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Distinct attention network topology and dynamics and their relations with pubertal hormones in preadolescent boys and girls with binge eating

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The increased prevalence of binge eating during puberty is predominantly in girls, coinciding with a surge in pubertal hormones. This suggests that hormone-activated alterations in widespread brain networks, such as attention network, can contribute to the pathophysiology of the disorder in girls, while distinct mechanisms may exist in boys. This study proposed to examine the topological properties and their temporal dynamics of the sustained attention network in preadolescent children with binge eating symptoms (BE) and matched controls and to test the relation of these properties to circulating levels of pubertal hormones. Data from 77 children with BE and 104 group-matched controls were analyzed. In a static network comprising the entire task duration, the nodal topological properties, i.e., nodal efficiency, betweenness-centrality and degree, of the caudate nucleus, hippocampus and inferior parietal gyrus (IPG) significantly differentiated children with and without BE; and that of left caudate were significantly associated with pubertal hormone levels in girls with and without BE, but not in boys. During different substages of sustained attention processing, Variability of the topological properties in key network nodes, such as bilateral IPG, bilateral precentral gyrus and left hippocampus, demonstrated significant between-group differences and/or unique group-by-sex interactions. These results suggest that the association between pubertal hormones and network topological organization may contribute towards the specific rise of BE in girls, while neural mechanisms of BE in boys may alternatively link to suboptimal functional dynamics associated with precentral gyrus, during their interactions with other cortical and subcortical regions when sustained attention is performed.

INTRODUCTION

Binge eating disorder (BED) is the most common eating disorder, affecting 1.1% of children and between 1 and 5% of adolescents [1, 2]. The risk for problematic binge eating (BE) increases from late childhood to early adolescence [1, 2], coincident with the pubertal surge of gonadal hormones [3] and may serve as a vulnerability for eating disorders in later life [4, 5]. However, the elevated risk is not spread uniformly, with a significantly greater increase in prevalence of BE during puberty in girls than boys [6]. This suggests that different neural developmental effects and pubertal hormones, as well as their distinct interactions, may be implicated in the pathophysiology of BE in boys and girls.

Widespread neural alterations have been identified in individuals with BE [7]. These include distinct patterns of dysconnectivity among distant brain regions or systems-level alterations of the functional brain networks subserving cognitive processes and/or at resting-state [8–11]. Several cognitive processes believed to be involved in BE, including attention, are supported by these widespread brain pathways and rely heavily on the maintenance of arousal [12–14]. Generalized brain arousal, which increases the excitation and activation of attention and behavior, may be implicated in these functional alterations [15].

The link between the pubertal hormone surge and generalized arousal has been established previously [16, 17]. These hormones have powerful direct and indirect influences on the noradrenergic pontine nucleus locus coeruleus that lies at the intersection of arousal and attention networks in the brain [18]. Estrogen binding to nuclear receptors in locus coeruleus enhances norepinephrine synthesis and reduces norepinephrine catabolism [19], thereby increasing synaptic levels of the neurotransmitter in coerulear terminal [20]. This in turn, drives neuronal activity in prefrontal regions that support attention [21] and basal forebrain regions that promote wakefulness [22].

This may contribute towards the increased vulnerability to BE during adolescence, particularly in girls, as gonadal hormones in particular estradiol, may drive the generalized arousal of the brain [23] and therefore, may serve as a vulnerability for BE in adolescence, especially in girls [24, 25]. Pubertal levels of the androgen testosterone and the estrogen estradiol have been divergently associated with ventral striatal activation and connectivity for reward responsivity and decision-making in young adolescent girls but not boys [26, 27]. While the aforementioned systems-wide alterations in brain function may point towards the aforementioned effects of generalized arousal, to date the

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relationship between pubertal hormones, and function in brain networks underpinned by generalized arousal underlying BE have not been investigated in children.

The current study proposed to assess firstly the systems-level topological properties and their temporal dynamics of the functional brain network subserving sustained attention processing in children with and without BE, and secondly the association of these functional brain properties to pubertal hormones. Graph theoretical techniques [28, 29] and sliding-window-based techniques [30, 31] were utilized to evaluate the topological properties of the functional brain network during a block-based attention task, as well as their temporal dynamics in the substages of attention initiation, stable attention, post-attention, and resting periods. Graph theoretical techniques allow the quantification of systems-level topological organization of the sustained attention network, by modelling the efficiency and connectedness of functional communications among all possible pairwise connections between remote brain regions in the network (network nodes) [28]. By analyzing the topological properties of a brain network highly dependent on generalized arousal, we aimed to link any observed alterations with the arousal-modulating pubertal hormone levels.

Our hypotheses are twofold: first, based on evidence of altered attentional processes [12, 14, 32] and of altered functional network properties in BE [11, 33], we hypothesized that relative to the matched control children, preadolescent children with symptoms of BE would show significant altered topological properties and their dynamics of the sustained attention network. Second, based on the association between pubertal hormones, generalized arousal and disordered eating risk, we further hypothesized that the topological property alterations in children with BE would be associated with levels of pubertal hormones, particularly in girls but not in boys.

METHODS
Participants
Neuroimaging and clinical data from 77 children with BE and 104 matched controls were included in this study. These data were obtained from the Adolescent Brain Cognitive Development (ABCD) Study baseline pool (Release 4) and downloaded from the National Institute of Mental Health Data Archive. The ABCD Study aimed to recruit a sample that reflects the sociodemographic variation of the US population including race and ethnicity [34]. The baseline pool included 11,875 children aged 9 and 10 years, from 21 sites across the United States.

The original exclusion criteria of the ABCD Study baseline enrollment were: a current diagnosis of schizophrenia, autism spectrum disorder (moderate, severe), mental retardation/intellectual disability, or alcohol/substance use disorder [34]. To further remove potential confound in our findings, subjects with a history of traumatic brain injury or bipolar disorder were also excluded. Subjects with incomplete structural MRI, fMRI and/or task performance data, or low-quality imaging data (using the Human Connectome Project imaging data quality check criteria [35]), or missing/low quality pubertal hormone data [36] in both measurement repetitions were further excluded.

A sample of children with BE was defined using multiple criteria, due to the complexity of diagnosis in pediatric BED. First, binge eating-related symptoms were assessed using the parent/guardian responses to the Kiddie Schedule for Affective Disorders and Schizophrenia (K-SADS) based on DSM-5 criteria [37]. An initial pool of 377 children with present binge eating were identified, based on parent reports indicating presence of binge eating (ABCD K-SADS item: Symptom - Binge Eating Present). From this initial pool, 106 subjects were excluded due to parents reporting 'no' to all 7 items in the binge eating supplementary scale used to characterize individual binge eating behaviors (e.g. "My child eats a lot even though he or she is not hungry", "My child feels disgusted or guilty after binge eating"). In the remaining 271 subjects with present binge eating diagnosis/behaviors, we defined a group of 123 as having BE using the following inclusion criteria: i) having a BED diagnosis ($n = 37$); ii) having a diagnosis of BED/Other Specified Feeding or Eating Disorders/not meeting full diagnostic criteria ($n = 28$); or iii) no diagnosis but reported at least one

binge eating episode per week for at least 3 months (diagnostically equivalent to full-threshold BED criteria) plus parent report of child displaying at least one binge eating behavior present on the KSADS ($n = 58$). Among the 123 subjects with BE, 46 were excluded from group-level analyses due to excessive head movements in the fMRI data (see below in the *Imaging Data Acquisition and Preprocessing* Section). The flow of BE group identification process is graphically depicted in Fig. 1.

A pool ($n = 2340$) of control participants was identified following the ABCD Study and the current study-specific exclusion criteria, without diagnosis of any eating disorder, and no participant or family history of psychiatric disorders. A study-specific control group was then defined from this pool, consisting of 104 participants, who were pseudo-randomly selected from participants with complete and high quality imaging data with head motion passing the motion-based criteria described in the Section of *Imaging Data Acquisition and Preprocessing*, and matched on age, height, IQ (age-corrected picture vocabulary), sex, handedness and combined parental income (to reflect socioeconomic status) to the group with BE.

As our sample size was determined by available data, we ran a power analysis to ensure the final sample size was sufficient, particularly to detect interaction effects. The power for a 2×2 interaction assuming rX = 0.45 and rX2 = 0.2 (one medium effect and one small effect on Y) and a correlation of r =0.4 between them (moderate correlation of predictors) and examining effects of the interaction ranging from 0.10 to 0.45 (small to medium effect), we estimated power with total sample size ranging from 100 to 700 using 10,000 simulations in InteractPowerR v0.2.2. We achieved at least 80% power with interaction effects at 0.25 with sample size of 100 [38]. For the main group effect we estimated power with total sample size ranging from 20 to 200 and achieved at least 80% power with sample size of 100. Figures S1 and S2 summarize our simulations.

### Ethics approval and consent to participate
The ABCD Study was approved by the institutional review board (IRB) of the University of California, San Diego and of each data collection site. Informed consent and informed assent were obtained from parents and participants, respectively. The current study is a secondary analysis of de-identified data and therefore IRB approval was waived.

Pubertal hormones
Testosterone, dehydroepiandrosterone (DHEA) and estradiol (in girls only) levels were obtained at ABCD study sites by salivary measurement. Details of the measurement procedures are described elsewhere [39]. Briefly, saliva was collected via passive drool method following 30 min of no eating, drinking or chewing of gum. Saliva samples were frozen on site and analyzed in duplicate by Salimetrics (Carlsbad, CA). Raw hormone assay values were standardized on age, and Pubertal Development Scale (PDS) subscale score, by sex using Bayesian mean estimation with priors derived from population age and race ethnicity norms. The remaining DHEA, testosterone, and estradiol values were standardized within the Bayesian model by averaging across age weighted for PDS subscale and derived by controlling for a number of factors that can impact hormone level: i) time of day of saliva collection; ii) color of the sample; iii) duration of sample collection; iv) caffeine and v) vigorous physical activity. Pubertal stage was estimated using the PDS completed by the parent. Pubertal stage in girls was calculated by summing responses for body hair and breast growth, combined with information about menarche. Pubertal stage in boys was calculated by summing responses for body hair, facial hair and voice changes [36, 40]. Final hormone values used in analysis were single values derived from averaging Bayesian estimates of each repetition.

Imaging data acquisition and preprocessing
We utilized fMRI data collected during the 0-back blocks of the emotional n-back task [41] (see supplementary material for full task description, and Table 1 for behavioral performance). Unlike the 2-back trials of the task which require working memory, the 0-back trials instead require only sustained attention without a working memory loading, and alone are sometimes referred to as the attentional 0-back task [41–43]. Contrasting 0-back trials with fixation trials shows significant activation in bilateral cortical regions involved in the dorsal and ventral attention networks (DVAN), including several regions of the frontal cortex, the inferior parietal gyrus (IPG), and subcortical regions, including the dorsal and ventral striatum and the thalamus [44].
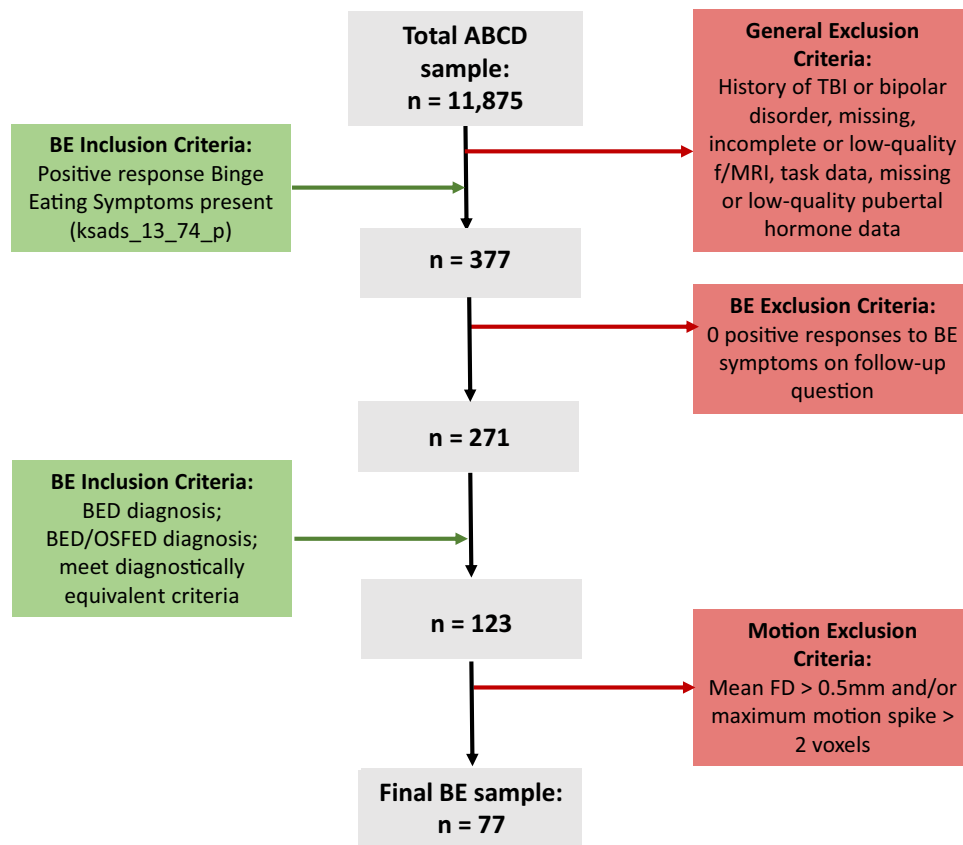
Fig. 1 Binge eating participant inclusion/exclusion flowchart. Inclusion criteria are shown on the left (green), exclusion criteria are shown on the right (red), participants included at each stage shown in the middle (grey). BE, binge eating; BED, binge eating disorder; FD, framewise displacement; fMRI, functional magnetic resonance imaging; OSFED, otherwise specified feeding or eating disorder; TBI, traumatic brain injury.

Detailed data acquisition protocols from the ABCD Study have been published elsewhere [41]. Briefly, two runs of the task-based scans lasting approximately 5 min were acquired using whole-brain multiband echo planar imaging depicting the blood oxygenation level-dependent (BOLD) signals (TR = 800 ms, TE = 30 ms, flip angle = 30°, slices = 60, resolution = 2.4 × 2.4 × 2.4, multiband acceleration factor = 6).

Raw fMRI data was downloaded and preprocessed using the FEAT toolbox (FMRIB Software Library, FSL, version 5.0). First, the initial volumes were removed from the time series, depending on the manufacturer (Philips and Siemens original n volumes = 370 and n removed = 8; GE DV25 series original n volumes = 367 and n removed = 5, GE DV26 s series original n volumes = 378 and n removed = 16). Next, slice time correction, and motion correction using MCFLIRT were performed on the time series, and a high-pass temporal filter with a 100-second cut-off (0.01 Hz) was applied to remove slow frequency drifts. Spatial smoothing using a 5 mm gaussian kernel was then applied. Finally, functional images were spatially normalized to a standard MNI space pediatric image [45], with a resolution of 1 ×1 x 1mm. Functional connectivity and network analyses are particularly sensitive to excessive motion [46, 47], and therefore stringent motion-based exclusion criteria were applied in this study. Subjects were excluded if framewise displacement [46] in both task runs exceeded 0.5 mm and/or if maximum motion exceeded 2 voxels in any direction (See Fig. 1 for subjects excluded).

Node selection and BOLD timeseries extraction
A combined activation map of the two groups was first generated for the contrast of interest (0-back versus fixation) (see Fig. 2A). This reference activation map was parcellated into 246 distinct regions using the Brainnettome Atlas [48]. Network nodes were defined as 4-mm spheres around peak activation in clusters thresholded at $T \geq 2.3$ in each region with at least 800 voxels of contiguous activation, and in the bilateral pulvinar nucleus. This resulted in 55 network nodes located in bilateral cortical and subcortical areas from the reference activation map. For each

subject, the BOLD signals of each node (averaged over voxels in each node) were extracted from a sequence of 208 brain volumes consecutively formed along each 0-back block and the rest block immediately following the 0-back block. To further remove head motion-related artifact in the signals, a six-level wavelet noise filtering process was applied to the resulting timeseries of each node, using the inverse Maximal Overlap Discrete Wavelet Transform with the Symlet wavelet family, in the GAT-FD toolbox [49, 50].

Static functional network construction
A 55 ×55 functional connectivity matrix was then calculated for each subject using Pearson's correlation of the BOLD signal timeseries in each pair of the network nodes. The connectivity matrix was binarized by using network cost as thresholds, defined as the fraction of existing edges relative to all possible edges in a network [51]. The appropriate cost range for thresholding the network was then determined to be between 0.14 and 0.45 and the topological properties of the network were calculated within this range at an increment of 0.1, at each increment retaining positive edges that exceed the threshold only. Details and justification of the determination of the appropriate cost range can be found in Supplementary Materials. The network global and local efficiencies were calculated for the overall network. The nodal efficiency, nodal degree and betweenness-centrality (BC) were obtained for each network node. Mathematical definitions of these topological properties can be found in Supplementary Materials. Neurobiologically, the network global efficiency reflects the ability of the network to efficiently transfer information across all distributed network nodes (i.e. the network as a whole). Network local efficiency reflects the network's efficiency/speed for information transfer between neighboring nodes. Nodal efficiency reflects the efficiency/speed with which any given node communicates with all other connected nodes, while nodal BC and nodal degree are measures of the extent of connectedness to other nodes in the network, or hubness of a given node.

Table 1. Participant characteristics and behavioral performance.

	BE N = 77 M(SD)	CON N = 104 M(SD)	T	P
Age	9.95 (0.62)	9.97 (0.60)	0.25	0.80
IQ	99.1 (11.8)	101.7 (16.1)	0.86	0.38
BMI percentile	0.89 (0.90)	0.67 (0.28)	6.0	<0.001
0-back n trials correct	64.5 (13.3)	66.8 (10.4)	-1.3	0.19
0-back RT	917.2 (140.6)	912.7 (122.0)	0.23	0.82
0-back SDRT	295.2 (59.1)	288.6 (55.1)	0.77	0.44
	n	**n**	**X^2**	**P**
Sex			0.64	0.42
Girls	44	52		
Boys	33	52		
Scanner Type			1.4	0.52
Siemens	50	34		
Phillips	10	68		
GE	17	31		
Race			13.6	0.057
American Indian/ Alaska Native	0	3		
Asian	0	1		
Black/ African American	15	12		
Mixed/ Other	23	16		
Native Hawaiian/ Pacific Islander	0	1		
White	35	65		
No Response	3	4		
Ethnicity			0.22	0.90
Hispanic	27	34		
Non-Hispanic	49	68		
No Response	1	2		
Pubertal Stage			10.2	0.07
Pre	23	46		
Early	15	23		
Mid	31	24		
Late	0	2		
Post	1	0		
Handedness			4.9	0.09
Left	8	10		
Right	53	98		
Mixed	16	15		
Parental Income			8.6	0.47

BE participants with binge eating, CON control, IQ intelligence quotient (age-corrected picture vocabulary), BMI body mass index, RT reaction time, SDRT standard deviation of the reaction time.

Network dynamics

Functional connectivity of brain regions can vary during processes of sensory and cognitive tasks or even in resting-state [30, 52]. An increasing number of studies suggest that temporal variance of functional brain networks contributes to cognitive performance, and alterations in this variance may play a significant role in neuropsychiatric conditions [31]. For example, while increased variance in networks has been associated with superior cognitive performance [53, 54] both increased and decreased network temporal variance is reported in schizophrenia, major depression and bipolar disorder [31]. To analyze the dynamics of the topological properties of the DVAN, we utilized the sliding window-based techniques from the GAT-FD toolbox [55]. A temporal window of 17 volumes was used with a sliding window step size of one volume. This resulted in a total of 192 temporal windows per task run per subject, and a network was constructed for each window. The dynamic network threshold was correlation coefficients between 0.24 and 0.78, corresponding to the top 45-15% strongest functional connectivity. This threshold range should retain the connections meeting the small-world network assumptions [50].

The first seven networks in each run were discarded to account for the slow BOLD response and fast repetition time (800 ms). The remaining 185 networks were then classified as during the substages of stable attention (n networks = 60), post-attention (n networks = 48), rest (n networks = 32) and attention initiation (n networks = 45), based on the temporal locations of the brain networks along the task (see Fig. 2B and C). To assess the temporal dynamics and variability of the topological properties of the DVAN along the task duration, Variance across each substage was calculated for nodal efficiency, BC and degree were calculated for each network node for each of the four substages. Variance was defined as:

$$Variance = \frac{1}{N-1} \sum_{i=1}^{N} |Ai - \mu|^2$$

Where A is a vector made up of N observations (i.e. networks) and μ is the mean of A.

Group-level statistical analysis

Participant characteristics including basic demographic information and pubertal stage were analyzed using t-test and chi-square tests for continuous and categorical data, respectively. Behavioral performance during the 0-back blocks of the task was analyzed using a t-test to assess group differences in accuracy, mean reaction time, and standard deviation of reaction time.

To analyze static and dynamic network properties, the following ANCOVA model was tested:

$Node\ Property \sim group + BMI\% + SES + IQ + sex + group \times sex$

Homogeneity of variance was confirmed using Levene's test ($p > 0.05$) and normality was confirmed by inspection of Q-Q plots. Results were considered in the two global network properties and the nodal properties in 15 key cortical and subcortical brain components, determined based on those regions defined as belonging to the DVAN [56, 57], including bilateral superior frontal gyri (SFG), middle frontal gyri (MFG), IPG, insula, inferior temporal gyri as well as the pulvinar nuclei of thalamus and dorsal striatum. Bilateral hippocampi were also included in analyses. Although hippocampus is not a core structure of the DVAN, there is solid evidence suggesting that it interacts with these networks through its role in memory retrieval, where it may be activated when attention needs to access stored information from memory, especially through connections with the dorsal attention network which manages top-down attentional control [58, 59]. Bonferroni correction was applied over results from these nodes.

A partial least squares (PLS) regression was used (using MATLAB function plsregress) to assess the relationship between pubertal hormones (testosterone, DHEA and estradiol in girls, testosterone and DHEA in boys) and the nodal network properties showing significant (uncorrected) group differences. For any given subject, covariance between network properties across the involved network nodes, as well as between circulating levels of pubertal hormones is expected. PLS regression allows assessment of the relationship between pubertal hormones and network properties by creating uncorrelated components, thus solving the issue of collinearity in these measurements [60]. The PLS latent brain component explaining a significant percentage of variance was identified separately for boys and girls with and without BE, as boys do not have data on estrogen levels. The loadings for the significant brain component were compared for the different groups. Significance of PLS components was tested using permutation with the number of iterations justified based on the sample size (n permutations = 500). Variable Importance in Projection (VIP) scores were calculated for each brain region. Brain components with a VIP scores
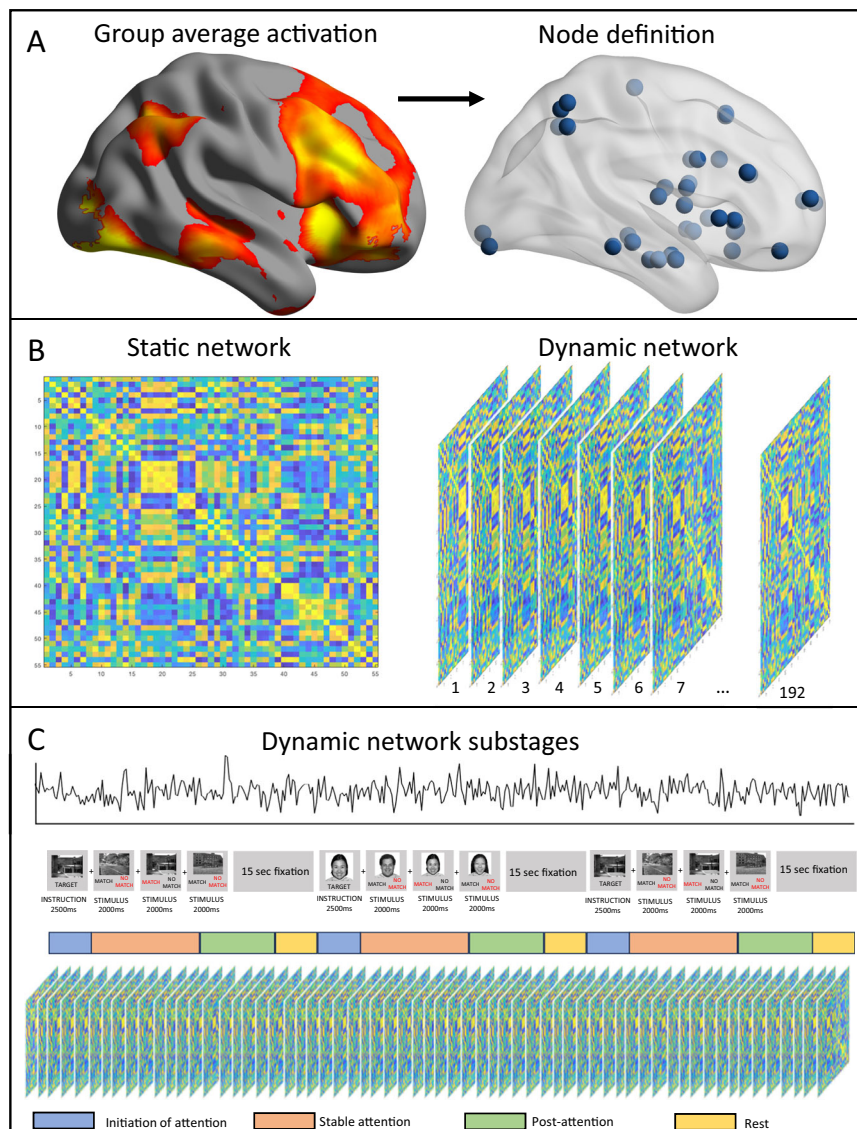
Fig. 2 Analysis pipeline. A: Nodes are defined first by calculating a group-average, then 4 mm spherical nodes are defined around activation peaks. **B** Correlation matrices (55 ×55) are calculated to reflect connections (Pearson correlation) between each node. The matrix is binarized to create a network. This is either done once (static network) or 192 times (sliding window dynamic network). For each network created, nodal global efficiency, degree and betweenness centrality are calculated. **C** Breakdown of concatenated sustained attention trials into four dynamic stages: initiation, stable attention, post-attention and rest.

> 1 are considered important in the association between brain and hormonal components [61].

RESULTS
Demographic measures
Participants with BE were in a significantly higher BMI percentile (95% CI: 0.14 – 0.29, p <0.001) than control participants. There were no significant group differences in sociodemographic measures, pubertal stage or scanner type. Statistical comparisons of participant characteristics are shown in Table 1.

Behavioral performance
There were no significant differences between BE and control children in 0-back accuracy (95% CI: -5.91 – 1.19; $p = 0.19$), reaction time (95% CI: -34.86 – 43.96; $p = 0.82$) or standard deviation of reaction time (95% CI: -10.49 – 23.89; $p = 0.44$). Group statistics for behavioral performance can be found in Table 1.

Pubertal Hormones There were no significant differences between BE and control children in pubertal hormone levels (all $p > 0.05$).
In participants with BE, the mean testosterone level for boys was 32.6 pg/mL (± 16.6 pg/mL), and for girls, it was 45.6 pg/mL (± 23 pg/mL). For DHEA, the average level in boys was 62 pg/mL (± 36 pg/mL), while for girls, it was 102 pg/mL (± 60 pg/mL). In girls with BE, the mean estradiol level was 1.14 pg/mL (± 0.5 pg/mL).
In control participants, the mean testosterone level for boys was 34.4 pg/mL (± 16.8 pg/mL) and for girls, it was it was 37.5 pg/mL (± 14 pg/mL). For DHEA, the average level in boys was 69.2 pg/mL (± 51.9 pg/mL) while for girls, it was 76 pg/mL (± 42 pg/mL). In control girls, the mean estradiol level was 1.03 pg/mL (± 0.5 pg/mL).

Static network topological properties
There were no significant differences between BE and control children in network global efficiency or network local efficiency ($p > 0.05$). Group means of all the significant nodal properties prior to

Table 2. Group Differences in Static Network Properties.

	Region	BE vs CON	BE M(SD)	CON M(SD)	$p_{uncorrected}$	p_{BON}	partial eta^2
Efficiency							
	L Hippocampus	↑	0.48 (0.11)	0.43 (0.12)	0.002	0.03	0.0276
	L Caudate	↑	0.57 (0.08)	0.55 (0.10)	<0.001	<0.001	0.0494
Degree							
	L Hippocampus	↑	10.8 (5.5)	8.6 (4.7)	0.002	0.03	0.0277
	L Caudate	↑	16.4 (4.9)	15.1 (5.9)	<0.001	0.01	0.0338
BC							
	L Inferior Parietal Gyrus	↑	64.0 (58.6)	41.8 (38.7)	0.001	0.015	0.031

L left, *R* right, *BE* participants with binge eating, *CON* control, P$_{BON}$ p-values bonferroni corrected for network, Symptoms, *BC* betweenness-centrality. significant results following bonferroni correction are shown in bold.

Bonferroni correction are included in Table 2. Children with BE showed significantly higher nodal efficiency in left hippocampus (95% CI: 6.99 – 12.90; $p_{uncorrected}$ = 0.002, p_{BON} = 0.03, η^{2}p = 0.0276) and left caudate (95% CI: 12.84 – 23.67; $p_{uncorrected}$ <0.001, p_{BON} = <0.001, η^{2}p = 0.0494); significant higher nodal degree in left hippocampus (95% CI: 7.0 – 12.99; $p_{uncorrected}$ = 0.002, p_{BON} = 0.03, η^{2}p = 0.0277) and left caudate (95% CI: 8.67 – 15.99; $p_{uncorrected}$ <0.001, p_{BON} = 0.01, η^{2}p = 0.0338); and significant higher nodal BC in left IPG (95% CI: 7.69 – 14.169; $p_{uncorrected}$ = 0.001, p_{BON} = 0.015, η^{2}p = 0.031). The BMI percentile covariate significantly contributed to the model for left caudate efficiency (p = 0.028), left hippocampus degree (p = 0.045) and left caudate degree (p = 0.046). However, these effects did not survive Bonferroni correction. Significant group-by-sex interactions of the static topological properties were not observed in any nodes within the DVAN (all p > 0.05). Group means for all significant nodal properties prior to Bonferroni correction are included in Table S1.

Dynamics of the nodal topological properties across substages of attention processing
Attention initiation substage. Following Bonferroni correction, children with BE showed significantly reduced Variance of nodal degree during the initiation of attention in right IPG (95% CI 6.47 – 11.93, $p_{uncorrected}$ = 0.003, p_{BON} = 0.045, η^{2}p = 0.026) compared to control children, and there was a significant group-by-sex interaction in Variance of nodal efficiency in right precentral gyrus (PrG). The BMI percentile covariate did not significantly contribute to the model for these measures during attention initiation (all p > 0.05). Post-hoc tests revealed reduced Variance of right PrG nodal efficiency in boys with BE compared to control boys (95% CI -0.004 – -0.0009, p = 0.002, Cohen's d = -0.62). There was no difference in the variability of PrG nodal efficiency between girls with and without BE (p > 0.05).

Stable attention substage. Children with BE showed significantly increased Variance of nodal BC during stable attention in right middle frontal gyrus (95% CI 6.85 – 12.63; $p_{uncorrected}$ = 0.003, p_{BON} = 0.045, η^{2}p = 0.027) compared to control children, and there was a significant group-by-sex interaction in the Variance of the right PrG following Bonferroni correction. The BMI percentile covariate did not significantly contribute to the model for these measures during stable attention (p > 0.05). Post-hoc tests revealed reduced Variance of right PrG degree in boys with BE compared to control boys (95% CI -11.6 – -0.07, p = 0.047, Cohen's d = -0.40). There was no difference in PrG efficiency between BE and control girls (p > 0.05).

Post-attention Substage. Analyses revealed no significant differences between BE and control children or group-by-sex interactions in the Variance of the nodal topological properties

in any nodes of the DVAN during the post-attention substage (all p > 0.05).

Rest substage. Children with BE showed significantly increased Variance of left IPG BC during rest (95% CI 6.66 – 12.28; $p_{uncorrected}$ = 0.003, p_{BON} = 0.045, η^{2}p = 0.026) compared to control children, and there were significant group-by-sex interactions in the Variance of right PrG nodal efficiency (p_{BON} = 0.015) and left hippocampus BC (p_{BON} = 0.03), all survived Bonferroni correction. The BMI percentile covariate did not significantly contribute to the model for these measures during stable attention (p > 0.05). Post-hoc T-tests showed increased Variance of nodal efficiency in PrG in girls with BE compared to control girls (95% CI 0.0003 – 0.003, p = 0.015, Cohen's d = 0.50), while in contrast, Variance of right PrG nodal efficiency was lower in boys with BE than control boys (95% CI -0.004 – -0.0004, p = 0.017, Cohen's d = -0.47). Post-hoc tests also revealed increased Variance in hippocampal BC in girls with BE compared to control girls (95% CI 444.9 – 2172.2, p = 0.003, Cohen's d = 0.62). There was no difference in hippocampal BC between boys with and without BE (p > 0.05).

Results of analyses in network dynamics during all substages of attention processing are reported in full in supplementary Tables S2 and S3, including all significant nodal properties prior to and post-Bonferroni correction.

Relationship with hormones
The first brain PLS component explained a significant amount of variance in the hormone measures in both girls with BE (p$_{perm500}$ = 0.021) and control girls (p$_{perm500}$ < 0.001). Weightings of factor loadings separately for girls with and without BE can be found in Fig. 3. For both groups of girls, the strongest factor loading was a negative loading for nodal efficiency in left caudate nucleus and left putamen and a negative loading for nodal degree in left caudate nucleus. The first PLS component did not explain a significant amount of variance in the hormone measure for either boys with BE or control boys (p$_{perm500}$ = 0.69 and p$_{perm500}$ = 0.052 respectively). In BE girls, efficiency in the left hippocampus, the left putamen and left caudate, BC in the right hippocampus and degree in the left caudate had VIP scores > 1. In control girls, efficiency in the right hippocampus, the left putamen and left caudate, BC in the right IFG and degree in the left IFG had VIP scores > 1. VIP scores are presented in Fig. 3.

DISCUSSION
The results of this study demonstrated that during sustained attention processing, the topological properties and their temporal dynamics associated with several key nodes of the DVAN distinguished children with BE from control children. Specifically, children with BE showed significantly increased nodal efficiency and degree of the functional subnetworks associated
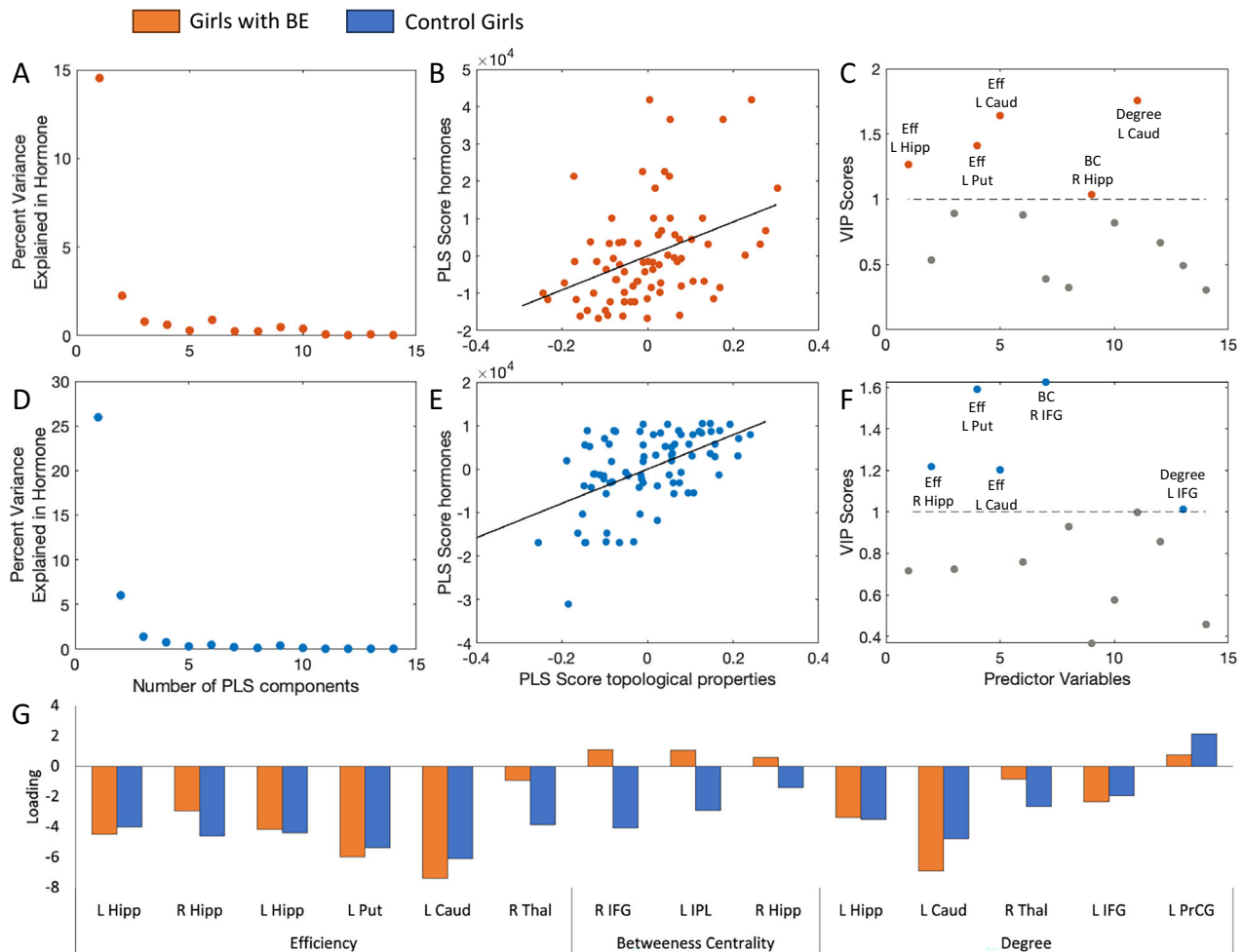
Fig. 3 PLS Regression Analysis of Gonadal Hormones and Attention Network Properties. A-C show the significant first PLS component and the significant correlation between hormone PLS scores and network properties PLS scores and VIP scores for the brain predictor variables for girls with BE (orange) and **D-F** show the equivalent for control girls (blue). **G** shows the network property loadings onto the significant PLS component.

with left caudate and left hippocampus and increased BC of the subnetwork associated with left IPG during the entire task period; as well as significantly altered dynamic variability of these nodal topological properties of the subnetworks associated with bilateral IPG and right MFG. Meanwhile, the nodal efficiency and degree of left caudate, in which between-group differences were identified, contributed to an association between circulating pubertal hormones and functional brain integrity in girls only, suggesting a female-specific pubertal-hormone dependent mechanism via altered efficiency and connectedness of left caudate during its functional communications with other brain regions for sustained attention processing. Alternatively, boys with BE were distinguished from control boys through reduced dynamic variability of nodal efficiency and connectedness of the subnetwork associated with of bilateral PrG. These sex-specific findings suggest differentiating mechanisms underlying binge eating in preadolescent boys and girls.

Participants with BE were distinct from control participants in several measures, notably through consistent differences associated with IPG, in both the topological properties and their functional dynamics along different substages of the attention task. During the entire task, children with BE showed increased overall speed for functional information transferring and hyper-communications among brain regions in the subnetwork associated with left IPG. Furthermore, the dynamic variability of speed

for information transferring and connectedness of the subnetwork associated with IPG in children with BE were found to be overly decreased during the attention initiation substage, while abnormally increased during resting-state. IPG is a major hub of the fronto-parietal system and plays a critical role in a range of cognitive functions, including attention [62]. Alterations in regional activation and seed-based connectivity in IPG have previously been implicated in binge eating, with reports of both increased and decreased functional connectivity in this region in participants with BED [10, 63], possibly contributing to the posited role of attentional processes in the disorder [13, 14, 32]. Our observation of differences in the functional organization of this junction of auditory and visual processing streams may indicate widespread impacts on functioning in children with BE, as would be expected if generalized arousal was impacted. Interestingly, the overall betweenness-centrality of left IPG loaded in opposite directions on the pubertal hormone component for girls with and without BE, with the former group showing a small, positive loading versus a stronger, negative loading in the latter group. This suggests that the relationship between circulating pubertal hormones and functional brain properties associated with IPG is distinct in girls with and without BE, and may contribute towards BE in girls.

Our results in girls support the hypothesized association between pubertal hormone levels and the function of a central

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node in the ventral attention network that may convey vulnerability for BE in young adolescent girls specifically. The finding of this association in girls but not boys suggests that estradiol actions at estrogen receptors may contribute towards this relationship. Caudate nucleus plays a critical role in goal-directed behavior through the prioritization of actions based on outcome [64] and has been implicated in the control of food intake [65, 66], with regional caudate fMRI activation positively associated with binge eating severity [10, 67]. Caudate spiny projection neurons and interneurons all express membrane-bound estrogen receptors [68], which increases neuronal excitability beginning during puberty [69] and impedes the synaptic plasticity that supports learning [70]. Estradiol indirectly promotes basal and stimulated dopamine release and dopamine receptor expression in dorsal striatum [71], and is linked to increased nucleus accumbens activation for decision-making in adolescent girls [27] and reduced caudate responses to reward cues. The significant associations of pubertal hormone levels in girls to the nodal efficiency and connectedness of left caudate nucleus suggest that, in early pubertal developmental stages, pubertal hormone levels are associated with organization of BE-relevant neurocircuitry [24, 25]. Although we did not find group differences in levels of pubertal hormones, this absence of significant difference may be due to the early pubertal developmental stages of participants. As pubertal development continues, significant differences in circulating pubertal hormones may become evident between adolescents with and without binge eating [6] and further contribute towards functional network alterations. The general arousing effects of the increasing pubertal levels of estradiol may disrupt the prioritization of actions in the caudate nucleus [64], although due to the cross-sectional nature of the evidence presented here, longitudinal research is required to test any lasting organizational impacts into adulthood of estradiol levels in puberty. Additionally, future research should consider whether similar relationships between pubertal hormone and network organization exist in bulimia nervosa, for which there is also a reported sex difference in prevalence [72], to understand if the associations identified here reflect a neurobiological risk for the transdiagnostic behavior of binge eating.

Intriguingly, the temporal dynamic patterns of topological properties associated with bilateral PrG showed significant group-by-sex differences in multiple substages of sustained attention processing. Particularly, boys with BE showed significantly reduced dynamic variability of nodal efficiency and degree of right PrG in attention initiation and resting substages, and reduced dynamic variability of nodal degree of left PrG during the stable attention substage. Girls with BE showed differences in variance in right PrG efficiency in the rest substage only, interestingly in the opposite direction to boys. PrG activation has been consistently reported to be associated with food motivation in children and adolescents [73], and differences of functional activation in this region have previously been observed in adults with BED compared to control adults [63]. The sex-specific distinct patterns of altered temporal dynamics of PrG-associated subnetwork suggest sex-specific differences in children with BE in the propensity for the DVAN to maintain its performance during different attentional substages. Specifically, consistent differences in boys with BE compared to control boys point towards a mechanisms contributing to binge eating in boys that does not consistently exist in girls, distinct from the sex-specific hormone-driven mechanism discussed above. It should be noted that group-by-sex interactions of the static topological properties (overall averaged across the entire task duration) associated with PrG were not observed in the analyses. While to-date there is not consensus about the direct impacts of reduced network variability, our results suggest that advanced investigations into the temporal dynamics of functional brain networks subserving sensory/cognitive processes could provide us more refined evaluations of the neurophysiological mechanisms associated with BE; while on the other hand, the relationship between sex, BE, and PrG properties requires further investigation.

Limitations
This study has limitations that need to be considered. First, as the study is cross-sectional, we cannot conclude any potential developmental effects of pubertal hormones on the DVAN organization. The majority of the sample used here were pre-, early- or mid-pubertal. It is likely that the influence of pubertal hormones will develop into adolescence, as pubertal development continues. Further studies should utilize the longitudinal nature of the ABCD study to assess how the relationships identified here cross-sectionally develop with age. Second, although sustained attention is dependent upon generalized arousal, we make conclusions here relating to generalized brain arousal using sustained attention as a proxy measure. While we believe that the relationship between systems-level brain alterations and pubertal hormones likely arises as a result of the known effect of pubertal hormones on generalized arousal, it is possible that these associations arise reflect more specific or localized effects. Finally, although we controlled for BMI percentile in our regression models, children with BE were in a significantly higher BMI percentile than control children, and this may have contributed towards group differences observed.

CONCLUSIONS
We observed for the first time alterations in topological properties of the DVAN during sustained attention in children with BE, supporting the evidence for alterations in attentional processes in BED. We identified an association between circulating hormones and nodal topological properties of the attention network in girls but not boys, which may be reflective of the impact of estrogen on widespread circuitry underlying generalized brain arousal, which in turn may contribute towards the increased risk for binge eating in girls during puberty by impacting widespread brain pathways. Alternatively, boys with BE showed consistent alterations associated with the PrG, potentially reflecting a distinct mechanism. Future longitudinal work will further elucidate the sex-specific mechanisms underlying binge eating and the impacts of gonadal hormones on binge eating-related neurocircuitry across pubertal development.

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AUTHOR CONTRIBUTIONS

Conceptualization, EM, XL, TH; methodology, EM and XL; formal analysis, EM; writing - original draft preparation, EM; writing - review and editing, XL, TH, KPS, LAB, RS. All authors have read and agreed to the published version of the manuscript.

COMPETING INTERESTS

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