

# Altered cortical thickness and attentional deficits in adolescent girls and women with bulimia nervosa

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**Background:** Frontostriatal and frontoparietal abnormalities likely contribute to deficits in control and attentional processes in individuals with bulimia nervosa and to the persistence of dysregulated eating across development. This study assessed these processes and cortical thickness in a large sample of adolescent girls and women with bulimia nervosa compared with healthy controls. **Methods:** We collected anatomical MRI data from adolescent girls and women (ages 12–38 yr) with full or subthreshold bulimia nervosa and age-matched healthy controls who also completed the Conners Continuous Performance Test-II (CPT-II). Groups were compared on task performance and cortical thickness. Mediation analyses explored associations among cortical thickness, CPT-II variables, bulimia nervosa symptoms and age. **Results:** We included 60 girls and women with bulimia nervosa and 54 controls in the analyses. Compared with healthy participants, those with bulimia nervosa showed increased impulsivity and inattention on the CPT-II, along with reduced thickness of the right pars triangularis, right superior parietal and left dorsal posterior cingulate cortices. In the bulimia nervosa group, exploratory analyses revealed that binge eating frequency correlated inversely with cortical thickness of frontoparietal and insular regions and that reduced frontoparietal thickness mediated the association between age and increased symptom severity and inattention. Binge eating frequency also mediated the association between age and lower prefrontal cortical thickness. **Limitations:** These findings are applicable to only girls and women with bulimia nervosa, and our cross-sectional design precludes understanding of whether cortical thickness alterations precede or result from bulimia nervosa symptoms. **Conclusion:** Structural abnormalities in the frontoparietal and posterior cingulate regions comprising circuits that support control and attentional processes should be investigated as potential contributors to the maintenance of bulimia nervosa and useful targets for novel interventions.

## Introduction

Bulimia nervosa is characterized by recurrent binge eating and compensatory behaviours to avoid weight gain.<sup>1</sup> The disorder affects 1%–3% of women and is associated with significant medical complications and substantial psychosocial impairment.<sup>2</sup> Empirically supported treatments for bulimia nervosa result in symptom abstinence in only 30%–50% of treatment completers,<sup>3</sup> thus identification of brain-based abnormalities that could serve as targets for novel treatments are crucial. As bulimia nervosa typically begins during adolescence,<sup>4</sup> prevention efforts require understanding of how brain abnormalities contribute to illness onset and how bulimic behaviours impact brain development.

Recurrent binge eating, defined most saliently by a sense of “loss of control” over eating,<sup>5</sup> and impaired performance on behavioural tasks<sup>6</sup> suggest difficulties with inhibitory control among individuals with bulimia nervosa. Attentional deficits

may also contribute to bulimia nervosa symptomatology, and self-reported inattention better predicts bulimic behaviour than does impulsivity.<sup>7,8</sup> However, attentional processes are understudied in bulimia nervosa, both behaviourally and in association with their neural correlates.

Neuroimaging data suggest that disturbances in control and attentional processes are linked to underlying functional<sup>9–12</sup> and anatomical<sup>13,14</sup> abnormalities within frontostriatal and temporoparietal regions in individuals with bulimia nervosa. Both women and adolescent girls with bulimia nervosa fail to activate frontostriatal circuits to the same extent as healthy participants when engaging control on a Simon task.<sup>9,10</sup> In addition, local cortical volumes are reduced in individuals with bulimia nervosa compared with healthy controls in frontal, temporoparietal and posterior cingulate cortices.<sup>14</sup> Reductions in inferior frontal cortices are associated with greater illness severity and Stroop interference in participants with bulimia nervosa.<sup>14</sup> Compared with healthy women,

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those with bulimia nervosa also show functional and structural alterations in attentional circuits, including insular, temporal and parieto-occipital regions.<sup>15–17</sup>

These cortical abnormalities may contribute to the development and persistence of bulimia nervosa from adolescence to adulthood,<sup>18</sup> but research on age-related structural alterations associated with bulimia nervosa onset and maintenance is sparse. Our previous anatomical findings suggest that volume reductions within inferior frontal cortices become more prominent with increasing age in bulimia nervosa,<sup>14</sup> but that study included only 35 participants with bulimia nervosa and used a unique software to assess cortical surface morphology. It is unknown whether changes in the thickness of frontal, temporoparietal and posterior cingulate cortices over adolescence and adulthood contribute to bulimia nervosa persistence, worsening of symptoms, or deficits in control and attentional processes. Prospective, longitudinal research is required to understand how brain alterations may contribute to and result from bulimia nervosa symptoms; however, an initial identification of bulimia nervosa-specific, age-related alterations in cortical thickness is necessary to inform hypotheses for such large-scale investigations.

We used the Conners Continuous Performance Test-II (CPT-II) to test our hypothesis that compared with healthy controls, adolescent girls and women with bulimia nervosa would show deficits in control and attentional processes that are more pronounced in older individuals. We also sought to extend our prior anatomical findings in a much larger sample, using Freesurfer to compare the bulimia nervosa and control groups on the thickness of frontal, temporoparietal and posterior cingulate regions. To begin to understand the effects of abnormal brain structure on the persistence of bulimia nervosa symptoms and control/attentional processes, we performed mediation analyses to explore associations between these symptoms, processes and age-related alterations in cortical thickness. Though cross-sectional, this study, specifically our exploratory mediation analyses, served to inform hypotheses for future longitudinal research aimed at delineating the effects of abnormal cortical maturation on the persistence of bulimia nervosa symptoms from the scarring effects of dysregulated eating behaviour on brain structure.

## Methods

### *Participants*

We acquired structural MRI scans from female adolescent and adult control participants and from adolescent girls and women with bulimia nervosa or a bulimia nervosa–spectrum disorder otherwise specified (bulimia nervosa with sub-threshold frequency or duration of symptoms). Adolescents with subthreshold bulimia nervosa were included because it is associated with significant distress and likely cross over to threshold bulimia nervosa.<sup>19</sup> Participants completed the CPT-II outside of the scanner. This sample included participants from previous fMRI studies,<sup>9,10</sup> and 28 bulimia nervosa and 21 control participants whose data were included in prior analyses of cerebral surface morphology.<sup>14</sup>

Participants were recruited via online advertisements, flyers posted in the surrounding community, and through the Eating Disorders Clinic at the New York State Psychiatric Institute (NYSPI), where participants with bulimia nervosa could receive treatment at no cost. Individuals with any history of neurologic disorder, seizures, head trauma with loss of consciousness, mental retardation, or pervasive developmental disorder were excluded. Controls with a history of lifetime Axis-I disorders were excluded, as were participants with bulimia nervosa who met criteria for any comorbid Axis-I disorders other than major depressive and anxiety disorders.<sup>1</sup> Bulimia nervosa diagnoses and comorbidities were established, full-scale IQs were estimated, and self-reported symptoms of inattention were quantified using standard measures (Appendix 1, available at [jpn.ca/170070-a1](http://jpn.ca/170070-a1)).

All participants older than 18 years of age provided informed consent; adolescents younger than 18 years provided informed assent, and their legal guardians provided informed consent. The NYSP's Institutional Review Board approved this study.

### *Conners' Continuous Performance Test-II*

Participants completed the standard computerized CPT-II<sup>20</sup> outside of the scanner within the same week as scanning, and we compared groups on CPT-II variables that index impulsivity, deficits in sustained attention, or both (Appendix 1).

### *MRI acquisition*

We acquired MRI scans on a GE Signa 3 T whole-body scanner (GE Medical Systems) using a body transmitter coil and an 8-channel head coil. High-resolution,  $T_1$ -weighted images were acquired with a fast-spoiled gradient echo (FSPGR) 3-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  $256 \times 256$ , field of view 25 cm, flip angle  $11^\circ$ , 164 slices, slice thickness 1 mm encoded for sagittal slice reconstruction, voxel dimensions  $0.976 \times 0.976 \times 1.0$  mm.

### *Image processing*

Image processing, including cortical surface reconstruction and volumetric segmentation was performed in FreeSurfer image analysis suite (version 5.3.0) using automated and semiautomated tools.<sup>21,22</sup> Briefly,  $T_1$ -weighted images were registered to Talairach space, intensity variations corrected, and nonbrain tissues (i.e., skull or extracerebral regions) removed. Data from each participant were segmented into grey and white matter, and a triangular tessellation cover was applied to each individual scan before the image was inflated for visualization of cortical surfaces within sulci. Each scan was then transformed into a parameterizable surface to ensure accurate alignment to a reference template, and the cerebral cortex was divided into parcels based on gyri and sulci positioning.<sup>23</sup> Last, we calculated cortical thickness at every point on the smoothed, aligned images by measuring the distance between the pial and white matter surfaces.

### Statistical analyses

All analyses were conducted using SAS software version 9.3 (SAS Institute Inc.).

### CPT-II performance

Distributions of CPT-II variables were examined before analysis. Highly skewed variables were log-transformed. Linear regressions examined main effects of group (controlling for age) and group  $\times$  age interactions as independent variables and CPT-II scores as dependent variables.

### Cortical thickness

We selected regions of interest (ROIs) a priori based on previous findings from individuals with bulimia nervosa<sup>10,14,17,24</sup> and fMRI findings from healthy individuals suggesting that frontoparietal, temporal, insular and posterior cingulate cortices support the control and attentional processes measured by the CPT-II.<sup>25–27</sup> We restricted our primary analyses to the following bilateral ROIs: pars triangularis, pars orbitalis and pars opercularis, rostral and caudal middle frontal gyrus (rMFG, cMFG), caudal anterior cingulate cortex (cACC), superior and inferior parietal cortex (SPC, IPC), paracentral gyrus (PCG), supramarginal gyrus (SMG), superior temporal gyrus (STG), insula, posterior cingulate cortex (PCC), isthmus cingulate, and precuneus (Appendix 1, Fig. S2). Using FreeSurfer's Query, Design, Estimate, Contrast (QDEC) application, we assessed group differences in and age effects on cortical thickness. A general linear model was fitted at each vertex within each ROI, first with cortical thickness as the dependent variable and group as the independent variable, with age included as a covariate. Next, we fitted a general linear model at each vertex with cortical thickness as the dependent variable and group and age, followed by the group  $\times$  age interaction as predictors. Assessing the significance of group  $\times$  age interactions allowed us to examine whether group differences in cortical thickness depend on age, or whether age effects on cortical thickness differed between participants with bulimia nervosa and healthy controls. Group difference maps and group  $\times$  age interaction maps were constructed in QDEC based on  $-\log_{10}(p \text{ value})$ . We report findings corrected for multiple comparisons, including all vertices within each ROI using `lme_mass_FDR2`, a MATLAB code from LME tools in FreeSurfer that implements a powerful 2-stage false discovery rate correction (FDR) procedure ( $\alpha = 0.05$ , 2-tailed).<sup>28–30</sup> We treated each ROI as a separate search region for multiple comparison correction rather than combining all ROIs into a single mask because our sample included a wide age range (12–38 yr), and normative developmental changes in cortical thickness occur at different rates across these regions.<sup>31,32</sup> Cortical thickness of some of these regions decreases, whereas in other regions it tends to increase with advancing age in healthy individuals.<sup>33</sup> Statistically significant clusters were mapped onto the Desikan-Killany atlas.<sup>23</sup>

### Exploratory analyses

Exploratory analyses examining symptom severity correlates, mediating effects of cortical thickness and effects of potential

confounds were performed within the bulimia nervosa group only in the ROIs listed previously. Consistent with an approach used in previous studies,<sup>34</sup> we extracted mean cortical thickness values for each ROI for each participant with bulimia nervosa from Desikan-Killany atlas parcels using automated segmentation in QDEC, and these values were included in subsequent analyses in R software.

### Symptom severity correlates and mediating effects of cortical thickness

We used Spearman correlations to examine associations of fronto- and temporoparietal cortical thickness with the frequency of symptoms in the bulimia nervosa group while controlling for age. Given our interest in the association between frontoparietal development and bulimia nervosa symptoms, structural equation models with bootstrapping (lavaan package, R version 3.2.3<sup>35</sup>) tested in the bulimia nervosa group whether lower cortical thickness mediated the association between age and symptoms and whether symptom frequency mediated the effect of advancing age on cortical thickness. Both models were tested given the equally strong theories that brain abnormalities could contribute to and result from symptoms of bulimia nervosa.<sup>36</sup> Additional models in both the bulimia nervosa and control groups explored whether lower cortical thickness mediated the association between advancing age and control and attentional processes and whether control and attentional processes mediated the effect of advancing age on cortical thickness (Appendix 1, Fig. S1). All models were restricted to ROIs in which cortical thickness was associated with age and to symptoms that were associated with age. Of note, these exploratory mediation analyses of cross-sectional data were conducted only to inform hypotheses for future longitudinal studies. They do not permit consideration of order effects, thereby limiting the conclusions that can be drawn herein.

An additional exploratory whole-brain vertex-wise analysis examining the effect of group on cortical thickness, controlling for age, was also conducted in QDEC (Appendix 1).

### Effects of potential confounds

We explored the effects of medication, illness duration and comorbid illnesses on group differences in cortical thickness, CPT-II performance, and on our mediation findings. Illness duration (2–192 mo) was strongly correlated with age ( $r = 0.78$ ,  $p < 0.001$ ), precluding its inclusion as a covariate in models with age. We therefore reran mediation analyses with illness duration substituted for age to confirm that exploratory mediation findings involving age were not better explained by long-standing illness.

## Results

### Participants

We included 60 adolescent girls and women with bulimia nervosa and 54 controls in the analyses. Groups were matched on age, body mass index (BMI), and full-scale IQ (Table 1). All participants were right-handed and postpubertal with regular menstrual cycles. The sample (aged 12–38 yr)

included 33 adolescents with bulimia nervosa and 30 adolescent controls (age ≤ 18 yr). Age distributions were similar across groups (Appendix 1, Fig. S3). Ten adolescent participants met criteria for bulimia nervosa of low frequency or limited duration (a BN-spectrum otherwise specified eating disorder).<sup>37</sup> Age was positively associated with binge eating frequency, such that older participants with bulimia nervosa reported more frequent objectively large bulimic episodes (OBEs) in the previous 3 months ( $p < 0.001$ ) and loss of control eating episodes (LOCEs) of any size in the previous month ( $p = 0.004$ ; Appendix 1). This association with OBEs remained after excluding participants with subthreshold bulimia nervosa ( $p = 0.024$ ).

*CPT-II performance and self-reported inattention*

Across all ages, participants with bulimia nervosa had higher commission error ( $p = 0.001$ ) and perseveration scores ( $p = 0.016$ ) than controls (Appendix 1, Table S1). They also showed an impaired ability to discriminate between targets and nontargets (higher  $d'$  scores;  $p = 0.001$ ). No significant group × age interactions were detected (all  $p > 0.20$ ). However, age was positively associated with response style ( $p = 0.003$ ) and hit reaction time variability (Hit RT (SE);  $p = 0.018$ ) in participants with bulimia nervosa but was not associated with performance in controls (all  $p > 0.17$ ). Self-reported symptoms of inattention were more severe in participants with bulimia nervosa than control participants ( $p < 0.001$ ), but were unrelated to CPT-II scores in either group (all  $p > 0.06$ ). In participants with bulimia nervosa, symptom severity was not associated with CPT-II scores or self-reported inattention (all  $p > 0.20$ ).

*Cortical thickness*

The ROI analyses revealed group differences in cortical thickness of right frontoparietal regions and the left PCC, with

reduced cortical thickness in participants with bulimia nervosa compared with controls in the right pars triangularis, right SPC, and left dorsal PCC (all  $p < 0.05$ , FDR-corrected; Fig. 1A and Appendix 1, Table S2). An analysis of group differences in cortical thickness unadjusted for age yielded similar findings (Appendix 1). Greater cortical thickness in participants with bulimia nervosa than in controls was detected in the left ventral PCC. A significant group × age interaction was detected in the right isthmus cingulate ( $p < 0.05$ , FDR-corrected; Appendix 1, Table S4), and a scatterplot of this interaction showed that isthmus cingulate thickness was inversely associated with age in controls and positively associated with age in participants with bulimia nervosa (Fig. 1B).

*Exploratory analyses*

**Symptom severity correlates and mediating effects of cortical thickness**

Controlling for age, OBEs (previous 3 months) were inversely associated with cortical thickness of the right pars triangularis, right pars opercularis, left rMFG and right IPC (all  $p < 0.05$ ; Fig. 2A and Appendix 1, Table S6). The LOCEs (previous month) were inversely associated with cortical thickness of the bilateral insula (both  $p < 0.05$ ; Fig. 2B).

In the bulimia nervosa group, cortical thickness of the bilateral insula mediated the association between advancing age and more LOCEs (previous month; Fig. 3A and Appendix 1, Table S7). Increased OBEs (previous 3 months) mediated the association between advancing age and cortical thickness of the left rMFG (Fig. 3B). However, increased LOCEs (previous month) did not mediate the association between age and cortical thickness of any region.

Cortical thickness of the right insula and bilateral fronto-parietal areas mediated the association between advancing age and increased CPT-II attentional scores in participants with bulimia nervosa (Fig. 3C and Appendix 1, Table S7). Specifically, cortical thickness of the right pars

**Table 1: Demographic, clinical and neuropsychological characteristics of study participants**

Characteristic	Group; mean ± SD or no. (%)		t	p value
	Control, n = 54	Bulimia nervosa, n = 60		
Age, yr	19.2 ± 5.5	18.8 ± 4.1	0.47	0.64
BMI (adults)	21.9 ± 2.1	22.4 ± 2.4	0.86	0.39
zBMI (adolescents)*	0.20 ± 0.65	0.40 ± 0.62	1.12	0.27
WASI full-scale IQ	113 ± 16	109 ± 11	1.66	0.10
OBEs (previous 3 mo)	—	76.3 ± 74.0	—	—
LOCEs (previous mo)	—	39.5 ± 32.2	—	—
Self-induced vomiting episodes (previous 3 mo)	—	145.6 ± 155.6	—	—
Duration of illness, mo	—	44.5 (40.9)	—	—
Subclinical bulimia nervosa	—	10 (16.7)	—	—
Comorbid anxiety disorder	—	6 (10.0)	—	—
Comorbid major depression	—	17 (28.3)	—	—
Past anorexia nervosa	—	10 (16.7)	—	—
Medication	—	15 (25.0)	—	—

BMI = body mass index; LOCEs = loss of control eating episodes of any size; OBEs = objective bulimic episodes; SD = standard deviation; WASI = Wechsler Abbreviated Scale of Intelligence.

\*BMI calculation in participants younger than 18 yr is adjusted for age.

triangularis and insula mediated the association between advancing age and increased omission errors and Hit RT (SE). Cortical thickness of the right and left pars opercularis mediated the association between age and omissions. In these mediation models, indirect effects were negative and direct effects were positive (Appendix 1, Table S7). Thus, cortical thickness of the right insula and bilateral frontoparietal cortices suppressed the association between advancing age and inattention in participants with bulimia nervosa.<sup>38</sup> Cortical thickness did not mediate the association between age and self-reported symptoms of inattention (all  $p > 0.10$ ).

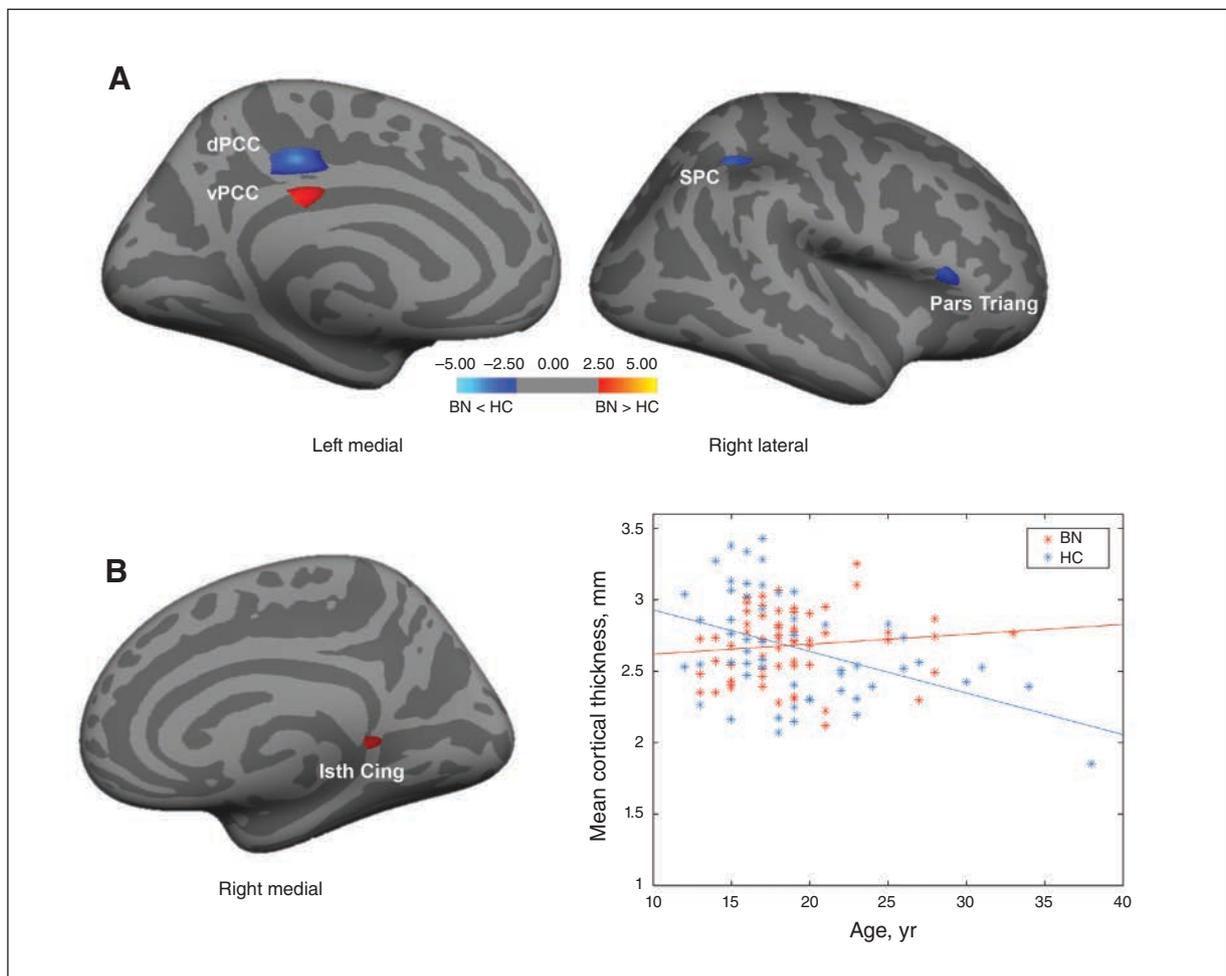
#### Effects of potential confounds

Results were qualitatively similar after excluding participants with comorbid major depressive disorder (MDD), anxiety,

current use of selective serotonin reuptake inhibitors, or a history of anorexia nervosa and when these comorbidities or self-reported inattention scores were included as covariates in the between-group CPT-II performance and within-group (bulimia nervosa) mediation analyses (Appendix 1). Substituting illness duration for age in our mediation analyses revealed no statistically significant findings (all  $p > 0.06$ ).

#### Discussion

To our knowledge, this is the first study of control and attentional processes, cortical thickness and symptom severity in a large sample of adolescent girls and women with bulimia nervosa. Across all ages, participants with bulimia nervosa compared with healthy participants made more commission errors and had difficulty discriminating between target and



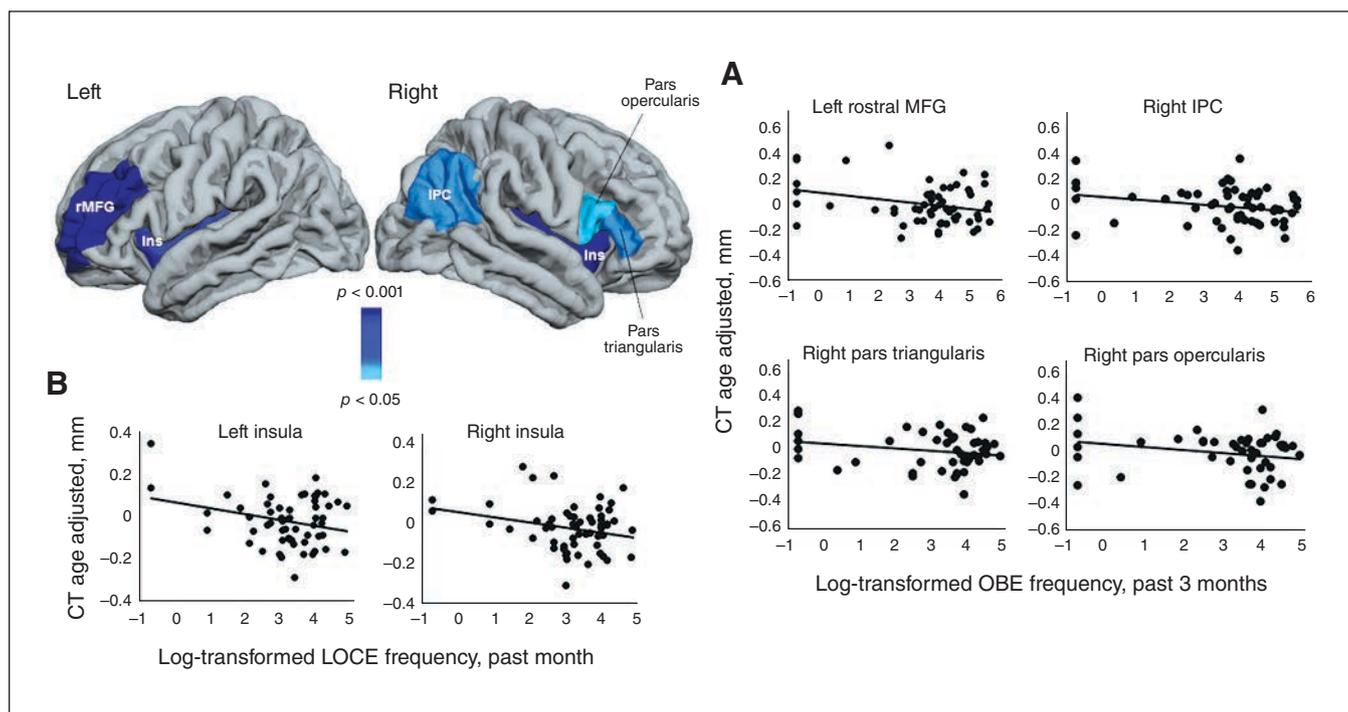
**Fig. 1:** (A) Group differences in cortical thickness ( $p < 0.05$ , false discovery rate [FDR]-corrected). Cool colours (blues) indicate reduced thickness, and warm colours (reds) indicate greater thickness in the bulimia nervosa (BN) compared with the control group (HC). Analyses include age as a covariate. The colour bar indicates  $t$  values. Corresponding statistics are presented in Appendix 1, Table S2. (B) Group  $\times$  age interaction effect on cortical thickness ( $p < 0.05$ , FDR-corrected). Cortical thickness of the right isthmus cingulate (Isth Cing) was inversely associated with age in the healthy control group and positively associated with age in the bulimia nervosa group, contributing to a group  $\times$  age interaction. Corresponding statistics are presented in Appendix 1, Table S4. dPCC = dorsal posterior cingulate cortex; pars triang = pars triangularis; SPC = superior parietal cortex; vPCC = ventral posterior cingulate cortex.

nontarget stimuli on the CPT-II. Consistent with these behavioural findings, our ROI analysis revealed structural alterations in participants with bulimia nervosa in frontoparietal and posterior cingulate regions underlying control and attentional processes. Controlling for age, thickness reductions of bilateral frontoparietal regions were most pronounced in the participants with bulimia nervosa who had the most frequent binge eating. Our exploratory whole-brain analysis revealed additional reductions of middle frontal, temporal and insular cortices consistent with prior findings of reduced volumes in these regions.<sup>14,16</sup> Though limited by cross-sectional data, our exploratory path analysis findings inform future longitudinal research by providing initial evidence that insular thickness mediates the association between advancing age and more frequent binge eating, which mediates the association between advancing age and rMFG thickness. Further, lower frontoparietal thickness suppressed the association between advancing age and inattention in participants with bulimia nervosa. Thus, thinning in frontoparietal cortices may have functional consequences for individuals with bulimia nervosa, contributing to their impaired control over eating but leaving their non-eating-specific attentional processes intact.

Participants with bulimia nervosa made more commission errors and responded faster and less accurately on the CPT-II

than controls. This impulsive performance profile is consistent with meta-analytic findings of inhibitory control deficits in individuals with bulimia nervosa.<sup>6</sup> Observed deficits in attentional processes (i.e., elevated  $d'$  T scores)<sup>20</sup> are consistent with findings of increased self-reported inattention in individuals with bulimia nervosa,<sup>39</sup> associations of inattention with bulimia nervosa symptoms,<sup>40</sup> and findings that self-reported inattention better explains bulimia nervosa symptom variance than does impulsivity or hyperactivity.<sup>7</sup> Although attentional measures and symptoms were uncorrelated in our sample, positive associations of age with CPT-II scores suggest that performance in the older participants with bulimia nervosa was more cautious, but more inattentive.<sup>41</sup> Although inhibitory control deficits may contribute to “loss of control” eating,<sup>9,10</sup> attentional deficits may contribute to difficulty planning and organizing eating behaviour in individuals with bulimia nervosa.<sup>7</sup>

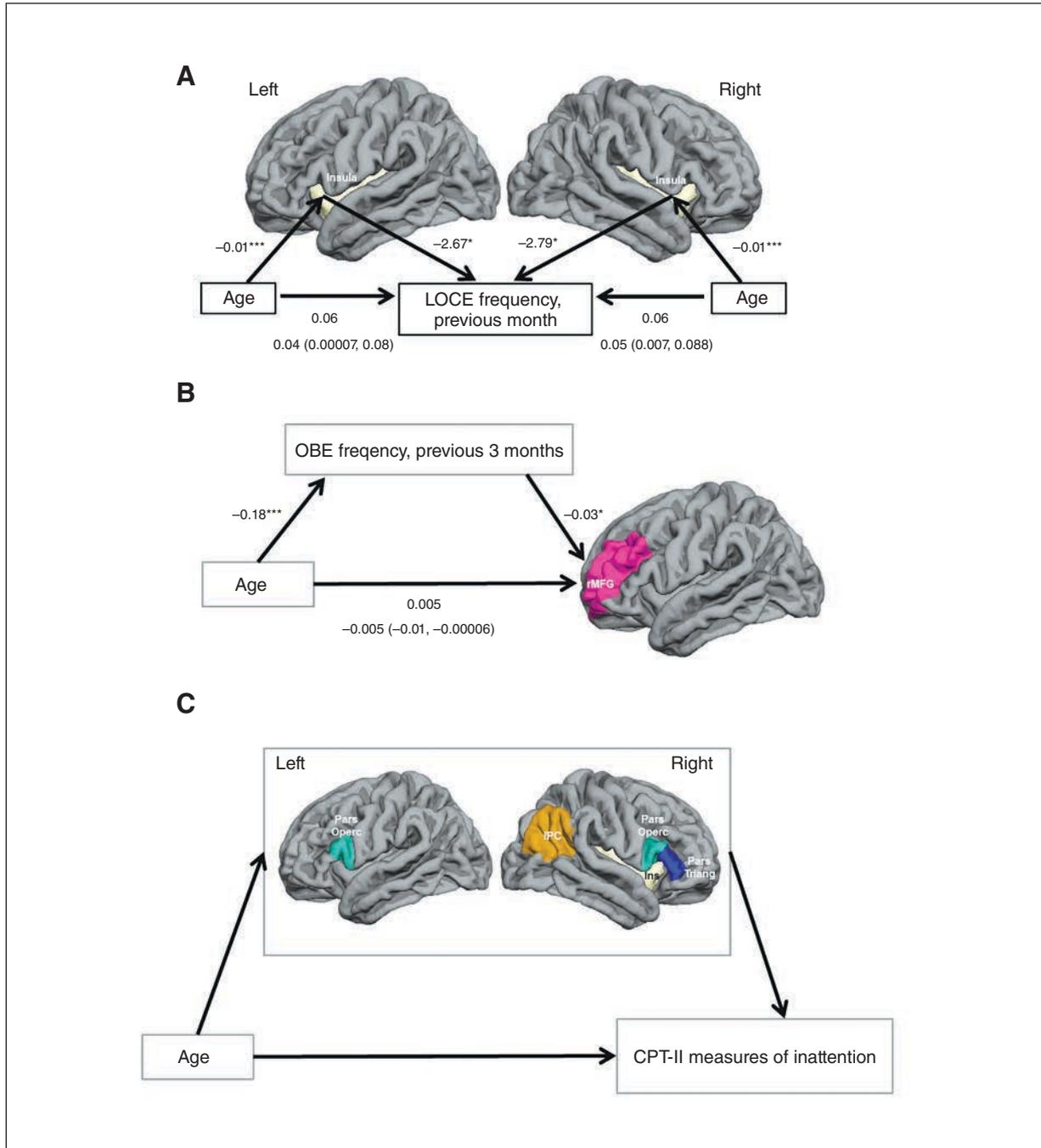
Our findings of lower cortical thickness of the right pars triangularis, SPC and dorsal PCC in bulimia nervosa are consistent with previous findings of local volume reductions in frontoparietal and posterior cingulate regions from a smaller sample of individuals with bulimia nervosa and healthy participants.<sup>14</sup> However, the previous findings suggested reductions in the left, rather than right, inferior frontal regions and



**Fig. 2:** Associations of cortical thickness (CT) with loss of control eating episodes (LOCEs) in the bulimia nervosa group. Blue colours indicate inverse associations of cortical thickness with the frequency of binge-eating episodes before MRI scanning, with smaller  $p$  values in darker shades. **(A)** Cortical thickness, adjusted for age, is plotted on the Y axis, with log-transformed objective bulimic episodes (OBEs; previous 3 months) plotted on the X axis. All effect sizes for associations between cortical thickness and OBEs were medium. **(B)** Cortical thickness, adjusted for age, is plotted on the Y axis, with log-transformed LOCEs (previous month) plotted on the X axis. Three outliers in the distribution of LOCEs were detected ( $p = 0.012$ ), but none were detected in the distribution of OBEs ( $p = 0.46$ ).<sup>62</sup> Studentized residuals of regression models<sup>63</sup> confirmed that effects in the bilateral insula were not outlier-driven (left  $p = 0.50$ ; right  $p = 0.69$ ), but effects in the right insula became marginally significant ( $p = 0.08$ ) after excluding 2 13-year-olds without LOCEs in the previous month. Ins = insula; IPC = inferior parietal cortex; rMFG = rostral middle frontal gyrus.

bilateral temporoparietal regions and PCC. That study used different image processing methods and included participants with less symptom variance, but both studies suggest reduced

volume and thickness of the frontoparietal and posterior cingulate regions that comprise networks underlying control and attentional processes in individuals with bulimia nervosa.



**Fig. 3:** Mediation models within the bulimia nervosa (BN) group. **(A)** Lower cortical thickness in the bilateral insula (yellow) mediated the association between advancing age and increased frequency of loss of control eating episodes (LOCEs; previous month). **(B)** More frequent objective bulimic episodes (OBEs; previous 3 months) mediated the association between age and lower cortical thickness in the left rostral middle frontal gyrus (rMFG; magenta). Indirect effects and 95% confidence intervals are shown below mediation models in panels **A** and **B**. **(C)** Lower thickness of bilateral pars opercularis (Pars Operc) and right pars triangularis (Pars Triang), inferior parietal cortex (IPC), and insula (Ins) mediated the association between age and Conners Continuous Performance Test-II (CPT-II) measures of inattention in the bulimia nervosa sample. Estimates and significance levels for each path in this model (model C in Appendix 1, Fig. S1) are presented in Appendix 1, Table S7.

Dorsal and ventral aspects of the PCC are both functionally connected with the default mode network at rest, but these subregions are functionally and structurally distinct,<sup>27</sup> and the dorsal PCC is more strongly associated with prefrontal cortices and cognitive control networks.<sup>42,43</sup> The dorsal PCC may in fact modulate the connection between internally focused (i.e., default mode) and externally focused (i.e., cognitive control) networks to ensure that attention is efficiently allocated.<sup>44</sup> Reduced thickness of the dorsal PCC along with frontoparietal control regions in individuals with bulimia nervosa compared with healthy participants may thus contribute to disturbances in the attentional processes that these networks support. Greater thickness of the left ventral PCC in individuals with bulimia nervosa is a novel finding, but it is consistent with prior data suggesting increased thickness of this region in individuals with MDD.<sup>45</sup> This finding remained after excluding the participants with bulimia nervosa with comorbid MDD, perhaps suggesting a common marker of dysfunctional emotion processing and regulation in those with bulimia nervosa<sup>46,47</sup> and MDD.<sup>48,49</sup>

We detected a group  $\times$  age interaction in the right isthmus cingulate. Age-related increases in the thickness of the right isthmus cingulate in participants with bulimia nervosa contrasted with age-related reductions in healthy controls. Future studies should assess whether altered structure and maturation of ventral cingulate cortices contributes to the persistence of emotion dysregulation in individuals with bulimia nervosa, as both the ventral PCC and isthmus cingulate are functionally involved in emotion processing and regulation.<sup>50</sup>

Consistent with our prior findings, cortical thickness reductions of inferior frontal cortices were most prominent in participants with bulimia nervosa with the most frequent OBEs. Inverse associations of OBEs with cortical thickness were additionally detected in other attentional control regions (left rMFG and right IPC), and lower cortical thickness of the bilateral insula was associated with the frequency of binge-eating episodes of any size. Functional MRI data suggest deficient activation of frontoparietal regions during the engagement of control in adults with bulimia nervosa<sup>9,12</sup> and adolescents<sup>10</sup> with the most frequent OBEs. Morphological<sup>16</sup> and functional insular abnormalities are associated with altered sensory processing of food stimuli,<sup>51,52</sup> excessive self-focus,<sup>53</sup> and preoccupation with shape/weight<sup>9</sup> in individuals with bulimia nervosa. Our results add to these findings to suggest a structure–function association within frontoparietal and insular cortices whereby lower thickness may underlie functional deficits that, in turn, contribute to an impaired capacity of individuals with bulimia nervosa to engage control over eating and thoughts about food, shape and weight.

Our exploratory mediation analyses suggest that lower insular thickness mediates the association between advancing age and binge-eating frequency and that binge-eating frequency mediates the association between advancing age and lower cortical thickness in the rMFG. Thus, lower cortical thickness in attentional and inhibitory control networks may both contribute to symptom severity and result from behaviours unique to the disorder, as has been suggested in studies of alcohol use disorders.<sup>54</sup> Such associations were not detected

with purging behaviours, but longitudinal, transdiagnostic research should delineate potential unique neurodevelopmental risks for and effects of purging and binge eating.<sup>55</sup>

Our mediation results also suggest that lower frontoparietal thickness suppressed age-related alterations in control and attentional processes in the bulimia nervosa group. Although scores on some CPT-II indices of inattention were higher in older than younger participants with bulimia nervosa, lower thickness of right IPC, pars triangularis/opercularis and insula was associated with lower scores. The direction of these effects indicates inconsistent mediation,<sup>38</sup> such that age-related reductions in frontoparietal and insular thickness could mitigate age-related increases in inattention in individuals with bulimia nervosa. As cortical thickness did not mediate the association between age and self-reported inattention, age-related thickness reductions may attenuate CPT-measured inattention, but not symptoms of inattention over the course of bulimia nervosa.

Age-related thickness reductions of the insular cortex were associated with increased binge-eating frequency, but attenuated CPT-measured inattention. The insula coordinates sustained attentional control,<sup>56</sup> and insular thinning is associated with improved self-regulatory control over healthy development,<sup>57</sup> perhaps explaining why age-related insular thinning suppressed the association between increasing age and inattention in participants with bulimia nervosa. However, as the insula also supports salience processing,<sup>58</sup> age-related insular thinning in individuals with bulimia nervosa may specifically impair attention to or control over motivationally salient food stimuli and responses to these stimuli (i.e., binge eating).

### Limitations

Important limitations should be noted. Our cross-sectional design precludes understanding of whether age-related changes in frontoparietal and insular thickness precede bulimia nervosa symptoms and deficits in control and attentional processes, or vice versa. Because the application of mediation analyses to cross-sectional data may produce biased results,<sup>59</sup> our findings from these analyses merely inform hypotheses for future longitudinal research and should be interpreted with caution. Future research is also needed to examine whether our findings may have been impacted by group differences in unassessed sociodemographic characteristics (e.g., socioeconomic status) and whether they extend to adolescent boys or men with bulimia nervosa or to individuals with binge-eating disorder. In addition, this study is unable to determine the origins of reduced cortical thickness in individuals with bulimia nervosa, as MRI cannot assess cellular changes (e.g., axonal or synaptic pruning, myelination, neuronal apoptosis) that may contribute to an altered age-related trajectory of cortical thickness in individuals with bulimia nervosa. Last, we did not measure hormone levels, which also may contribute to group differences in and age effects on cortical thickness,<sup>60</sup> or schedule scans to control for menstrual cycle phase or hunger, which may impact inhibition and attention.<sup>61</sup>

Despite these limitations, this is to our knowledge the largest anatomical MRI study of bulimia nervosa to date. We used a well-validated neuropsychological task of control and attentional processes and open-source software to permit replication and potential transdiagnostic extension. Our between-group findings of reduced frontoparietal thickness are consistent with previous findings of lower local volumes in the same cortical regions in individuals with bulimia nervosa,<sup>14</sup> suggesting that these patterns are replicable. Inclusion of participants with subthreshold bulimia nervosa likely diminished between-group effects, but the wide range of illness severity advantageously permitted examination of severity as a continuous variable.

## Conclusion

Our findings support a potential role of frontoparietal, posterior cingulate and insular cortices in the persistence of binge eating and cognitive deficits associated with bulimia nervosa; however, cross-sectional data allow us to conclude little regarding the maintenance of the disorder. Prospective, longitudinal studies are necessary to characterize the association between functional and structural alterations that may contribute to the progression of bulimia nervosa from adolescence to adulthood. Future research should examine control and attentional processes as targets for early bulimia nervosa interventions and prevention efforts.

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