Appendix 1 to Berner LA, Stefan M, Lee S, et al. Altered cortical thickness and attentional deficits in adolescent girls and women with bulimia nervosa. *J Psychiatry Neurosci* 2017.

DOI: 10.1503/jpn.170070

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Method

Participants

Diagnosis of bulimia nervosa (BN) and Axis I comorbidities in adults (aged 18 and older) were established using the *Structured Clinical Interview for DSM-IV-TR Axis I Disorders*,[1] and in adolescents using the Schedule for Affective Disorders and Schizophrenia for School-Age Children—Present and Lifetime Version.[2] Full Scale IQs were estimated using the four subtests of the Wechsler Abbreviated Scale of Intelligence.[3] The DuPaul-Barkley Attention-Deficit Hyperactivity Disorder (ADHD) Rating Scale quantified self-reported symptoms of inattention.[4]

The Eating Disorder Examination (EDE)[5, 6] was used to assess objective bulimic episodes (OBEs; objectively large loss-of-control eating episodes) and self-induced vomiting in the three months prior to scanning. Data collection for participants included in this sample began prior to the publication of the 16.0 D edition of the EDE. As a result, some participants completed the EDE 12.0 D, which only assesses for subjective bulimic episodes (SBEs; loss-of-control eating episodes that are not objectively large but are perceived as large by the participant) in the last 28 days rather than the last 3 months. Given that loss-of-control eating (regardless of episode size) may be a more relevant construct in pediatric and young adolescent samples,[7] we also examined associations of our brain and behavioral measures with the frequency of loss-of-control eating episodes (LOCEs), defined as the sum of OBEs and SBEs in the past 28 days.

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Ten adolescent BN participants did not meet full *DSM-5* criteria for BN (nine endorsed sub-threshold frequency of objectively large binge-eating episodes and one had a 2-month illness duration). Four of these adolescent participants with subthreshold BN endorsed loss-of-control eating episodes of any size and compensatory episodes that occurred at least once per week on average over the past 3 months. Thus, these four participants engaged in regular LOC eating and compensatory behaviors, but did not meet full diagnostic criteria for BN because of the size of their LOCEs.

BN participants with comorbid *DSM-IV-TR* anxiety disorders included posttraumatic stress disorder (n = 3), panic disorder without agoraphobia (n = 1), social phobia (n = 1), and specific phobia (n = 1). BN participants who were taking psychotropic medication included methylphenidate hydrochloride *(*n = 1); methylphenidate hydrocloride with fluoxetine (n = 1); fluoxetine and buspirone (n =1); paroxetine (n =1); fluoxetine alone (n = 4); bupropion hydrochloride (n = 1); sertraline (n = 3), aripiprazole, bupropion, and topiramate (n =1); amphetamine, dextroamphetamine mixed salts and fluoxetine (n =1); duloxetine, aripiprazole, PRN clonazepam, and PRN trazodone (n = 1)).

The BN group included 17 inpatients and 22 outpatients who completed study procedures within 1 month of admission or before starting outpatient treatment; the remaining 21 were not seeking treatment in our clinic.

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Conners' Continuous Performance Test-II

Participants completed the computerized Conners' Continuous Performance Test-II (CPT-II) outside the scanner. During this task, participants were instructed to watch a black screen and press a button as quickly and accurately as possible upon presentation of all letters (except X) that appear on the screen at varying intervals. Participants were instructed to withhold responding upon presentation of an X (a no-go stimulus). Performance is summarized over six consecutive blocks. The CPT is one of the most widely used tests of inattention, and a large body of evidence indicates that individuals with ADHD and other psychiatric disorders demonstrate impaired performance on the task.[8, 9] Unlike the original Conners' CPT, CPT-II stimuli are 90% targets, which makes withholding responses particularly difficult. Some argue that commission errors may indicate a failure to inhibit a habitual response, and that the CPT-II may best be characterized as a classic test of executive functioning.[10] Results of factor analysis indicate that the CPT-II assesses multiple sub-processes of attention, including focused attention, impulsivity-hyperactivity, sustained attention, vigilance, and change in control.[11]

We compared groups on CPT-II variables that index impulsivity: commission errors and response style; deficits in sustained attention: omission errors, variability in hit reaction time (Hit RT (SE)), discriminability (*d'*); or both: hit reaction time (Hit RT), perseverations.[11, 12]

CPT-II raw scores are converted to T scores adjusted for an age-matched normative sample. In general, higher CPT-II T-scores indicate worse performance, except in the cases of

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Hit RT T scores and response style T scores. Slow Hit RT (corresponding to higher Hit RT T scores) may indicate inattentiveness and a fast Hit RT may indicate impulsivity (especially in combination with a high frequency of commission errors). A low response style T score indicates a cautious response style, but an excessively cautious response style may come at the cost of missing some targets; a high response style T score indicates a more impulsive response style.[10, 12]

MRI Acquisition

To ensure acquisition of at least one high-quality anatomical image, we acquired two high-resolution T1-weighted anatomical scans from each participant. We visually inspected these two scans and selected one for analyses. If the two scans appeared identical, the first scan was used.

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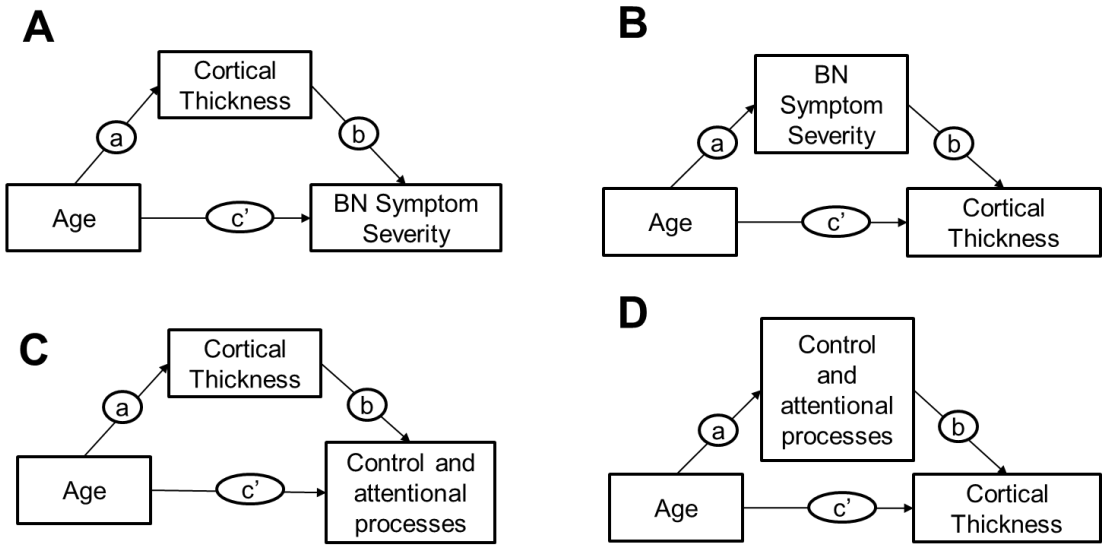

Figure S1. Mediation models used to explore relationships among cortical thickness, advancing age, BN severity, and control and attentional processes. Primary models tested **A)** whether reduced cortical thickness mediated the association between age and symptom frequency, and **B)** whether increased symptom frequency mediated the effect of advancing age on cortical thickness. Additional models tested **C)** whether reduced cortical thickness mediated the relationship between advancing age and cognitive abilities, and **D)** whether cognitive abilities mediated the effect of advancing age on cortical thickness. The letters labeling each arrow in the figure correspond to the parameters in the equations and labeled paths in Table S7.

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Exploratory Analyses

Age and CPT-II Raw Scores. To confirm that increasing age was associated with fewer errors in our healthy control sample, we conducted exploratory Spearman correlation analyses examining the association between age and CPT-II raw scores.

Self-reported Inattention. As our cortical thickness and CPT-II performance findings indicated an important role for inattention in BN, we conducted exploratory analyses examining self-reported inattention on the DuPaul Barkley Attention-Deficit Hyperactivity Disorder (ADHD) Rating Scale. Data from this measure were obtained only for a subset of the full sample (42 BN and 44 healthy controls [HC]). We tested whether reduced CT in our regions of interest also mediated the relationship between age and self-reported inattention in the BN group. The same analysis was conducted using total ADHD scores, even though no participant had a comorbid diagnosis of ADHD.

Effects of Medication and Comorbid Disorders. *Post-hoc* analyses were conducted to ensure that any between-group differences in CT were not due to the effects of medication or comorbid psychiatric illnesses. We conducted sensitivity analyses for the between-group comparisons of CT excluding participants with BN with comorbid major depressive disorder (MDD), anxiety disorder, current medication, and history of AN. In addition, we conducted between-group CPT-II performance analyses and within-BN mediation analyses including as

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covariates comorbid major depressive disorder (MDD), anxiety disorder, current medication, and history of anorexia nervosa (AN).

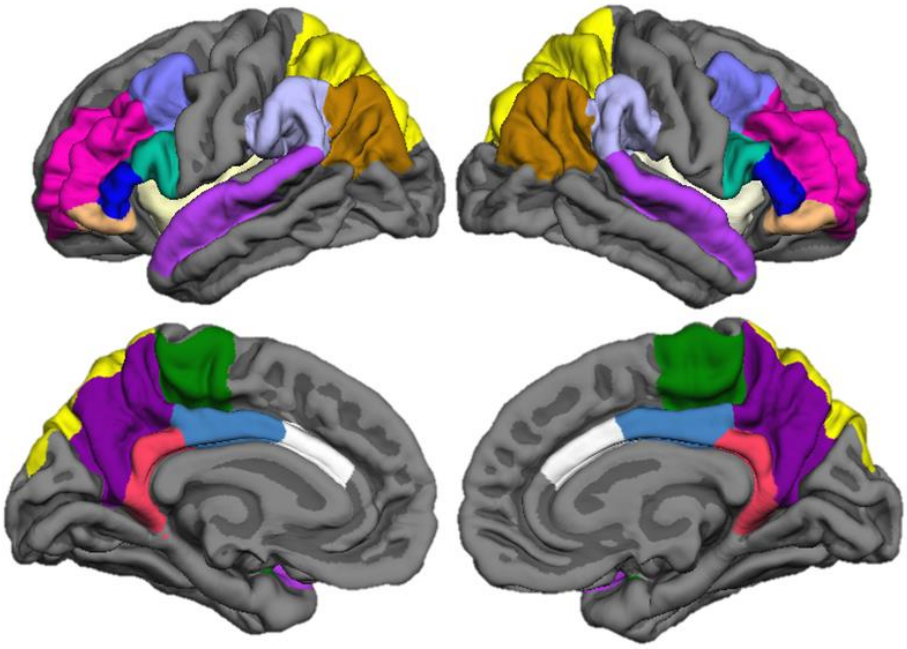

Figure S2. Frontoparietal regions of interest included in cortical thickness analyses. Colors were selected based on those automatically displayed in Freesurfer's *tksurfer* for these regions. These colors are used to label each region in Figure 3.

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Results

Participants

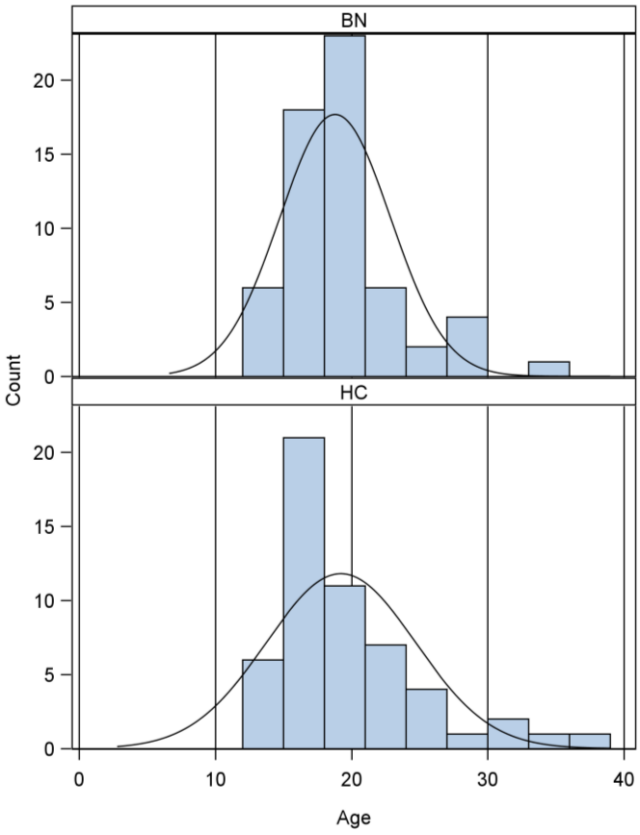

Figure S3. Age distributions in bulimia nervosa and healthy control groups. Groups did not differ on age (see Table 1) and age distributions were similar across groups. Abbreviations: BN, bulimia nervosa; HC, healthy controls.

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Table S1. Between-group Differences in CPT-II T Scores, Controlling for Age

CPT-II T Score[a]	Estimate	S.E.	*t*	*p*
Omission Errors	0.03	0.03	0.85	0.399
Commission Errors	0.14	0.04	3.47	0.001
Hit RT	-0.06	0.04	-1.31	0.192
Discriminability (*d'*)	0.13	0.04	3.28	0.001
Perseverations	0.10	0.04	2.45	0.016
Response style (*β*)	-0.05	0.03	-1.91	0.059
Hit RT (SE)	0.07	0.04	1.62	0.108

[a]Log-transformed. Age was centered for all analyses. Abbreviations: CPT-II, Conners' Continuous Performance Test-II; Hit RT, hit reaction time; Hit RT (SE), hit reaction time variability.

Table S2. Region of Interest Analysis: Between-group Differences in Cortical Thickness Controlling for Age ($p < 0.05$, FDR corrected)

Hem	Region	Max	Size (mm^2)	X	Y	Z	Vertices	p^a
Lower CT in BN vs. HC								
R	Superior parietal cortex	-3.83	139.16	32.0	-43.7	37.2	408	0.0020
R	Pars triangularis	-3.30	140.62	50.4	21.1	8.5	248	0.0055
L	Posterior cingulate	-4.12	264.53	-12.8	-28.3	36.3	721	0.0188
Greater CT in BN vs. HC								
L	Posterior cingulate	3.07	68.19	-8.4	-28.7	29.0	227	0.0188

[a]Age included as a covariate. Abbreviations: Hem, hemisphere; Max, maximum; BN, bulimia nervosa; HC, healthy control; CT, cortical thickness.

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Table S3. Region of Interest Analysis: Between-group Differences in Cortical Thickness ($p < 0.05$, FDR corrected)

Hem	Region	Max	Size (mm^2)	X	Y	Z	Vertices	*p*
Lower CT in BN vs. HC								
R	Superior parietal cortex	-3.60	60.37	33.6	-46.2	39.5	299	0.0003
L	Posterior cingulate	-3.64	219.91	-13.4	-30.6	40.5	674	0.0001
Greater CT in BN vs. HC								
L	Posterior cingulate	3.16	42.15	-5.2	-31.0	28.2	140	0.0003
L	Isthmus cingulate	2.74	114.65	-5.7	-35.4	27.1	341	0.0018

Abbreviations: Hem, hemisphere; Max, maximum; BN, bulimia nervosa; HC, healthy control; CT, cortical thickness.

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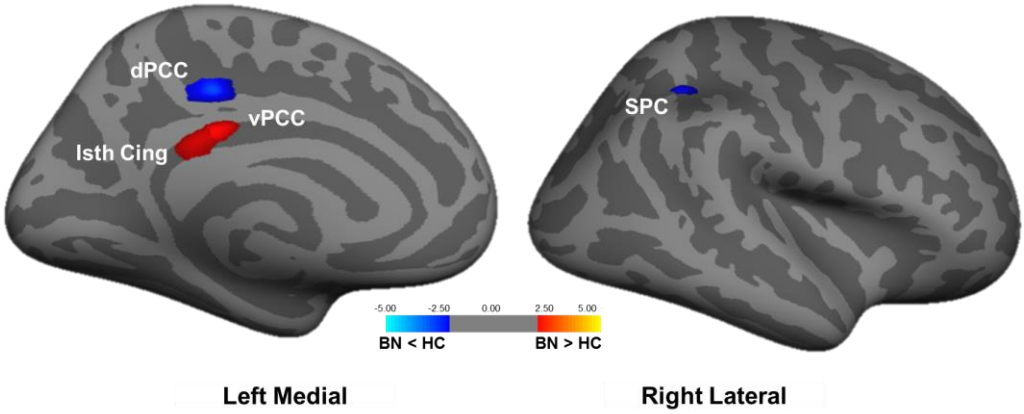

Figure S4. Group Differences in Cortical Thickness ($p < 0.05$, FDR corrected). Cool colors (blues) indicate lower thickness and warm colors (reds) indicate greater thickness in the BN compared to HC group. The color bar indicates *t* values. Corresponding statistics are presented in Table S3.

Table S4. Region of Interest Analysis: Interactions of Group with Age on Cortical Thickness ($p < 0.05$, FDR corrected)

Hem	Region	Max	Size (mm^2)	X	Y	Z	Vertices	*p*
R	Isthmus cingulate	2.87	27.94	11.8	-42.5	5.9	95	0.0047

Abbreviations: Hem, hemisphere; Max, maximum.

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Exploratory Analyses

A whole-brain analysis revealed reduced CT in BN compared to HC participants in bilateral pars opercularis, left rMFG and cMFG, SMG, right PCG, bilateral STG and insular cortices, and a cluster spanning right PCC, isthmus cingulate, and precuneus ($p < 0.005$, uncorrected; Table S5). Greater CT in BN compared to HC participants was detected in left isthmus cingulate cortex ($p < 0.005$, uncorrected).

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Table S5. Exploratory Whole-Brain Analysis: Between-group Differences in Cortical Thickness ($p < 0.005$, uncorrected)

Hem	Region	Max	Size (mm^2)	X	Y	Z	Vertices	p^a
Lower CT in BN vs. HC								
L	Posterior cingulate	-3.85	263.73	-12.3	-30.1	38	622	0.0001
L	Superior temporal gyrus/insula	-3.35	365.75	-43.9	-21.8	-5.8	676	0.0004
R	Superior parietal cortex	-3.09	165.76	32.1	-44.6	40.4	482	0.0008
L	Superior parietal/supramarginal/postcentral gyrus	-3.00	384.72	-32.7	-34.6	39.7	1069	0.0010
R	Pars triangularis/pars opercularis	-2.84	261.95	54.4	23.4	10.4	468	0.0015
R	Supramarginal gyrus	-2.76	100.87	57.9	-23.3	29.8	264	0.0018
R	Superior temporal gyrus/insula	-2.73	84.28	41.9	-14.8	-11.3	247	0.0019
L	Rostral middle frontal gyrus	-2.65	70.24	-45.3	23.1	34.4	154	0.0022
L	Caudal middle frontal gyrus	-2.62	141.59	-29	-1.7	46.2	338	0.0024
R	Paracentral gyrus	-2.61	129.17	16.9	-28.4	41.9	388	0.0024
R	Posterior cingulate/isthmus cingulate/precuneus	-2.57	162.49	11.2	-46.3	30.8	426	0.0027
L	Pars opercularis	-2.32	98.38	-50.9	14.4	16.3	164	0.0048
Lower CT in BN vs. HC								
L	Posterior cingulate/isthmus cingulate	3.29	258.24	-8.7	-31.1	29.7	590	0.0005

[a]Age included as a covariate. Abbreviations: Hem, hemisphere; Max, maximum; BN, bulimia nervosa; HC, healthy control; CT, cortical thickness.

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Table S6. Associations of Cortical Thickness and BN Severity, controlling for age ($p < 0.05$)

Symptom Severity Index	Region of Interest	Hemisphere	Estimate	S.E.	*p*
OBE Frequency (previous 3 months)	IPC	R	-3.04	1.45	0.035
	Pars opercularis	R	-2.64	1.31	0.044
	Pars triangularis	R	-3.31	1.54	0.032
	rMFG	L	-3.05	1.28	0.017
LOCE Frequency (previous month)	Insula	L	-2.67	1.19	0.025
		R	-2.79	1.17	0.017

Abbreviations: BN, bulimia nervosa; OBE, objective bulimic episodes; LOCE, loss of control eating episodes; IPC, inferior parietal cortex; rMFG, rostral middle frontal gyrus.

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Table S7. Exploratory Within-BN Mediation Models ($p < 0.05$)

Model	Mediator	Outcome	Paths	*p*	Beta	S.E.	95% CI	
A	Left insula	LOCEs (past month)	a	***	-0.015	0.004	-0.022	-0.008
			b	*	-2.671	1.189	-5.000	-0.342
			DE		0.060	0.038	-0.014	0.135
			IDE	*	0.040	0.020	0.000	0.079
			total	**	0.100	0.035	0.031	0.169
	Right insula		a	***	-0.015	0.004	-0.022	-0.008
			b	*	-2.793	1.167	-5.081	-0.506
			DE		0.058	0.038	-0.016	0.132
			IDE	*	0.042	0.020	0.002	0.082
			total	**	0.100	0.035	0.031	0.169
B	OBEs (past 3 months)	Left rMFG	a	***	0.184	0.052	0.083	0.286
			b	*	-0.029	0.012	-0.053	-0.005
			DE		0.005	0.005	-0.005	0.016
			IDE	*	-0.005	0.003	-0.011	0
			total		0	0.005	-0.01	0.01
C	Right IPC	Omission T score	a	**	-0.016	0.005	-0.026	-0.006
			b	**	0.390	0.150	0.096	0.685
			DE		0.010	0.006	-0.002	0.023
			IDE	*	-0.006	0.003	-0.013	0.000
			total		0.004	0.006	-0.008	0.016
	Right pars opercularis		a	***	-0.019	0.006	-0.030	-0.008
			b	**	0.350	0.135	0.085	0.615
			DE		0.011	0.006	-0.002	0.023
			IDE	*	-0.007	0.003	-0.013	0.000
			total		0.004	0.006	-0.008	0.016
	Right pars		a	***	-0.019	0.005	-0.028	-0.009

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	triangularis		b		0.372	0.163	0.052	0.692
			DE		0.011	0.007	-0.002	0.024
			IDE	*	-0.007	0.003	-0.014	-4.77E-05
			total		0.004	0.006	-0.008	0.016
	Right insula	Hit RT (SE) T score	a	***	-0.015	0.004	-0.023	-0.008
			b	**	0.594	0.23	0.144	1.045
			DE	***	0.026	0.007	0.011	0.04
			IDE	*	-0.009	0.004	-0.017	-0.001
			total	*	0.016	0.007	0.003	0.03
	Right pars triangularis		a	***	-0.017	0.004	-0.025	-0.009
			b	**	0.543	0.204	0.144	0.942
			DE	***	0.026	0.007	0.011	0.04
			IDE	*	-0.009	0.004	-0.017	-0.001
			total	*	0.016	0.007	0.003	0.03
	Left pars opercularis	Hit RT T score	a	***	-0.019	0.005	-0.029	-0.01
			b	*	0.109	0.173	-0.23	0.449
			DE	*	0.012	0.007	-0.002	0.027
			IDE	*	-0.002	0.003	-0.009	0.005
			total		0.01	0.007	-0.003	0.023

*$p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. Mediation Model A: Age → Cortical Thickness → Symptom Severity; Mediation Model B: Age → Symptom Severity → Cortical Thickness; Mediation Model C: Age → Cortical Thickness → Inattention. All symptom severity and inattention measures were log-transformed. Abbreviations: BN, bulimia nervosa; S.E., standard error; CI, confidence interval; DE, direct effect; IDE, indirect effect; OBEs, objective bulimic episodes; LOCEs, loss-of-control eating episodes of any size; IPC, inferior parietal cortex; rMFG, rostral middle frontal gyrus.

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Age and CPT-II Raw Scores. As expected based on CPT-II norms,[10] increasing age was associated with fewer omission errors and commission errors, improved discriminability, and a less impulsive response style in the HC group (all raw CPT-II scores unadjusted for normative age-matched sample; Table S8).

Table S8. Association among Age and CPT-II Raw Scores in HC group

Raw CPT-II	*n*	*r*	*p*
Omission Errors	54	-0.48	< 0.001
Commission Errors	54	-0.30	0.028
Hit RT	54	0.03	0.849
Discriminability (*d'*)	54	0.37	0.006
Perseverations	53	-0.16	0.259
Response style (β)	54	-0.28	0.037
Hit RT (SE)	54	-0.23	0.092

Abbreviations: CPT-II, Conners' Continuous Performance Test-II; HC, healthy control; Hit RT, hit reaction time; Hit RT (SE), hit reaction time variability.

Self-reported Inattention. Inclusion of self-reported inattention (or total ADHD scores) as covariates in between-group comparisons of CPT-II performance did not alter results, and CPT-II performance was unrelated to self-reported inattention in either group (all *p*s > 0.30). Within the BN group, inattention scores did not mediate the relationship between age and CT, and CT did not mediate the relationship between age and symptoms of inattention (all *p*s > 0.10).

Effects of Medication and Comorbid Disorders. CPT-II performance in the BN group was not correlated with illness duration (*p*s > 0.07).

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Inclusion of covariates (comorbid depression or anxiety, current SSRI treatment, history of AN) in our between-group comparisons of CPT-II performance revealed qualitatively similar findings with reduced significance of group differences in Hit RT and response style, likely due to reduced power in these analyses.

Analyses excluding individuals with comorbid MDD, anxiety, or those taking medication revealed reduced CT in BN in right precuneus, an additional region that was not implicated in our primary analysis including all participants. Excluding these participants did not otherwise change our findings of reduced CT in fronto-parietal and insular regions in BN, but these group differences were associated with higher *p* values, likely attributable to reduced power.

After inclusion of these covariates in our mediation analyses, reduced CT in bilateral insula still mediated the relationship between age and LOC episode frequency in the past month, but these findings became marginally significant ($ps > 0.051$).

We also included these covariates in our models testing whether BN severity mediates the relationship between advancing age and reduced CT. Including comorbid depression as a covariate did not impact our findings but inclusion of comorbid anxiety and AN history as covariates revealed that BN severity still mediated the relationship between advancing age and reduced thickness of left rMFG, albeit less significantly ($0.05 < ps < 0.06$). Likewise, including current SSRI treatment as a covariate showed that BN severity still mediated the relationship between advancing age left rMFG.

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Results of models testing whether reduced CT mediates the relationship between age and inattention in BN were unchanged with the inclusion of medication status or comorbidities (depression or anxiety) as covariates. With inclusion of AN history as a covariate, reduced thickness of right pars triangularis no longer mediated the relationship between age and omission T score ($p = .058$).

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