

# Subcortical Shape Abnormalities in Bulimia Nervosa

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## ABSTRACT

**BACKGROUND:** Bulimia nervosa (BN) is associated with functional abnormalities in frontostriatal and frontolimbic circuits. Although structural alterations in the frontal portions of these circuits have been observed, this is the first study of subcortical surface morphometry and the largest study of subcortical volume in BN.

**METHODS:** Anatomical magnetic resonance scans were acquired from 62 female participants with full and sub-threshold BN (mean age  $\pm$  SD,  $18.7 \pm 4.0$  years) and 65 group-matched healthy control participants (mean age  $\pm$  SD,  $19.3 \pm 5.7$  years). General linear models were used to compare groups and assess the significance of group-by-age interactions on the shape and total volume of 15 subcortical structures ( $p < .05$ , familywise error corrected). Associations with illness severity and duration were assessed in the BN group.

**RESULTS:** Subcortical volumes did not differ across groups, but vertexwise analyses revealed inward shape deformations on the anterior surface of the pallidum in BN relative to control participants that were associated with binge-eating frequency and illness duration. Inward deformations on the ventrolateral thalamus and dorsal amygdala were more pronounced with advancing age in the BN group, and inward deformations on the caudate, putamen, and amygdala were associated with self-induced vomiting frequency.

**CONCLUSIONS:** Our findings point to localized deformations on the surface of subcortical structures in areas that comprise both reward and cognitive control circuits. These deformations were more pronounced among older BN participants and among those with the most severe symptoms. Such precise localization of alterations in subcortical morphometry may ultimately aid in efforts to identify markers of risk and BN persistence.

**Keywords:** Amygdala, Basal ganglia, Bulimia nervosa, Structural MRI, Subcortical shape, Vertex analysis

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Bulimia nervosa (BN) affects 1% to 3% of women (1–3) and is associated with significant medical complications, high rates of comorbid psychopathology, and considerable psychosocial impairment (1,4). Only 30% to 50% of individuals with BN respond to first-line treatments (5,6). Structural and functional brain abnormalities that may maintain recurrent binge eating [defined by a sense of “loss of control over eating” (7)] and compensatory behaviors [e.g., self-induced vomiting (1)] could serve as direct targets for novel treatments. As such, improved identification and characterization of these abnormalities are vital.

Little is known about structural alterations that may contribute to the development or persistence of BN, and it is not clear what alterations pre-date or result from BN symptoms (8). To date, the relatively few anatomical magnetic resonance imaging (MRI) studies of BN have focused on cortical surface morphology and white and gray matter volume. Adults and adolescents with BN show reduced volume and thickness in frontoparietal and temporal cortices relative to control participants and in association with behavioral and cognitive symptoms of BN (9–12). Volume reductions on the surface of inferior frontal cortices are more pronounced with advancing age and are associated with greater illness severity and greater deficits in

cognitive control processes (9). In contrast, adult women with BN show increased volumes of ventral anterior insula and medial orbitofrontal cortex, the latter of which has been associated with sucrose pleasantness ratings (13,14). Together, these findings point to structural abnormalities in cortical regions involved in both control and reward processes in BN.

Findings focused on subcortical structures are mixed, with voxel-based morphometry (VBM) approaches showing increased gray matter density in ventral striatum (13) and with traditional volumetric (i.e., total volume) approaches showing normal (15) nucleus accumbens volumes in individuals with BN compared with control participants. Other VBM and traditional volumetric findings suggest decreased (14–16) or normal (17) gray matter density and volumes of dorsal striatum, specifically the caudate nucleus. These disparate results may be related to small sample sizes, different analytic tools and volumetric measurements, or the inherent limitations of VBM. Although VBM can detect more localized alterations than can total volume analyses, VBM results reflect a mix of variations in size, shape, and position of brain structures (18). In addition, VBM findings depend on smoothing extents and accurate classification of tissue type (19).

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Shape (i.e., vertex) analysis has been used to overcome these limitations in studies of subcortical morphology in healthy individuals (20) and in individuals with psychiatric and neurological disorders (21–24). This approach does not depend on tissue-type classification and includes no additional smoothing. Therefore, compared with VBM, vertex analysis permits comparison of subcortical morphology across groups of individuals with much greater anatomical precision and sensitivity to detect subtle regional differences (e.g., inward or outward deformations). To date, vertex analysis has been used in the eating disorders field only to characterize thalamic shape abnormalities associated with anorexia nervosa (AN) (25).

In the current study, we used high-resolution anatomical MRI and a validated, model-based segmentation toolbox in FSL (FIRST) (19) to examine the volume and shape of subcortical structures in a large sample of adolescent and adult female participants with BN compared with group-matched healthy control (HC) participants. Consistent with some prior findings of reduced gray matter density and total volumes (14–16), we hypothesized that BN would be associated with localized inward deformations, or “inversions,” on the surface of the caudate and putamen, along with reduced total caudate and putamen volume. As this is the first application of shape analysis in BN, we also examined whether BN was associated with localized morphometric alterations in other subcortical structures (nucleus accumbens, pallidum, thalamus, hippocampus, amygdala, and brain stem). Exploratory analyses tested whether alterations were more pronounced in older individuals and associated with more chronic BN (i.e., longer durations of illness) and more severe acute bulimic symptoms (i.e., more frequent current bulimic symptoms). The subcortical structures previously implicated in BN by functional MRI (fMRI) and volumetric studies consist of subregions with distinct projections that comprise distinct corticobasal ganglia and corticolimbic circuits that support specific functions (26). Thus, more accurate and precise localization of subcortical alterations that are associated with BN and scale with age and bulimic symptom measures is an important next step to inform future longitudinal research. Such focal alterations may be more sensitive biomarkers for the disorder.

## METHODS AND MATERIALS

### Participants and Study Design

Structural MRI scans were acquired from HC female participants and adolescent and adult female participants with BN or a BN-spectrum otherwise specified eating disorder (BN with subthreshold frequency or duration of symptoms). Participants were recruited via flyers posted in the surrounding community, via online advertisements, and through the Eating Disorders Clinic at the New York State Psychiatric Institute, where BN participants could receive no-cost treatment. Participants in the BN group were enrolled in the study if they engaged in an average of at least one loss-of-control eating episode (regardless of episode size) or one compensatory behavior episode per week within the past 3 months. BN symptom severity in the past 3 months was assessed using an abbreviated version of the Eating Disorders Examination (27).

Individuals with any history of neurological illness, seizures, head trauma with loss of consciousness, intellectual

developmental disorder, or pervasive developmental disorder were excluded. HC participants had no lifetime history of any Axis I disorder, and BN participants did not meet criteria for any comorbid Axis I disorder other than major depression or anxiety disorders. BN diagnoses and comorbidities were established (28–31) and full-scale IQs were estimated (32) using standard measures (see the Supplement).

All participants over 18 years of age provided written, informed consent. Legal guardians of adolescents under 18 years provided written informed consent and adolescents provided written assent to participate. The New York State Psychiatric Institute’s Institutional Review Board approved this study.

### Image Acquisition

Imaging was performed on a 3T GE Signa whole-body scanner (GE Healthcare, Milwaukee, WI) using an eight-channel coil. High-resolution, T1-weighted images were acquired with a fast-spoiled gradient echo three-dimensional pulse sequence using the following parameters: inversion time, 500 ms; echo time, 1.3 ms; repetition time, 4.7 ms; 1 excitation; matrix size, 256 × 256; field of view, 25 cm; flip angle, 11°; number of slices, 164; slice thickness, 1 mm; voxel dimensions, 0.976 × 0.976 × 1.0 mm.

### Subcortical Shape Analyses

Image preprocessing, including intensity correction and skull stripping, was performed using the DARTEL algorithm from the VBM8 toolbox for SPM (<http://www.neuro.uni-jena.de/vbm/download>). A Bayesian model-based segmentation toolbox in FSL (FIRST; <http://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST>) (19) was used to segment each anatomical image and create vertex meshes for 15 subcortical structures (brain stem, and bilateral nucleus accumbens, putamen, caudate, pallidum, thalamus, hippocampus, and amygdala).

Quality control of the subcortical segmentations was performed by an experienced image analyst (ZW) following FSL FIRST guidelines (<https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FIRST/UserGuide>) and included the following procedures: 1) each raw T1-weighted structural image was visually inspected for distortion or tissue loss; 2) output of the DARTEL algorithm, which performed skull stripping, removed bias and noise, and corrected the global intensity of each raw T1-weighted image, was visually inspected for artifacts or distortion; and 3) for each participant, FSL FIRST output was overlaid onto the corresponding participant-specific skull-stripped T1-weighted image and visually inspected to ensure correct subcortical structural segmentation. No participant had poor structural segmentation.

Vertex analysis was conducted using standard FIRST procedures (19) via the `first_utils` command. For each participant and subcortical structure, vertex indices were calculated based on the signed perpendicular distance from the surface mesh of the corresponding structure in the Montreal Neurological Institute template. Positive indices represented outward deformations on the surface of a given structure, and negative indices represented inward deformations or inversions. These values were then submitted to statistical analysis. Additionally, we computed the volume of each subcortical structure by

generating a mask file in three-dimensional volume space for each structure and multiplying the number of voxels in the mask by voxel size (mm).

### Statistical Analyses

Group differences in subcortical shape were assessed with general linear model-based group comparisons in FSL randomise that included age as a covariate. The significance of group-by-age interactions was assessed to determine the differential effect of age on subcortical shape in the BN and control groups. We report results corrected for multiple comparisons using threshold-free cluster enhancement with a familywise error rate of  $p < .05$  (two-tailed) by running 5000 random permutations. Group differences in subcortical volumes were assessed via general linear models including age as a covariate, and group-by-age interactions tested the differential effects of age on subcortical volume across groups. These volumetric analyses were Bonferroni-corrected for multiple comparisons (two-tailed  $\alpha = .003$ ).

Given the wide range of current illness severity and duration in our sample, exploratory analyses within the BN group using FSL randomise examined associations of the shape of each subcortical structure with acute illness severity, as measured by bulimic symptoms in the past 28 days (9,10,33–39), and months with BN ( $p < .05$ , familywise error corrected). Clinical variables were logarithmically transformed because of significant skewness and included 1) objectively large binge-eating episodes (“objective bulimic episodes”), 2) self-induced vomiting episodes, and 3) illness duration (months).

Sensitivity analyses, presented in detail in the Supplement, assessed potential confounding effects of subthreshold BN ( $n = 11$ ), comorbid major depressive disorder (MDD;  $n = 19$ ), comorbid anxiety disorders ( $n = 8$ ), a lifetime history of AN ( $n = 11$ ), psychotropic medications ( $n = 16$ ), and treatment seeking ( $n = 39$ ).

## RESULTS

### Participants

Scans were acquired from 65 HC participants and 62 participants with BN. Of the 62 participants in the BN group, 11 endorsed loss-of-control eating frequency that was subthreshold for DSM-5 BN diagnosis (40). The BN group included 17 inpatients and 22 outpatients who completed study procedures  $\leq 1$  month before admission or before starting outpatient treatment; the remaining 23 participants were not seeking treatment in our clinic (see the Supplement for further detail). Duration of illness ranged from 2 to 192 months. This sample included 26 HC and 29 BN participants whose data were included in prior analyses of cerebral surface morphology (9). The BN and HC groups did not differ on age, body mass index, full-scale IQ, or race and/or ethnicity (Table 1).

### Group Differences in Subcortical Morphology

Significantly smaller vertex indices (i.e., inward deformations) were detected in the BN group compared with the HC group on the surface of anterior aspects of the lateral and medial right

pallidum ( $p = .038$ ) (Table 2; Figure 1). Projecting this area to a three-dimensional volume atlas (41) using a K-nearest neighbors algorithm revealed that the peak group difference and 57% of the vertices were located in the internal globus pallidus, and 43% were in the external globus pallidus (GPe). Groups did not differ in total volume of any subcortical structure (Supplemental Table S1).

Group-by-age interactions were detected on the surface of left thalamus ( $p = .028$ ) and right amygdala ( $p = .0002$ ) (Figure 2). Scatter plots of these interactions revealed associations of age with inward deformations on these structures in the BN group ( $p$  values  $< .05$ ) in contrast to outward deformations on the surface of the right amygdala in the HC group ( $p < .001$ ) (Figure 2B) and no association of age with thalamus shape in the HC group ( $p = .661$ ). Similarly, a group-by-age interaction for right amygdala volume ( $p = .0009$ ) revealed that age was associated with decreased volume in the BN group in contrast to increased volume in the HC group (Supplemental Table S1).

### Exploratory Symptom Severity Correlates Within the BN Group

In the BN group, the frequency of objective bulimic episodes was associated with inward deformations on lateral and medial right pallidum ( $p = .013$ ) and anterior medial and dorsal aspects of the left pallidum ( $p = .043$ ) (Supplemental Table S2; Figure 3A). A total of 35.7% of the vertices of the right pallidum associated with objective bulimic episode frequency also showed inward deformations relative to those of HC participants.

Vomiting episode frequency was associated with inward deformations on dorsolateral and ventromedial aspects of the right caudate body and tail and anterior ventromedial aspects of the right caudate head ( $p = .042$ ) (Figure 3B), predominantly lateral aspects (dorsal posterior and ventral anterior) of the left putamen ( $p = .011$ ), and dorsal anterior aspects of the right amygdala ( $p = .008$ ). Illness duration was associated with inward deformations on the right ( $p = .005$ ) and left ( $p = .002$ ) pallidum, left caudate ( $p = .021$ ), and right amygdala ( $p = .013$ ) (Supplemental Table S2; Supplemental Figure S1). Because age, illness duration, and objective bulimic episode frequency were themselves intercorrelated ( $r$  values = .42–.74;  $p$  values  $\leq .001$ ), an additional exploratory model included all three variables simultaneously. None of these variables were associated with subcortical shape when controlling for the others.

### Sensitivity Analyses

Excluding BN-group participants who were taking medications or those with subthreshold BN or a comorbid anxiety disorder did not appreciably affect findings of group differences in subcortical shape or interactions with age (see the Supplement). After we excluded those with a history of AN, group differences in right pallidum shape were no longer statistically significant ( $p = .093$ ), but inward deformations on the surface of the right nucleus accumbens emerged in the BN compared with HC group ( $p = .010$ ). Excluding those with comorbid MDD revealed significant inward deformations on the surface of lateral, medial, and ventral aspects of left caudate head ( $p = .045$ ). However, caudate shape was

**Table 1. Demographic, Clinical, and Neuropsychological Characteristics of Participants**

Characteristic	BN Group			HC Group			t or $\chi^2$	p
	n <sup>a</sup>	Mean	SD	n <sup>a</sup>	Mean	SD		
Age, Years	62	18.8	4.0	65	19.3	5.7	-0.63	.53
BMI, Adults <sup>b</sup>	37	22.4	2.5	35	22.6	2.8	-0.34	.74
zBMI, Adolescents	25	0.4	0.6	30	0.1	0.7	1.48	.15
WASI Full-Scale IQ	62	109	11	65	112	16	-1.22	.23
Eating Disorder Severity								
Duration of illness, months	62	43.7	40.5		-	-		
Objective bulimic episodes in past 28 days	62	24.6	27.8		-	-		
Self-induced vomiting episodes in past 28 days <sup>c</sup>	62	44.9	49.8		-	-		
Comorbid Symptoms								
BDI-II score	50	19.0	11.9	53	2.6	4.6	9.11	<.001
Prior AN	11	11	17.7		-	-		
Medication	16	16	25.8		-	-		
Comorbid MDD	19	19	30.6		-	-		
Comorbid anxiety disorder	8	8	12.9		-	-		
Race/Ethnicity							5.14	.40
White/Caucasian	41			35				
African American/Black	4			10				
Hispanic	7			11				
Asian	6			7				
Native American/American Indian	1			0				
Other/Mixed	3			2				

AN, anorexia nervosa; BDI-II, Beck Depression Inventory-II; BMI, body mass index; BN, bulimia nervosa; HC, healthy control; MDD, major depressive disorder; WASI, Wechsler Abbreviated Scale of Intelligence; zBMI, BMI z-score.

<sup>a</sup>Number of participants with available data (continuous variables) or number of participants (categorical variables).

<sup>b</sup>BMI calculation in youths <18 years of age is adjusted for age.

<sup>c</sup>Most of the BN sample (92%) endorsed self-induced vomiting, whereas only 39% endorsed driven exercise, 20% endorsed laxative misuse, and 2% endorsed diuretic misuse.

unassociated with scores on the Beck Depression Inventory-II (42) in the full BN group. Excluding BN participants with comorbid MDD additionally revealed a group-by-age interaction in right pallidum, deriving from an association of age with inward deformations on the lateral surfaces of this region in the BN group ( $p = .039$ ).

## DISCUSSION

This is the first study to examine subcortical shape abnormalities in a large sample of adolescents and adults with BN. As has been observed in studies of other disease states (21,22,24,43), vertexwise shape analyses were more sensitive than volumetric analyses, permitting detection of surface deformations in localized areas that comprise reward (44,45) and cognitive control (46) circuits. Our findings suggest a link between morphometric alterations of basal ganglia structures and BN symptoms. Compared with group-matched control participants, BN-group participants had significant inward deformations on the surface of the anterior right pallidum that were more pronounced among individuals with more frequent binge-eating episodes and longer illness durations. Inversions on the surface of the striatum (right caudate and left putamen) were specifically associated with self-induced vomiting. In addition, our findings of group-by-age interactions on the surface of left thalamus and the surface and total volume of right amygdala may indicate altered developmental trajectories within these structures in BN (47). Inward

surface deformations are thought to reflect atrophy in neurodegenerative disorders (48) and aberrant neurodevelopment (e.g., dendritic arborization) in developmental disorders (49). Although we can only speculate about the functional significance of our findings, the localization of these subcortical shape alterations is a first step toward identifying precise structural markers of the trajectory or maintenance of BN from adolescence to adulthood.

Structural and functional imaging findings from healthy individuals and primates implicate the specific anatomical locations of our findings within the pallidum, striatum, and amygdala in reward and control circuits (26,50–52). Reward

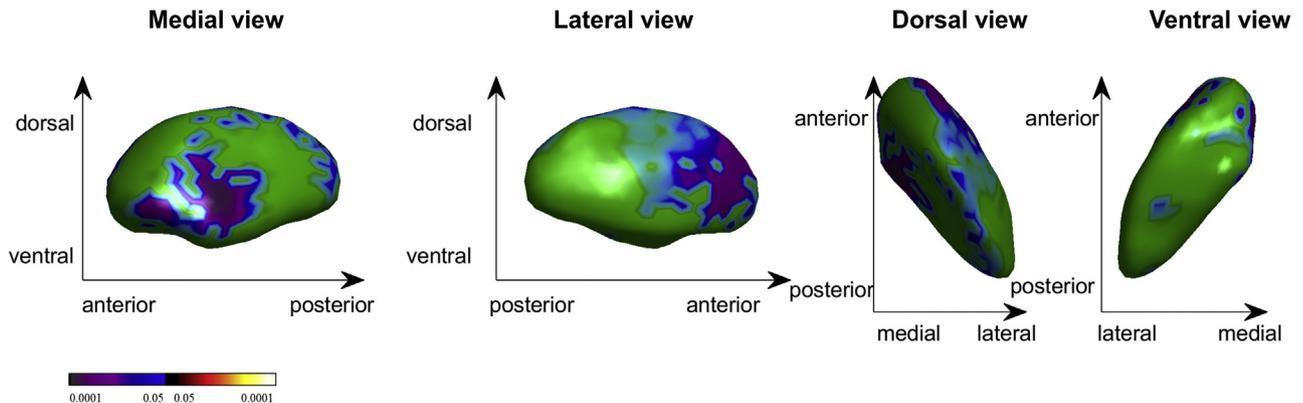
**Table 2. Group Differences and Interactions of Group With Age on Subcortical Shape**

Hem	Structure	Vertices	Peak MNI Coordinates			t	p <sup>a</sup>
			x	y	z		
Group Differences <sup>b</sup>							
R	Pallidum	28	14	-4	-4	-3.40	.038
Group-By-Age Interactions							
L	Thalamus	42	-12	-26	-3	-3.90	.028
R	Amygdala	483	1714	-7	-13	-4.05	.0002

Hem, hemisphere; L, left; MNI, Montreal Neurological Institute; R, right.

<sup>a</sup> $p < .05$ , familywise error corrected.

<sup>b</sup>Group differences were adjusted for age.

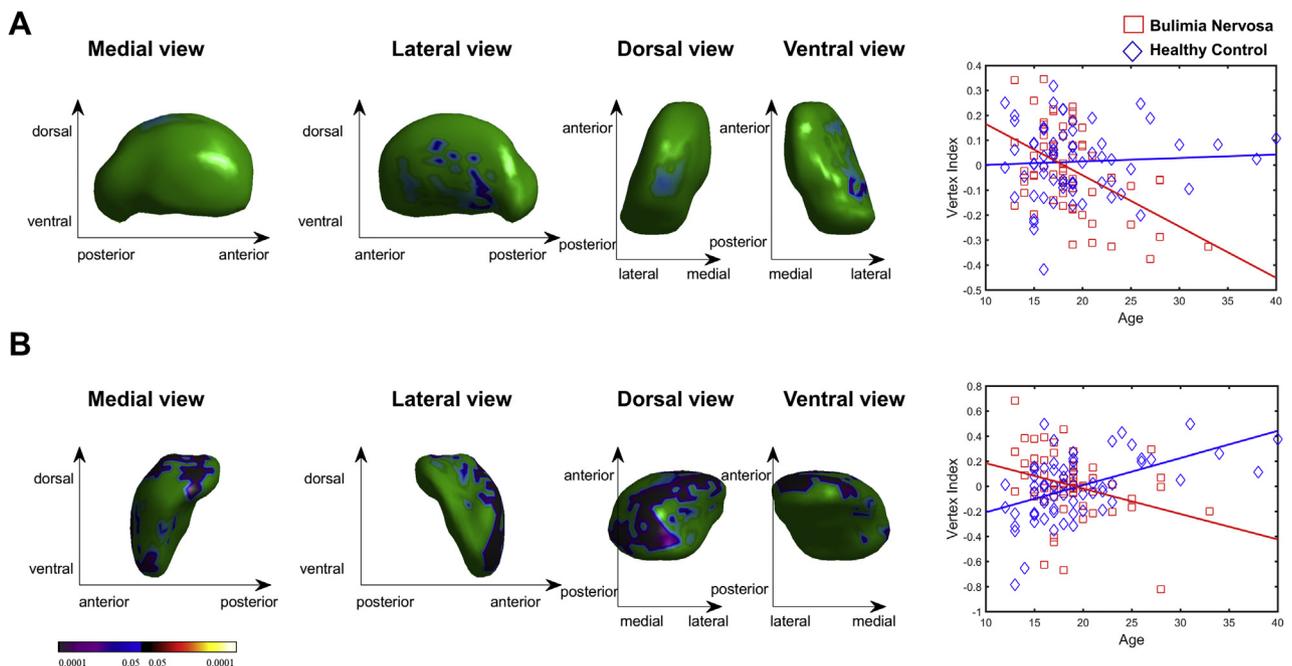


**Figure 1.** Group differences in right pallidum shape ( $p < .05$ , familywise error corrected). Cool colors (blues) indicate shape inversions in the bulimia nervosa group compared with the healthy control group. The color bar indicates  $t$  values.

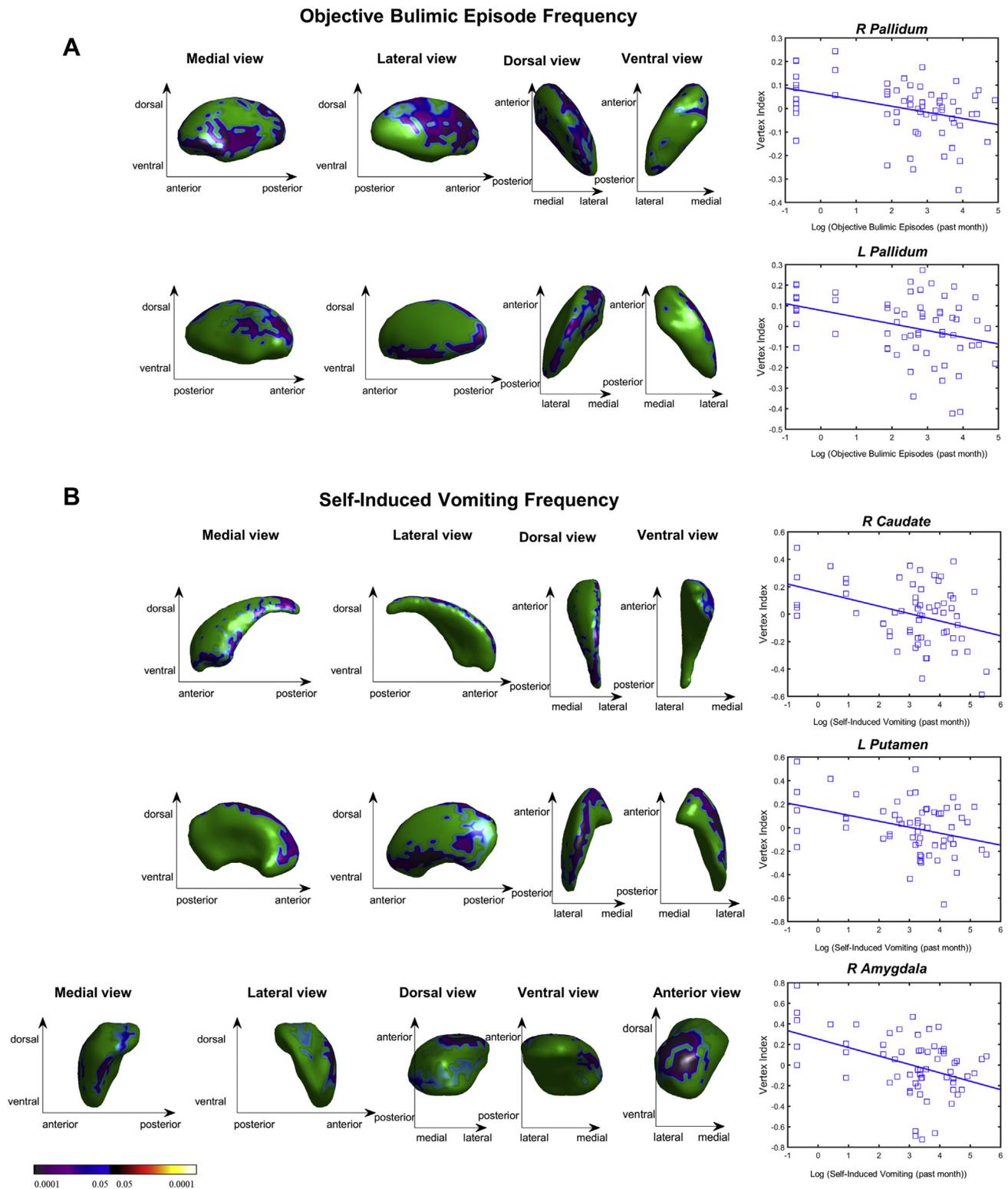
circuitry includes dopaminergic projections from the midbrain to the nucleus accumbens, ventral pallidum, ventral caudate, ventral putamen, amygdala, and prefrontal cortex (44,45). The ventral pallidum is specifically involved in “liking” palatable foods (53), the consumption of preferred foods (54,55), eating past satiety (56), and predicting how pleasant future food consumption will be (57). Across all ages, we detected inward shape deformations in BN on anterior ventromedial aspects of the pallidum—areas that project to medial and orbitofrontal cortices involved in reward valuation (26). These deformations were associated with increased binge-eating frequency in the BN group. More pronounced inward shape deformations

were detected among older participants with BN on subregions of the amygdala that are also involved in reward valuation, learning, and feeding regulation (58,59). However, inward deformations on the surface of right amygdala were also associated with illness duration, suggesting that these surface abnormalities may reflect an altered developmental trajectory, a consequence of prolonged bulimic symptoms, or both.

Although we did not replicate prior findings of decreased caudate or putamen gray matter density and volume in BN (14–16), caudate shape was associated with illness duration, and caudate and putamen shape were associated with self-



**Figure 2.** Interaction of group with age on subcortical shape ( $p < .05$ , familywise error corrected). **(A)** The shape of the left thalamus was inversely associated with age in the bulimia nervosa group (shown in red) and unassociated with age in the healthy control group (shown in blue), contributing to a group-by-age interaction. **(B)** The shape of the right amygdala was inversely associated with age in the bulimia nervosa group and positively associated with age in the healthy control group, contributing to a group-by-age interaction. The color bar indicates  $t$  values.



**Figure 3.** Associations of subcortical shape with episodes of binge eating and self-induced vomiting in the bulimia nervosa group ( $p < .05$ , familywise error corrected). Blue colors indicate inverse associations of shape with the frequency of bulimic symptom episodes in the month prior to magnetic resonance imaging scanning, with stronger associations in darker, more purple shades. **(A)** Right (R) pallidum shape, as measured by vertex index, is plotted on the y-axis with binge eating (logarithmically transformed objective bulimic episodes) plotted on the x-axis. **(B)** Right caudate, left (L) putamen, and right amygdala shape, as measured by vertex index, is plotted on the y-axis with logarithmically transformed self-induced vomiting episodes plotted on the x-axis. The color bar indicates  $t$  values.

induced vomiting. Participants with BN who engaged in more frequent vomiting episodes and were ill for longer had more prominent inward shape deformations on the ventral anterior putamen, caudate head, and ventral caudate body—areas that are structurally and functionally connected to orbito-frontal cortices in limbic reward circuits (26,51). The directionality of these associations is inconsistent with previous findings linking increased caudate gray matter volume to purging severity in BN (13); however, inward deformations in these areas have been implicated in other psychiatric disorders (21,60–61), and the current findings add to evidence linking ventral striatal abnormalities to BN symptoms (62,63). Without additional behavioral and self-report measures, we can only speculate that ventral pallidum, ventral striatal, and amygdala shape alterations may relate to the reward circuit dysfunction and altered reward-based learning hypothesized to promote binge eating among individuals with BN (8,62–67). This interpretation is consistent with findings of altered activation in the ventral striatum and amygdala during the anticipation or receipt of food stimuli (8,62,63,68–70) and monetary rewards (67) among participants with BN relative to control participants.

We detected inversions on the surface of other subcortical regions that are critical components of basal ganglia pathways that control voluntary actions. Projections from the dorsal caudate and putamen to the medial and lateral aspects of the pallidum comprise the “direct” and “indirect” pathways that are thought to mediate “go” and “stop” signals via the ventral anterior and lateral thalamus (48). Mid and anterior aspects of the pallidum project to the premotor cortex and dorsolateral prefrontal cortex and are parts of the “motor” and “associative” corticobasal ganglia circuits that control cognition and behavior (26,52). Anterior portions of the right and left lateral pallidum (i.e., the GPe) are specifically involved in action cancellation and prevention, respectively (71). Thus, inward shape deformations of the anterior GPe and age-associated deformations on the surface of the ventrolateral thalamus, which projects to the motor cortex (72), could contribute to or result from altered action initiation and inhibition signaling and relate to a wide range of impulsive behaviors in BN (40,73). Inward deformations on the surface of the GPe and on localized areas of the dorsal caudate and dorsal posterior putamen that project to lateral prefrontal and premotor cortices (26) were associated with the frequency of BN symptoms and illness duration. Similar inward deformations on the surface of the dorsal striatum have been detected in trichotillomania, a disorder characterized by poor control over compulsive behaviors (24). In BN, dorsal striatal and GPe structural abnormalities may relate to impaired control over eating behaviors and urges to self-induce vomiting. Consistent with this interpretation, girls and women with BN show reduced pallidum activation when engaging inhibitory control (39,74), and binge-eating frequency is associated with deficient caudate activation during the engagement of control in adults with BN (39,75).

Results of sensitivity analyses also point to inward surface deformations of areas involved in reward and control circuits in BN. For example, inward deformations were detected on the surface of right nucleus accumbens in BN-group participants without a history of AN, which may relate to increased

reward sensitivity in individuals with BN compared with AN (76) and to the central role of the nucleus accumbens in reward circuitry. Excluding BN participants with comorbid MDD revealed age effects on the surface of the right pallidum and inward shape deformations on the left caudate head and lateral caudate body. As Beck Depression Inventory-II scores were unrelated to caudate shape in the full BN sample, and outward shape deformations of the caudate have not been documented in individuals with MDD (21), this result may be better explained by BN duration than by depressive symptoms. Illness duration tended to be shorter in the BN-group participants with compared to without comorbid MDD ( $p = .053$ ,  $d = 0.58$ ), but these subgroups did not differ in age or in the severity of their BN symptoms ( $p$  values  $> .143$ ). Since longer illness duration was associated with inward deformations on the left caudate in the full BN sample, excluding those with MDD (and therefore less persistent BN) may have revealed left caudate inversions relative to control participants that were only apparent among those with the longest BN durations. Future transdiagnostic, longitudinal studies should assess developmental changes in caudate and accumbens structure in BN participants with and without MDD and AN to delineate how such changes may contribute to the reward and cognitive control circuit alterations characteristic of all three disorders (77–80).

This study has several limitations. First, our cross-sectional design cannot determine whether any of the subcortical shape abnormalities detected herein precede BN symptoms, precipitating their development, or instead represent sequelae of these behaviors. Relatedly, age, illness duration, and objective bulimic episode frequency were intercorrelated, and none of these variables were associated with subcortical shape when we controlled for the others. Future studies of samples in which these variables are uncorrelated are required to disentangle potential effects of altered neurodevelopment from illness duration. Prospective longitudinal studies are needed to delineate causes from consequences and to distinguish state-specific from traitlike subcortical shape alterations in BN. Second, assumptions about the functional implications of structural abnormalities in certain regions of the brain are only speculative. Future studies of subcortical morphology in BN should include behavioral measures of control and reward processes to determine whether the shapes of the pallidum, caudate, putamen, thalamus, and amygdala are in fact associated with impairments in these functions. Third, our sample was not large enough to conclusively determine the impact of comorbidities. Given that 25% to 41% of individuals with BN have a history of AN (2,81,82) and that the population comorbidity of BN is 50.1% with MDD and 80.6% with anxiety disorders, the heterogeneity of our BN sample (17.7% with prior AN, 30.6% with MDD, 17.7% with an anxiety disorder) likely bolsters the external validity of our findings. Nevertheless, future studies should include larger samples of individuals with and without these comorbidities to better understand their impact on subcortical morphology in BN. Fourth, our use of an automated segmentation procedure may be viewed as a limitation to this study, but these procedures now are commonly used in studies of subcortical morphology [e.g., Lu *et al.* (21)], are replicable, and are less biased and time-consuming than

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manual methods are. Fifth, our results are applicable only to female individuals with BN, and further study is needed to examine whether inversions on the surface of the pallidum are also present in male individuals with BN. In addition, we did not limit scanning to a specific menstrual cycle phase or time of day, nor did we systematically collect information on other factors that may affect brain structure, including acute weight change, hydration, length of treatment, hormonal contraceptive use, sleep, or pubertal stage among adolescents (83,84).

Despite these limitations, this is one of the largest anatomical MRI studies of BN to date and the first to employ vertexwise subcortical shape analysis, which can reveal subtler, more precisely localized alterations than volumetric approaches can. Our findings indicate that inward deformations of the basal ganglia are exaggerated in more symptomatic individuals with BN and that deformations on the thalamus and amygdala are more pronounced in older individuals with BN. Shape analysis is particularly advantageous for heterogeneous structures like the pallidum, which integrates motivational and emotional information (85) and plays a central role in processing food reward and controlling consummatory behavior (86). Our findings of inward shape deformations in BN are consistent with previously documented functional alterations in brain regions and circuits involved in control and reward processes (8,39,62,63,67–70,74,75,87,88), and they may reflect synaptic loss, premorbid abnormal maturation, or both. Postmortem tissue analyses and future longitudinal, multimodal investigations are necessary to understand relationships among shape, volume, and functional changes in subcortical structures and their contribution to BN maintenance. Ultimately, precisely localized structural alterations may prove useful in detecting early risk for BN, predicting outcome, evaluating change over time, or evaluating mechanistic effects of interventions.

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ClinicalTrials.gov: An fMRI Study of Self-regulation in Adolescents With Bulimia Nervosa; <https://clinicaltrials.gov/ct2/show/NCT00345943>; NCT00345943.

## ARTICLE INFORMATION

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