Title: Earlier onset of menstruation is related to increased body mass index in adulthood and altered functional correlations between visual, task control, and somatosensory brain networks.

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Acknowledgments:

GES was responsible for the design, data analysis, and writing of the manuscript. JRS and KSB were responsible for design considerations and editing of the manuscript. AP was responsible for editing the manuscript. Data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657) funded by the 16 NIH Institutes and Centers that support the NIH Blueprint for Neuroscience Research; and by the McDonnell Center for Systems Neuroscience at Washington University. This work was supported by the National Institute of Diabetes and Digestive and Kidney Diseases R01 DK112317 and the American Diabetes Association 1-17-JDF-031. The authors have no competing financial interests to disclose.

Data Availability

The data that support the findings of this study are openly available in connectomeDB at <https://db.humanconnectome.org/app/template/Login.vm;jsessionid=FDE86FD272E119A1708AC55CDC5D3BAF>, reference number HCP1200 PTN.

Abstract:

Onset of puberty has been associated with lower body mass index (BMI) in adulthood independent of childhood BMI. However, how the relationship between time of onset of puberty and BMI in adulthood is associated with neurocognitive outcomes is largely unstudied. Here, women were sampled from the Human Connectome Project 1200 PTN release. Inclusion criteria were: 4 (15 minute) resting state fMRI scans, current measured BMI, self-reported age at onset of menstruation (a proxy of age at onset of puberty), and no endocrine complications (e.g., polycystic ovarian syndrome). The effect of age at onset of menstruation, measured BMI at scan date, and the interaction of age at onset of menstruation by BMI on brain functional correlation was modeled using FSLnets controlling for race and age at scan. Corrected significance was set at $p_{FWE} < 0.05$. A final sample of $n=510$ (age $29.5y \pm 3.6$; BMI at scan 25.9 ± 5.6 ; age at onset of menstruation 12.7 ± 1.6) were included. Age at onset of menstruation was negatively associated with BMI at scan ($r = -0.19$, $p < 0.001$). The interaction between age at onset of menstruation and BMI at scan was associated with stronger correlation between a somatosensory and visual network ($t = 3.45$, $p_{FWE} = 0.026$), and a visual network and cingulo-opercular task control network ($t = 4.74$, $p_{FWE} = 0.0002$). We show increased correlation between visual, taste-associated, and self-control brain regions in women at high BMI with later age at onset of menstruation. Together, this implies that the association between later menarche and lower BMI may impart improved self-control during exposure to visual cues.

Keywords:

Puberty, fMRI, cingulo-opercular, somatosensory, BMI

Introduction

Obesity is a global epidemic, with the burden of obesity and related comorbidities greater among women (1). The majority of obesity research in women has focused on reproductive capacity, noting that women with elevated body mass index (BMI) have decreased reproductive capacity and higher infant mortality (2). The health risks associated with high BMI and reproduction are well known, yet the onset of reproductive maturation - puberty - represents an understudied and potentially modifiable childhood risk factor for adult obesity (3).

Puberty, the rapid development of reproductive capacity, represents a period of high physical and cognitive development (4). This sudden increase in development presents challenges for all children, however developing earlier than one's peers conveys additional challenges especially for girls (5). Earlier puberty is related to a host of health problems including gynecological, psychiatric, musculoskeletal, and respiratory conditions (6). Previous research shows that early puberty independently increases the risk of diseases that are seemingly unrelated to reproduction or development, such as: cardiovascular disease (7), metabolic syndrome (8–10), type 2 diabetes (T2D) (9–12), asthma (13), certain cancers (14), and overall reduced life expectancy (15). A common element associated with all of these disease states is elevated BMI (3,16,17). It is possible that BMI drives the increased risk of these conditions associated with early puberty. In support, Gill and colleagues demonstrated a potential causal positive effect of earlier puberty on elevated BMI in adulthood in a large European sample, with the stipulation that hormonal and psychological effects may drive this relationship (18).

Both psychological and hormonal responses are coordinated in the brain, making the brain a strong candidate site for changes contributing to the health problems associated with earlier puberty. Despite the known relationship between earlier onset of puberty, elevated BMI, and psychosocial problems, no study to date has examined the relationship between the onset of puberty, adult BMI, and the brain. This gap in knowledge is surprising considering that the onset of puberty is rooted in neuroendocrine function driven by the brain and body weight. The brain integrates somatic condition, energy balance, genetic predisposition, and seasonality signals, which together trigger human gonadotropin releasing hormone (GnRH) secretion from the hypothalamus. GnRH drives the production and release of luteinizing and follicular stimulating hormones from the pituitary, and stimulates steroid hormone production (4). In turn, the brain, which initiated this increased production of steroid hormones, is sensitive to hormonal reorganization of the hypothalamic, limbic, and prefrontal executive control systems (19–21). The premature flood of steroid hormones in early puberty has been hypothesized to abbreviate adolescent brain reorganization and may potentially underlie the increased onset of psychiatric disorders (19,21). Considering that psychological disturbances in childhood can last through adulthood (21), premature exposure to pubertal hormones may underlie the higher rate of psychological and physical diseases such as anxiety, depression, disordered eating, and obesity in women (22).

While there is a paucity of longitudinal resting state functional magnetic resonance imaging (rfMRI) studies evaluating neural risk factors for obesity from childhood to adulthood, some cross sectional studies (23–25) and two task-based longitudinal imaging studies suggest neural differences exist across the BMI spectrum and may predict weight gain (26,27). Therefore, the present study aimed to assess the relationship between onset of puberty (operationalized as age at onset of menstruation), adult BMI, and resting state functional neural correlations in a large sample of women from the Human Connectome Project (28). We hypothesized that earlier puberty will be related to increased BMI in adulthood and the interaction between earlier puberty and BMI will be related to increased connectivity between reward-related (striatum, somatosensory cortex, and limbic) regions of the brain.

Methods

Sample

Female subjects were selected from the Human Connectome Project (HCP) 1200 parcellation, timeseries, and netmats release (PTN) (29). Participants in the HCP gave written informed consent approved by both the Washington University in St. Louis and the University of Minnesota Institutional Review Boards. Of the 656 females in the full sample, 648 reported their first menstrual cycle was before 24 years of age, 628 did not report any endocrine problems, and 510 had full scan data. Sample characteristics are described in **Table 1**.

Data description and preprocessing

Data collection, preprocessing, and generation of the PTN release has been detailed extensively previously (28,30,31). Briefly, participants completed 4 rfMRI over two days on a 3T Siemens Skyra magnet, totaling 58 min and 12 s of rfMRI data per participant. The HCP data was gathered with a standard protocol using an eight-factor multiband, gradient echo EPI sequence (TR: 720 ms, TE: 33.1 ms, flip angle: 52 degrees, slice thickness: 2.0 mm) (32,33). Participants viewed a light crosshair on a dark background projected into their field of view. The PTN release was extensively preprocessed, and no additional preprocessing was performed locally (30).

Group ICA

Dense connectomes were generated using the incremental group-principal components analysis (PCA) from the Multivariate Exploratory Linear Optimized Decomposition into Independent Components (MELODIC) software (34,35). These dense connectomes were subsequently parcellated using group-independent components analysis (ICA) to create 15 spatial-ICA network maps (36). Because multiple components in a network may include overlap of anatomical regions with other components, independent components (IC) will be referred to by their number and anatomical regions(s) (ex. IC 3 primary visual network).

Individual component timeseries and creation of netmats

Participant timeseries from the 4 scans were concatenated and spatially mapped to the corresponding network map. Dual regression was used to regress each group network map against the individual timeseries to create individual participant network matrices (netmats). Therefore, the netmats represent neural activity in the IC over time.

Statistical analyses

Imaging analyses were performed in FSLNets (Version 0.6, FMRIB, Oxford, UK). Each IC was correlated with every other IC (15x15) to create individual correlation matrices with normalized covariances. A general linear model was then fitted assessing the interaction between BMI at scan, age at onset of menstruation (37,38) (as a proxy of pubertal status) on functional correlations between ICs controlling for race and age at scan.

$$\text{Functional correction matrices (netmat)} = \text{BMI at scan} + \text{Age at onset of menses} + \text{BMI} * \text{Age at onset of menses} + \text{race} + \text{age at scan}$$

The following contrasts were assessed: 1) positive interaction between BMI and age at onset of menses on brain connectivity; 2) negative interaction between BMI and age at onset of menses; 3) positive effect of BMI; 4) negative effect of BMI; 5) positive effect of age at onset of menses; 6) negative effect of age at onset of menses. To correct for potential false positives, non-parametric permutation testing was used through FSL's Randomize tool with 10,000 permutations (39). Results were considered significant at $p_{FWE} < 0.05$. Results were visualized using workbench view <https://github.com/Washington-University/workbench>. To better

characterize what functional networks were present, each IC was parcellated into the 333 area Gordon 2016 functional parcellation for finer detail (40), and Yeo 2011 17-resting state parcellation to assess larger network participation (41). Non-imaging data analyses were performed in R (v. 3.6.1) (42). To visualize the interactions, the top and bottom age at onset of menstruation tertiles were selected and graphed against BMI and the pearson-z corrected correlations between ICs.

Post hoc cognitive performance and twin analyses

The relationship between the interaction of BMI and the onset of menses was also assessed on cognitive performance measures, glycemia, stress, taste sensitivity, physical activity, socio-economic status (SES), and genetic contributions. Cognitive performance measures included: delayed discounting for \$200 and \$4000, NIH Toolbox Picture Sequence Memory, NIH Toolbox Dimensional Change Card Sort Test, NIH Toolbox Flanker Inhibitory Control and Attention Test, NIH Toolbox Cognition Fluid Composite, NIH Toolbox Cognition Total Composite Score, NIH Toolbox Cognition Crystallized Composite.

A subsample of twins ($n = 227$) was selected to test for genetic effects on the interaction between BMI, onset of menses, and functional connectivity. Genetic effects were assessed through the “Mets” package (v. 1.2.6) in R using the “twinlm” function to fit a classical twin model for quantitative traits (43,44). This assessed the following variation: Additive genetic (A), common shared family (C), genetic dominance (D), and nonshared environmental (E) effects. Bonferroni corrections were used to prevent false positives. Significance was set at $p < 0.003$.

Results

Demographics

Sample characteristics can be found in **Table 1** and relationship to BMI and age at onset of menstruation in **Figure 1**. Overall, the sample was predominantly white (73%), with an average age just under 30 years (mean= 29.5 y, SD= 3.6 y). On average women in this sample reported their first menses just before 13 years (mean= 12.7 y, SD= 1.6 y), which is in line with United States national average (45). Compared to white women, Black or African American women reported their first menses earlier ($\beta = -0.11$, $p = 0.02$) and Native American women reported their first menses slightly later ($\beta = 0.08$; $p = 0.04$). Additionally, compared to white women, Asian American, Native Hawaiian, and or Pacific Islander women had lower BMI ($\beta = -0.17$, $p = 0.00005$) whereas Black or African American women had higher BMI on average in this sample ($\beta = 0.22$, $p = 0.0000002$). Asian American, Native Hawaiian, and or Pacific Islander women ($\beta = -0.20$, $p = 0.000006$) and women reporting more than one race ($\beta = -0.15$, $p = 0.0003$) were also on average younger at time of scan than the white women.

Relationship Between Puberty and BMI

Age at onset of menses was negatively related to BMI as an adult controlling for age at scan and race (partial $\eta^2 = 0.03$, $\beta = -0.16$, CI= -0.86, -0.27, $p = 0.0002$).

Brain Correlation Results

The interaction between age at onset of menstruation and BMI was positively associated with functional correlations between IC 12 comprised of the visual cortex and IC 13 comprised of the mouth somatosensory area (**Figure 2A**, $t = 3.45$, $p_{FWE} = 0.026$). Additionally, the interaction of BMI and age at onset of menstruation was positively associated with the functional correlation between IC 3 of the primary visual cortex and IC 6 comprised of the cingulo-opercular network and dorsolateral prefrontal cortex (**Figure 2B**, $t = 4.74$, $p = 0.0002$). Overall, those women who reported earlier menses showed decreased connectivity between the visual cortex and the somatosensory area and cingulo-opercular network with increasing BMI.

The interaction between age at onset of menstruation and BMI was negatively associated with functional correlation between IC 2 the default mode network and IC 3 the primary visual area (**Figure 2C**, $t = 4.03$, $p = 0.004$). As such, those women who reported later onset of menses showed decreased functional correlations between the DMN and primary visual area.

Post Hoc Cognitive Performance and Twin Analysis Results

SES, cognitive function, glycemia, stress, physical activity, and taste were not related to the interaction of BMI and age at onset of menstruation (p 's = 0.24-10.1). The HCP dataset is enriched with twin pairs. **Table 3** outlines the distribution of twins in the sample. Additive genetic (A), common shared family (C), genetic dominance (D), and nonshared environmental (E) effects are shown in **Table 4** and **Figure 3**. Overall, nonshared environment (E) accounted for the most variance for adult BMI, age at onset of menstruation, and correlations between IC 12 and IC 13, and IC 3 and IC 6. Interestingly, age at onset of menstruation remained significantly associated with adult BMI ($z = -3.30$, $SE = 0.23$, $p = 0.001$) when accounting for potential genetic effects. Dominant genetic effects appear to account for the most variance between the correlation between IC 12 and IC 13 as the interaction between BMI and age at onset of menstruation was no longer significantly related. However, the BMI by age at onset of menstruation interaction trended towards significance ($z = 2.61$, $SE = 0.02$, $p = 0.009$) after accounting for potential genetic effects. Comparison of Akaike's Information Criterion between models with heritability estimates versus those without are summarized in **Table 5**. Overall, the inclusion of quantitative heritability factors resulted in more parsimonious models, even with the smaller sample sizes overall (46).

Discussion

The present study assessed the relationship between self-reported onset of puberty, adult BMI, and functional correlation of resting state BOLD response. We confirmed previous research (7,18) showing a negative relationship between age at onset of menstruation and adult BMI. Further, the interaction between age at onset of menstruation and adult BMI was associated with increased connectivity between the visual and cingulo-opercular network. For those with late-onset puberty, visual and cingulo-opercular connectivity increased with increasing BMI, while for women with earlier puberty, decreased visual and cingulo-opercular connectivity was associated with increased BMI. Similarly, women with earlier puberty showed decreased connectivity between the somatosensory network and visual network, whereas this relationship was slightly positive in women with later puberty. Conversely, we found, overall decreased connectivity between the DMN and the visual network in women with later puberty onset, compared to those with earlier onset of puberty.

Post hoc tests did not show any associations between cognitive performance measures, glycemia, stress, taste sensitivity, physical activity, or socio-economic status on the interaction between age at onset of puberty and BMI as an adult. Using a subset of twins, a post hoc quantitative heritability analyses showed unshared environmental factors explained most variation in adult BMI, age at onset of puberty, and functional correlation of brain networks and that the addition of heritability factors resulted in more parsimonious models overall. Notably, the relationship between the interaction of adult BMI and age at onset of menstruation with functional correlation between the somatosensory and visual networks was nullified with the addition of heritability parameters. However, the relationship between functional correlations between the cingulo-opercular and visual networks and the interaction of adult BMI and age at onset of puberty trended toward significance with the addition of heritability parameters. Together, these results indicate the relationship between the cingulo-opercular and visual network accounts for a unique relationship with the interaction of BMI and age at onset of puberty outside of heritability factors, whereas the relationship with the somatosensory and

visual networks and the interaction of BMI and age at onset of menstruation is encompassed within the heritability framework. In conjunction with age at onset of menstruation showing little heritability between twins, this may indicate that childhood obesity is an important unmeasured variable as proposed previously (7,18).

Overall, the interaction between BMI and age at onset of menstruation was related to functional correlation between brain networks associated with top-down control (47), interoception (48), emotional regulation (49), visualization (50), and taste perception (51). Earlier onset of menstruation was related to decreased connectivity between the visual and somatosensory networks with increasing adult BMI. The opposite was found in those with later onset of menstruation, where increased correlations between the somatosensory and visual networks was found with increasing BMI. The somatosensory cortex is canonically made up of the pre- and postcentral gyri, the insula, and anterior opercular areas (51). Connectivity of the somatosensory cortex and visual areas are shown to be important for bodily perception and decision making (52,53). The intersection of taste, bodily perception, and decision making is important for the study of eating behaviors and disordered eating. Positron emission tomography (PET) studies have shown that individuals with high BMI have higher resting state activity in the somatosensory cortex compared to peers with BMI between 18 and 25 (54). Further, elevated BMI has also is related to decreased cohesion between somatosensory and visual networks (55). Both the increased resting state activity of the somatosensory cortex and its reduced cohesion with the visual cortex are hypothesized to increase sensory driven behaviors, such as overeating (54,55). This pattern of decreased cohesion, or correlation, between the visual and somatosensory networks is similar to the pattern seen in our sample, specifically in individuals with earlier onset of menstruation, but not in those with later menstruation. Further, reduced correlations between the somatosensory and visual network has been observed with increasing bulimia symptoms (56). These findings along with our own suggest that the relationship between earlier onset of puberty and adult BMI may be related to increased sensory driven behaviors, but decreased bodily perception (53,55,56). Similarities between functional correlations in individuals who went through puberty early and disordered eating is in line with previous research demonstrating that being more developmentally advanced compared to one's peers is a risk factor for disordered eating in adolescence and adulthood (57–59), specifically for clinical diagnosis of bulimia nervosa (60). Similar retrospective research shows that adult women who reported going through puberty earlier than their peers were more dissatisfied with the physical changes accompanying pubertal development and this predicted eating disorder symptoms (61). Thus, the differences in functional correlation by onset of menstruation and adult BMI may be rooted in a psychosocial etiology.

The insula has been shown to be an integral region for not only somatosensory/taste processing, but also top-down long term task control (51,62,63). Previous research from our group shows increased correlations between a functional network including the occipital pole and another comprised of the insula, central operculum, precentral gyrus, and anterior cingulate in twins with lower BMI compared to their higher BMI twin (24). On the contrary, adolescents with an elevated BMI exhibited reduced global connectivity in a region containing the insula, frontal operculum, and middle temporal gyrus (64). While the insula is important in both studies, these networks appear distinct from the somatosensory and seem to comprise the cingulo-opercular task control network (62). As the name suggests, the cingulo-opercular task control network is implicated in long term task maintenance and goals (62). In the context of the cingulo-opercular network, the insula and dorsal anterior cingulate have specific roles signaling behaviorally important events and updating attentional processes accordingly (65). It is not surprising that the cingulo-opercular network and visual network are functionally correlated, as behaviorally important information and attention often requires visual cue processing (66). Visual processing speed is highly correlated to cingulo-opercular activity (67). The present

analysis showed an inverse relationship between age at onset of menstruation and adult BMI on functional correlations between the cingulo-opercular network and the primary visual network. Similar to the relationship between the somatosensory network and the visual network, individuals who went through puberty early showed decreased connectivity between the cingulo-opercular and primary visual network with increasing BMI. Alternately, women who went through puberty later exhibited increasing connectivity between the cingulo-opercular network and the primary visual network with increasing BMI. This dichotomy in cingulo-opercular network connectivity has been seen across obesity research. Increased insula and superior frontal gyrus activity has been associated with elevated BMI (66), while decreased connectivity between the cingulo-opercular and other networks has also been seen in individuals with high BMI (63). The present results suggest that, in women, age at onset of puberty may contribute to these contrasting results. In a singular, longitudinal weight loss trial, increased functional correlation between the insula and visual cortex was associated with a decrease in BMI (weight loss) (68). Weygandt and colleagues hypothesize that the increased correlation between the insula and visual areas may reflect better goal maintenance in the face of visual food cues (68). Therefore, women who go through puberty later in childhood may have better success losing weight compared to women who go through puberty earlier. This change in the connectivity of the cingulo-opercular network and visual network may occur in adolescence. Executive function networks, including the cingulo-opercular, are in place by middle childhood similar to when puberty occurs (69). This is in accordance with Schulz and colleagues' organizational activational hypothesis, in which earlier exposure to sex hormones results in altered neural organization and adult behavior (20). The present study takes this hypothesis one step further, suggesting that earlier puberty not only results in altered neural organization and behavior, but also altered physiology and sensitivity to weight loss (68).

The interaction of adult BMI and age at puberty onset may additionally influence visual bias toward food related stimuli. Women who went through puberty earlier showed increased functional correlation between the default mode network (DMN) and visual network, whereas women who went through puberty later showed decreased correlation between the areas with increasing adult BMI. The DMN is a peculiar network as it is traditionally characterized by its decrease in activity during external attention tasks (70). This has led to many suggesting that the DMN is simply a rest network, or encoding subconscious neural activity (71). However, the DMN is activated in self-referential tasks, such as autobiographical memory (71). Based on the anatomical structure of the DMN, others have suggested that it represents a "sensory-visceromotor link" (70). Evidence of the sensory-visceromotor function of the DMN has been previously observed in overfed individuals with healthy BMI who exhibited increased activation in the DMN compared to those with an overweight BMI (72). This suggests the DMN is not only inactivated during a task, but also integrates internal visceral and external sensory signals (70). In light of the "sensory-visceromotor" definition, the increased connectivity between the DMN and visual network with increasing BMI and earlier puberty may suggest a shift in the DMN from visceral signals towards sensory stimuli. Similarly, increased DMN and visual network correlations with increased BMI, were previously reported in other studies using the HCP data (24,55). Additionally, regional assessment of the DMN showed an increase in the inferior parietal cortex and posterior cingulate cortex integrates food images with visual attention (73) and generates a bias towards food cues, respectively (74). Therefore, the interaction between age at onset of puberty and high adult BMI may be a unique phenotype of women who are less sensitive to internal visceral signals with a visual bias to food cues.

The novel nature of the findings presented here warranted further characterization, therefore we ran a series of post hoc tests to assess the relation of socio-economic (education, household income), physiological (glycemia, taste sensitivity, physical activity, stress), cognitive (delayed discounting, working memory, inhibitory control), and heritable factors to our results. While we did not have a priori hypotheses related to these measures, all were chosen based on

previous published work: socio-economic (75), physiological (22,58,66,76), cognitive (77–79), and heritability (80,81). Despite these previous relationships, we did not find any association between socio-economic, physiological, nor cognitive measures and the interaction of age at onset of puberty and adult BMI. The lack of association between HCP behavioral measures and BMI is not unique (Doucet et al. 2018; Sadler et al. 2019; Sadler et al. 2018), and could be due to a lack of specificity of the tasks.

Previous genome wide association studies have identified multiple loci related to both earlier puberty and high BMI in adulthood independent of childhood BMI (80). The high frequency of both monozygotic and dizygotic twin pairs within the HCP dataset allowed us to run post hoc analyses exploring potential quantitative genetic factors: additive genetic (A), common environmental (C), dominant genetic (D), and unique environmental factors (E) (82). The ACDE model presumes that monozygotic twins completely share their genetic material, therefore any differences between the twins is attributed to unique environment (which also includes measurement error) (82). Dizygotic twins share an average of half of their genetic material, therefore differences between dizygotic twins could be due to non-shared genetic or non-shared environmental factors (82). Genetic effects can be further divided into additive or dominant effects (82). A factor is considered additive if the correlation of genetic effects is 50%, whereas if the correlation is near 25% it is assumed to be a dominant effect (82). Under these model assumptions, we found that dominant genetic variance ($z = 10.40$, $p < 0.003$) eliminated the significant effect of the age at onset of puberty by adult BMI interaction on functional correlation between the somatosensory and visual networks ($z = 1.46$, $p = 0.14$). Unshared environmental factors accounted for the most variance describing the functional correlation between the cingulo-opercular and visual networks ($z = 11.05$, $p < 0.003$). However, the interaction between age at onset of puberty and adult BMI trended toward significance even after controlling for heritability factors ($z = 2.61$, $p = 0.009$). Age at onset of puberty remained associated with adult BMI after controlling for heritability estimates. In conjunction with age at onset of menstruation showing little heritability between twins, this may indicate that childhood obesity is an important unmeasured variable as proposed previously (7,18). Further, this post hoc analysis highlights the importance of environmental factors in the development of high BMI in adulthood and on functional networks.

Although the cross-sectional nature of this study precludes mechanistic analysis, the dopamine literature suggests a potential mechanism for future research. Dopamine synthesis has been positively correlated with cingulo-opercular network connectivity (83). Additionally, defective dopamine synthesis has been implicated in the overexpression of the orexigenic hypothalamic neuro-peptide Y (84). The cingulo-opercular network has been shown to be preferentially connected to the dopamine sensitive nucleus accumbens (NAcc) (85). Therefore, impaired dopamine synthesis may act via the NAcc to decrease cingulo-opercular connectivity, while simultaneously promoting eating behaviors through the hypothalamus. Earlier onset of menarche has been associated with higher levels of sex hormones and decreased sex hormone binding globulin, allowing for an increase in free sex hormones (12). The limbic-hypothalamic pituitary-adrenal (LHPA) axis is sensitive to sex hormones (22) and dopaminergic projections from the limbic system modulate NAcc activity (86). This additionally aligns with the organizational-activational hypothesis, and hypothesizes that early puberty in women increases free sex hormones which create a cascade effect: decreasing dopamine production and thereby protracting cingulo-opercular connectivity via the NAcc, functionally reorganizing the brain as presented here. The longitudinal adolescent, brain, cognition, and development dataset will facilitate testing this hypothesis, and shed light on the importance of childhood BMI (87).

This study has several notable limitations. First, this is a cross-sectional study with a retrospective proxy of pubertal development. While use of age at onset of menstruation has been reported to have high reproducibility (37), the validation between self-report in adolescents and again in adulthood is only moderate (88). Second, because this study relies on age at onset

of menstruation it precludes subjects who do not menstruate. Therefore, these results are not generalizable to other populations. Third, this sample is predominantly white and was screened to be generally healthy. Given the known differences between racial categories on the age at onset of menstruation (89), further work is needed using more diverse samples. Fourth and finally, evidence exists of a reciprocal relationship between childhood BMI, age at onset of puberty, and adult BMI (7,9,80). These factors may not be independent, but rather synergistic. Childhood BMI may influence the onset of puberty, which in turn may predispose children to metabolic, psychological, and social adversity culminating in poor health in adulthood.

Conclusions

In a large sample of adult women, we found that pubertal onset, operationalized as age of onset of menstruation, was negatively associated with adult BMI. The interaction of pubertal onset and adult BMI was associated with resting state functional correlation of networks. The interaction was associated with decreased connectivity of visual network with somatosensory and cingulo-opercular networks. Early onset of menstruation is established as a risk factor for disease states such as obesity (18), but the present study is the first to show that the interaction of pubertal onset and adult BMI is related to neural connectivity. Our study adds to a growing body of evidence suggesting puberty is a critical period of development for immediate and distal health outcomes.

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672 **Table 1: Sample characteristics by reported race**

	n	BMI (kg/m ²)		Age at Scan (y)		Age of Menses Onset (y)		Hemoglobin A1c (mmol/mol)		
		mean	SD	mean	SD	mean	SD	n	mean	SD
Native American	1	29.23	NA	35.00	NA	16.00	NA	1	5.90	NA
Asian, Native Hawaiian, or Pacific Islander	33	21.62	3.62	26.97	4.29	12.33	1.49	21	5.23	0.31
Black or African American	78	29.12	6.42	29.54	3.43	12.35	1.84	44	5.40	0.35
More than one race	12	25.15	4.13	26.17	3.49	12.92	1.51	8	5.39	0.26
Unknown or chose not to report	10	28.53	4.73	28.10	4.23	12.30	1.83	8	5.29	0.40
White	376	25.60	5.31	29.87	3.43	12.82	1.51	245	5.21	0.37
Total	510	25.94	5.62	29.52	3.61	12.72	1.58	347	5.25	0.37

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675 **Table 2: Relationship between BMI and age of onset of menses**

	Estimate	Standard Error	T value	P value
Intercept	33.84	6.25	5.41	0.00
Menstrual age began (y)	-0.56	0.15	-3.74	0.00
Age (y)	0.13	0.07	1.86	0.06
Asian, Native Hawaiian, or Pacific Islander	-8.66	5.43	-1.60	0.11
Black or African American	-1.48	5.37	-0.28	0.78
More than one race	-4.70	5.56	-0.85	0.40
Unknown or chose not to report	-1.92	5.60	-0.34	0.73
White	-4.77	5.34	-0.89	0.37

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678 **Table 3:** Description of twins in sample

	Monozygotic	Dizygotic	Total
Pairs	64	31	95
Singletons [†]	16	21	37
Total	144	83	227

[†]Singletons refer to individuals who are reported being twins, but their twin was not included in the sample.

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Table 4. Variance estimates and confidence intervals from heritability analysis

Outcome	h^2	a^2	c^2	d^2	e^2
BMI [†]	0.64 (-19.5, 20.8)	0.12 (-60.2, 60.5)	0.01 (-20.1, 20.2)	0.52 (-39.7, 40.7)	0.35 (0.2, 0.5)
Age at onset of menstruation [‡]	0.37 (-3.9, 4.4)	0.17 (-11.7, 12.1)	0.12 (-3.8, 4.1)	0.19 (-7.7, 8.1)	0.50 (0.3, 0.7)
Correlation between IC 12 and IC 13 [§]	0.58 (0.4, 0.7)	0 (0, 0)	0 (0, 0)	0.58 (0.4, 0.7)	0.41 (0.3, 0.6)
Correlation between IC 3 and IC 6 [§]	0.51 (-5.4, 6.4)	0.19 (-17.4, 17.7)	0.05 (-5.8, 5.9)	0.32 (-11.4, 12.1)	0.43 (0.3, 0.6)

Bold indicates p value < 0.003; [†] model adjusted for age at scan, race, and age at onset of menstruation; [‡] model adjusted for age at scan and race; [§] model adjusted for age at scan, age at onset of menstruation, BMI, and the interaction between age at onset of menstruation and BMI. h^2 is the total heritability, a^2 is the additive genetic effect, c^2 is the common environment, d^2 is the dominant genetic effect, and e^2 is the non-shared environmental effect.

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685 **Table 5.** Akaike's Information Criterion of heritability and standard linear models

Model outcome	df	AIC	AICc
BMI [†]			
Linear model	9	3157.73	3158.09
ACDE model	11	1363.04	1365.24
Age at onset of menstruation [‡]			
Linear model	8	1915.63	1915.91
ACDE model	10	818.54	820.35
Correlation between IC 12 and IC13 [§]			
Linear model	11	2971.95	2972.48
ACDE heritability model	13	1306.67	1309.75
Correlation IC 3 and IC [§]			
Linear model	11	2675.86	2676.39
ACDE heritability model	13	1182.99	1186.08
[†] model adjusted for age at scan, race, and age at onset of menstruation; [‡] model adjusted for age at scan and race; [§] model adjusted for age at scan, age at onset of menstruation, BMI, and the interaction between age at onset of menstruation and BMI.			

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688 **Figure 1. Relationship between BMI and Age of Onset of Menses (n=510)**

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690 Caption: Age of onset of menstruation (years) is negatively associated with adult body mass
691 index.

Figure 2. Interaction of Body Mass Index (BMI) and Age at Onset of Menses on Functional Correlation of Brain Networks (n=510)

Caption: A) shows the overall negative relationship between functional correlation of visual cortex (IC13) and mouth somatosensory area (IC12) with body mass index (BMI) in bottom (early) and top (late) age at onset of menstruation tertiles. The interaction with age at onset of menses is such that for women with early onset, the relationship is negative, and for those with late onset the relationship is positive. B) shows the relationship between functional correlation of

primary visual cortex (IC3) and cingulo-opercular network (IC6) with BMI and the interaction with age at onset of menses, which shows that for women with early onset, the relationship is negative, and for those with late onset the relationship is positive. C) shows the overall positive functional correlation of default mode network (IC2) and primary visual cortex (IC3) with BMI. The interaction with age at onset of menses is such that for women with early onset, the relationship is positive, and for those with late onset the relationship is negative. Raw maps represent the fisher z-correlation values per independent component. Standardized maps represent the fisher z-correlation per the Gordon parcellation (40). This allows for better generalization of the IC within the framework of an established map.

Figure 3. Effects of Additive Genetic (A), Common Environmental (C), Dominant Genetic (D), and Unique Environmental Factors (E) on BMI, Age at Onset of Menses, and Functional Neural Correlations

A) shows the effect of additive genetic (A), common environmental (C), dominant genetic (D), and unique environmental Factors (E) on BMI. B) shows the ACDE effects on age at onset of menses. C) shows ACDE effects on the correlation between IC12 (visual cortex) and IC13 (mouth somatosensory area). D) shows the ADCE effect on the correlation between IC3 (visual cortex) and IC6 (cingulo-opercular network).