses and the mean reaction times on trials immediately following correct responses (these subsequent trials were always congruent stimuli because incongruent trials were never preceded by incongruent trials in our version of the Simon task). F, Diagnosis  $\times$  posterior interactions in the dorsal anterior cingulate cortex (dACC) indicate that the controls who engaged this area the most during correct responses to conflict stimuli were those who slowed down most following correct conflict trials (all,  $P < .05$ , cluster  $> 25$  adjacent voxels). Cd indicates caudate nucleus; DLPFC, dorsolateral prefrontal cortex; IFG, inferior frontal gyrus; Ins, insula; Lent, lenticular nucleus; SMA, supplementary motor area; and vACC, ventral anterior cingulate cortex.

cies. Increasing deficiencies in activating these circuits in patients accompanied proportionately faster (more impulsive) responses during conflict trials.

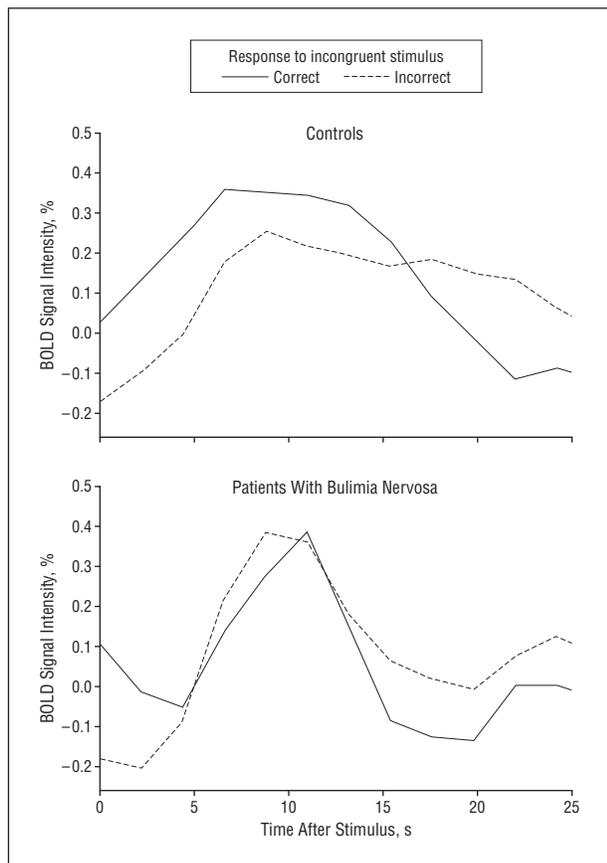
Our findings of deficient frontostriatal circuits are consistent with a previous report of decreased activation of the lateral PFC in response to food stimuli in patients with BN compared with anorexia nervosa patients and controls<sup>50</sup> who were instructed to focus on feelings elicited by food vs non-food stimuli. Because the lateral PFC is thought to contribute to the suppression of undesirable behaviors,<sup>51</sup> diminished activity in this region may account for the impulsivity and loss of control in BN patients when eating.

#### ERROR-RELATED ACTIVITY

Analyses of brain activity during the commission of errors relative to activity when responding correctly to conflict stimuli further suggested that frontostriatal systems may

function abnormally in patients with BN. Controls activated the dorsal ACC more during correct than during incorrect responses to conflict stimuli (Figure 4B). Furthermore, greater dorsal ACC activation during correct vs incorrect responses accompanied more posterror slowing (Figure 5D), likely reflecting a role for dorsal ACC activation in supporting correct responses to conflict trials (Figure 4B) and in adjusting performance to ensure a correct response following an error.

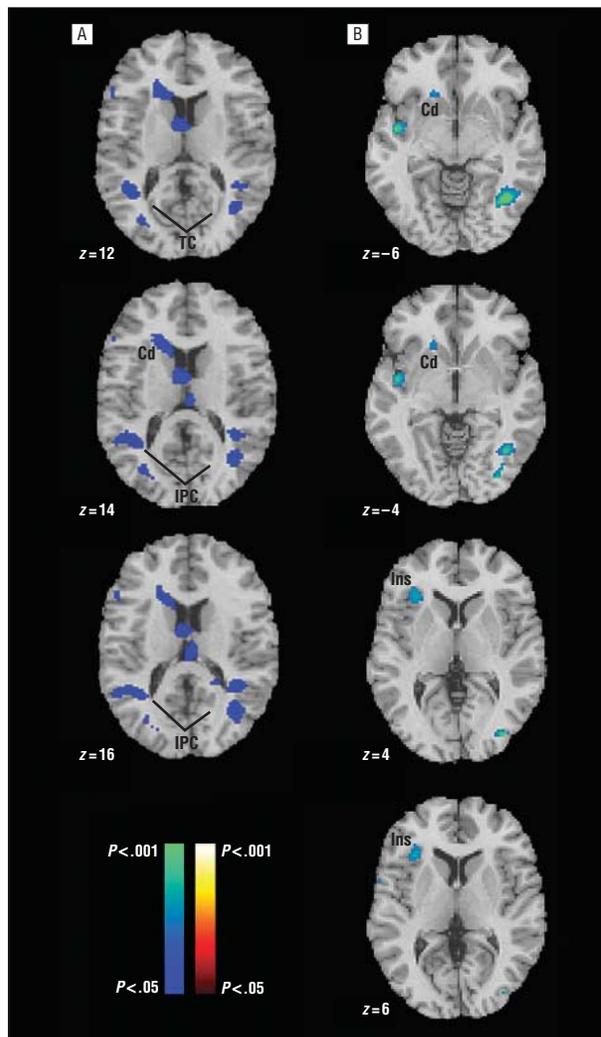
Patients with BN, in contrast, activated the dorsal ACC slightly more during incorrect than correct responses to conflict trials (Figure 4C); its activation did not modulate their performance on subsequent trials (Figure 5E). These findings may suggest the presence of heightened error detection, but limited attempts at error correction, in patients with BN, as their reaction times did not slow following errors. In contrast, an electrophysiological study of persons with anorexia nervosa reported lower error



**Figure 6.** Temporal patterns of maximum dorsal anterior cingulate cortex ( $x=-4$ ,  $y=34$ ,  $z=26$ ) activations following correct and incorrect responses to incongruent stimuli in healthy controls and patients with bulimia nervosa (extracted from Figure 3). Time courses were averaged across voxels in each region of interest for both groups. BOLD indicates blood oxygenation level-dependent.

rates than in controls on a flanker task and reduced error-related negativity, suggesting deficient error detection.<sup>29</sup> Differences across patients with anorexia nervosa and BN in their ability to detect errors, however, may reflect their respective personality characteristics of perfectionism and impulsiveness that distinguish patients with restricting-type from those with binge-type eating disorders.<sup>52</sup> Moreover, less activation of the dorsal ACC and prefrontal and parietal cortices accompanied more errors in patients (Figure 5B), indicating that deficient activation in these regions during correct responses (Figure 2C) was associated with less interference (Figure 3B) and the commission of more errors in patients (Figure 5B). Deficient cortical activation in the patients thus likely accounted for their more impulsive, error-prone performances compared with controls (Figure 1). The differential role of dorsal ACC activity in correct and incorrect responding in controls is consistent with evidence that this area of the brain activates during both error<sup>11</sup> and conflict<sup>10</sup> responses and may have more than a single unitary function in healthy individuals.

Controls activated the striatum without activating cortical regions during incorrect but not during correct responses (Figure 4B). The more they activated the striatum, even during correct responses, the more errors they made (Figure 5A). Thus, when generating more striatal



**Figure 7.** Main effects of symptom severity in patients with bulimia nervosa. A, Inverse correlations of the number of objective bulimic episodes (from the Eating Disorders Examination) with the magnitude of activation during correct responding suggest that the patients with the most episodes of binge eating and purging engaged cortical areas (medial prefrontal cortex, temporal cortex [TC], and inferior parietal cortex [IPC]) and the head of the caudate the least. B, Inverse associations of ratings of preoccupation with weight and shape with task-related activations indicated that the most preoccupied patients engaged the caudate and insula (Ins) the least (all,  $P < .05$ , cluster  $>25$  adjacent voxels). Cd indicates caudate nucleus.

activity, controls were likely engaging an automatic response tendency based within that region.<sup>53,54</sup> In contrast, the more the patients activated both cortical and subcortical regions (ie, the less deficient their overall pattern of brain activation) (Figure 2), the fewer errors they made. Deficient striatal activity in the patients seemed simply to represent a deficient overall frontostriatal activation that likely contributed to impulsive, erroneous responses (Figure 4C).

Although the patients reported more depressive symptoms than did controls, covarying for depressive symptoms did not affect our findings. In addition, the dorsal ACC activated in patients during the commission of errors, whereas the rostral ACC has been shown to activate during affective responses to errors and has been implicated in the pathogenesis of depression.<sup>15</sup>

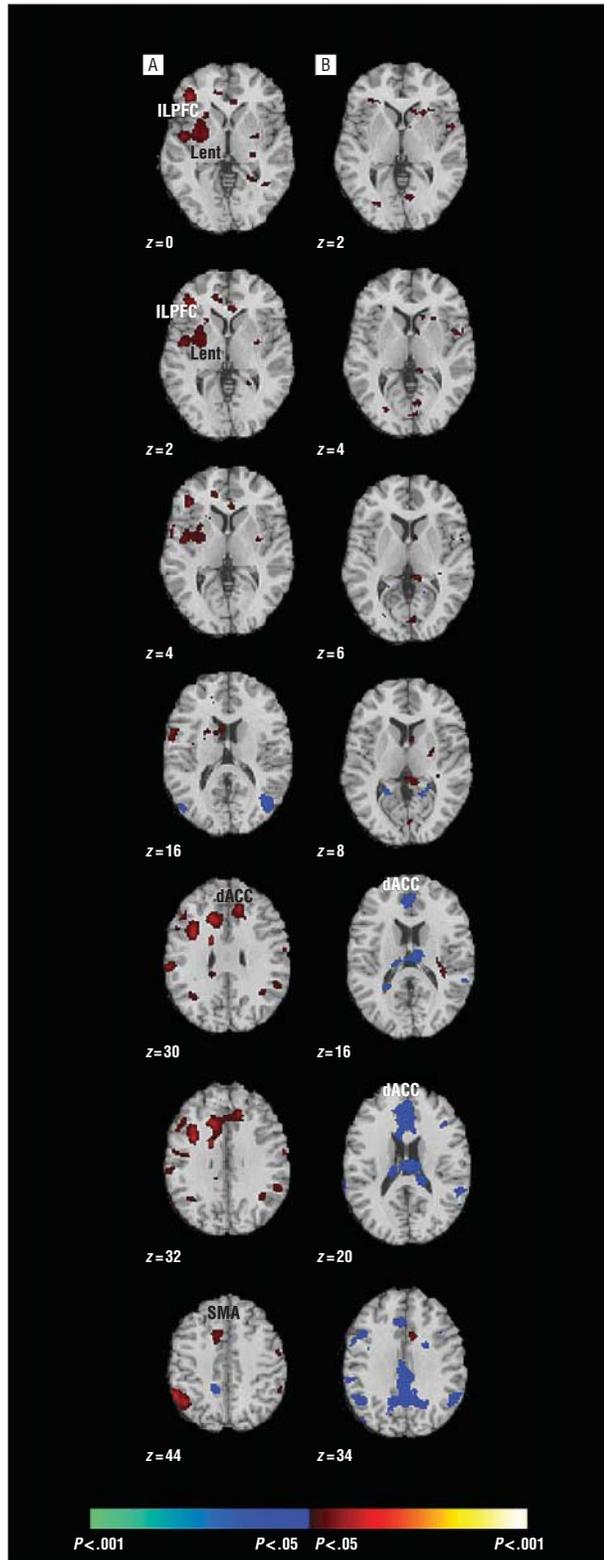
## TIME COURSE OF ACTIVATION

The time course of the blood oxygenation level–dependent response in the dorsal ACC during processing of incongruent stimuli differed in patients and controls (Figure 6). Activation in controls following both correct and incorrect responses rose earlier and declined later than in patients. Peak activity also occurred earlier in controls. Given that patients made more errors that increased across runs (Figure 1), the association of more errors with less dorsal ACC activity (Figure 5) suggests that the reduced duration of the blood oxygenation level–dependent response in patients likely contributed to their reduced activation of this region during correct responses on conflict trials (Figure 2), thereby contributing to their impulsive, erroneous responses. Reduced dorsal ACC activation in controls during incorrect responses (Figure 4 and Figure 5) suggests that the dorsal ACC mediates resolution of cognitive conflict induced by incongruent stimuli, presumably through the exertion of top-down control over automatic response tendencies. In controls, these automatic response tendencies were likely represented by increased activity in the lenticular nucleus during the commission of errors (Figure 4 and Figure 5). Thus, the shorter duration of dorsal ACC activity in patients may have contributed to their poorer performance throughout the task, whereas failure to generate sufficient amplitude of the response in this region contributed to erroneous responses in the controls. Both groups generated activations that declined more slowly following incorrect responses than following correct ones (Figure 6), suggesting the invocation of either compensatory strategies or error-monitoring activities in both groups. Posterror adjustments in performance, however, were not associated with dorsal ACC activity in patients (Figure 5E), which may indicate that this compensatory strategy or error-monitoring activity failed to reduce their errors on subsequent trials.

## STRIATAL AND ANTERIOR CINGULATE ACTIVATION

An excessive reliance on automatic responding, perhaps in the service of responding quickly, would produce incorrect responses on incongruent trials. Indeed, self-regulatory control is required to overcome automatic and habitual responses, such as the stimulus-response mappings that are acquired during the more frequent congruent trials. The dorsal striatum mediates the gradual acquisition of stimulus-response associations, variously termed *procedural* or *habit-based learning*.<sup>53</sup> Top-down control from the PFC via projections to the striatum is required to modulate processing in these areas and to produce a desired action.<sup>44,55</sup> Thus, in controls, incorrect responding on incongruent trials was associated with increased striatal activity, whereas correct responding on these trials (the desired action) engaged both prefrontal and striatal regions. A proper balance of cortical and subcortical activity is likely required to respond correctly and rapidly to incongruent stimuli.

Multiple functions have been assigned to roles that the ACC plays in self-regulation.<sup>10,43,56</sup> Some functional magnetic resonance imaging studies indicate that healthy par-



**Figure 8.** Group differences in brain activations accounting for comorbid depression in patients with bulimia nervosa. A, Group  $\times$  stimulus (congruent vs incongruent) interactions were detected in frontostriatal regions (red). Activations were still greater in healthy controls than in patients with bulimia nervosa when we accounted for Beck Depression Inventory II scores. B, Group  $\times$  response (incorrect vs correct) interactions also remained the same when we accounted for Beck Depression Inventory II scores ( $P < .05$ , cluster  $> 25$  adjacent voxels). dACC indicates dorsal anterior cingulate cortex; ILPFC, inferolateral prefrontal cortex; Lent, lenticular nucleus; and SMA, supplementary motor area.

ticipants activate the rostral ACC during incorrect responses on the go/no-go<sup>9,13</sup> and stop<sup>8</sup> tasks, suggesting that this portion of the ACC preferentially monitors response errors. A conflict-monitoring theory maintains that ACC function enhances cognitive control during the processing of conflicting stimuli, thereby reducing conflict on subsequent trials.<sup>10,41-43</sup> For example, conflict monitoring of the dorsal ACC on a Simon task predicted adjustments in reaction times to incongruent stimuli in healthy participants.<sup>37</sup> Another study of healthy individuals reported significantly less dorsal ACC activity for incorrect than for correct incongruent trials on a Stroop task,<sup>41</sup> consistent with our findings. Thus, dorsal ACC engagement likely helps healthy individuals override conflict to respond correctly on both tasks. Discrepant findings regarding the roles of the ACC and other prefrontal regions may reflect differences in the control processes that are elicited by different tasks.<sup>57</sup> Failing to distinguish the conflict-mediating and error-processing functions of the dorsal ACC from the performance-monitoring functions of the rostral ACC may have added to the discrepant findings.<sup>14,58</sup>

#### ASSOCIATIONS WITH SYMPTOM SEVERITY

The number of objective bulimic episodes correlated inversely with activation of the left caudate nucleus and temporal and inferior parietal cortices, indicating that the most symptomatic patients engaged these regions the least, suggesting the presence of a dose-dependence in the association of cortical-subcortical activation with symptom severity. The most symptomatic patients also performed the worst on the task, further suggesting that disturbances in self-regulatory control in individuals with BN may be a consequence of their reduced engagement of frontostriatal systems. Patient ratings of their preoccupation with shape and weight also correlated inversely with activations in the left caudate nucleus and left insula, indicating that the most preoccupied patients engaged these brain areas the least, consistent with evidence showing that the insula-opercular region is involved in the resolution of cognitive interference.<sup>57</sup>

#### POSSIBLE MECHANISMS UNDERLYING DEFICIENT SELF-REGULATORY CONTROL

The causes of the impulsive, erroneous responding and deficient frontostriatal activation in women with BN during performance of the Simon task are unknown. We speculate that these deficits may be caused by previously reported decreases in serotonin metabolism in frontal cortices in persons with BN.<sup>59,60</sup> Altered serotonergic function likely contributes to their disturbances in self-regulatory control and mood.<sup>59,61</sup> Even in healthy individuals, transient decreases in serotonergic neurotransmission (induced through the acute depletion of dietary tryptophan) produce impulsive and aggressive behaviors<sup>62</sup> and reduces inferior PFC activity during tasks that require inhibitory control.<sup>63</sup> Thus, the impulsive responding and reduced prefrontal activation in our patients, with prior reports of abnormalities in various serotonin indi-

ces in BN, suggests that altered serotonergic neurotransmission likely decreased frontostriatal activation and impaired self-regulatory control. In addition, reduced serotonin transporter availability in the thalami of persons with BN<sup>61</sup> is consistent with our finding of reduced activation in thalamic portions of frontostriatal circuits. The thalamus plays a crucial intermediary role in transmitting information through frontostriatal circuits,<sup>64</sup> which suggests that abnormal serotonin transmission in thalamic nuclei contributes to the overall dysfunction of frontostriatal circuits in individuals with BN. Also noteworthy, frontostriatal regions depend heavily on dopaminergic transmission for proper functioning.<sup>65</sup> Failure to sufficiently activate frontostriatal regions in patients therefore argues *prima facie* for the future study of dopaminergic systems in BN.

#### CONCLUSIONS

The few extant neuroimaging studies in persons with BN have investigated brain function at rest under controlled conditions using body shape- or food-related stimuli to elicit symptom-related processes in the brain.<sup>50,66</sup> We instead used a task to assess the functioning of self-regulatory control processes in individuals with BN in the absence of disorder-specific stimuli. A limitation of this study was the absence of a control group consisting of impulsive individuals with healthy weights and eating behaviors, which would permit assessment of the specificity of frontostriatal abnormalities in persons with BN. In addition, we did not account for menstrual status, which can affect neural functioning in women.<sup>67</sup> We have no reason to suspect, however, that menstrual status differed systematically across groups to confound our findings. Our inclusion of only adult women makes impossible the generalization of findings to men or adolescents with BN. Moreover, impaired self-regulatory control could be a consequence of chronic illness in the patients. Thus, future studies should evaluate the functioning of frontostriatal systems in adolescents with BN closer to the onset of illness. Our sample was heterogeneous in symptom severity, and patients were at differing stages of treatment. Thus, future studies should include larger samples of patients with eating disorders. Studying patients after the remission of symptoms would provide insight into whether impairments in self-regulation are trait- or state-related.

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### Correction

**Error in Funding/Support.** In the Original Article by Strigo et al titled "Association of Major Depressive Disorder With Altered Functional Brain Response During Anticipation and Processing of Heat Pain," published in the November issue of the *Archives* (2008;65[11]:1275-1284), there was an error in the Funding/Support section. It should have said that Drs Paulus and Simmons were supported by the University of California San Diego Center of Excellence for Stress and Mental Health, not Drs Paulus and Strigo.